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New bispyrazoline derivatives built around aliphatic chains: Synthesis, characterization and antimicrobial studies

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Abstract. The bispyrazolines **3a–3h** built around the alkyl chains of varying lengths have been synthesized from the cyclization reactions of bischalcones with phenyl hydrazine. The bischalcones **2a–2h** were obtained from the Claisen–Schmidt reactions of acetophenone with various bisaldehydes **1a–1h**. The intermediate bischalcones and final bisheterocyclic compounds have been characterized by means of IR, ^{1}H-NMR, ^{13}C-NMR, Mass (ESI) and elemental analysis. The antibacterial and antifungal activities of the synthesized compounds were also evaluated against the *Klubsellia pneumoniae*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Staphylococcus aureus*, *Bacillius subtilis* and *Aspergillius janus*, *Aspergillus niger* and *Pencillium glabrum*, respectively. The antimicrobial behaviour of the bispyrazolines **3a–3h** is found to be dependent on the length of internal spacer unit.

Keywords. Cyclization reactions; bischalcones; internal spacer; bispyrazolines; alkyl chains and antimicrobial activity.

1. Introduction

The study of heterocyclic systems has attracted the attention of organic chemists in the past decades because of their natural occurrence and large numbers of their derivatives are essential to human life in various forms. Chalconoids are the natural compounds that exhibit a wide spectrum of biological activity. The most common compounds among the chalconoid group are the chalcones which are open chain molecule having two aromatic ring linked by the three carbon fragment. Many of these molecules show beneficial biological activities like antiinflammatory[1] and antiinvasive.[2] These molecules are not only significant because of their biological significances but also act as intermediate in the synthesis of pyrazolines and related heterocyclics. Pyrazolines have gained much interest because of wide range of applications in clinical and pharmaceutical chemistry such as bacterial,[3] depression,[4] pyretic and antiinflammatory,[1] and many industrial applications.[5–9] Thus, chalcones[10–13] are the valuable synthones for the synthetic organic chemists and with proper planning and designing these molecules can be subjected to the synthesis of many exotic heterocyclic compounds. Bischalcones[10,14–17] are the molecules which are formed by joining two chalcone moieties together with the carbon chains of varying lengths and structures. By keeping this aspect in view, the present researches are focussed on the transformations of bischalcones **2a–2h** to bispyrazolines **3a–3h** built around the alkyl chains consisting of three to twelve methylene groups. The major interest behind this study was to investigate the effect of the central spacer length on the formation and antimicrobial behaviour of the final bispyrazolines.

2. Experimental

Melting points reported are uncorrected. IR spectra were scanned in KBr pellets on a Perkin Elmer RXIFT Infrared spectrophotometer. ^{1}H-NMR spectra were recorded on a 400 MHz Bruker spectrometer using TMS as the internal standard. The mass spectra have been scanned on the Waters Micromass Q-T of Micro (ESI) spectrometer. UV-Vis spectra were recorded in MeOH with Shimadzu UV-1800 Spectrophotometer. TLC plates were coated with silica gel suspended in MeOH–$CHCl_3$ and iodine vapours were used as visualizing agent. Bisaldehydes **1a–1h** were prepared according to the reported methods.[18,19]

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2.1 *Synthesis of (2E,2′E)-3,3′-(4,4′-(ethane-1,2-diylbis(oxy))bis(4,1-phenylene)) bis(1-phenylprop-2-en-1-one)* ***2a***

A mixture of acetophenone (0.910 g, 0.0072 mol), bisaldehyde **1a** (1.0 g, 0.0036 mol) and NaOH (0.01 mol) in EtOH (25.0 ml) was stirred for 12 h at room temperature. The reaction was monitored by TLC and after the completion of reaction, the mixture was poured into iced-HCl to provide a crude material which was crystallized from CH_3OH:$CHCl_3$ (3:1) to yield a pure compound **2a**.

2a: Brown solid; Yield 64%; m.p.: 102–104°C. UV-Vis (MeOH) λ_{max}(nm): 328, 250; IR (KBr) cm^{-1} 2964, 2856 (methylene C-H), 1602 (C=C), 1657 (C=O); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.01 (4H, dd, $J_{p,o}$ = 1.1, 8.8 Hz, H-2', 6'), 7.73 (2H, d, J_{trans} = 15.6 Hz, H-3), 7.52 (6H, m, H-3', 4', 5'), 7.42 (4H, td, $J_{p,o}$ = 1.2, 8.8 Hz, H-2", 6"), 7.39 (2H, d, J_{trans} = 15.6 Hz, H-2), 6.90 (4H, td, $J_{p,o}$ = 1.2, 8.8 Hz, H-3", 5"), 4.01 (4H, t, J_{vic} = 6.3 Hz, O***CH***$_2$$CH_2$); (MS-ESI): m/z $(M+H)^+$ 475. Anal. Calc. for $C_{33}O_4H_{28}$: Calc. C, 81.01%; H, 5.48%; Found: C, 81.07%; H, 5.42%.

2.2 *Synthesis of (2E,2′E)-3,3′-(4,4′-(propane-1,3-diylbis(oxy))bis(4,1-phenylene)) bis(1-phenylprop-2-en-1-one)* ***2b***

The bischalcone **2b** was synthesized from the reaction of bisaldehyde **1b** (1.0 g, 0.0035 mol) with acetophenone (0.864 g, 0.0070 mol) under the similar conditions as used for **2a**.

2b: Brown solid; Yield 77%; m.p.: 156–158°C. UV-Vis (MeOH) λ_{max}(nm): 353, 246; IR (KBr) cm^{-1} 2960, 2850 (methylene C-H), 1600 (C=C), 1658 (C=O); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.00(4H, dd, $J_{p,o}$ = 1.1, 8.8 Hz, H-2', 6'), 7.78 (2H, d, J_{trans} = 15.6 Hz, H-3), 7.58 (6H, m, H-3', 4', 5'), 7.49 (4H, td, $J_{p,o}$ = 1.2, 8.8 Hz, H-2", 6"), 7.41 (2H, d, J_{trans} = 15.6 Hz, H-2), 6.94 (4H, td, $J_{p,o}$ = 1.2, 8.8 Hz, H-3", 5"), 4.23 (4H, t, J_{vic} = 6.3 Hz, O***CH***$_2$$CH_2$), 2.31 (2H, quintet, J_{vic} = 6.3 Hz, OCH_2***CH***$_2$); (MS-ESI): m/z $(M+H)^+$ 489. Anal. Calc. for $C_{33}O_4H_{28}$: Calc. C, 81.14%; H, 5.73%; Found: C, 81.20%; H, 5.78%.

2.3 *Synthesis of (2E,2′E)-3,3′-(4,4′-(butane-1,4-diylbis(oxy))bis(4,1-phenylene)) bis(1-phenylprop-2-en-1-one)* ***2c***

The bischalcone **2c** was prepared from the reaction of bisaldehyde **1c** (1.0 g, 0.0034 mol) with acetophenone (0.816 g, 0.0068 mol) under the similar conditions as used for **2a**.

