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Synthesis, Characterization and Antibacterial Activity of Some Novel Pyrido[2,3-*b*]indole, Morpholine and Chalcone Hybrid Compounds

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In present investigation, a novel series of (*E*)-3-(2-morpholino-9*H*-pyrido[2,3-*b*]indol-3-yl)-1-phenylprop-2-en-1-one and its derivatives (**5a-f**) were synthesized by condensation reaction from the final intermediate, 2-morpholino-9*H*-pyrido[2,3-*b*]indol-3-carbaldehyde (**4**). The synthesis of the title compounds commenced from commercially available 21*H*-indol-2-amine (**1**) and by involving *N*-(1*H*-indol-2-yl)-acetamide (**2**) and 2-chloro-9*H*-pyrido[2,3-*b*]indole-3-carbaldehyde (**3**) as reactive intermediates. The chemical structure of synthesized compounds was characterized by IR, ^{1}H NMR, mass spectral data and elemental analysis. The final compounds were used to screen for their antibacterial activity against various strains of bacteria.

Keywords: Indole, Morpholine, Pyridines, Antibacterial activity.

INTRODUCTION

The nitrogen containing heterocycles are widely distributed in nature and have long been of interest to synthetic organic chemists [1,2]. Such compounds have also become privileged motifs in medicinal chemistry and there is an ongoing need for development of new synthetic methodology towards these heterocycles [3]. Many nitrogen heterocycles are therapeutically useful, for example as anticancer [4], antifungal [5] and antiviral [6] agents.

Pyridine is a fundamental organic heterocyclic molecule and its precursor, dihydropyridine, are among the most common structural units in the pharmaceutical industry [7]. Extensively pyridine and its derivative containing drugs are mostly used as antimicrobial [8], antiviral [9], anticancer [10], antioxidant [11], antimycobacterial [12], antidiabetic, antimalarial [13], antihypertensive [14], anti-inflammatory agents [15] and anti-HIV [16]. The pyridine derivative is established in several medicinal drugs like sorafenib and in different agrochemicals like picloram, nitapyrin and pyridinenitrile. The pyridine ring is also present in a numerous vitamins and alkaloids, such as niacin, pyridoxine and nicotine [17-21].

Pyrido[2,3-*b*]indole is a three-membered aromatic system and its related compounds are established in a wide range of natural products [22,23]. These analogous are also identified with various pharmacological activities such as anticancer [24], anti-inflammatory [25] and potential treatment of type II diabetes [26]. Additionally, these derivatives are also performing diversified practices in material science like fluorescent molecular probes and sensors [27,28] and also as organic semi-conductors [29].

Pyrido[2,3-*b*]indole based bi- or trifunctional hybrids have attracted researchers towards this architecture for selection as a linker to join two or more bioactive functionalities [30-32], therefore, in this work, a novel series of (*E*)-3-(2-morpholino-9*H*-pyrido[2,3-*b*]indol-3-yl)-1-phenylprop-2-en-1-one and its derivatives were synthesized in a multi-step reactions. The synthesized compounds were characterized and also screened for their antimicrobial activity to display a pronounced efficiency against the tested microorganisms as part of the structure-activity relationship (SAR).

EXPERIMENTAL

All the chemicals and solvents were used as acquired commercially. The melting points were determined on a Stuart

Scientific melting point apparatus and are uncorrected. Thin layer chromatography was performed analytically on precoated silica gel $60F_{254}$ plates applying UV absorption or iodine staining for visualization and 100-200 mesh silica gel was used for column chromatography. The IR spectra were obtained on a Perkin-Elmer-781 IR spectrophotometer using KBr disc. The PMR spectra were recorded in $CDCl_3$ solution at 300 MHz on a Bruker™ 300 MHz spectrometer and position of the signals (chemical shifts in δ ppm) is relatively reported using TMS as an internal standard. Mass spectra were acquired from a PE-SCIEX AP1 3000 LC/MS/MS system using electron spray ionization at 80-250 ºC.

