Design and synthesis of an indol derivative as antibacterial agent against *Staphylococcus aureus*

Hau-Heredia Lenin¹ · Figueroa-Valverde Lauro¹ · Rosas-Nexticapa Marcela² ·
Herrera-Meza Socorro³ · López-Ramos Maria¹ · Díaz-Cedillo Francisco⁴ ·
García-Cervera Elodia¹ · Pool-Gómez Eduardo¹ · Paat-Estrella Josefa¹ ·
Cauich-Carrillo Regina¹ · Euan-Hau Saidy¹

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Abstract Several indole derivatives with antibacterial activity have been prepared using different protocols; however, some require special reagents and conditions. The aim of this study involved the synthesis of some indole derivatives using estrone and OTBS-estrone as chemical tools. The synthesis of the indole derivatives involves reactions such as follows: (1) synthesis of two indol derivatives (**4** or **5**) by reaction of estrone or OTBS-estrone with phenylhydrazine in medium acid; (2) reaction of **4** or **5** with 6-cloro-1-hexyne in medium basic to form two hexynyl-indol (**7** or **8**); (3) preparation of indol-propargylic alcohol derivatives (**10** or **11**) by reaction of benzaldehyde with **7** or **8** in medium basic; (4) synthesis of indol-aldehydes (**12** or **13**) via oxidation of **10** or **11** with DMSO; (5) synthesis of indeno-indol-carbaldehyde (**15** or **16**) via alkynylation/cyclization of **12** or **13** with hexyne in presence of copper(II); (6) preparation indeno-indol-carbaldehyde complex (**19** or **20**) via alkynylation/cyclization of **12** or **13** with 1-(hex-5-yn-1-yl)-2-phenyl-1*H*-imidazole.

The antibacterial effect exerted by the indol-steroid derivatives against *Streptococcus pneumoniae* and *Staphylococcus aureus* bacteria was evaluated using dilution method and the minimum inhibitory concentration (MIC). The results showed that only the compound **19** inhibit the growth bacterial of *S. aureus*. In conclusion, these data indicate that antibacterial activity of **19** can be due mainly to functional groups involved in the chemical structure in comparison with the compounds studied.

Keywords Synthesis · Indole · Estrone · Hexyne · Benzaldehyde · Antibacterial

Introduction

Staphylococcus aureus have been associated with several community-acquired and nosocomial diseases [1, 2]. There are some pharmacological agents for their treatment; however, this pathogen has acquired bacterial resistance with any of these drugs. For example, there are studies which indicate that penicillin induces bacterial resistance in *S. aureus* strains [3, 4]. Therefore, in the search of a therapeutic alternative, some indole-steroid derivatives have been prepared. For example, there is a study that showed the preparation of a series of substituted 1,2,3,4-tetrahydropyrazino [1,2-*a*] indole derivatives with antibacterial activity against *S. aureus* [5]. Other data indicate the preparation of 2,9-disubstituted-1,2,3,4-tetrahydropyrido[3,4-*b*]indoles as potential antibacterial agents on *S. aureus* [6]. In addition, several 1-dialkylaminoacetyl-5/6-fluoroindole-2,3 diones were synthesized with antibacterial activity against *S. aureus* and *Escherichia coli* [7]. Also, a study showed the

✉ Figueroa-Valverde Lauro
lauro_1999@yahoo.com

¹ Laboratory of Investigation, Faculty Chemical-Biological Sciences, University Autonomous of Campeche, Agustin Melgar s/n, C.P. 24039 Bellavista, Campeche, Mexico

² Facultad de Nutrición, Universidad Veracruzana, Médicos y Odontólogos s/n, 91010 Xalapa, Veracruz, Mexico

³ Instituto de Investigaciones Psicológicas, Universidad Veracruzana, Av. Dr. Luis Castelazo Ayala s/n Col Industrial Animas, C.P. 91190 Xalapa, Veracruz, Mexico

⁴ Escuela Nacional de Ciencias Biológicas del Instituto Politécnico Nacional Col. Santo Tomas, Prol. Carpio y Plan de Ayala s/n, D.F. C.P. 11340 México, Mexico

preparation of some hiazolidinonyl-1,3,4-thiadiazino[6,5-b]indoles with bacterial activity on against *S. aureus* and *E. coli* [8]. Other report indicated the preparation of pyridazino[4,3-b]indole-4-carboxylic acids which exert antibacterial activity on *S. aureus* [9]. In addition, a study showed the synthesis of some isoxazolo[4,3-*e*]indoles as antibacterial agents on *S. aureus* [10]. Other study showed the synthesis of 3-aminoalkylated indoles with antibacterial activity against *S. aureus* [11]. All these experimental results show different methods for the preparation of indole derivatives; nevertheless, it is important to mention that some protocols require hazardous reagents as well as different experimental conditions for the preparation of these compounds. Therefore, in this study, an indol-steroid derivative with antibacterial activity against *S. aureus* was prepared using estrone and 3[(*tert*-butyldimethylsilyl)oxy] estrone-1,3,5(10)-trien-17-one (OTBS-estrone) as chemical tools.

Material and methods

General methods

The compound 3[(*tert*-butyldimethylsilyl)oxy]estra-1,3,5-(10)-trien-17-one (OTBS-estrone) was prepared by a previously method reported [12]. In addition, all the compounds evaluated in this study were purchased from Sigma-Aldrich Co. Ltd. The melting points for the different compounds were determined on an Electrothermal (900 model). Infrared spectra (IR) were recorded using KBr pellets on a Perkin Elmer Lambda 40 spectrometer. ¹H and ¹³C NMR spectra were recorded on a Varian VXR-300/5 FT NMR spectrometer at 300 and 75.4 MHz in CDCl₃ using TMS as internal standard. EI-MS spectra were obtained with a Finnigan Trace GCPolaris Q. spectrometer. Elementary analysis data were acquired from a Perkin Elmer Ser. II CHNS/O 2400 elemental analyzer.

Preparation of indole-steroids derivatives via Fisher method

A solution of estrone or compound **2** (100 mg), phenylhydrazine (150 mg, 0.72 mmol), and potassium hydroxide (28 mg, 0.5 mmol) in 5 ml of acetic acid was stirring for 72 h to room temperature. The reaction mixture was evaporated to a smaller volume. After, the mixture was diluted with water and extracted with chloroform. The organic phase was evaporated to dryness under reduced pressure, the residue was purified by crystallization from methanol/water/hexane (4:2:1).

(8*aS*)-8*a*-methyl-1,2,6*b*,7,8,8*a*,8*b*,9,14,14*a*,14*b*-decahydronaphtho[2',1':4,5]indeno[1,2-*b*]indol-4-ol (**4**)

The product yield was 67%; m.p. 106–108 °C; IR (*V*_{max}, cm⁻¹): 3400, 3330, and 1245; ¹H NMR (300 MHz, CDCl₃) δ_H: 1.30–1.52 (m, 2H), 1.60 (s, 3H), 1.66–2.06 (m, 6H), 2.66–6.64 (m, 7H), 6.94 (broad, 2H), 7.20 (m, 1H), 7.22–7.42 (m, 4H) ppm. ¹³C NMR (75.4 Hz, CDCl₃) δ_C: 19.25 (C-25), 26.76 (C-14), 27.56 (C-17), 29.88 (C-18), 31.10 (C-16), 35.30 (C-10), 35.36 (C-15), 36.80 (C-12), 44.50 (C-13), 48.94 (C-11), 110.85 (C-3), 113.22 (C-22), 114.76 (C-8), 115.58 (C-24), 118.22 (C-6), 119.00 (C-5), 121.00 (C-4), 125.64 (C-7), 126.45 (C-21), 134.27 (C-20), 134.86 (C-2), 137.48 (C-19), 153.30 (C-9), 155.00 (C-23) ppm. EI-MS *m/z*: 343.19. Anal. Calcd. for C₂₄H₂₅NO: C, 83.93; H, 7.34; N, 4.08; O, 4.66. Found: C, 83.86; H, 7.26.

(8*aS*)-8*a*-methyl-4-((2-(trimethylsilyl)propan-2-yl)oxy)-1,2,6*b*,7,8,8*a*,8*b*,9,14,14*a*,14*b*-decahydronaphtho[2',1':4,5]indeno[1,2-*b*]indol (**5**)

The product yield was 54%; m.p. 140–142 °C; IR (*V*_{max}, cm⁻¹): 3328, 1248; ¹H NMR (300 MHz, CDCl₃) δ_H: 0.26 (s, 6H), 1.02 (s, 9H), 1.30–1.52 (m, 2H), 1.60 (s, 3H), 1.66–2.06 (m, 6H), 2.66–6.80 (m, 7H), 7.10–7.24 (m, 3H), 7.28 (m, 1H), 7.44 (m, 1H), 8.38 (broad, 1H) ppm. ¹³C NMR (75.4 Hz, CDCl₃) δ_C: -4.48 (C-28, C-29), 18.15 (C-30), 19.30 (C-25), 25.70 (C-31, C-32, C-33), 26.76 (C-14), 27.56 (C-17), 29.78 (C-18), 31.10 (C-16), 35.30 (C-10), 35.36 (C-15), 36.80 (C-12), 44.50 (C-13), 48.94 (C-11), 110.82 (C-3), 112.70 (C-24), 114.76 (C-8), 117.18 (C-22), 118.22 (C-6), 119.00 (C-5), 119.94 (C-24), 121.00 (C-4), 125.65 (C-7), 126.12 (C-21), 133.90 (C-20), 134.86 (C-2), 137.68 (C-19), 153.30 (C-9), 153.40 (C-23) ppm. EI-MS *m/z*: 457.28. Anal. Calcd. for C₃₀H₃₉NOSi: C, 78.72; H, 8.59; N, 3.06; O, 3.50; Si, 6.14. Found: C, 78.60; H, 8.44.

Synthesis of hexynyl-indol derivatives

A solution of **4** or **5** (200 mg), 6-chloro-1-hexyne (90 μl, 0.69 mmol), and potassium hydroxide (28 mg, 0.5 mmol) in 5 ml of methanol was stirring for 72 h to room temperature. The reaction mixture was evaporated to a smaller volume. After, the mixture was diluted with water and extracted with chloroform. The organic phase was evaporated to dryness under reduced pressure, the residue was purified by crystallization from methanol/water (4:2).