2c: White solid; Yield 80%; m.p.: 70–72°C. UV-Vis (MeOH) λ_{max}(nm): 347, 245; IR (KBr) cm^{-1} 2931, 2875 (methylene C-H), 1598 (C=C), 1659 (C=O); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.01 (4H, dd, J_o = 8.5, 1.1 Hz, H-2', 6'), 7.78 (2H, d, J_{trans} = 15.6 Hz, H-3), 7.57 (6H, m, H-3', 4', 5'), 7.47 (4H, m, H-2", 6"), 7.41 (2H, d, J_{trans} = 15.6 Hz, H-2), 6.92 (4H, d, J_o = 8.4 Hz, H-3", 5"), 4.10 (4H, t, J_{vic} = 5.3 Hz, O***CH***$_2$$CH_2$), 2.02 (4H, quintet, J_{vic} = 5.3 Hz, OCH_2***CH***$_2$); (MS-ESI): m/z $(M+H)^+$ 503. Anal. Calc. for $C_{34}O_4H_{30}$: Calc. C, 81.20%; H, 5.97%; Found: C, 81.14%; H, 5.92%.

2.4 *Synthesis of (2E,2′E)-3,3′-(4,4′-(pentane-1,5-diylbis(oxy))bis(4,1-phenylene)) bis(1-phenylprop-2-en-1-one)* ***2d***

The bischalcone **2d** was synthesized from the reaction of bisaldehyde **1c** (1.0 g, 0.0032 mol) with acetophenone (0.778 g, 0.0065 mol) under the similar conditions as used for **2a**.

2d: Yellow solid; Yield 68%; m.p.: 120–122°C. UV-Vis (MeOH) λ_{max}(nm): 312, 238; IR (KBr) cm^{-1} 2945, 2860 (methylene C-H), 1597 (C=C), 1658 (C=O); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.00 (4H, d, J_o = 7.2 Hz, H-2', 6'), 7.78 (2H, d, J_{trans} = 15.8 Hz, H-3), 7.58 (4H, d, J_o = 7.6 Hz, H-2", 6"), 7.52 (6H, m, H-3', 4', 5'), 7.40 (2H, d, J_{trans} = 15.8 Hz, H-2), 6.92 (4H, d, J_o = 7.6 Hz, H-3", 5"), 4.06 (4H, t, J_{vic} = 6.3 Hz, O***CH***$_2$$CH_2CH_2$), 1.87 (4H, quintet, J_{vic} = 6.3 Hz, OCH_2***CH***$_2$$CH_2$), 1.69 (2H, quintet, J_{vic} = 6.3 Hz, OCH_2CH_2***CH***$_2$); (MS-ESI): m/z $(M+Na)^+$ 539. Anal. Calc. for $C_{35}O_4H_{32}$: Calc. C, 81.39%; H, 6.20%; Found: C, 81.32%; H, 6.26%.

2.5 *Synthesis of (2E,2′E)-3,3′-(4,4′-(hexane-1,6-diylbis(oxy))bis(4,1-phenylene)) bis(1-phenylprop-2-en-1-one)* ***2e***

The bischalcone **2e** was obtained from the reaction of bisaldehyde **1e** (1.0 g, 0.0030 mol) with acetophenone (0.744 g, 0.0062 mol) under the similar conditions as described earlier for **2a**.

2e: Brown solid; Yield 75%; m.p.: 80–82°C. UV-Vis (MeOH) λ_{max}(nm): 320, 235; IR (KBr) cm^{-1} 2938, 2863 (methylene C-H), 1593 (C=C), 1654 (C=O); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.01 (4H, d, J_o = 7.3 Hz, H-2', 6'), 7.78 (2H, d, J_{trans} = 15.7 Hz, H-3),

7.58 (4H, dd, $J_{p,o}$ = 1.1, 8.8 Hz, H-2", 6"), 7.50 (6H, m, H-3', 4', 5'), 7.41 (2H, d, J_{trans} = 15.7 Hz, H-2), 6.91 (4H, $J_{p,o}$ = 1.1, 8.8 Hz, H-3", 5"), 4.02 (4H, t, J_{vic} = 6.4 Hz, O***CH***$_2$CH$_2$CH$_2$), 1.84 (4H, quintet, J_{vic} = 6.4 Hz, OCH$_2$***CH***$_2$CH$_2$), 1.56 (4H, t, J_{vic} = 6.4 Hz, OCH$_2$CH$_2$***CH***$_2$); (MS-ESI): m/z (M+H)$^+$ 531. Anal. Calc. for $C_{36}O_4H_{34}$: Calc. C, 81.50%; H, 6.40%; Found: C, 81.57%; H, 6.45%.

2.6 *Synthesis of (2E,2′E)-3,3′-(4,4′-(octane-1,8-diylbis(oxy))bis(4,1-phenylene)) bis(1-phenylprop-2-en-1-one)* ***2f***

The bischalcone **2f** was prepared from the reaction of bisaldehyde **1f** (1.0 g, 0.0026 mol) with acetophenone (0.714 g, 0.0058 mol) under the similar conditions as used for **2a**.

2f: Yellow solid; Yield 60%; m.p.: 64–66°C. UV-Vis (MeOH) λ_{max}(nm): 318, 253; IR (KBr) cm^{-1} 2940, 2845 (methylene C-H), 1599 (C=C), 1655 (C=O); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.00 (4H, dd, $J_{p,o}$ = 1.1, 8.2 Hz, H-2', 6'), 7.80 (2H, d, J_{trans} = 15.5 Hz, H-3), 7.60 (6H, m, H-3', 4', 5'), 7.50 (4H, m, H-2", 6"), 7.41 (2H, d, J_{trans} = 15.5 Hz, H-2), 6.39 (4H, d, J_o = 8.8 Hz, H-3", 5"), 4.00 (4H, t, J_{vic} = 6.9 Hz, O***CH***$_2$CH$_2$CH$_2$CH$_2$), 1.81 (4H, quintet, J_{vic} = 6.4 Hz, OCH$_2$***CH***$_2$CH$_2$CH$_2$), 1.48 (4H, t, J_{vic} = 5.4 Hz, OCH$_2$CH$_2$***CH***$_2$CH$_2$), 1.41 (4H, t, J_{vic} = 5.6 Hz, OCH$_2$CH$_2$CH$_2$***CH***$_2$); (MS-ESI): m/z (M+H)$^+$ 559. Anal. Calc. for $C_{38}O_4H_{38}$: Calc. C, 82.31%; H, 6.85%; Found: C, 82.36%; H, 6.89%.

2.7 *Synthesis of (2E,2′E)-3,3′-(4,4′-(decane-1,10-diylbis(oxy))bis(4,1-phenylene)) bis(1-phenylprop-2-en-1-one)* ***2g***

The bischalcone **2g** was synthesized by reacting bisaldehyde **1g** (1.0 g, 0.0024 mol) with acetophenone (0.650 g, 0.0056 mol) under the similar conditions as described earlier for **2a**.