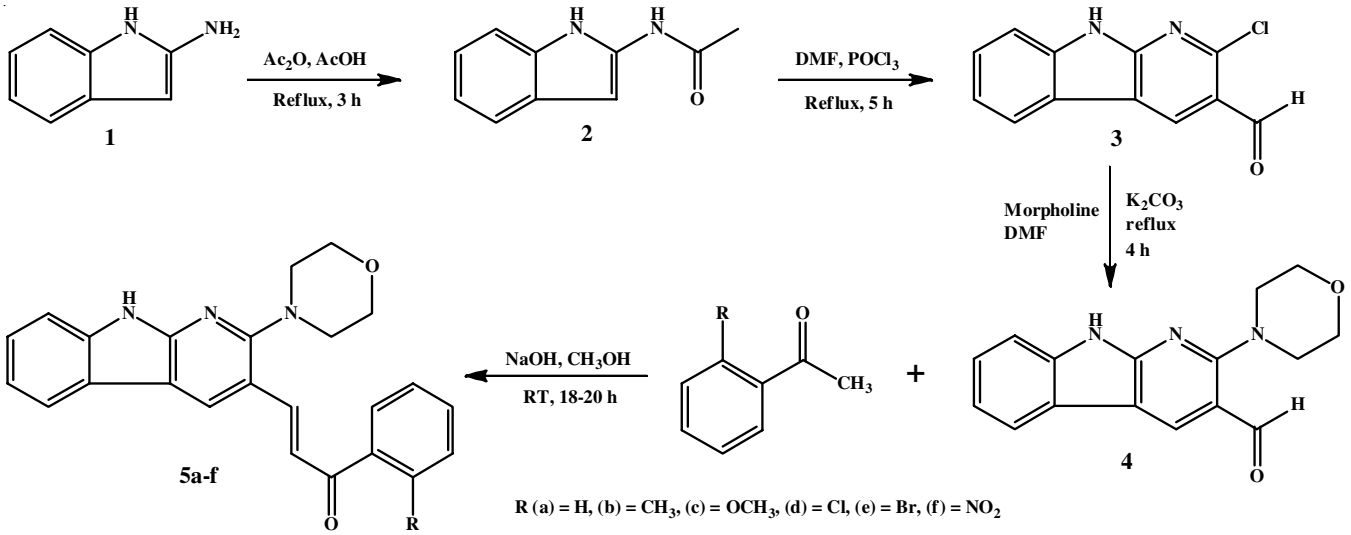
Synthesis of *N*-(1*H*-indol-2-yl)acetamide (2): A solution of 1*H*-indol-2-amine (**1**, 1.32 g, 0.01 mol) and acetic anhydride (0.01 mol) in 10 mL acetic acid was refluxed with a magnetic stirrer at reflux temperature. After 3 h, the reaction mixture was cooled to room temperature and then residual mass was poured into cool water. Thus, the yielded solid was filtered off and crystallized from a mixture of ethanol-DMF (1:1) to offer pure *N*-(1*H*-indol-2-yl)acetamide (**2**). Colour: pale yellow; yield: 74%; m.p.: 120-122 ºC; IR (KBr, ν_{max}, cm^{-1}): 3236 (N-H), 3185 (N-H), 3045 (C-H, Ar), 2972 (C-H, CH_3), 1685 (C=O), 1607 (C=C); ^{1}H NMR ($CDCl_3$, 300 MHz), δ ppm: 7.70-7.29 (m, 4H, Ar-H), 6.71 (s, 1H, NHCO), 5.20 (s, 1H, =CH), 4.38 (s, 1H, NH), 2.41 (s, 3H, CH_3); MS (*m/z*, $M^+ + 1$): 175; Elemental analysis of $C_{10}H_{10}N_2O$: Calcd. (found) %: C, 68.26 (68.95); H, 5.78 (5.79); N, 16.06 (16.08); O, 9.17 (9.18).