(8*aS*)-9-(hex-5-yn-1-yl)8*a*-methyl-1,2,6*b*,7,8,8*a*,9,14,14*a*,14*b*-decahydronaphtho[2',1':4,5]indeno[1,2-*b*]indol-4-ol (**7**)

The product yield was 44%; m.p. 202–204 °C; IR (*V*_{max}, cm⁻¹): 3400, 2120, and 1210; ¹H NMR (300 MHz, CDCl₃)

δ_{H} : 1.30 (m, 1H), 1.56 (s, 3H), 1.58 (m, 1H), 1.66 (t, 2H, $J = 1.89$ Hz), 1.70 (m, 1H), 1.80 (t, 2H, $J = 1.00$ Hz), 1.88 (m, 1H), 1.90 (s, 1H), 2.04–2.06 (m, 4H), 2.18 (t, 2H, $J = 1.00$ Hz), 2.68–3.20 (m, 5H), 4.16 (t, 2H, $J = 1.89$ Hz), 5.60 (broad, 1H), 6.60–6.66 (m, 2H), 7.16–7.18 (m, 2H), 7.20 (m, 1H), 7.24–7.34 (m, 2H) ppm. ^{13}C NMR (75.4 Hz, CDCl_3) δ_{C} : 18.04 (C-28), 20.00 (C-31), 25.86 (C-27), 26.00 (C-14), 27.60 (C-17), 28.42 (C-26), 29.88 (C-18), 31.60 (C-16), 35.60 (C-15), 36.16 (C-12), 40.82 (C-10), 44.50 (C-13), 44.73 (C-25), 53.34 (C-11), 68.54 (C-30), 84.00 (C-29), 107.52 (C-3), 113.00 (C-8), 113.24 (C-22), 115.58 (C-24), 117.22 (C-6), 117.64 (C-4), 118.10 (C-5), 122.20 (C-7), 126.44 (C-21), 133.12 (C-2), 134.14 (C-20), 137.48 (C-19), 151.54 (C-9), 155.00 (C-23) ppm. EI-MS m/z : 423.25. Anal. Calcd. for $\text{C}_{30}\text{H}_{33}\text{NO}$: C, 85.06; H, 7.85; N, 3.30; O, 3.78. Found: C, 85.00; H, 7.76.

(8a*S*)-4-((*tert*-butyldimethylsilyl)oxy)-9-(hex-5-yn-1-yl)-8a-methyl-1,2,6b,7,8,8a,8b, 9,14,14a,14b-decahydronaphtho[2',1':4,5]indeno[1,2-*b*]indole (8)

The product yield was 38%; m.p. 175–178 °C; IR (V_{max} , cm^{-1}): 2124, 1246, and 1212; ^1H NMR (300 MHz, CDCl_3) δ_{H} : 0.26 (s, 6H), 1.02 (s, 9H), 1.30 (m, 1H), 1.54 (s, 3H), 1.58 (m, 1H), 1.66 (t, 2H, $J = 6.00$ Hz), 1.70 (m, 1H), 1.80 (t, 2H, $J = 6.50$ Hz), 1.88–2.06 (m, 6H), 2.18 (t, 2H, $J = 6.50$ Hz), 2.66–3.18 (m, 5H), 4.16 (t, 2H, $J = 7.00$ Hz), 6.70–6.78 (m, 2H), 7.12–7.24 (m, 3H), 7.28 (m, 1H), 7.38 (m, 1H) ppm. ^{13}C NMR (75.4 Hz, CDCl_3) δ_{C} : -4.48 (C-34, C-35), 18.05 (C-28), 18.16 (C-36), 20.00 (C-31), 25.70 (C-37, C-38, C-39), 25.86 (C-27), 25.96 (C-14), 27.56 (C-17), 28.40 (C-26), 29.80 (C-18), 31.60 (C-16), 35.60 (C-15), 36.16 (C-12), 40.82 (C-10), 44.50 (C-13), 44.70 (C-25), 53.34 (C-11), 68.50 (C-30), 84.00 (C-29), 107.50 (C-3), 113.00 (C-8), 117.18 (C-22), 117.30 (C-6), 117.64 (C-4), 118.12 (C-5), 119.94 (C-24), 122.20 (C-7), 126.12 (C-21), 133.10 (C-2), 133.86 (C-20), 137.68 (C-19), 151.60 (C-9), 153.40 (C-23) ppm. EI-MS m/z : 537.34. Anal. Calcd. for $\text{C}_{36}\text{H}_{47}\text{NOSi}$: C, 80.39; H, 8.81; N, 2.60; O, 2.97; Si, 5.22. Found: C, 80.22; H, 8.74.

Preparation of indol-propargylic alcohol derivatives

A solution of **7** or **8** (200 mg), benzaldehyde (100 μl , 0.98 mmol), and potassium hydroxide (20 mg, 0.50 mmol) in 5 ml of methanol was stirring for 72 h to room temperature. The reaction mixture was evaporated to a smaller volume. After, the mixture was diluted with water and extracted with chloroform. The organic phase was evaporated to dryness under reduced pressure, the residue was purified by crystallization from methanol/water: (4:3).

(8a*S*)-9-(7-hydroxy-7-phenylhept-5-yn-1-yl)-8a-methyl-1,2,6b,7,8,8a,9,14,14a,14b-decahydronaphtho[2',1':4,5]indeno[1,2-*b*]indol-4-ol (10)

The product yield was 52%; m.p. 98–100 °C; IR (V_{max} , cm^{-1}): 3402, 2122, and 1210; ^1H NMR (300 MHz, CDCl_3) δ_{H} : 1.30 (m, 1H), 1.56 (s, 3H), 1.58 (m, 1H), 1.66 (t, 2H, $J = 6.00$ Hz), 1.70 (m, 1H), 1.80 (t, 2H, $J = 6.50$ Hz), 1.88–2.06 (m, 5H), 2.20 (t, 2H, $J = 6.78$ Hz), 2.68–3.20 (m, 5H), 3.90 (broad, 2H), 4.16 (m, 2H), 5.50 (s, 1H), 6.58–6.66 (m, 2H), 7.14–7.18 (m, 2H), 7.20 (m, 1H), 7.24–7.34 (m, 2H), 7.40–7.50 (m, 5H) ppm. ^{13}C NMR (75.4 Hz, CDCl_3) δ_{C} : 18.70 (C-28), 20.00 (C-33), 25.96 (C-14), 26.36 (C-27), 27.60 (C-17), 28.42 (C-26), 29.88 (C-18), 31.60 (C-16), 35.60 (C-15), 36.16 (C-12), 40.82 (C-10), 44.50 (C-13), 44.73 (C-25), 53.34 (C-11), 63.34 (C-31), 80.32 (C-30), 84.30 (C-29), 107.52 (C-3), 113.00 (C-8), 113.24 (C-22), 115.58 (C-24), 117.26 (C-6), 117.64 (C-4), 118.10 (C-5), 122.20 (C-7), 126.36 (C-36, C-40), 126.44 (C-21), 128.22 (C-37, C-39), 128.26 (C-38), 133.12 (C-2), 134.10 (C-20), 137.48 (C-19), 141.14 (C-35), 151.52 (C-9), 155.00 (C-23) ppm. EI-MS m/z : 529.29. Anal. Calcd. for $\text{C}_{37}\text{H}_{39}\text{NO}_2$: C, 83.89; H, 7.42; N, 2.64; O, 6.04. Found: C, 83.74; H, 7.32.

7-((8a*S*)-4-((*tert*-butyldimethylsilyl)oxy)-8a-methyl-2,6b,7,8,8a,14,14a,14b-octahydro-naphthol[2',1':4,5]indeno[1,2-*b*]indol-9(1H)-yl)-1-phenylhept-2-yn-1-ol (11)

The product yield was 87%; m.p. 88–90 °C; IR (V_{max} , cm^{-1}): 2120, 1246, and 1212; ^1H NMR (300 MHz, CDCl_3) δ_{H} : 0.26 (s, 6H), 1.02 (s, 9H), 1.30 (m, 1H), 1.56 (s, 3H), 1.58 (m, 1H), 1.64 (t, 2H, $J = 6.00$ Hz), 1.70 (m, 1H), 1.76 (t, 2H, $J = 6.50$ Hz), 1.88–2.06 (m, 5H), 2.20 (t, 2H, $J = 6.78$ Hz), 2.24 (broad, 1H), 2.68–3.28 (m, 5H), 4.16 (m, 2H), 5.50 (s, 1H), 6.70–6.78 (m, 2H), 7.12–7.22 (m, 3H), 7.26 (m, 1H), 7.36 (m, 1H), 7.40–7.50 (m, 5H) ppm. ^{13}C NMR (75.4 Hz, CDCl_3) δ_{C} : -4.46 (C-36, C-43), 18.12 (C-44), 18.70 (C-28), 20.00 (C-33), 25.70 (C-45, C-46, C-47), 26.00 (C-14), 26.36 (C-37), 27.56 (C-17), 28.40 (C-26), 29.84 (C-18), 31.64 (C-16), 35.36 (C-15), 36.12 (C-12), 40.82 (C-10), 44.50 (C-13), 44.70 (C-25), 53.36 (C-11), 63.36 (C-31), 80.36 (C-30), 84.30 (C-29), 107.50 (C-3), 113.00 (C-8), 117.16 (C-22), 117.28 (C-6), 117.60 (C-4), 118.11 (C-5), 119.90 (C-24), 122.20 (C-7), 126.14 (C-21), 126.35 (C-38, C-42), 128.20 (C-39, C-41), 128.26 (C-40), 133.10 (C-2), 133.80 (C-20), 137.68 (C-19), 141.20 (C-37), 151.52 (C-9), 153.32 (C-23) ppm. EI-MS m/z : 643.38. Anal. Calcd. for $\text{C}_{43}\text{H}_{53}\text{NO}_2\text{S}$: C, 80.20; H, 8.30; N, 2.18; O, 4.97; Si, 4.36. S, 6.95; Found: C, 80.06; H, 8.22.

Synthesis of indol-aldehyde derivatives

A solution of **10** or **11** (200 mg, 0.38 mmol) in 5 ml of dimethyl sulfoxide was stirring for 72 h to room temperature. The reaction mixture was evaporated to a smaller volume. After, the mixture was diluted with water and extracted with chloroform. The organic phase was evaporated to dryness under reduced pressure, the residue was purified by crystallization from methanol/water (4:2).