2g: Brown solid; Yield 69%; m.p.: 96–98°C. UV-Vis (MeOH) λ_{max}(nm): 320, 246; IR (KBr) cm^{-1} 2920, 2835 (methylene C-H), 1603 (C=C), 1665 (C=O); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.02 (4H, dd, $J_{p,o}$ = 1.1, 8.2 Hz, H-2', 6'), 7.78 (2H, d, J_{trans} = 15.5 Hz, H-3), 7.56 (6H, m, H-3', 4', 5'), 7.47 (4H, d, J_o = 8.9 Hz, H-2", 6"), 7.39 (2H, d, J_{trans} = 15.5 Hz, H-2), 6.36 (4H, d, J_o = 8.8 Hz, H-3", 5"), 3.99 (4H, t, J_{vic} = 6.9 Hz, O***CH***$_2$CH$_2$CH$_2$CH$_2$CH$_2$), 1.80 (4H, quintet, J_{vic} = 6.4 Hz, OCH$_2$***CH***$_2$CH$_2$CH$_2$CH$_2$), 1.46 (4H, t, J_{vic} = 5.4 Hz, OCH$_2$CH$_2$***CH***$_2$CH$_2$CH$_2$), 1.40 (4H, t, J_{vic} = 5.6 Hz, OCH$_2$CH$_2$CH$_2$***CH***$_2$CH$_2$), 1.20 (4H, t, J_{vic} = 6.9 Hz, OCH$_2$CH$_2$CH$_2$CH$_2$***CH***$_2$); (MS-ESI): m/z (M+Na)$^+$ 609. Anal. Calc. for $C_{40}O_4H_{42}$: Calc. C, 83.04%; H, 7.26%; Found: C, 82.97%; H, 7.21%.

2.8 *Synthesis of (2E,2′E)-3,3′-(4,4′-(dodecane-1,12-diylbis(oxy))bis(4,1-phenylene)) bis(1-phenylprop-2-en-1-one)* ***2h***

The bischalcone **2h** was synthesized by reacting bisaldehyde **1h** (1.0 g, 0.0022 mol) with acetophenone (0.617 g, 0.0054 mol) under the similar conditions as described earlier for **2a**.

2h: Brown solid; Yield 61%; m.p.: 86–88°C. UV-Vis (MeOH) λ_{max}(nm): 314, 259; IR (KBr) cm^{-1} 2918, 2849 (methylene C-H), 1596 (C=C), 1654 (C=O); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.00 (4H, dd, $J_{p,o}$ = 1.1, 8.2 Hz, H-2', 6'), 7.75 (2H, d, J_{trans} = 15.5 Hz, H-3), 7.54 (6H, m, H-3', 4', 5'), 7.42 (4H, d, J_o = 8.9 Hz, H-2", 6"), 7.34 (2H, d, J_{trans} = 15.5 Hz, H-2), 6.32 (4H, d, J_o = 8.8 Hz, H-3", 5"), 3.96 (4H, t, J_{vic} = 6.9 Hz, O***CH***$_2$CH$_2$CH$_2$CH$_2$CH$_2$CH$_2$), 1.78 (4H, quintet, J_{vic} = 6.4 Hz, OCH$_2$***CH***$_2$CH$_2$CH$_2$CH$_2$CH$_2$), 1.48 (4H, t, J_{vic} = 5.4 Hz, OCH$_2$CH$_2$***CH***$_2$CH$_2$CH$_2$CH$_2$), 1.38 (4H, t, J_{vic} = 5.6 Hz, OCH$_2$CH$_2$CH$_2$***CH***$_2$CH$_2$CH$_2$), 1.15 (8H, t, J_{vic} = 6.9 Hz, OCH$_2$CH$_2$CH$_2$CH$_2$***CH***$_2$***CH***$_2$); (MS-ESI): m/z (M+Na)$^+$ 637. Anal. Calc. for $C_{42}O_4H_{46}$: Calc. C, 83.21%; H, 7.49%; Found: C, 83.29%; H, 7.54%.

2.9 *Synthesis of 1,2-bis(4-(1,3-diphenyl-4,5-dihydro-1H-pyrazol-5-yl) phenoxy)ethane* ***3a***

A mixture of bischalcone **2a** (1.0 g, 0.0020 mol), phenyl hydrazine (0.4426 g, 0.0040 mol) and glacial AcOH (5 ml) in dry EtOH (30 ml) was refluxed for 8 h. The progress of reaction was monitored by TLC. The resulting reaction mixture was concentrated under vacuum to obtain a solid product which was crystallized from $CHCl_3$:CH_3OH (1:3) to yield pure bispyrazoline **3a**.

3a: Brown solid; Yield 70%; m.p.: 90–92°C. UV-Vis (MeOH) λ_{max}(nm): 355, 252, 230; IR (KBr) cm^{-1} 1590, 1505 (C=N, C=C), 2922, 2846 (methylene C-H); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.67 (4H, dd, $J_{p,o}$ = 1.1, 8.8 Hz, H-2", 6"), 7.36 (6H, m, H-3", 4", 5"), 7.25 (4H, m, H-2', 6'), 7.18 (6H, m, H-3', 4', 5'), 7.12 (4H, dd, $J_{p,o}$ = 1.1, 8.8 Hz, H-2"', 6"'), 6.80 (4H, dd, $J_{p,o}$ = 1.1, 8.8 Hz, H-5"', 3"'), 5.23 (2H, dd, J_{XA} = 7.1, J_{XM} = 12.1 Hz, H_X), 4.00 (4H, t, J_{vic} = 6.3 Hz, O***CH***$_2$CH$_2$),

3.76 (2H, dd, J_{AM} = 17.0, J_{MX} = 12.00 Hz, H_M), 3.10 (2H, dd, J_{AX} = 7.1, J_{AM} = 17.2 Hz, H_A); (MS-ESI): m/z $(M+H)^+$655. Anal. Calc. for $C_{45}O_2N_4H_{40}$: Calc. C, 80.73%; H, 5.81%; N, 8.56%; Found: C, 80.78%; H, 5.88%; N, 8.49%.

2.10 *Synthesis of 1,3-bis(4-(1,3-diphenyl-4,5-dihydro-1H-pyrazol-5-yl) phenoxy)propane **3b***

The bispyrazoline **3b** was obtained from the reaction of bischalcone **2b** (1.0 g, 0.00200 mol) with phenyl hydrazine (0.443 g, 0.00400 mol) under the similar conditions as described earlier for **3a**.

3b: Mustard brown solid; Yield 75%; m.p.: 95–97°C. UV-Vis (MeOH) λ_{max}(nm): 356, 253, 218; IR (KBr) cm^{-1} 1597, 1503 (C=N, C=C), 2926, 2849 (methylene C-H); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.70 (4H, dd, $J_{p,o}$ = 1.1, 8.8 Hz, H-2", 6"), 7.38 (6H, m, H-3", 4", 5"), 7.30 (4H, m, H-2', 6'), 7.20 (6H, m, H-3', 4', 5'), 7.08 (4H, dd, $J_{p,o}$ = 1.1, 8.8 Hz, H-2"', 6"'), 6.85 (4H, dd, $J_{p,o}$ = 1.1, 8.8 Hz, H-5"', 3"'), 5.20 (2H, dd, J_{XA} = 7.1, J_{XM} = 12.1 Hz, H_X), 4.08 (4H, t, J_{vic} = 6.3 Hz, O***CH***$_2$$CH_2$), 3.78 (2H, dd, J_{AM} = 17.0, J_{MX} = 12.00 Hz, H_M), 3.08 (2H, dd, J_{AX} = 7.1, J_{AM} = 17.2 Hz, H_A), 2.20 (2H, quintet, J_{vic} = 6.3 Hz, OCH_2***CH***$_2$); (MS-ESI): m/z $(M+H)^+$ 669. Anal. Calc. for $C_{45}O_2N_4H_{40}$: Calc. C, 80.51%; H, 5.98%; N, 8.38%; Found: C, 80.56%; H, 5.93%; N, 8.44%.