Synthesis of 2-chloro-9*H*-pyrido[2,3-*b*]indole-3-carbaldehyde (3): *N*-(1*H*-Indol-2-yl)acetamide (**2**, 1.75 g, 0.01 mol) dissolved in DMF (15 mL) and $POCl_3$ (0.01 mol) was added with steady stirring under reflux for 5 h. The residual product was precipitated by placing in ice-cold water, filtered and washed with ethanol, dried and crystallized from ethanol-H_2O to obtain 2-chloro-9*H*-pyrido[2,3-*b*]indole-3-carbaldehyde (**3**) in pure form. Colour: yellow; yield: 81%; m.p.: 102-104 ºC; IR (KBr, ν_{max}, cm^{-1}): 3325 (N-H), 3038 (C-H, Ar), 1736 (C=O), 1638 (C=N), 1580 (C=C, Ar); ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm: 10.25 (s, 1H, CHO) 7.60-7.42 (m, 4H, Ar-H), 7.52 (s, 1H, Ar-H), 4.66 (s, 1H, NH); MS (*m/z*, $M^+ + 1$): 231; Elemental analysis of $C_{12}H_7N_2OCl$: Calcd. (found) %: C, 62.02 (62.49); H, 3.06 (3.06); Cl, 15.35 (15.37); N, 12.13 (12.15), O, 6.93 (6.94).

Synthesis of 2-morpholino-9*H*-pyrido[2,3-*b*]indol-3-carbaldehyde (4): To a mixture of 2-chloro-9*H*-pyrido[2,3-*b*]-indole-3-carbaldehyde (**3**, 2.31 g, 0.01 mol) and K_2CO_3 (0.01 mol) in DMF (10 mL), morpholine (0.01 mol) was added slowly. The composition was then refluxed for 4 h with constant stirring and the reaction mixture was poured into ice-cold water. The precipitated solid was filtered, washed with water thoroughly and then recrystallized from ethyl acetate to obtain pure 2-morpholino-9*H*-pyrido[2,3-*b*]indol-3-carbaldehyde (**4**). Colour: brown; yield: 83%; m.p.: 130-132 ºC; IR (KBr, ν_{max}, cm^{-1}): 3248 (N-H), 3048 (C-H, Ar), 2965 (C-H, CH_2), 1740 (C=O), 1656 (C=N), 1594 (C-H, Ar), 1233 (C-O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm: 10.72 (s, 1H, CHO), 7.79-7.45 (m, 4H, Ar-H), 7.65 (s, 1H, Ar-H), 3.68 (s, 1H, NH), 2.82 (t, 4H, J = 5.4 Hz, 2 × OCH_2), 2.57 (t, 4H, J = 5.4 Hz, 2 × NCH_2); MS (*m/z*, $M^+ + 1$): 282; Elemental analysis of $C_{16}H_{15}N_3O_2$: Calcd. (found) %: C, 68.01 (68.31); H, 5.37 (5.37); N, 14.92 (14.94); O, 11.35 (11.37).

Synthesis of (*E*)-3-(2-morpholino-9*H*-pyrido[2,3-*b*]-indol-3-yl)-1-phenylprop-2-en-1-one and derivatives (5a-f): A solution of 2-morpholino-9*H*-pyrido[2,3-*b*]indol-3-carbaldehyde (**4**, 2.82 g, 0.01 mol), aromatic ketone (0.01 mol), NaOH solution (10 %, 10 mL) in methanol (15 mL) was stirred at ambient temperature for 18-20 h. The product was filtered off, concentrated, diluted with water and neutralized with HCl. The crude product was collected and crystallized from ethanol to yield (*E*)-3-(2-morpholino-9*H*-pyrido[2,3-*b*]indol-3-yl)-1-phenylprop- 2-en-1-ones (**5a-f**) (**Scheme-I**).

(*E*)-3-(2-Morpholino-9*H*-pyrido[2,3-*b*]indol-3-yl)-1-phenylprop-2-en-1-one (5a): Colour: white; yield: 78%; m.p.: 95-97 ºC; IR (KBr, ν_{max}, cm^{-1}): 3165 (N-H), 3065 (C-H, Ar), 2971 (C-H, CH_2), 1752 (C=O), 1644 (C=N), 1578 (C=C, Ar), 1239 (C-O); ^{1}H NMR ($CDCl_3$, 300 MHz) (δ ppm): 7.82-7.36 (m, 8H, Ar-H), 7.65(s, 1H, Ar-H), 4.98 (d, 1H, J = 15.3 Hz,



Scheme-I

=CH), 4.47 (d, 1H, *J* = 15.3 Hz, =CH), 4.23 (s, 1H, NH), 2.89 (t, 4H, *J* = 5.9 Hz, 2 × OCH_2), 2.28 (t, 4H, *J* = 5.9 Hz, 2 × OCH_2); MS (*m/z*, M^+ + 1): 384; Elemental analysis of $C_{24}H_{21}N_3O_2$: Calcd. (found) %: C, 75.04 (75.18); H, 5.52 (5.52); N, 10.94 (10.96); O, 8.34 (8.35).