(8a*S*)-8a-methyl-9-(8-oxo-7-phenyloct-5-yn-1-yl)-1,2,6b,7,8,8a,9,14,14a,14b-decahydro naphtho [2',1':4,5] indeno [1,2-*b*]indole-4-carbaldehyde (**12**)

The product yield was 67%; m.p. 120–122 °C; IR ($V_{\max}$, cm^{-1}): 2112, 1728, and 1210; ^1H NMR (300 MHz, CDCl_3) δ_{H} : 1.30 (m, 1H), 1.56 (s, 3H), 1.58 (m, 1H), 1.64 (t, 2H, $J = 6.00$), 1.70 (m, 1H), 1.76 (t, 2H, $J = 6.50$), 1.88–2.06 (m, 5H), 2.12 (t, 2H, $J = 6.78$), 2.68–3.18 (m, 5H), 4.14 (m, 2H), 4.40 (s, 1H), 7.12 (m, 1H), 7.14 (m, 1H), 7.19 (m, 1H), 7.20–7.23 (m, 2H), 7.28 (m, 2H), 7.36 (m, 1H), 7.48 (m, 1H), 7.60 (m, 2H), 7.62 (m, 1H), 9.70–10.06 (m, 2H) ppm. ^{13}C NMR (75.4 Hz, CDCl_3) δ_{C} : 18.90 (C-28), 20.00 (C-34), 26.00 (C-14), 26.40 (C-27), 27.60 (C-17), 28.44 (C-26), 29.60 (C-18), 31.68 (C-16), 35.60 (C-15), 36.16 (C-12), 39.00 (C-31), 40.85 (C-10), 44.53 (C-13), 44.70 (C-25), 53.32 (C-11), 79.77 (C-30), 81.76 (C-29), 107.50 (C-3), 113.00 (C-8), 117.30 (C-6), 117.66 (C-4), 118.10 (C-5), 122.16 (C-7), 124.76 (C-21), 125.44 (C-22), 125.90 (C-38, C-42), 126.10 (C-24), 127.00 (C-40), 131.50 (C-39, C-41), 133.08 (C-2), 135.34 (C-37), 135.90 (C-23), 136.70 (C-19), 150.80 (C-20), 151.56 (C-9), 191.80 (C-32), 192.18 (C-35) ppm. EI-MS m/z : 553.29. Anal. Calcd. For $\text{C}_{39}\text{H}_{39}\text{NO}_2$: C, 84.59; H, 7.10; N, 2.53; O, 5.78. Found: C, 84.48; H, 7.02.

8-((8a*S*)-4-((*tert*-butyldimethylsilyl)oxy)-8a-methyl-2,6b,7,8,8a,14,14a,14b-octahydro-naphthol[2',1':4,5] indeno[1,2-*b*] indol-9(1H)-yl)-2-phenyloct-3-ynal (**13**)

The product yield was 54%; m.p. 100–102 °C; IR ($V_{\max}$, cm^{-1}): 2122, 1728, 1248, and 1212; ^1H NMR (300 MHz, CDCl_3) δ_{H} : 0.26 (s, 6H), 1.02 (s, 9H), 1.30 (m, 1H), 1.56 (s, 3H), 1.58 (m, 1H), 1.64 (t, 2H, $J = 6.00$ Hz), 1.70 (m, 1H), 1.76 (t, 2H, $J = 6.50$ Hz), 1.88–2.06 (m, 5H), 2.12 (t, 2H, $J = 6.78$ Hz), 2.68–3.18 (m, 5H), 4.16 (m, 2H), 4.40 (s, 1H), 6.70–6.78 (m, 2H), 7.12 (m, 1H), 7.14–7.22 (m, 3H), 7.26 (m, 2H), 7.28 (m, 1H), 7.36 (m, 1H), 7.60 (m, 2H), 9.70 (d, 1H, 0.90) ppm. ^{13}C NMR (75.4 Hz, CDCl_3) δ_{C} : -4.46 (C-37, C-44), 18.12 (C-44), 18.90 (C-28), 20.00 (C-34), 25.70 (C-46,

C-47, C-48), 26.00 (C-14), 26.36 (C-27), 27.56 (C-17), 28.40 (C-26), 29.84 (C-18), 31.64 (C-16), 35.60 (C-15), 36.12 (C-12), 39.00 (C-31), 40.82 (C-10), 44.50 (C-13), 44.70 (C-25), 53.36 (C-11), 79.78 (C-30), 81.76 (C-29), 107.50 (C-3), 113.00 (C-8), 117.16 (C-22), 117.28 (C-6), 117.60 (C-4), 118.11 (C-5), 119.90 (C-24), 122.20 (C-7), 125.86 (C-39, C-43), 126.14 (C-21), 126.95 (C-41), 131.50 (C-40, C-42), 133.10 (C-2), 133.80 (C-20), 135.30 (C-38), 137.68 (C-19), 151.52 (C-9), 153.32 (C-23), 191.80 (C-32), ppm. EI-MS m/z : 655.38. Anal. Calcd. for $\text{C}_{44}\text{H}_{53}\text{NO}_2\text{Si}$: C, 80.56; H, 8.14; N, 2.14; O, 4.88; Si, 4.28 Found: C, 80.44; H, 8.06.

Preparation of indeno-indol-carbaldehyde derivatives via alkynylation/cyclization

A solution of **12** or **13** (200 mg), hexyne (100 μl , 0.88 mmol), and copper(II) (100 mg, 0.72 mmol) in 3 ml of MeOH was stirring for 72 h at room temperature. The reaction mixture was evaporated to dryness under reduced pressure. After, the residue was purified by crystallization from methanol/water (4:1).

(8a*S*)-9-(4-(2-formyl-5-pentyl-3-phenylcyclopenta-1,4-dien-1-yl)butyl)-8a-methyl-1,2,6b,7,8,8a,9,14,14a,14b-decahydronaphtho[2',1':4,5] indeno[1,2-*b*]indole-4-carbaldehyde (**15**)

The product yield was 45%; m.p. 82–84 °C; IR ($V_{\max}$, cm^{-1}): 1726 and 1210; ^1H NMR (300 MHz, CDCl_3) δ_{H} : 1.00 (s, 3H), 1.32 (m, 1H), 1.44–1.50 (m, 4H), 1.54 (t, 2H, $J = 6.00$), 1.56 (s, 3H), 1.58–1.70 (m, 2H), 1.76 (t, 2H, $J = 6.50$), 1.86–2.06 (m, 5H), 2.30 (t, 2H, $J = 13.80$), 2.46 (t, 2H, $J = 13.80$), 2.68–4.00 (m, 6H), 4.02 (t, 2H, $J = 14.00$), 6.78 (d, 1H, 1.58 Hz), 7.12 (m, 1H), 7.16 (m, 2H), 7.18 (m, 1H), 7.20–7.24 (m, 2H), 7.30 (m, 1H), 7.36 (m, 1H), 7.46 (m, 1H), 7.50 (m, 2H), 7.60 (m, 1H), 9.20 (d, 1H, $J = 0.90$), 10.02 (d, 1H, $J = 0.75$), ppm. ^{13}C NMR (75.4 Hz, CDCl_3) δ_{C} : 14.10 (C-48), 20.00 (C-34), 22.52 (C-47), 26.00 (C-14), 26.60 (C-27), 27.60 (C-17), 28.70 (C-28), 29.00 (C-26), 29.60 (C-18), 30.88 (C-46), 31.66 (C-16), 32.00 (C-45), 35.60 (C-15), 36.18 (C-12), 40.85 (C-10), 43.76 (C-25), 44.50 (C-13), 51.60 (C-31), 53.34 (C-11), 107.50 (C-3), 113.00 (C-8), 117.30 (C-6), 117.66 (C-4), 118.10 (C-5), 122.16 (C-7), 124.76 (C-21), 125.44 (C-22), 126.10 (C-24), 126.70 (C-40, C-44), 127.65 (C-42), 127.67 (C-32), 128.84 (C-41, C-43), 133.06 (C-2), 135.00 ((C-39), 135.90 (C-23), 136.70 (C-19), 141.30 (C-30), 150.80 (C-20), 151.60 (C-9), 152.70 (C-33), 168.22 (C-29), 186.20 (C-37), 192.18 (C-35) ppm. EI-MS m/z : 635.37. Anal. Calcd. for $\text{C}_{45}\text{H}_{49}\text{NO}_2$: C, 85.00; H, 7.77; N, 2.20; O, 5.03. Found: C, 84.90; H, 7.62.

3-butyl-2-(4-((8a*S*)-4-((*tert*-butyldimethylsilyl)oxy)-8a-methyl-2,6b,7,8,8a,14,14a,14b-octahydronaphtho[2',1':4,5]indeno[1,2-*b*]indol-9(1*H*)-yl)butyl)-5-phenylcyclopenta-1,3-diene-1-carbaldehyde (16)

The product yield was 47%; m.p. 104–106 °C; IR ($V_{\max}$, cm^{-1}): 1728, 1246, and 1212; ^1H NMR (300 MHz, CDCl_3) δ_{H} : 0.26 (s, 6H), 0.98 (s, 3H), 1.04 (s, 9H), 1.30 (m, 1H), 1.44–1.50 (m, 4H), 1.54 (t, 2H, $J = 6.00$ Hz), 1.56 (s, 3H), 1.58–1.70 (m, 2H), 1.76 (t, 2H, $J = 6.50$ Hz), 1.88–2.06 (m, 5H), 2.30 (t, 2H, $J = 13.80$ Hz), 2.46 (t, 2H, $J = 13.80$ Hz), 2.68–3.18 (m, 5H), 4.00 (d, 1H, $J = 1.58$), 4.02 (m, 2H), 670 (m, 1H), 6.74 (d, 1H, $J = 1.00$), 6.78 (m, 1H), 7.12 (m, 1H), 7.16 (m, 2H), 7.20–7.24 (m, 2H), 7.28 (m, 1H), 7.30 (m, 1H), 7.36 (m, 1H), 7.50 (m, 2H), 9.20 (d, 1H, 0.90) ppm. ^{13}C NMR (75.4 Hz, CDCl_3) δ_{C} : -4.46 (C-37, C-50), 14.12 (C-49), 18.14 (C-51), 20.00 (C-34), 22.52 (C-48), 25.70 (C-52, C-53, C-54), 26.00 (C-14), 26.60 (C-27), 27.56 (C-17), 28.70 (C-28), 29.00 (C-26), 29.84 (C-18), 30.84 (C-47), 31.66 (C-16), 32.00 (C-46), 35.60 (C-15), 36.12 (C-12), 40.82 (C-10), 43.80 (C-25), 44.50 (C-13), 51.56 (C-31), 53.36 (C-11), 107.50 (C-3), 113.00 (C-8), 117.16 (C-22), 117.28 (C-6), 117.60 (C-4), 118.11 (C-5), 119.90 (C-24), 122.20 (C-7), 126.14 (C-21), 126.74 (C-41, C-45), 127.66 (C-32, C-43), 128.84 (C-42, C-44), 133.10 (C-2), 133.80 (C-20), 135.00 (C-40), 137.68 (C-19), 141.30 (C-30), 151.60 (C-9), 152.72 (C-33), 153.32 (C-23), 168.22 (C-29), 186.20 (C-38), ppm. EI-MS m/z : 737.46. Anal. Calcd. for $\text{C}_{50}\text{H}_{63}\text{NO}_2\text{Si}$: C, 81.36; H, 8.60; N, 1.90; O, 4.34; Si, 3.80 Found: C, 81.22; H, 8.54.