2.11 *Synthesis of 1,4-bis(4-(1,3-diphenyl-4,5-dihydro-1H-pyrazol-5-yl) phenoxy)butane **3c***

The bispyrazoline **3c** was obtained from the reaction of bischalcone **2c** (1.0 g, 0.00198 mol) with phenyl hydrazine (0.430 g, 0.00398 mol) under the similar conditions as described earlier for **3a**.

3c: Pale yellow solid; Yield 70%; m.p.: 110–112°C. UV-Vis (MeOH) λ_{max}(nm): 368, 246, 220; IR (KBr) cm^{-1} 1590, 1513 (C=N, C=C), 2930, 2850 (methylene C-H); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.65 (4H, dd, $J_{p,o}$ = 1.4, 8.5 Hz, H-2", 6"), 7.30 (4H, m, H-3", 5"), 7.22 (2H, m, H-4"), 7.10 (8H, m, H-2', 3', 5', 6'), 7.00 (4H, dt, $J_{p,o}$ = 1.1, 8.5 Hz, H-2"', 6"'), 6.74 (4H, dt, $J_{p,o}$ = 1.1, 8.6 Hz, H-3"', 5"'), 6.68 (2H, dt, $J_{m,o}$ = 2.6, 4.6 Hz, H-4'), 5.14 (2H, dd, J_{XM} = 12.2, J_{XA} = 7.04 Hz, H_X), 3.73 (4H, brs, O***CH***$_2$$CH_2$), 3.69 (2H, dd, J_{XM} = 12.2, J_{MA} = 17.6 Hz, H_M), 3.04 (2H, dd, J_{AX} = 7.2, J_{AM} = 17.0 Hz, H_A), 1.85 (4H, brs, OCH_2***CH***$_2$); (MS-ESI): m/z $(M+Na)^+$ 705. Anal. Calc. for $C_{46}O_2N_4H_{42}$: Calc. C, 80.93%; H, 6.15%; N, 8.21%; Found: C, 80.88%; H, 6.10%; N, 8.15%.

2.12 *Synthesis of 1,5-bis(4-(1,3-diphenyl-4,5-dihydro-1H-pyrazol-5-yl) phenoxy)pentane **3d***

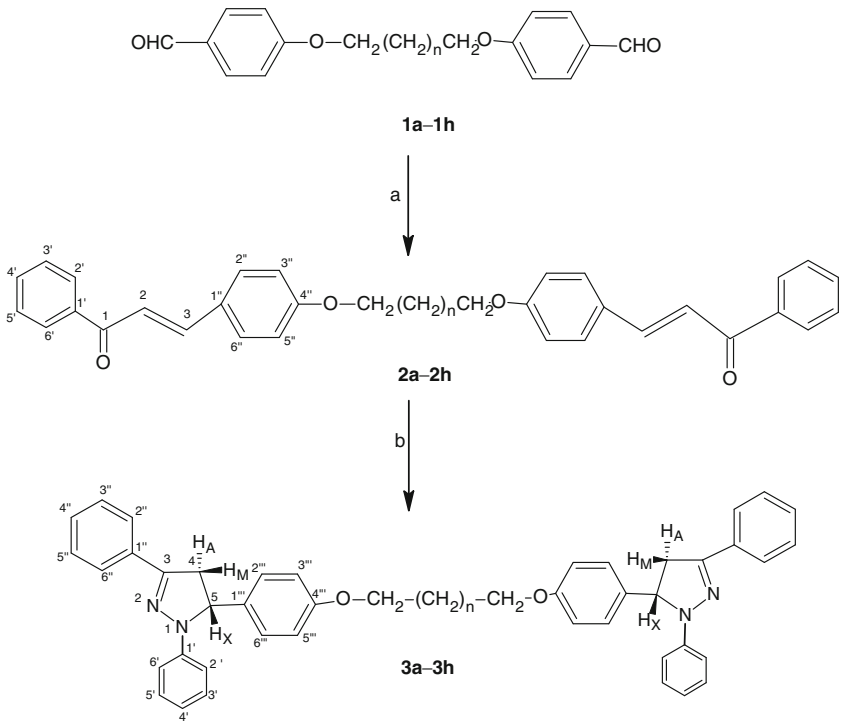
The bispyrazoline **3d** was prepared by reacting bischalcone **2d** (1.0 g, 0.00192 mol) with phenyl hydrazine (0.4186 g, 0.003874 mol) under the similar conditions as described earlier for **3a**.

3d: Yellow solid; Yield 73%; m.p. 125–127°C. UV-Vis (MeOH) λ_{max}(nm): 356, 240, 212; IR (KBr) cm^{-1} 1598, 1508 (C=N, C=C), 2946, 2830 (methylene C-H); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.72 (4H, d, J_o = 7.8 Hz, H-2", 6"), 7.37 (4H, dd, $J_{p,o}$ = 1.1, 8.8 Hz, H-2"', 6"'), 7.30 (6H, m, H-3", 4", 5"), 7.20 (6H, m, H-3', 4', 5'), 7.11 (4H, m, H-2', 6'), 6.85 (4H, dd, $J_{p,o}$ = 1.1, 8.8 Hz, H-3"', 5"'), 5.22 (2H, dd, J_{XA} = 7.1, J_{XM} = 1.1 Hz, H_X), 3.95 (4H, t, J_{vic} = 6.3 Hz, O***CH***$_2$$CH_2$$CH_2$), 3.80 (2H, dd, J_{MX} = 1.1, J_{MA} = 16.2 Hz, H_M), 3.11 (2H, dd, J_{AX} = 7.1, J_{AM} = 16.2 Hz, H_A), 1.82 (4H, quintet, J_{vic} = 6.3 Hz, OCH_2***CH***$_2$$CH_2$), 1.64 (2H, quintet, J_{vic} = 6.3 Hz, OCH_2CH_2***CH***$_2$); (MS-ESI): m/z $(M)^+$ 696. Anal. Calc. for $C_{47}O_2N_4H_{44}$: Calc. C, 81.10%; H, 6.32%; N, 8.04%; Found: C, 81.15%; H, 6.26%; N, 8.00%.

2.13 *Synthesis of 1,6-bis(4-(1,3-diphenyl-4,5-dihydro-1H-pyrazol-5-yl) phenoxy)hexane **3e***

The bispyrazoline **3e** was prepared from the treatment of bischalcone **2e** (1.0 g, 0.00188 mol) with phenyl hydrazine (0.4074 g, 0.003773 mol) under the same conditions as used earlier for **3a**.