(*E*)-3-(2-Morpholino-9*H*-pyrido[2,3-*b*]indol-3-yl)-1-*o*-tolylprop-2-en-1-one (5b): Colour: white; yield: 74%; m.p.: 142-144 ºC; IR (KBr, ν_{max}, cm^{-1}): 3174 (N-H), 3058 (C-H, Ar), 2962 (C-H, CH_2), 1748 (C=O), 1635 (C=N), 1575 (C=C, Ar), 1232 (C-O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm: 7.79-7.35 (m, 8H, Ar-H), 7.68 (s, 1H, Ar-H), 4.87 (d, 1H, *J* = 16.2 Hz, =CH), 4.52 (d, 1H, *J* = 16.2 Hz, =CH), 4.25 (s, 1H, NH), 2.91 (t, 4H, *J* = 6.0 Hz, 2 × OCH_2), 2.32 (t, 4H, *J* = 6.0 Hz, 2 × OCH_2); MS (*m/z*, M^+ + 1): 398; Elemental analysis of $C_{25}H_{23}N_3O_2$: Calcd. (found) %: C, 75.10 (75.54); H, 5.83 (5.83); N, 10.55 (10.57); O, 8.04 (8.05).

(*E*)-1-(2-Methoxyphenyl)-3-(2-morpholino-9*H*-pyrido-[2,3-*b*]indol-3-yl)-prop-2-en-1-one (5c): Colour: red; yield: 77%; m.p.: 104-106 ºC; IR (KBr, ν_{max}, cm^{-1}): 3192 (N-H), 3035 (C-H, Ar), 2960 (C-H, CH_2), 1746 (C=O), 1630 (C=N), 1564 (C=C, Ar), 1234 (C-O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm: 7.78-7.26 (m, 8H, Ar-H), 7.58 (s, 1H, Ar-H), 4.87 (d, 1H, *J* = 14.0 Hz, =CH), 4.52 (d, 1H, *J* = 14.0 Hz, =CH), 4.28 (s, 1H, NH), 2.74 (t, 4H, *J* = 6.2 Hz, 2 × OCH_2), 2.31 (t, 4H, *J* = 6.2 Hz, 2 × OCH_2); MS (*m/z*, M^+ + 1): 414; Elemental analysis of $C_{25}H_{23}N_3O_3$: Calcd. (found) %: C, 72.21 (72.62); H, 5.61 (5.61); N, 10.15 (10.16); O, 11.60 (11.61).

(*E*)-1-(2-Cholophenyl)-3-(2-morpholino-9*H*-pyrido-[2,3-*b*]indol-3-yl)-prop-2-en-1-one (5d): Colour: brown; yield: 84%; m.p.: 128-130 ºC; IR (KBr, ν_{max}, cm^{-1}): 3189 (N-H), 3070 (C-H, Ar), 2977 (C-H, CH_2), 1769 (C=O), 1646 (C=N), 1582 (C=C, Ar), 1245 (C-O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm: 7.90-7.30 (m, 8H, Ar-H), 7.62 (s, 1H, Ar-H), 4.95 (d, 1H, *J* = 14.8 Hz, =CH), 4.43 (d, 1H, *J* = 14.8 Hz, =CH), 4.19 (s, 1H, NH), 2.85 (t, 4H, *J* = 5.7 Hz, 2 × OCH_2), 2.23 (t, 4H, *J* = 5.7 Hz, 2 × OCH_2); MS (*m/z*, M^+ + 1): 418; Elemental analysis of $C_{24}H_{20}N_3O_2Cl$: Calcd. (found) %: C, 68.32 (68.98), H, 4.82 (4.82); Cl, 8.47 (8.48), N, 10.05 (10.06); O, 7.65 (7.66).