Preparation of hexynyl-imidazole

A solution of 2-phenyl-1*H*-imidazole (200 mg), 6-chloro-1-hexyne (90 μl , 0.69 mmol), and potassium hydroxide (28 mg, 0.5 mmol) in 5 ml of methanol was stirring for 72 h to room temperature. The reaction mixture was evaporated to a smaller volume. After, the mixture was diluted with water and extracted with chloroform. The organic phase was evaporated to dryness under reduced pressure, the residue was purified by crystallization from methanol/water/hexane (2:1:2).

1-(hex-5-yn-1-yl)-2-phenyl-1*H*-imidazole (18)

The product yield was 45%; m.p. 58–60 °C; IR ($V_{\max}$, cm^{-1}): 2122 and 1210; ^1H NMR (300 MHz, CDCl_3) δ_{H} : 1.66 (t, 2H, $J = 6.00$ Hz), 1.90 (s, 1H), 1.96–4.40 (m, 6H), 6.50 (d, 1H, $J = 0.90$ Hz), 7.20 (m, 2H), 7.21–7.24 (m, 3H), 7.30–7.48 (m, 3H), 7.56 (m, 1H) ppm. ^{13}C NMR (75.4 Hz, CDCl_3) δ_{C} : 18.08 (C-13), 25.82 (C-12), 28.50 (C-11), 44.36 (C-10), 68.50 (C-15), 84.00 (C-14), 102.06 (C-9), 110.60 (C-7), 120.20 (C-6), 12.10 (C-5), 121.50 (C-4), 127.12 (C-17, C-21), 127.70 (C-19), 128.72 (C-3), 129.22 (C-18, C-20), 133.76 (C-8), 138.40

(C-2), 148.56 (C-16) ppm. EI-MS m/z : 273.15. Anal. Calcd. for $\text{C}_{20}\text{H}_{19}\text{N}$: C, 87.87; H, 7.01; N, 5.12. Found: C, 87.74; H, 6.94.

Synthesis of indol-indeno-indol-carbaldehyde derivatives via alkynylation/cyclization

A solution of **12** or **13** (200 mg), 1-(hex-5-yn-1-yl)-2-phenyl-1*H*-imidazole (100 μl , 0.88 mmol), and copper(II) (100 mg, 0.72 mmol) in 3 ml of MeOH was stirring for 72 h at room temperature. The reaction mixture was evaporated to dryness under reduced pressure. After, the residue was purified by crystallization from methanol/hexane/water (4:1:1).

(8a*S*)-9-(4-(2-formyl-3-phenyl-5-(4-(2-phenyl-1*H*-indol-1-yl)butyl)cyclopenta-1,4-dien-1-yl)butyl)-8a-methyl-1,2,6b,7,8,8a,9,14,14a,14b-decahydronaphtho[2',1':4,5]indeno[1,2-*b*]indole-4-carbaldehyde (19)

The product yield was 67%; m.p. 138–140 °C; IR ($V_{\max}$, cm^{-1}): 1728 and 1210; ^1H NMR (300 MHz, CDCl_3) δ_{H} : 1.32 (m, 1H), 1.54 (t, 2H, $J = 6.00$ Hz), 1.56 (s, 3H), 1.58 (m, 1H), 1.60 (t, 2H, $J = 6.00$), 1.70 (m, 1H), 1.76 (t, 2H, $J = 6.50$), 1.86 (m, 1H), 1.96 (t, 2H, $J = 6.50$ Hz), 2.02–2.08 (m, 4H), 2.30 (t, 2H, $J = 13.80$ Hz), 2.50 (t, 2H, $J = 13.80$ Hz), 2.68–3.18 (m, 5H), 4.00 (t, 2H, $J = 14.00$ Hz), 4.05 (m, 1H), 4.30 (t, 2H, $J = 14.00$ Hz), 6.50 (d, 1H, 0.90 Hz), 6.66 (d, 1H, 0.90 Hz), 7.12 (m, 1H), 7.16 (m, 2H), 7.18 (m, 1H), 7.19 (m, 1H), 7.20 (m, 2H), 7.21–7.22 (m, 2H), 7.23 (m, 1H), 7.24 (m, 1H), 7.30 (m, 2H), 7.32 (m, 1H), 7.36 (m, 1H), 7.46 (m, 1H), 7.48 (m, 1H), 7.50 (m, 2H), 7.56 (m, 1H), 7.60 (m, 1H), 9.20 (d, 1H, $J = 0.90$), 10.02 (d, 1H, $J = 0.75$), ppm. ^{13}C NMR (75.4 Hz, CDCl_3) δ_{C} : 20.00 (C-34), 26.00 (C-14), 26.32 (C-46), 26.60 (C-27), 27.60 (C-17), 28.50 (C-28), 29.00 (C-26), 29.18 (C-47), 29.60 (C-18), 31.58 (C-45), 31.66 (C-16), 35.60 (C-15), 36.18 (C-12), 40.85 (C-10), 43.40 (C-48), 43.76 (C-25), 44.50 (C-13), 50.80 (C-31), 53.34 (C-11), 102.10 (C-56), 107.50 (C-3), 110.62 (C-56), 113.00 (C-8), 107.50 (C-3), 110.60 (C-51), 113.00 (C-8), 117.30 (C-6), 117.66 (C-4), 118.10 (C-5), 120.26 (C-52), 121.10 (C-53), 121.50 (C-54), 122.16 (C-7), 124.76 (C-21), 125.44 (C-22), 126.10 (C-24), 126.80 (C-40, C-44), 127.06 (C-59, C-63), 127.27 (C-32), 127.67 (C-42), 127.70 (C-61), 128.70 (C-55), 128.84 (C-41, C-43), 129.20 (C-60, C-62), 133.06 (C-2), 133.70 (C-2), 135.18 (C-39), 135.90 (C-23), 136.70 (C-19), 138.40 (C-50), 141.90 (C-30), 148.54 (C-58), 150.80 (C-20), 151.60 (C-9), 161.30 (C-33), 172.42 (C-29), 186.20 (C-37), 192.18 (C-35) ppm. EI-MS m/z : 826.44. Anal. Calcd. for $\text{C}_{59}\text{H}_{58}\text{NO}_2$: C, 85.68; H, 7.07; N, 3.39; O, 3.87. Found: C, 85.54; H, 7.00.

2-(4-((8a*S*)-4-((*tert*-butyldimethylsilyl)oxy-8a-methyl-2,6*b*,7,8,8*a*,14,14*a*,14*b*-octadeca hydronaphto[2',1':4,5]indeno[1,2-*b*]indol-9(1*H*)-yl)butyl)5-phenyl-3-(4-(2-phenyl-*H*-indol-1-yl)butyl)cyclopenta-1,3-diene-1-carbaldehyde (20)

The product yield was 54%; m.p. 128–130 °C; IR ($V_{\max}$, cm^{-1}): 1726, 1248, and 1212; ^1H NMR (300 MHz, CDCl_3) δ_{H} : 0.26 (s, 6H), 1.04 (s, 9H), 1.32 (m, 1H), 1.54 (t, 2H, $J = 6.00$ Hz), 1.56 (s, 3H), 1.58 (m, 1H), 1.60 (t, 2H, $J = 6.00$), 1.70 (m, 1H), 1.76 (t, 2H, $J = 6.50$), 1.86 (m, 1H), 1.98 (t, 2H, $J = 6.50$ Hz), 2.02–2.08 (m, 4H), 2.30 (t, 2H, $J = 13.80$ Hz), 2.50 (t, 2H, $J = 13.80$ Hz), 2.68–3.18 (m, 5H), 4.00 (t, 2H, $J = 14.00$ Hz), 4.04 (m, 1H), 4.30 (t, 2H, $J = 14.00$ Hz), 6.50 (d, 1H, 0.90 Hz), 6.66 (d, 1H, 0.90 Hz), 6.70–6.78 (m, 2H), 7.12 (m, 1H), 7.16 (m, 2H), 7.18 (m, 1H), 7.20 (m, 2H), 7.22 (m, 1H), 7.23 (m, 1H), 7.24 (m, 1H), 7.28 (m, 1H), 7.30 (m, 2H), 7.32 (m, 1H), 7.36 (m, 1H), 7.46 (m, 1H), 7.48 (m, 2H), 7.56 (m, 1H), 7.60 (m, 1H), 9.20 (d, 1H, $J = 0.90$) ppm. ^{13}C NMR (75.4 Hz, CDCl_3) δ_{C} : -4.50 (C-37, C-59), 18.18 (C-60), 20.00 (C-34), 25.72 (C-61, C-68, C-69), 26.00 (C-14), 26.32 (C-47), 26.60 (C-27), 27.60 (C-17), 28.50 (C-28), 29.00 (C-26), 29.18 (C-48), 29.80 (C-18), 31.58 (C-46), 31.66 (C-16), 35.60 (C-15), 36.18 (C-12), 40.85 (C-10), 43.40 (C-48), 43.76 (C-25), 44.50 (C-13), 50.80 (C-31), 53.34 (C-11), 102.10 (C-57), 107.50 (C-3), 110.62 (C-52), 113.00 (C-8), 117.18 (C-22), 117.30 (C-6), 117.60 (C-4), 118.10 (C-5), 119.90 (C-24), 120.26 (C-53), 121.10 (C-54), 121.50 (C-55), 122.16 (C-7), 126.10 (C-21), 126.80 (C-41, C-45), 127.06 (C-63, C-67), 127.27 (C-32), 127.67 (C-43), 127.70 (C-65), 128.70 (C-56), 128.84 (C-42, C-44), 129.24 (C-64, C-66), 133.06 (C-2), 133.68 (C-58), 133.85 (C-20), 135.18 (C-40), 137.70 (C-19), 138.46 (C-51), 141.88 (C-30), 148.54 (C-62), 151.60 (C-9), 153.34 (C-23), 161.30 (C-33), 172.42 (C-29), 186.20 (C-38) ppm. EI-MS m/z : 928.53. Anal. Calcd. for $\text{C}_{64}\text{H}_{72}\text{N}_2\text{O}_2\text{Si}$: C, 82.71; H, 7.81; N, 3.01; O, 3.44; Si, 3.02. Found: C, 82.60; H, 7.70.

Biological evaluation

Strains The microorganisms in this study belonged to the strain bank at the Department of Pharmaco-Chemistry at the Facultad de Ciencias Químico-biológicas of the University Autonomous of Campeche. The strains are certified by the Center for Disease Control in Atlanta and were as follows. *S. aureus* (ATCC 25923). The strains are kept under refrigeration at 4 °C in special gel (BBL).