3e: Brown solid; Yield 60%; m.p.: 160–162°C. UV-Vis (MeOH) λ_{max}(nm): 357, 238, 214; IR (KBr) cm^{-1} 1588, 1501 (C=N, C=C), 2932, 2846 (methylene C-H); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.64 (4H, dd, $J_{p,o}$ = 1.2, 8.6 Hz, H-2", 6"), 7.32 (4H, m, H-3", 5"), 7.20 (2H, m, H-4"), 7.14 (8H, m, H-2', 3', 5', 6'), 7.00 (4H, dt, $J_{p,o}$ = 1.1, 8.4 Hz, H-2"', 6"'), 6.78 (4H, dt, $J_{p,o}$ = 1.1, 8.4 Hz, H-3"', 5"'), 6.67 (2H, td, $J_{m,o}$ = 2.4, 4.8 Hz, H-4'), 5.15 (2H, dd, J_{XA} = 7.2, J_{XM} = 12.24 Hz, H_X), 3.84 (4H, t, J_{vic} = 6.4 Hz, O***CH***$_2$$CH_2$$CH_2$), 3.73 (2H, dd, J_{MX} = 12.2, J_{MA} = 17.1 Hz, H_M), 3.04 (2H, dd, J_{AX} = 7.2, J_{AM} = 17.1 Hz, H_A), 1.70 (4H, quintet, J_{vic} = 6.1 Hz, OCH_2***CH***$_2$$CH_2$), 1.45 (4H, m, OCH_2CH_2***CH***$_2$); (MS-ESI): m/z $(M+Na)^+$ 733. Anal. Calc. for $C_{48}O_2N_4H_{46}$: Calc. C, 81.12%; H, 6.47%; N, 7.88%; Found: C, 81.07%; H, 6.41%; N, 7.93%.



Reaction Conditions: a) NaOH/EtOH/$PhCOCH_3$; b) EtOH/AcOH/$PhNHNH_2$/ Δ

Scheme 1. Synthesis of bispyrazolines **3a**–**3h**.

2.14 *Synthesis of 1,8-bis(4-(1,3-diphenyl-4,5-dihydro-1H-pyrazol-5-yl) phenoxy)octane **3f***

The bispyrazoline **3f** was obtained from the reaction of bischalcone **2f** (1.0 g, 0.00178 mol) with phenyl hydrazine (0.387 g, 0.003584 mol) under the similar conditions as described above for **3a**.

3f: Brown solid; Yield 67%; m.p.: 175–177°C. UV-Vis (MeOH) λ_{max}(nm): 370, 243, 225; IR (KBr) cm^{-1}

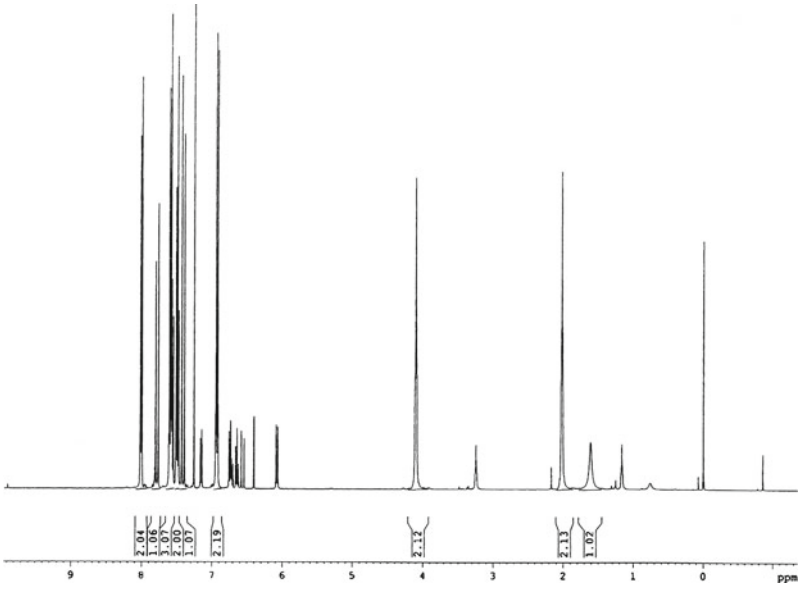


Figure 1. ^{1}H-NMR (400 MHz) spectrum of bischalcone **3c**.

1596, 1502 (C=N, C=C), 2925, 2852 (methylene C-H); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.62 (4H, dd, $J_{,p,o}$ = 1.0, 8.7 Hz, H-2", 6"), 7.32 (4H, m, H-3", 5"), 7.20 (2H, m, H-4"), 7.10 (8H, m, H-2', 3', 5', 6'), 7.02 (4H, dt, $J_{p,o}$ = 1.0, 8.4 Hz, H-2"', 6"'), 6.76 (4H, dt, $J_{p,o}$ = 1.0, 8.4 Hz, H-3"', 5"'), 6.68 (2H, td, $J_{m,o}$ = 2.6, 4.8 Hz, H-4'), 5.12 (2H, dd, J_{XA} = 7.2, J_{XM} = 12.2 Hz, H_X), 3.81 (4H, t, J_{vic} = 6.4 Hz, O***CH***$_2$CH$_2$CH$_2$CH$_2$), 3.70 (2H, dd, J_{MX} = 12.3, J_{MA} = 17.0 Hz, H_M), 3.02 (2H, dd, J_{AX} = 7.2, J_{AM} = 17.0 Hz, H_A), 1.66 (4H, quintet, J_{vic} = 6.0 Hz, OCH$_2$***CH***$_2$CH$_2$CH$_2$), 1.35 (4H, m, OCH$_2$CH$_2$***CH***$_2$CH$_2$), 1.28 (4H, m, OCH$_2$CH$_2$CH$_2$***CH***$_2$); (MS-ESI): m/z $(M)^+$ 738. Anal. Calc. for $C_{49}O_2N_4H_{48}$: Calc. C, 81.21%; H, 6.62%; N, 7.73%; Found: C, 81.15%; H, 6.58%; N, 7.68%.

2.15 *Synthesis of 1,10-bis(4-(1,3-diphenyl-4,5-dihydro-1H-pyrazol-5-yl)phenoxy)decane **3g***

The bispyrazoline **3g** was synthesized by reacting bischalcone **2g** (1.0 g, 0.0017064 mol) with phenyl hydrazine (0.3686 g, 0.003412 mol) under the similar conditions as used earlier for **3a**.

3g: Brown solid; Yield 62%; m.p.: 240–242°C. UV-Vis (MeOH) λ_{max}(nm): 362, 247, 218; IR (KBr) cm^{-1} 1602, 1509 (C=N, C=C), 2925, 2854 (methylene C-H); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.60 (4H, dd, $J_{p,o}$ = 1.0, 8.7 Hz, H-2", 6"), 7.29 (4H, m, H-3", 5"), 7.21 (2H, m, H-4"), 7.15 (8H, m, H-2', 3', 5', 6'), 7.02 (4H, dt, $J_{p,o}$ = 1.0, 8.9 Hz, H-2"', 6"'), 6.75 (4H, dt, $J_{p,o}$ = 1.0, 8.9 Hz, H-3"', 5"'), 6.63 (2H, td, $J_{m,o}$ = 2.6, 4.9 Hz, H-4'), 4.88 (2H, dd, J_{XA} = 7.2, J_{XM} = 12.0 Hz, H_X), 3.84 (4H, t, J_{vic} = 6.2 Hz, O***CH***$_2$CH$_2$CH$_2$CH$_2$CH$_2$), 3.70 (2H, dd, J_{MX} = 12.1, J_{MA} = 17.0 Hz, H_M), 3.30 (2H, dd, J_{AX} = 7.2, J_{AM} = 17.2 Hz, H_A), 1.67 (4H, quintet, J_{vic} = 6.4 Hz, OCH$_2$***CH***$_2$CH$_2$CH$_2$CH$_2$), 1.36 (4H, m, OCH$_2$CH$_2$***CH***$_2$CH$_2$CH$_2$), 1.24 (4H, m, OCH$_2$CH$_2$CH$_2$***CH***$_2$CH$_2$), 1.10 (4H, quintet, J_{vic} = 6.3 Hz, OCH$_2$CH$_2$CH$_2$CH$_2$***CH***$_2$); (MS-ESI): m/z $(M+H)^+$ 767. Anal. Calc. for $C_{50}O_2N_4H_{50}$: Calc. C, 81.30%; H, 6.77%; N, 7.58%; Found: C, 81.36%; H, 6.82%; N, 7.63%.