(*E*)-1-(2-Bromophenyl)-3-(2-morpholino-9*H*-pyrido-[2,3-*b*]indol-3-yl)-prop-2-en-1-one (5e) Colour: pink; yield: 80%; m.p.: 150-152 ºC; IR (KBr, ν_{max}, cm^{-1}): 3181 (N-H), 3066 (C-H, Ar), 2958 (C-H, CH_2), 1743 (C=O), 1650 (C=N), 1567 (C=C, Ar), 1233 (C-O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm: 7.84-7.35 (m, 8H, Ar-H), 7.70 (s, 1H, Ar-H), 4.88 (d, 1H, *J* = 15.5 Hz, =CH), 4.52 (d, 1H, *J* = 15.5 Hz, =CH), 4.23 (s, 1H, NH), 2.78 (t, 4H, *J* = 6.2 Hz, 2 × OCH_2), 2.30 (t, 4H, *J* = 6.2 Hz, 2 × OCH_2); MS (*m/z*, M^+ + 1): 462; Elemental analysis of $C_{24}H_{20}N_3O_2Br$: Calcd. (found) %: C, 62.03 (62.35); H, 4.36 (4.36); Br, 17.26 (17.28); N, 9.08 (9.09); O, 6.92 (6.92).

(*E*)-1-(2-Nitrophenyl)-3-(2-morpholino-9*H*-pyrido-[2,3-*b*]indol-3-yl)-prop-2-en-1-one (5f): Colour: brown; yield: 76%; m.p.: 136-138 ºC; IR (KBr, ν_{max}, cm^{-1}): 3135 (N-H), 3056 (C-H, Ar), 2968 (C-H, CH_2), 1761 (C=O), 1640 (C=N), 1575 (C=C, Ar), 1226 (C-O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm: 7.85-7.40 (m, 8H, Ar-H), 7.58 (s, 1H, Ar-H), 4.85 (d, 1H, *J* = 15.5 Hz, =CH), 4.51 (d, 1H, *J* = 15.5 Hz, =CH), 4.25 (s, 1H, NH), 2.90 (t, 4H, *J* = 6.2 Hz, 2 × OCH_2), 2.30 (t, 4H, *J* = 6.2 Hz, 2 × OCH_2); MS (*m/z*, M^+ + 1): 429; Elemental analysis of $C_{24}H_{20}N_4O_4$: Calcd. (found) %: C, 67.01 (67.28); H, 4.71 (4.71); N, 13.06 (13.08); O, 14.92 (14.94).

RESULTS AND DISCUSSION

In view of our ongoing interest in the development of new synthetic heterocyclic derivatives, the present study aims to design and synthesize a novel series pyrido[2,3-b]indole, morpholine and chalcone hybrids compounds using 1*H*-indol-2-amine as the starting compound. The purity of the compounds was estimated by TLC and elemental analysis. All the newly synthesized compounds were characterized with the spectral data obtained from ^{1}H NMR, FTIR and Mass data of in full agree-ment with the proposed structures.

The synthesis of the target pyrido[2,3-*b*]indole containing morpholine and chalcone hybrid compounds was executed by following the multi-steps as outlined in **Scheme-I**. The starting compound, 1*H*-indol-2-amine (**1**) was *N*-acylated with acetic anhydride in hot acetic acid with constant stirring for 3 h to afford *N*-(1*H*-indol-2-yl)acetamide (**2**) in good yield as initial inter-mediate. The ^{1}H NMR spectrum of compound **2** shows the CH_3 singlet signal at δ 2.41 ppm of the acetamide group. In the IR spectrum, the absorption frequency at 1685 cm^{-1} of the C=O group indicates the formation of an acetamide group.

In further step, 2-chloro-9*H*-pyrido[2,3-*b*]indole-3-carbaldehyde (**3**) was obtained in superior yield by the treating compound **2** with $POCl_3$ for cyclization in presence of DMF under reflux temperature with constant stirring. The chemical conversation from compound **2** to compound **3** was confirmed based on the appearance of new signals in PMR and new peaks in the IR spectrum, along with the recording of molecular weight in the mass spectrum. Thus, both new singlet signals at δ 7.52 ppm and δ 10.25 ppm corresponding to the pyridine ring and aldehyde group, respectively. The absorption band at 1736 cm^{-1} indicates the emerging of an aldehyde C=O group which does not appear in its precursor.