Antimicrobial agents The steroids derivatives and the other compounds studied were dissolved in methanol and diluted with distilled water. *Cefotaxime*, *gentamycin*, and *methicillin* were used as control drugs.

Antimicrobial activity The evaluation of antimicrobial effect of the different compounds on the bacterial species was made by a previously method reported [13].

The bacterial specie was incubated on *Staphylococcus* 110 (*S. aureus*) agars for 24 h at 37 °C. After 24 h, it was determined whether growth had taken place or not. In addition, a series of tubes were prepared, the first of which contained 2 ml of culture medium (tripticase soye) at double concentration, and the remainder (11 tubes), contained the same quantity of medium at single concentrations. From the first tube (double concentration), an aliquot of 2 ml of the studied compound (1 mg/ml) was added and stirred, from this tube an aliquot of 2 ml was taken and added to the following tube (simple concentration) and the process was successively repeated until the last 2 ml of dissolution had been used up. After this process, each tube was inoculated with 0.1 ml of the bacterial suspension, whose concentration corresponded to McFarland scale (9×10^8 cells/ml) and all the tubes were incubated at 37 °C for 24 h. Subsequently, a loop was taken from each of them and inoculated into the appropriate cultures for different bacterial organisms and were incubated for 24 h at 37 °C.

Docking Server

Docking calculations were carried out using Docking Server [14]. The MMFF94 force field [15] was used for energy minimization of ligand molecule using the Docking Server. Gasteiger partial charges were added to the ligand atoms. Non-polar hydrogen atoms were merged, and rotatable bonds were defined. Docking calculations were carried out on the HERD2 [16] and PARP [17] protein model. Essential hydrogen atoms, Kollman united atom type charges, and solvation parameters were added with the aid of AutoDock tools. Affinity (grid) maps of $20 \times 20 \times 20$ -Å grid points and 0.375-Å spacing were generated using the Autogrid program [18]. AutoDock parameter set and distance-dependent dielectric functions were used in the calculation of the Vander Waals and the electrostatic terms, respectively. Docking simulations were performed using the Lamarckian genetic algorithm (LGA) and the Solis and Wets local search method [19]. Initial position, orientation, and torsions of the ligand molecules were set randomly. Each docking experiment was derived from two different runs that were set to terminate after a maximum of 250,000 energy evaluations. The population size was set to 150. During the search, a translational step of 0.2 Å and quaternion and torsion steps of 5 were applied.

Statistical analysis

The obtained values are expressed as average $\pm$ S.E, using the SPSS 12.0 program [20].

Fig. 1 Chemical structure of estrone (**1**) and 3[(*tert*-butyldimethylsilyl)oxy]estra-1,3,5(10)-trien-17-one (OTBS-estrone) (**2**)

Results and discussion

In this study, we report a straightforward route for the synthesis of an indol-steroid derivative using estrone and OTBS-estrone (see Fig. 1) to evaluate their antibacterial activity on *S. aureus*.

Preparation of indol-steroid derivatives

In this study, two indol-steroid derivatives (compounds **4** or **5**) were synthesized using different strategies; the first stage (Fig. 2) was achieved by the synthesis of two indol-steroid derivatives (**4** and **5**) using as chemical tools estrone or OTBS-estrone (Figs. 2 and 3). It is noteworthy that there are procedures for preparation of several indole derivatives; however, despite its wide scope, have some drawbacks such as the use of some agents that have limited stability and require special conditions [21–23]. In this study, either estrone or OTBS-estrone was reacted with phenylhydrazine in

presence of acetic acid via Fisher mechanism [24] to form **4** or **5**. The ^1H NMR spectrum of compound **4** showed several signals at 1.60 ppm for methyl group for steroid nucleus; at 1.30–1.52, 1.66–6.64, and 7.20 ppm for steroid moiety; at 7.10, 7.22, and 7.42 ppm for indol group; and at 6.94 ppm for hydroxyl group. The ^{13}C NMR spectrum exhibits the following signals at 19.25 ppm for methyl group bound to steroid nucleus; at 26.76–48.94, 113.22–115.58, 126.45–134.27/137.48, and 155.00 ppm for steroid moiety 110.85, 118.22–125.64, 134.86, and 153.30 ppm for indol group. In addition, the mass spectrum of **4** exhibited molecular ion peak at m/z 343.19.

On the other hand, the compound **5** showed several signals at 0.26–1.02 ppm for methyl groups of the *tert*-butylsilyl fragment; at 1.30–1.52 and 1.66 ppm for steroid moiety; at 7.10–7.24 and 7.44 ppm for indol group; and at 8.38 ppm for amino group. ^{13}C NMR spectrum exhibits the following signals at 4.48–18.15 and 25.70 ppm for methyl groups; at 19.30 for methyl

Fig. 2 Synthesis of two indol derivatives (**4** or **5**). Reaction of estrone (**1**) or OTBS-estrone (**2**) with phenylhydrazine in acid medium to form **4** or **5**. *i* = acetic acid

Fig. 3 Mechanism of reaction involved in the synthesis of indol derivatives

group bound to steroid nucleus; at 26.70–48.94, 114.76–117.18, 119.94, 126.12–133.90, and 137.68–153.40 ppm

for steroid moiety; and at 110.82, 118.22–119.00, 121.00–125.60, and 134.86 ppm for indol group.

Fig. 4 Reaction of indol derivatives (**4** or **5**) with 6-Chloro-1-hexyne (**6**) in medium basic to form two hexynyl-indol (**7** or **8**).
ii = NaOH

Fig. 5 Mechanism of reaction involved in the synthesis of hexynyl-indol derivatives

Finally, the mass spectrum of this compound exhibited molecular ion peak at m/z 457.28.

Functionalization of indol group

There are several reports on the functionalization of indoles; for example, the Dakin oxidation of 4,6-dimethoxyindole-7-carbaldehydes, with $\text{H}_2\text{O}_2/\text{HCl}$ to form several 6-methoxy-4,7-indoloquinones [25]. Other data [26] indicate the 1,4-addition of indoles to enones in presence of $\text{BF}_3 \cdot \text{OEt}_2$. In addition, another study showed the reaction of 5-indole derivatives with aldehyde/ketones in presence of $\text{Dy}(\text{OTf})_3$ in ionic liquid [27]; in this work, the compounds **4** or **5** were reacted with 6-chloro-1-hexyne (Fig. 4) in basic conditions to form the compounds **7** or **8** through a $\text{S}_\text{N}2$ mechanism (Fig. 5). The ^1H NMR spectrum of compound **7** showed several signals at 1.56 ppm for methyl group bound to steroid nucleus; at

1.30, 1.58, 1.70, 1.88, 2.04–2.06, 2.68–3.20, 6.60–6.66, and 7.20 ppm for steroid moiety; at 1.66, 1.80, 2.18, and 4.16 ppm for methylene groups bound to both amino and alkyne groups; at 1.90 ppm for alkyne group; at 5.60 ppm for hydroxyl group; and at 7.10–7.18 and 7.24–7.34 ppm for indol group. The ^{13}C NMR spectrum exhibits the following signals at 20.00 ppm for methyl group; at 18.04, 25.86, 28.40, and 44.70 ppm for methylene groups bound to both amino and alkyne groups; at 26.00–27.60, 29.84–44.50, 53.34, 115.58, 126.44, and 134.14–155.00 ppm for steroid moiety; at 68.54–84.00 ppm for alkyne group; and at 107.52–113.00, 117.22–122.20, and 133.12 ppm for indol group. In addition, the presence of compound **7** was confirmed with mass spectrum which showed a molecular ion at m/z 423.25.

On the other hand, several signals involved in the ^1H NMR spectrum for the compound **8** were found at 0.26–1.02 for protons involved in the *tert*-butyldimethylsilane

Fig. 6 Reaction of hexynyl-indol (**7** or **8**) with benzaldehyde to form two indol-propargylic alcohol derivatives (**10** or **11**). *iii* = NaOH

Fig. 7 Mechanism of reaction involved in the synthesis of indol-propargylic alcohol derivatives

Fig. 8 Synthesis of indol aldehydes (**12** or **13**) via oxidation of **10** or **11** with DMSO (*iv*)

Fig. 9 Synthesis of indeno-indol-carbaldehyde (**15** or **16**) via alkynylation/cyclization of **12** or **13** with hexyne. v = copper(II)/rt

fragment; at 1.54 ppm for methyl bound to steroid nucleus; at 1.30, 1.58, 1.70, 1.88–2.06, 2.66–3.18, 6.70–6.78, and 7.28 ppm for steroid moiety; at 1.66, 1.80, 2.18, and 4.14 ppm for methylene bound to both amino and alkyne groups; and at 7.12–7.24 and 7.38 ppm for indol group. The ^{13}C NMR spectrum showed several signals at –4.48, 18.12, and 25.70 ppm for carbons involved in the *tert*-butyldimethylsilane fragment; at 20.00 ppm for methyl group bound to steroid moiety; at 18.05, 25.56, and 29.80–44.50 ppm for methylene bound to both amino and alkyne groups; at 25.96–27.56, 29.80–49.50, 53.44, 117.18, 119.94, 126.12, and 133.86–153.40 ppm for steroid moiety; at 68.50–84.00 ppm for alkyne group; and at 107.50–113.00, 117.30–118.12, 122.20, and 133.10 ppm for indol group. Finally, the presence of compound **8** was

confirmed with mass spectrum which showed a molecular ion at m/z 537.34.

Propargylic-alcohols derivatives via reaction of terminal alkynes with aldehydes

Since several years ago, several propargylic-alcohols have been prepared using different methods which involve some reagents such as disulfide-oxazolidine [28], $\text{Ti}(\text{O}-i\text{-Pr})_4$ -BINOL complex [29], chiral diamine-coordinated tin(II) triflate [24], $\text{P}(\text{PhCH}_2\text{NCH}_2\text{CH}_2)_3\text{N}$ [30], and others; however, some of these reagents are difficult to handle and require special conditions. Therefore in this study, the compounds **7** or **8** were reacted with benzaldehyde in basic conditions to form the compounds **10** or **11** (Fig. 6); the

Fig. 10 Synthesis of 1-(hex-5-yn-1-yl)-2-phenyl-1*H*-imidazole (**18**). Reaction of 2-phenyl-1*H*-imidazole with 6-Chloro-1-hexyne to form **18**. vi = KOH

Fig. 11 Synthesis of indeno-indol-carbaldehyde complex (19 or 20) via alkylation/cyclization of 12 or 13 with 1-(hex-5-yn-1-yl)-2-phenyl-1H-imidazole (18). *vii* = copper(II)/rt

mechanism of reaction involves a mechanism via S_N2 (Fig. 7). The 1H NMR spectrum for compound 10 showed signals at 1.56 ppm for methyl group bound to steroid nucleus; at 1.30, 1.58, 1.70, 1.88–2.06, 2.68–3.20, 6.58–6.66, and 7.20 ppm for steroid moiety; at 1.66, 1.80, 2.20, and 4.16 ppm for methylene groups bound to both alkyne and amino groups; at 3.90 ppm for hydroxyl group; at 5.50 ppm for methylene group bound to both alkyne and phenyl groups; at 7.14 and 7.24–7.34 ppm for indol group; and at 7.40–7.50 ppm for phenyl group. The ^{13}C NMR spectrum showed several signals at 18.70, 26.36, 28.42, and 44.73 ppm for methylene groups bound to both alkyne and amino groups; at 20.00 ppm for methyl group; at 25.96, 27.60, 29.88–44.50, 53.34, 113.22–115.58, 126.44, 134.10–17.48, and 151.52–155.00; at 63.34 ppm for methylene group bound to both alkyne and phenyl groups; at 80.32–84.30 ppm for alkyne group; at 107.50–113.00, 117.26–122.20, and 133.12 ppm for indol group; and at 126.36, 128.22–128.66, and 141.14 ppm for phenyl bound to carbon of methanol group. In addition, the presence of compound 10 was confirmed with mass spectrum which showed a molecular ion at m/z 529.29.