2.16 *Synthesis of 1,12-bis(4-(1,3-diphenyl-4,5-dihydro-1H-pyrazol-5-yl)phenoxy) dodecane **3h***

The bispyrazoline **3h** was synthesized by reacting bischalcone **2h** (1.0 g, 0.00167 mol) with phenyl hydrazine (0.3482 g, 0.003387 mol) under the similar conditions as used earlier for **3a**.

3h: Brown solid; Yield 60%; m.p.: 150–152°C. UV-Vis (MeOH) λ_{max}(nm): 359, 243, 216; IR (KBr) cm^{-1} 1603,

Table 1. ^{13}C-NMR data (δ) of bischalcones **2a–2h**.

Compound	C-1	C-4"	C-3	C-4'	C-1'	C-2',6'	C-2",6"	C-3',5'	C-1"	C-2	C-3",5"	$OCH_2(CH_2)_n$-
2a	190.22	160.98	144.62	138.50	138.40	130.22	128.50	128.44	127.71	119.90	114.95	64.20
2b	190.64	160.90	144.66	138.59	138.48	130.26	128.57	128.42	127.76	119.93	114.93	64.44, 29.12
2c	200.27	161.07	144.69	138.51	132.57	130.20	128.59	128.48	127.62	119.77	114.91	67.58, 25.90
2d	195.17	161.27	144.65	132.53	135.50	129.26	128.12	128.37	127.42	117.75	115.61	65.55, 25.70, 23.72
2e	190.37	161.25	144.45	132.33	133.50	128.10	126.22	128.17	125.42	115.25	115.21	65.50, 25.70, 21.33
2f	190.17	160.25	142.45	132.31	131.50	128.15	126.32	127.17	125.02	115.75	114.21	63.45, 24.33, 23.89, 14.03
2g	190.13	157.25	142.15	132.11	135.50	128.19	123.12	126.20	122.32	112.35	111.31	65.45, 25.89, 24.13, 15.03,11.23
2h	190.10	157.22	142.11	132.10	135.45	128.11	123.10	126.22	122.31	112.32	111.30	65.43, 25.84, 24.11, 24.05, 15.00, 11.21

1505 (C=N, C=C), 2920, 2850 (methylene C-H); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.62 (4H, dd, $J_{p,o}$ = 1.0, 8.7 Hz, H-2", 6"), 7.25 (4H, m, H-3", 5"), 7.19 (2H, m, H-4"), 7.12 (8H, m, H-2', 3', 5', 6'), 7.00 (4H, dt, $J_{p,o}$ = 1.0, 8.9 Hz, H-2"', 6"'), 6.72 (4H, dt, $J_{p,o}$ = 1.0, 8.9 Hz, H-3"', 5"'), 6.61 (2H, td, $J_{m,o}$ = 2.6, 4.9 Hz, H-4'), 4.85 (2H, dd, J_{XA} = 7.2, J_{XM} = 12.0 Hz, H_X), 3.80 (4H, t, J_{vic} = 6.2 Hz, O***CH***$_2$CH$_2$CH$_2$CH$_2$CH$_2$CH$_2$), 3.72 (2H, dd, J_{MX} = 12.1, J_{MA} = 17.0 Hz, H_M), 3.28 (2H, dd, J_{AX} = 7.2, J_{AM} = 17.2 Hz, H_A), 1.63 (4H, quintet, J_{vic} = 6.4 Hz, OCH$_2$***CH***$_2$CH$_2$CH$_2$CH$_2$), 1.32 (4H, m, OCH$_2$CH$_2$***CH***$_2$CH$_2$CH$_2$CH$_2$), 1.20 (4H, m, OCH$_2$CH$_2$CH$_2$***CH***$_2$CH$_2$CH$_2$), 1.12 (8H, quintet, J_{vic} = 6.3 Hz, OCH$_2$CH$_2$CH$_2$CH$_2$***CH***$_2$***CH***$_2$); (MS-ESI): m/z $(M+Na)^+$ 817. Anal. Calc. for $C_{52}O_2N_4H_{54}$: Calc. C, 81.41%; H, 6.82%; N, 7.40%; Found: C, 81.47%; H, 6.87%; N, 7.34%.

3. Results and discussion

3.1 *Chemistry*

The bispyrazolines **3a–3h** needed for the present investigations were synthesized starting from the Claisen–Schmidt reactions[20] of acetophenone with various bisaldehydes[18,19] **1a–1h** which yielded bischalcones **2a–2h**. The cyclizations[10] of later with phenyl hydrazine under alcoholic medium led to the formation of bispyrazolines **3a–3h** which were crystallized from $CHCl_3$:CH_3OH (1:3) to give pure compounds in moderate yields. The starting bisaldehydes **1a–1h** were obtained in good yields from the *O*-alkylation of 4-hydroxybenzaldehyde with suitable 1, ω-dibromoalkanes in the presence of KOH/EtOH/DMF (scheme 1). The structures of prepared compounds (**2a–2h** and **3a–3h**) were analysed from the rigorous analysis of their IR, UV-Vis, ^{1}H-NMR, ^{13}C-NMR and Mass spectral data.

The electronic spectra (MeOH) of the bischalcones **2a–2h** had two major absorptions at 353–312 and 259–235 nm. The later band may be ascribed to the $\pi \rightarrow \pi^*$ transitions of the conjugated double bond while the former band could be given by the n$\rightarrow$ π^* transition of the C=O group of the chalcone moiety. In the IR spectra of compounds **2a–2h**, strong bands were observed at 1665–1654 cm^{-1} which may be attributed to the conjugated C=O group and other significant absorptions were found at 2964–2835 (methylene C-H), 1603–1593 (C=C) and cm^{-1}. The major feature of the ^{1}H-NMR spectra of **2a–2h** was the two broad doublets centred at δ 7.80–7.73 and δ 7.41–7.34 which could be generated by H-3 and H-2 protons, respectively. The coupling value of 15.8 Hz between theses hydrogens describes the *trans* geometry around the C-2 and C-3 double bond. The downfield resonance of the H-3 as compared to H-2 could be ascribed to the electron deficient nature of the β-carbon (H-3) in the enone moiety (figure 1). Other significant signals in the aromatic region appeared at δ 7.58–7.42 (H-2″, 6″) and 6.94–6.32 (H-3″, 5″) having coupling value of 8.4 Hz (J_o); the electron releasing effect of the C-4′ alkoxy group causes the upfield resonance of the later hydrogens. The signal for internal chain OC***H***$_2$ protons were found