In the subsequent step to achieve the final intermediate, 2-morpholino-9*H*-pyrido[2,3-*b*]indol-3-carbaldehyde (**4**), compound **3** was reacted with morpholine in the presence of K_2CO_3 in DMF solvent at reflux temperature for 4 h on steady stirring. The IR spectrum of compound **4** shows a strong absorption band at 1233 cm^{-1} characteristic of the C-O group. The PMR spectrum showed the appearance of both triplet signals at δ 2.82 ppm and δ 2.57 ppm for eight protons with equal coupling constants (*J* = 5.4 Hz) indicating the attachment of morpholine ring. Finally, the conversion through the condensation of compound **4** with various aromatic ketones in alkaline medium in methanol at ambient temperature for 18-24 h with constant stirring furnished the corresponding title compounds, (*E*)-3-(2-morpholino-9*H*-pyrido[2,3-*b*]indol-3-yl)-1-phenylprop-2-en-1-ones **(5a-f)** in good yields. The structure of compound **5d** was confirmed on the basis of its IR, PMR and MS spectral data. The signal of the aldehyde fragment of compound **4** is replaced by two characteristic signals from both alkene protons and located at δ 4.95 ppm and δ 4.43 ppm in the PMR spectrum of compound **5d**. Additionally, four aromatic protons of acetophenone are incorporated in the multiplet signal and have

resonance in the aromatic region. Thus, these signals clearly demonstrate the formation of the target molecule. The broad band at 1769 cm^{-1} of compound **4** is absent in the IR spectrum of product **5d** indicating that the reaction has occurred at the aldehyde group. The mass spectrum exhibits the molecular ion peak at *m/z* 418.

Antibacterial activity: The antibacterial activity of the synthesized compounds, (*E*)-3-(2-morpholino-9*H*-pyrido[2,3-*b*]-indol-3-yl)-1- phenylprop-2-en-1-ones (**5a-f**) were examined against four bacteria strains *viz*. *Staphylococcus aureus*, *Bacillus megaterium*, *Pseudomonas aeruginosa* and *Escherichia coli* by selecting tetracycline as standard compound and DMSO as solvent. The activity of the synthesized compounds in the present study is presented in terms of the zone of inhibition in mm. The results show that compounds **5c** and **5f** were equally ineffective against *P. aeruginosa*, with a zone of inhibition of 11 mm (Fig. 1). However, compounds **5f**, **5e**, **5a**, **5d** and **5b** exhibited the maximum effectiveness against *B. megaterium* (zone of inhibition 16 mm, 15 mm, 14 mm, 18 mm and 20 mm, respectively). The rest of the compounds yielded low to moderate activity.

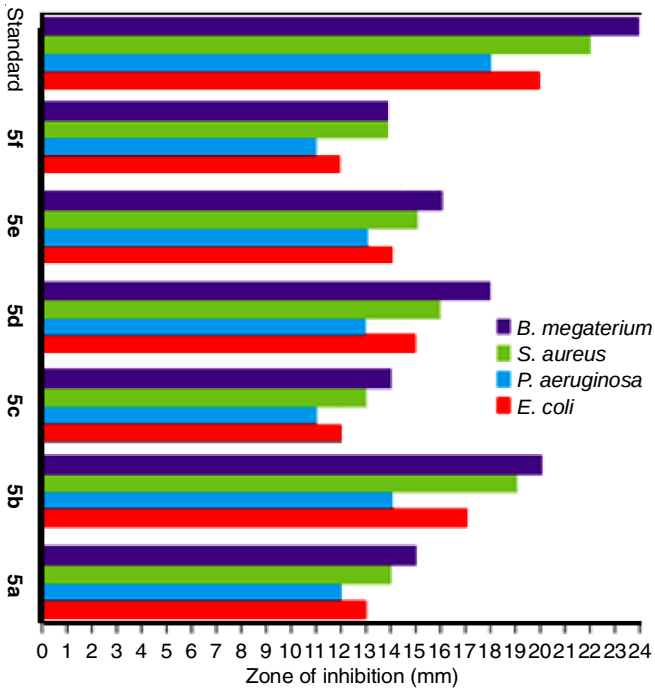


Fig. 1. Antibacterial activity of compounds **5a-f**

Conclusion

The present study offers a facile and convenient method for the synthesis of new hybrid compounds consisting of pyrido-[2,3-*b*]indole, morpholine and chalcone moieties using inexpensive available materials. The title compounds may act as drug candidates based on the pharmacological activity of indole, morpholine and chalcone moieties.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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