On the other hand, 1H NMR spectrum for compound 11 showed signals at 0.26–1.02 ppm for protons involved in the *tert*-butyldimethylsilane fragment; at 1.56 ppm for methyl group bound to steroid nucleus; at 1.30, 1.58, 1.70, 1.88–2.06, 2.68–3.28, 6.70–6.78, and 7.28 ppm for steroid moiety; at 1.64, 1.76, 2.20, and 4.16 ppm for methylene groups bound to both alkyne and amino groups; at 2.24 ppm for hydroxyl group; at 5.50 for methylene group bound to both alkyne and phenyl groups; at 7.14–7.22 and 7.36 ppm for indol group; and at 7.40–7.50 ppm for phenyl group. The ^{13}C NMR spectrum showed several signals at –4.46 to 18.12 and 25.70 ppm for carbons involved in the *tert*-butyldimethylsilane fragment; at 18.70, 26.36, 28.40, and 44.70 ppm for methylene groups bound to both alkyne and amino groups; at 20.00 for methyl group bound to steroid nucleus; at 26.00, 27.56, 29.80–44.50, 53.36, 117.16, 119.90, 126.14, 133.80–137.68, and 151.52–153.32 ppm for steroid moiety; 63.36 ppm for carbon bound to both alkyne and phenyl groups; at 80.36–84.30 ppm for alkyne group; and at 107.50–113.00, 117.28–118.11, 122.20, and 133.10 ppm for phenyl bound to carbon of methanol group. Finally, the presence of compound 11 was confirmed with mass spectrum which showed a molecular ion at m/z 643.38.

Fig. 12 Mechanism of reaction involved in the synthesis of indeno-indol-carbaldehyde derivatives

Preparation of indole-carbaldehyde derivatives

Several indol aldehyde have been prepared using different protocols; for example, the synthesis of 2-carbethoxyindole-3-aldehyde by the reaction of 2-carbethoxyindole with phosphoryl chlorid [31]. Other data [32] showed that $TiCl_4/t-BuNH_2$ -promoted hydroamination/annulation of δ -keto-acetylenes to form 2-acylindoles. In addition, a study indicates the preparation of 3-formylindole by the reaction of indole with *N*-methyl aniline using $RuCl_3$ as catalyst [33]. Another report indicated the formylation of indole using tertiary amines and molecular oxygen [34]. Recently, two triazonine-carbaldehyde derivatives were prepared via oxidation of the two triazoninol analogs with dimethyl sulfoxide [35]. Analyzing these data in this study, the compounds **10** and **11** were reacted with 6-chlorohex-1-yne in basic medium to form **12** and **13** (Fig. 8). The 1H NMR spectrum for

compound **12** showed signals at 1.56 ppm for methyl group bound to steroid nucleus; at 1.30, 1.58, 1.70, 1.88–2.06, 2.68–3.18, 7.19, 7.48, and 7.62 ppm for steroid moiety; 1.64, 1.76, 2.12, and 4.14 ppm for methylene groups bound to both alkyne and amino groups; at 4.40 ppm for methylene bound to both aldehyde and phenyl groups; at 7.12, 7.28, and 7.60 ppm for phenyl bound to acetaldehyde group; at 7.14, 7.20–7.23, and 7.36 ppm for indol group; and at 9.79–10.06 ppm for aldehyde groups. The ^{13}C NMR spectrum showed several signals at 20.00 ppm for methyl group bound to steroid nucleus; at 18.90, 26.40, 28.44, 44.70, 79.77, and 124.76–125.40 ppm for methylene groups bound to both alkyne and amino groups; at 26.00, 27.60, 29.60–36.16, 40.85–44.53, 53.32, 126.10, and 135.90–151.56 ppm for steroid moiety; at 39.00 for methylene bound to both aldehyde and phenyl groups; at 191.80–192.18 ppm for aldehyde groups; and at 81.76 ppm for alkyne groups. In addition, the presence of

Fig. 13 Antibacterial activity exert by an indol derivative (compound **19**) against *S. aureus*. The bacterial growth of *S. aureus* was inhibited by cefotaxime (*CEFOT*, 2.61×10^{-4} mg/ml), gentamicin (1.29×10^{-4} mg/ml), ciprofloxacin (*CIPROF*, 1.88×10^{-4} mg/ml), and the compound **19** (2.60×10^{-4} mg/ml). Each bar represents the mean $\pm$ S.E. of nine experiments

compound **12** was confirmed with mass spectrum which showed a molecular ion at m/z 553.29.

On the other hand, the ^1H NMR spectrum showed several signals at 0.26–1.02 ppm for methyl group bound to steroid nucleus; at for protons involved in the *tert*-butyldimethylsilane fragment; at 1.56 ppm for methyl group; at 1.30, 1.58, 1.70, 1.88–2.06, 2.48–3.18, 6.70–6.78, and 7.28 ppm for steroid nucleus; at 1.64, 1.76, 2.12, and 4.16 ppm for methylene groups bound to both alkyne and amino groups; at 4.40 ppm for methylene bound to both aldehyde and phenyl groups; at 7.12, 7.26, and 7.58 ppm for

phenyl bound to acetaldehyde group; at 7.14, 7.22, and 7.36 ppm for indol group; and at 9.72 ppm for aldehyde group. The ^{13}C NMR spectrum showed several signals at -4.46 to 18.12 and 25.70 ppm for carbons involved in the *tert*-butyldimethylsilane fragment; at 18.90, 26.36, 28.40, 44.70 ppm for methylene groups bound to both alkyne and amino groups; at 39.00 ppm for methylene bound to both aldehyde and phenyl groups; at 26.00, 27.56, 29.84–36.12, 40.82–44.50, 53.36, 117.16, 119.90, 126.14, 133.80, 137.68, and 153.32 ppm for steroid moiety; 79.78–81.76 ppm for alkyne group; at 107.50–113.00, 117.28–118.11, 122.20,

Fig. 14 Site of binding for penicillin binding protein from *S. aureus* (3hum) with the compounds 19. Visualized with GLMolViewer after docking analysis with one-click docking

Fig. 15 The scheme shown the contact site of amino acid residues involved in the interaction of penicillin binding protein from *S. aureus* (3hum) with the compound **19**. Visualized with GLMolViewer after docking analysis with one-click docking

133.10, and 151.52 ppm for indol group; and at 191.80 ppm for aldehyde group. Finally, the presence of compound **13** was confirmed with mass spectrum which showed a molecular ion at m/z 655.38.

Preparation of cyclopentadiene via reaction alkynylation/cyclization

Several protocols have been used for the alkynylation/cyclization of terminal alkynes; for example, a study showed that Zn(II)-mediated alkynylation/cyclization of *o*-trifluoroacetyl anilines [36]. Other data [37] indicate the alkynylation/cyclization of 2-aminoaryl ketones in presence of $\text{In}(\text{OTf})_3$. In addition, a report [38] showed that silver-phosphines complex-catalyzed stereoselective cascade alkynylation/cyclization of terminal alkynes. Other data [39, 40] indicates that gold(I)-catalyzed cascade addition/cyclization of terminal alkynes with *ortho*-alkynylaryl aldehyde. In this study, the compound **15** or **16** (Fig. 9) was prepared via alkynylation/cyclization of **12** or **13** using cupric(II). The ^1H NMR spectrum of compound **15** showed several

signals at 1.00 ppm for methyl of arm bound to cyclopentadiene ring; at 1.32, 1.58–1.70, 1.86–2.06, 2.68, 4.00, 7.18, 7.46, and 7.60 ppm for steroid fragment; at 1.44–1.50 and 2.30 ppm for methylene groups bound to cyclopentadiene ring; at 1.54, 1.76, 2.46, and 4.02 ppm for methylene bound to both cyclopentadiene ring and amino group; at 1.56 ppm for methyl group bound to steroid fragment; at 6.78 ppm for cyclopentadiene ring; at 7.12, 7.20–7.24, and 7.36 ppm for indol group; at 7.16, 7.30, and 7.50 ppm for phenyl group bound to cyclopentadiene ring; and at 9.20–10.02 ppm for aldehyde groups. The ^{13}C NMR spectrum showed several signals at 26.00, 27.60, 29.60, 31.66, 35.60, 40.85, 44.50, 53.34, 124.76–126.10, 135.90–136.70, and 150.80 ppm for steroid fragment; at 26.60, 28.70–29.00, and 43.76 ppm for methylene groups bound to both cyclopentadiene ring and amino group; at 51.60, 127.67, 141.30, and 152.70–168.22 ppm for cyclopentadiene ring; at 107.50–12.16, 133.06, and 151.60 ppm for indol group; at 126.70–127.65, 128.84, and 135.00 ppm for phenyl groups bound to cyclopentadiene ring; and at 186.10–192.18 ppm for aldehyde group. Additionally, the presence of compound **15**

Table 1 Amino acid residues involved between the interactions of the compound **19** with the penicillin binding protein from *S. aureus* (3hum) surface

Interactions	Amino acids residues
Hydrogen bonds	Ser ₁₂₉ Lys ₂₅₉
Polar	Leu ₁₁₅ Ala ₁₈₂ Phe ₂₄₁ Tyr ₂₉₁
pi-pi	Phe ₂₄₁
Others	Ser ₇₅ Glu ₁₁₄ Ser ₁₁₆ Ser ₁₃₉ Arg ₁₈₆ Thr ₂₆₀ Ser ₂₆₂ Ser ₂₆₃ Asp ₂₆₄ Tyr ₂₉₁ Glu ₂₉₇

was confirmed with mass spectrum which showed a molecular ion at m/z 635.37.