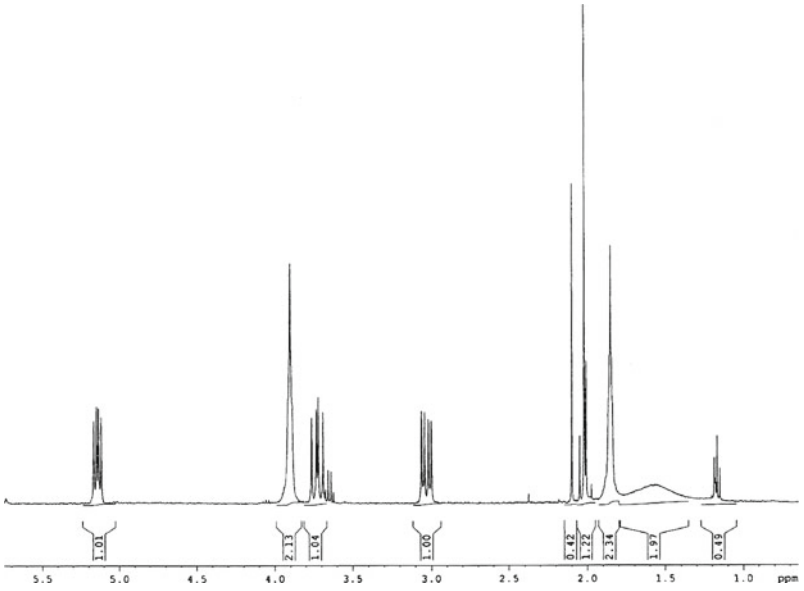


Figure 2. Partial 400 MHz ^{1}H-NMR spectrum of H_X, H_M and H_A in bispyrazoline **4c**.

resonating at δ 4.23–3.96 as triplet and for $\{(CH_2)_n\}$ it appeared at δ 2.31–1.15. In the ^{13}C-NMR spectra of **2a**–**2h**, the internal chain methylene groups were resonating at δ 67.58–63.45 (OCH_2) and δ 29.12–11.21 $\{(CH_2)_n\}$; the downfield resonance of the former suggests its placement near an electronegative oxygen atom. Other major signals were located at δ 200–190, 119–112 and 144–142 which could be very well attributed to C-1, C-2 and C-3 of the enone moiety (see table 1).

The UV-Vis (MeOH) spectra of the pyrazoline derivatives **3a**–**3h** exhibited two major absorption bands in the UV region of the spectra. The band at 370–355 nm may be assigned to the n $\rightarrow\pi^*$ transition of C=N moiety while absorption bands at 253–238 nm may be resulted by $\pi \rightarrow \pi^*$ transition of phenyl ring. IR spectra of **3a**–**3h** did not have any absorption in the region of 1665–1654 cm^{-1} which describes the absence of C=O group in these compounds. In the ^{1}H-NMR spectra of these compounds, the signals corresponding to the double bond hydrogens (H-2 and 3) at δ 7.80–7.73 and 7.41–7.34 in the bischalcones **2a**–**2h** were found missing altogether which indicates the involvement of the enone moiety in the cyclization reactions. The pyrazoline ring protons H_X, H_M and H_A produced resonances at δ 5.23–4.85 (dd), 3.80–3.70 (dd) and 3.30–3.02 (dd), respectively. The vicinal coupling constant (^3J) between H_X and H_M was found to be 12.1 Hz which reflects that these hydrogens are *cis* to each other while coupling value $J_{XA} = 6.8$ Hz and $J_{MA} = 17.7$ Hz describes the *trans* relationship between H_X and H_A while H_M and H_A are geminally placed at C-4′ (figure 2). In the ^{13}C-NMR spectra, signals corresponding to C=O group of bischalcones at δ 200–190 were not present which also corroborate the transformation of this functionality in the formation of pyrazoline moiety. The pyrazoline ring carbons C-3, C-4 and C-5 were very well placed at δ 159–158, 43–41 and 67–66, respectively (see table 2).

3.2 *Antimicrobial activity*

The newly prepared compounds were screened for their antibacterial and antifungal activity using paper disc method[21] *in vitro* against *Escherichia coli*, *Klubsellia pneumeniae*, *Bacillius subtilis*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* and *Aspergillius janus*, *Aspergillius niger* and *Pencillium glabrum* at conc. 100 µg/ml. In this method, the standard 5 mm diameter sterilized filter paper discs impregnated with the prepared compounds (**2a**–**2h** and **3a**–**3h**) were placed on an agar plate seeded with the test organisms. The plates were incubated for 24 h at 37°C for bacteria and

Table 2. ^{13}C-NMR data (δ) of bispyrazolines **3a–3h.**

Compound	C-3	C-4‴	C-1′	C-1‴	C-2″,6″	C-3″,5″	C-1″	C-3′,5′	C-2″, 6‴	C-4″	C-4′	C-3‴,5‴	C-2′,6′	OCH_2–$(CH_2)_n$	C-5	C-4
3a	158.40	146.59	143.90	132.56	132.10	129.16	126.00	125.90	125.70	125.83	119.12	113.16	114.30	63.10	67.32	43.40
3b	158.33	146.31	143.70	132.61	132.15	129.26	126.03	125.94	125.78	125.71	117.01	113.19	112.44	63.20, 25.92	66.41	43.72
3c	158.10	146.51	144.70	134.51	130.05	128.66	127.03	125.44	125.70	125.91	119.01	113.39	114.44	64.00, 25.96	67.41	43.62
3d	158.33	146.45	144.60	134.21	132.02	127.46	125.03	123.42	123.60	120.91	119.21	111.29	114.40	64.22, 25.76, 20.76	67.39	41.62
3e	158.49	146.71	144.90	134.49	132.84	128.92	127.03	125.36	125.85	125.71	119.03	113.40	115.01	64.03, 30.96, 29.19	67.79	43.63
3f	158.41	146.74	144.36	134.46	132.85	128.85	129.97	125.84	125.35	125.73	119.04	113.43	114.66	64.34, 29.31, 29.26, 26.01	67.95	43.65
3g	158.18	146.30	143.32	134.24	133.63	127.96	129.63	125.55	125.23	125.47	119.01	113.22	114.38	67.81, 29.22, 29.06, 26.04, 19.11	67.33	43.45
3h	158.15	146.33	143.30	134.22	133.60	127.94	129.61	125.50	125.20	125.42	119.00	113.20	114.34	67.80, 29.20, 29.02, 26.08, 24.00, 19.10	67.30	43.42

Table 3. *In vitro* MIC (μg/mL) of bischalcones **2a**–**2h**.

Compound No.	Gram (−ve) bacteria			Gram (+ve) bacteria		Fungi		
	Escherichia coli	*Klubsellia pneumoniae*	*Pseudomonas aeruginosa*	*Staphylococcus aureus*	*Bacillius subtilis*	*Aspergillus janus*	*Pencilluim glabrum*	*Aspergillus niger*
2a	16	8	8	16	32	16	8	32
2b	16	16	16	16	8	8	8	32
2c	32	16	16	8	8	8	8	16
2d	16	8	8	8	16	8	16	8
2e	4	8	8	8	16	8	4	8
2f	8	8	8	8	16	16	4	16
2g	8	16	16	16	8	16	8	4
2h	8	8	8	8	16	16	4	8
Amoxicillin	2	2	2	2	2			
Fluconazole						1	1	1

at 28°C for fungi. The minimum inhibitory concentration (MIC-μg/mL) of the studied compounds were also determined by using serial tube dilution method[22] at conc. 128, 64, 32, 16, 8, 4, 2, 1 μg/mL and the observed MIC values are given in tables 3 and 4 (figures 3 and 4). Compounds **2e**, **2h**, **2g**, **3c**, **3d**, **3e** and **3f** showed significant activity against the tested microorganisms. The zones of inhibitions of bacteria and fungi growth around the discs were observed. DMSO was used as a control and it did not show any activity against the strains of microorganisms used. The results are recorded as average diameter of inhibition zone in mm (figures 5 and 6).