On the other hand, the ^1H NMR spectrum of compound **16** showed several signals at 0.26, 1.04 for protons involved in the *tert*-butyldimethylsilane fragment; at 0.98 ppm for methyl group bound to cyclopentadiene ring; at 1.56 ppm for methyl bound to steroid nucleus; at 1.30, 1.58–1.70, 1.88–2.06, 2.68, 3.18, 6.70, 6.78, and 7.28 ppm for steroid moiety; at 1.44–1.50 and 2.20 ppm for methylene bound to cyclopentadiene ring; at 1.54, 1.76, 2.46, and 4.02 ppm for methylene groups

Table 2 Decomposed interaction energies (kcal/mol) involved between the compound **19** and the penicillin binding protein from *S. aureus* (3hum) surface

Interactions	Amino acids residues
Hydrogen bonds	Thr ₂₆₀ (−0.1532)
Polar	Lys ₂₅₉ (−0.2010) Ser ₁₃₉ (−0.1767)
Hydrophobic	Phe ₂₄₁ (−1.5019) Tyr ₂₉₁ (−1.4997) Leu ₁₁₅ (−0.8683) Ala ₁₈₂ (−0.1418)
Others	Ser ₁₁₆ (−1.1282) Ser ₂₆₂ (−1.0888) Glu ₂₉₇ (−0.7750) Asp ₂₆₄ (−0.7626) Glu ₁₁₄ (−0.7292) Arg ₁₈₆ (−0.6343) Ser ₂₆₃ (−0.5573) Ser ₇₅ (−0.3518)

bound to both cyclopentadiene and amino groups; at 4.00 and 6.74 ppm for cyclopentadiene ring; at 7.12, 7.20–7.24, and 7.36 ppm for indol group; and at 7.16, 7.30, and 7.50 ppm for phenyl bound to cyclopentadiene ring. The ^{13}C NMR spectrum showed several signals at −4.46, 18.14, and 25.70 ppm for carbons involved in the *tert*-butyldimethylsilane fragment; at 14.12 ppm for methyl of arm which bound to cyclopentadiene ring; at 20.00 ppm for methyl group bound to steroid nucleus; at 22.52, 30.84, and 43.80 for methylene groups bound to cyclopentadiene ring; at 26.00, 27.56, 29.84, 31.66, 35.60–40.82, 44.50, 53.36, 117.16, 119.90, 126.14, 133.80, 137.68, and 153.32 ppm for steroid moiety; at 26.60 and 28.70–29.00 for both cyclopentadiene and amino groups; at 51.56, 127.65, 141.30, 152.72, and 168.22 ppm for cyclopentadiene ring; at 107.50–113.10, 117.28–118.11, 122.20, 133.10, and 151.60 ppm for indol group; at 126.74–127.64, 128.84, and 135.00 for phenyl group bound to cyclopentadiene ring; and at 186.20 ppm for aldehyde group. Finally, the presence of compound **16** was confirmed with mass spectrum which showed a molecular ion at m/z 737.46.

Preparation of 1-hex-5-ynyl-2-phenyl-1H-indole

The synthesis of compound **18** (hexyl-phenylindole) was made by techniques described above for indole derivatives-hexynyl (Fig. 10). It is noteworthy that this compound was prepared to be used as a chemical tool for the following reactions. The ^1H NMR spectrum of compound **18** showed several signals at 1.66, 1.96–4.44 for methylene groups bound to amino group; at 1.90 ppm for alkyne group; at 6.50, 7.21–7.54, and 7.56 for indol group; and at 7.20 and 7.30–7.48 ppm for phenyl group bound to indol. The ^{13}C NMR spectrum showed several signals at 18.08–44.38 ppm for methylene groups bound to amino group; at 68.50–84.00 ppm for alkyne group; 102.06–121.50, 128.72, and 133.76–138.40 ppm for indol group; and at 127.12–127.70, 129.22, and 148.56 ppm for phenyl group bound to indol rings. In addition, the presence of compound **18** was confirmed with mass spectrum which showed a molecular ion at m/z 273.15.

Preparation of phenyl-indol-indeno-indol-carbaldehyde complex via reaction alkynylation/cyclization

The compounds **19** or **20** were prepared by reaction of **18** with **12** or **13** through alkynylation/cyclization of terminal alkynes (Figs. 11 and 12). The ^1H NMR spectrum of compound **19** showed several signals at 1.32, 1.58, 1.70, 1.86, 2.02–2.08, 2.68–3.18, 7.18, 7.48, and 7.60 ppm for steroid moiety; at 1.54, 1.76, 2.50 for methylene groups bound to both cyclopentadiene-carbaldehyde and indol ring; at 1.56 for

methyl group bound to steroid nucleus; 1.60, 1.98, 2.30, 4.00, and 4.30 ppm for methylene groups bound to both cyclopentadiene and indol rings; at 4.05 and 6.66 ppm for cyclopentadiene ring; at 6.50, 7.24, and 7.56 ppm for indol bound to phenyl group; at 7.12, 7.19, 7.23, and 7.36 ppm for indol group bound to steroid nucleus; at 7.16 and 7.32 ppm phenyl group bound to cyclopentadiene ring; and 7.20, 7.30, 7.46, and 7.50 ppm for phenyl group bound to indol group; and at 9.20–10.02 ppm for aldehyde groups. The ^{13}C NMR spectrum showed several signals at 20.00 ppm for methyl group bound to steroid nucleus; at 26.00, 27.60, 29.60, 31.66–40.85, 44.50, 53.34, 124.76, 126.10, 135.90, 136.70, and 150.80–151.60 ppm for steroid moiety; at 26.32, 29.18, 31.58, and 43.76 ppm for methylene groups bound to both cyclopentadiene-carbaldheyde and indol ring; at 26.60, 28.50–29.00, and 43.40 ppm for both cyclopentadiene-carbaldheyde and indol-steroid complex; at 126.80, 127.67, 18.84, and 135.18 ppm for phenyl bound to cyclopentadiene ring; at 107.50, 113.00–118.10, 122.16, 133.06, 133.70, and 138.40 ppm for indol group bound to cyclopentadiene-carbaldheyde; 102.10, 110.62, 120.26–121.50, and 128.70 ppm for indol bound to phenyl group; at 127.06, 127.70 and 129.20, 148.54 ppm for phenyl bound to indol; at 50.80, 127.27, 141.90, 161.30, 172.42 ppm for cyclopentadiene ring; and at 186.20–192.18 ppm for aldehyde groups. In addition, the presence of compound **19** was confirmed with mass spectrum which showed a molecular ion at m/z 826.44.

On the other hand, The ^1H NMR spectrum of compound **20** showed several signals at 0.26, 1.04 ppm for protons involved in the *tert*-butyldimethylsilane fragment; at 1.30, 1.58, 1.70, 1.86, 2.02–2.08, 2.18–3.18, 4.04, 6.70–6.78, and 7.28 ppm for steroid moiety; at 1.56 ppm for methyl group bound to steroid nucleus; at 1.60, 1.98, 2.30, and 4.30 ppm for methylene groups bound to both cyclopentadiene-carbaldheyde and indol ring; at 6.50, 7.22, 7.24, 7.36, and 7.56 ppm for indol bound to phenyl group; at 6.66 ppm for cyclopentadiene ring; at 7.12, 7.18, 7.23 for indol bound to steroid fragment; at 7.16, 7.32, and 7.48 ppm for phenyl bund to cyclopentadiene ring; at 7.20, 7.30, and 7.46 ppm for phenyl bund to indol group; and at 9.20 ppm for aldehyde group. The ^{13}C NMR spectrum showed several signals at –4.50, 18.18, and 25.72 ppm for carbons involved in the *tert*-butyldimethylsilane fragment; at 26.00, 27.60, 29.80, 31.66–40.85, 44.50, 53.34, 117.18, 119.90, 126.10, 133.85, 137.70, and 153.34 ppm for steroid moiety; at 26.32, 29.18, 31.58, and 43.40 ppm for methylene groups bound to both cyclopentadiene-carbaldheyde and indol ring; 26.60, 28.50–29.00, and 43.76 ppm for methylene groups bound to both cyclopentadiene-carbaldheyde and indol-steroid complex; at 126.80, 127.67, 128.84, and 135.18 ppm for phenyl bound to cyclopentadiene ring; at 50.80, 127.27, 141.88, 161.30, and 172.42 ppm for cyclopentadiene ring; at 102.10, 110.62, 120.26–121.50,

128.70, 133.68, and 138.46 ppm for indol bound to phenyl group; at 107.50, 113.00, 117.30–118.10, 122.16, 133.06, and 151.60 ppm for indol-steroid fragment; at 127.06, 127.70, 129.24, and 148.54 ppm for phenyl group bound to indol group; and at 186.20 for aldehyde group. Finally, the presence of compound **20** was confirmed with mass spectrum which showed a molecular ion at m/z 928.53.

Biological activity

On the other hand, in the second step the antibacterial activity of indol-steroid derivative on *S. aureus* was evaluated by means of dilution method and the minimum inhibitory concentration (MIC), using gentamicin, ampicillin, and cefotaxime as control in this study. The results (Fig. 13) indicate that bacterial growth of *S. aureus* was inhibited with *cefotaxime* ($\text{MIC} = 5.23 \times 10^{-4}$ mmol) and *gentamicin* ($\text{MIC} = 2.68 \times 10^{-5}$ mmol). In addition, the bacterial growth of *S. aureus* only in presence of compound **19** ($\text{MIC} = 7.44 \times 10^{-4}$ mmol) was blocked. These data indicate that antibacterial activity of the compound **19** can be due mainly to functional groups involved in the chemical structure of indol-steroid derivative in comparison with the compounds studied. In addition, also this phenomenon could be conditioned by interaction of carbonyl group with some substance involved on *S. aureus* bacteria.

Docking evaluation

In order to evaluate the possibility that the compound **19** could interact with the surface of penicillin binding protein from *S. aureus* (3hum) [41] in this study, a molecular docking model (serverdocking) [42, 43] was used. Theoretical results indicate that hydrogen interaction between the compound **19** with 3hum (Figs. 14 and 15) involves several amino acids residues (Table 1); however, it should be mentioned here that the inhibition of bacterial growth of *S. aureus* could be due in part to the interaction between carbonyl group involved in compound **19** with the amino acid residue Phe₂₄₁. In addition, other theoretical results showed different the decomposed interaction energies (kcal/mol) between the compounds **19** and the amino acid residues from 3hum (Table 2). All these data suggest that the interaction of these compounds with the penicillin binding protein from *S. aureus* is conditioned by their physicochemical properties.