In vitro antimicrobial MIC results of the bischalcones **2a**–**2h** and bispyrazolines **3a**–**3h** have been presented in tables 3 and 4, respectively. Most of the compounds showed good activities against the tested microorganisms (MIC: 8–16 μg/mL). The compound **2e** showed significant activity against *Escherichia coli* and *Pencilluim glabrum* (MIC: 4 μg/mL) and similar activity was also observed in **2f**, **2h** and **2g** against the strain *Pencilluim glabrum* and *Aspergillus niger*, respectively. Among the bispyrazolines, significant results (MIC: 4 μg/mL) were observed in **3c**, **3e** and **3f** against *Klubssila pneumoniae* and **3d** also revealed the activity of same order against *Staphylococcus aureus*.

It is evident from the above MIC data that bischalcones linked through the internal chain of six, eight and twelve carbon atoms were more active in the present investigations. Similarly, the bispyrazolines built around four, six and eight methylene spacer units also provided significant results. Thus, compounds involving longer internal chain consisting of even number of carbon atoms seem to be better antimicrobial products. The importance of this work lies in the possibility that the new compounds might be more efficacious derivatives against the strains for which investigation regarding the more biological studies could be helpful in designing the potent antimicrobial agents.

Table 4. *In vitro* MIC (μg/mL) for bispyrazolines **3a**–**3h.**

Compound No.	Gram (−ve) bacteria			Gram (+ve) bacteria		Fungi		
	Escherichia coli	*Klubsellia pneumoniae*	*Pseudomonas aeruginosa*	*Staphylococcus aureus*	*Bacillius subtilis*	*Aspergillus janus*	*Pencilluim glabrum*	*Aspergillus niger*
3a	16	16	16	16	16	16	8	16
3b	16	8	8	32	32	8	16	16
3c	16	4	16	8	16	16	8	6
3d	32	32	8	4	32	8	16	32
3e	16	4	8	8	16	16	8	16
3f	16	4	16	16	8	8	16	16
3g	16	8	32	16	16	8	16	32
3h	32	8	32	8	32	16	16	8
Amoxicillin	2	2	2	2	2			
Fluconazole						1	1	1

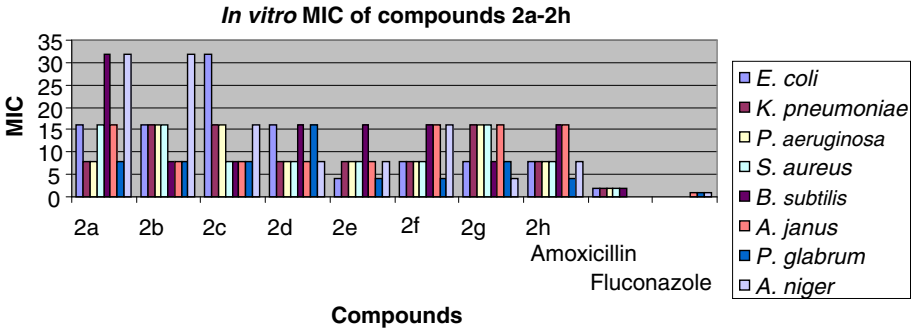


Figure 3. *In vitro* MIC (μg/mL) of compounds **2a–2h**.

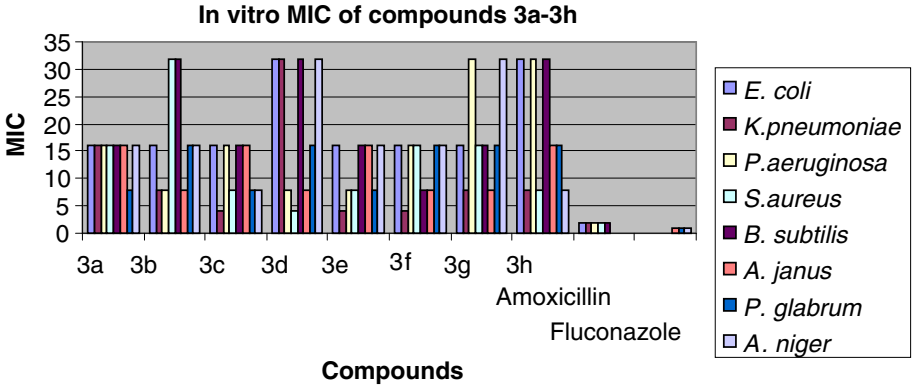


Figure 4. *In vitro* MIC (μg/mL) of compounds **3a–3h**.

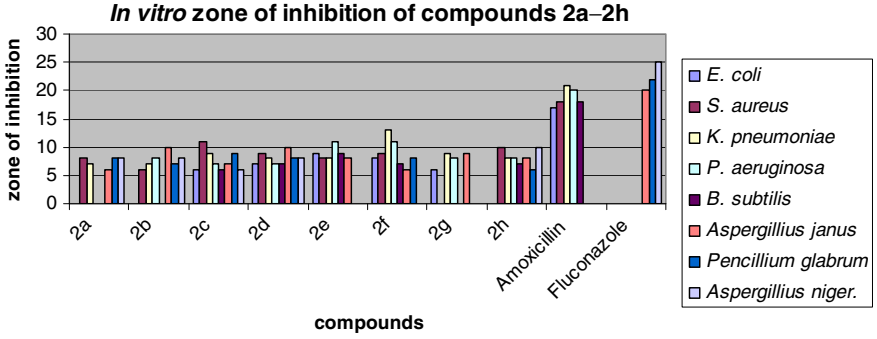


Figure 5. Zone of inhibition (mm) of compounds **2a–2h**.

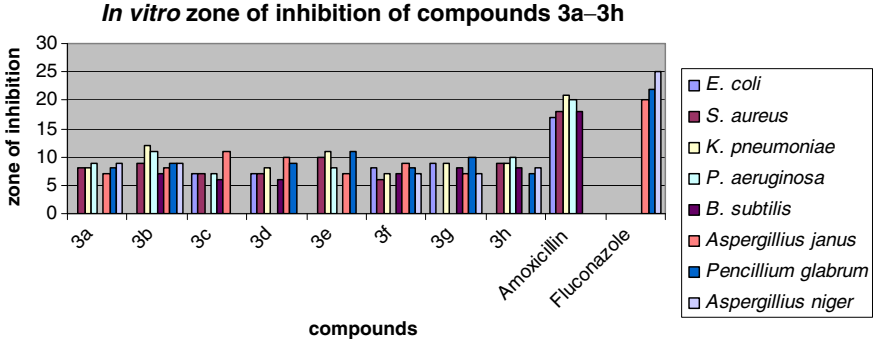


Figure 6. Zone of inhibition (mm) of compounds **3a–3h**.

4. Conclusion

It may be concluded that this study describe the general method for the synthesis of new bispyrazolines linked through the alkyl chains under the normal conditions. The significant antimicrobial activities were provided by the bischalcones and bispyrazolines linked through the intermediate chain containing even number of methylene groups

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