Conclusions

The indol-steroid derivative (compound **19**) is a particularly interesting drug, because its antibacterial activity exerted against *S. aureus* involves a molecular mechanism different

in comparison with other drugs; this phenomenon may constitute a novel therapy for infectious diseases.

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Compliance of ethical standards

Conflict of interest We declare that this manuscript does not have any conflict of financial interests (political, personal, religious, ideological, academic, intellectual, commercial or otherwise) for its publication.

References

- Steinberg J, Clark C, Hackman B (1996) Nosocomial and community-acquired *Staphylococcus aureus* bacteremias from 1980 to 1993: impact of intravascular devices and methicillin resistance. *Clin Infect Dis* 23:255–259
- Emori T, Gaynes R (1993) An overview of nosocomial infections, including the role of the microbiology laboratory. *Clin Microbiol Rev* 6:428–442
- Roman R, Smith J, Walker M, Byrne S, Ramotar K, Dyck B, Kabani A, Nicolle L (1996) Rapid geographic spread of a methicillin-resistant *Staphylococcus aureus* strain. *Clin Infect Dis* 25:698–705
- Speller D, Johnson A, James D, Marples R, Charlett A, George R (1996) Resistance to methicillin and other antibiotics in isolates of *Staphylococcus aureus* from blood and cerebrospinal fluid, England and Wales, 1989–1995. *Lancet* 250:323–325
- Rakesh K, Devender S, Jaspal S, Vibha Y, Ajay K (2006) Synthesis and antibacterial activity of substituted 1,2,3,4-tetrahydropyrazino [1,2-*a*] indoles. *Bioorg Med Chem Lett* 16:413–416
- Seefeld M, Miller W, Newlander K, Burgess W, Payne D, Rittenhouse S (2001) Inhibitors of bacterial enoyl acyl carrier protein reductase (FabI): 2,9-disubstituted 1,2,3,4-tetrahydropyrido[3, 4-*b*]indoles as potential antibacterial agents. *Bioorg Med Chem Lett* 11:2241–2244
- Joshi K, Pathak V, Jain S (1980) Studies of potential organofluorine antibacterial agents. Part 5: synthesis and antibacterial activity of some new fluorine-containing indole-2,3-dione derivatives. *Die Pharm* 35:677–679
- Panwar H, Verma R, Srivastava V, Kumar A (2006) Synthesis of some substituted azetidinonyl and thiazolidinonyl-1,3,4-thiadiazino[6,5-*b*]indoles as prospective antimicrobial agents. *Indian J Chem* 45B:2099–2104
- Palluotto F, Campagna F, Carotti F, Ferappi A, Rosato M, Vitali A (2002) Synthesis and antibacterial activity of pyridazino[4,3-*b*]indole-4-carboxylic acids carrying different substituents at N-2. *Farmaco* 67:63–69
- Pordel M, Abdollahi A, Razavi B (2009) Synthesis and biological evaluation of novel isoxazolo[4,3-*e*]indoles as antibacterial agents. *Russian J Bioorg Chem* 39:211–214
- Ambrus J, Kelso M, Bremner J, Ball A, Casadei G, Lewis K (2008) Structure–activity relationships of 2-aryl-1*H*-indole inhibitors of the NorA efflux pump in *Staphylococcus aureus*. *Bioorg Med Chem Lett* 18:4294–4297
- Fevig T, Katzenellenbogen J (1987) A short, stereoselective route to 16a-(substituted-alkyl)estradiol derivatives. *J Org Chem* 52:247–251
- Stuart D, Bertrand-Laperle M, Burgess Fagnou K (2008) Indole synthesis via rhodium catalyzed oxidative coupling of acetanilides and internal alkynes. *J Am Chem Soc* 130:16474–16475
- Bikadi Z, Hazai E (2009) Application of the PM6 semi-empirical method to modeling proteins enhances docking accuracy of AutoDock. *J Chem Inform*:1–16
- Halgren T (1999) MMFFVI. MMFF9s option for energy minimization studies. *J Comput Chem* 20:720–729
- Nahta R, Yu D, Hung M, Hortobagyi G, Esteva F (2006) Mechanisms of disease: understanding resistance to HER2-targeted therapy in human breast cancer. *Nature Clin Pract Oncol* 3:269–280
- Bièche I, Murcia G, Lidereau R (1996) Poly(ADP-ribose) polymerase gene expression status and genomic instability in human breast cancer. *Clin Cancer Res* 2(7):1163–1167
- Morris M, Goodsell M, Hallyday D, Huey R (1999) Automated docking using a Lamarckian genetic algorithm and an empirical binding free energy function. *J Comput Chem* 19:1639–1662
- Solis F (1981) Minimization by random search techniques. *Mathem Meth Oper Res*:19–30
- Hocht C, Opezzo J, Gorzalczy S, Bramuglia G, Tiara C (1997) Una aproximación cinética y dinámica de metildopa en ratas con coartación aórtica mediante microdiálisis. *Rev Argentina Cardiol* 67:769–773
- Hayakawa K, Yasukouchi T, Kanematsu K (1987) A new approach to the efficient indole synthesis by allene intramolecular cycloaddition. *Tetrahedron Lett* 27:1837–1987
- Barluenga J, Rodríguez F, Fañanás F (2009) Recent advances in the synthesis of indole and quinoline derivatives through cascade reactions. *Chem Asian J* 4:1036–1048
- Ketcha D, Gribble G (1985) A convenient synthesis of 3-acylindoles via Friedel-Crafts acylation of 1-(phenylsulfonyl) indole. A new route to pyridocarbazole-5, 11-quinones and ellipticine. *J Org Chem* 50:5451–5457
- Figueroa-Valverde L, Díaz-Cedillo F, García-Cervera E, Pool-gomez E, Rosas-Nexticapa M (2014) Design and synthesis of two indol-steroid derivatives. *Asian J Chem* 26:4959–4962
- Mahiuddin A, Mitchell P, Bowyer P, Kumar N, Black D (2008) Synthesis of 4,7-indoloquinones from indole-7-carbaldehydes by Dakin oxidation. *Tetrahedron* 64:7136–7142
- Poupaert H, Bukuru J, Gozzo A (1999) Clay (Montmorillonite K10) catalysis of the Michael addition of α,β -unsaturated Jacques carbonyl compounds to indoles: the beneficial role of alcohols. *Monats Für Chem* 130:929–932
- Xueling M, Sanzhong L, Jiaqi H, Pei J (2004) Dy(OTf)₃ in ionic liquid: an efficient catalytic system for reactions of indole with aldehydes/ketones or imines. *Tetrahedron Lett* 45:4567–4570
- Braga L, Appelt H, Silveira C, Wessjohann L, Schneider P (2002) Facile and practical enantioselective synthesis of propargylic alcohols by direct addition of alkynes to aldehydes catalyzed by chiral disulfide–oxazolidine ligands Antonio. *Tetrahedron* 58:10413–10416
- Marshall J, Bourbeau M (2003) Synthesis of enantioenriched propargylic alcohols related to polyketide natural products. A comparison of methodologies. *Org Lett* 5:3197–3199
- Mukaiyama T, Furuya M, Ohtsubo A, Kobayashi S (1991) Highly enantioselective of propargylic alcohols by way of the asymmetric aldol reaction. *Chem Lett* 20:989–992
- Wadhwa K, Chintareddy V, Verkade J (2009) P(PhCH₂NCH₂CH₂)₃N: an efficient lewis base catalyst for the synthesis of propargylic alcohols and Morita-Baylis-Hillman adducts via aldehyde alkynylation. *J Org Chem* 74:6681–6690
- Hong L, Sun W, Liu C, Wang L, Wang R (2010) Asymmetric organocatalytic N-alkylation of indole-2-carbaldehydes with α,β -unsaturated aldehydes: one-pot synthesis of chiral pyrrolo[1,2-*a*]indole-2-carbaldehydes. *Chem Eur J* 16:440–444
- Abbiati G, Casoni A, Canevari V, Nava D, Rossi E TiCl₄/t-BuNH₂-promoted hydroamination/annulation of δ -keto-acetylenes:

- synthesis of novel pyrrolo[1,2-a]indol-2-carbaldehydes. *Org Lett* 8: 4839–4842
34. Shabica C, Howe E, Ziegler J, Tishler M (1946) Improved syntheses of indole-3-aldehyde. *J Am Chem Soc* 68:1156–1157
35. Chen J, Liu B, Liu D, Liu S, Cheng J (2012) The Copper-catalyzed C-3-formylation of indole CH bonds using tertiary amines and molecular oxygen. *Adv Syn Cat* 354:2438–2442
36. Figueroa-Valverde L, Diaz-Cedillo F, Garcia-ervera E, Pool-Gomez E, Rosas-Nexticapa M, Lopez-Ramos M, Vera-Escobedo I (2016) Design and synthesis of two triazonine-carbaldehyde derivatives using several chemical tools. *J Saudi Chem Society* In Press, Doi: [10.1016/j.jscs.2016.03.003](https://doi.org/10.1016/j.jscs.2016.03.003)
37. Jiang B, Si Y (2002) Zn(II)-mediated alkynylation-cyclization of o-trifluoroacetyl anilines: one-pot synthesis of 4-trifluoromethyl-substituted quinoline derivatives. *J Org Chem* 67:9449–9451
38. Lekhok K, Prajapati D, Borua R (2008) Indium(III) trifluoro methanesulfonate: an efficient reusable catalyst for the alkynylation-cyclization of 2-aminoaryl ketones and synthesis of 2,4-disubstituted quinolines. *Synlett* 5:655–658
39. Yu M, Skouta R, Zhou L, Jiang H, Yao X, Li C (2009) Water-triggered, counter-anion-controlled, and silver-phosphines complex-catalyzed stereoselective cascade alkynylation/cyclization of terminal alkynes with salicylaldehydes. *J Org Chem* 74:3378–3383
40. Yao X, Li C (2006) Water-triggered and gold(I)-catalyzed cascade addition/cyclization of terminal alkynes with ortho-alkynylaryl aldehyde. *Org Lett* 8:1953–1955
41. Greninger AL, Chatterjee SS, Chan LC, Hamilton SM, Chambers HF, Chiu CY (2016) Whole-genome sequencing of methicillin-resistant *Staphylococcus aureus* resistant to fifth-generation cephalosporins reveals potential non-mecA mechanisms of resistance. *PLoS One* 18:1–9
42. Liu R, Perez J, Liang D, Saven J (2012) Binding site and affinity prediction of general anesthetics to protein targets using docking. *Anesth Analg* 114:947–955
43. Rosales M, Correa J (2015) The importance of employing computational resources for the automation of drug discovery. *Expert Opinion Drug Dis* 10:213–219