Synthesis and antimicrobial activity of some hybrid 2-aryl-4-(1-phenyl-3-(p-tolyl)-1H-pyrazol-4-yl)-2,3-dihydro-1H-benzo[b][1,4]diazepine derivatives

N C Desai* & Surbhi B Joshi
Division of Medicinal Chemistry, Department of Chemistry (DST-FIST Sponsored and UGC NON-SAP), Mahatma Gandhi Campus, Maharaja Krishnakumarsinhji Bhavnagar University, Bhavnagar 364 002, India
E-mail: dnisheeth@rediffmail.com
Received 3 September 2019; accepted (revised) 30 December 2019

Some new hybrid 2-aryl-4-(1-phenyl-3-(p-tolyl)-1H-pyrazol-4-yl)-2,3-dihydro-1H-benzo[b][1,4]diazepines have been synthesized which possessed the pyrazole and benzodiazepine heterocycles 2a-t. Antimicrobial evaluation of the synthesized compounds have been carried out against different strains of bacteria like E. coli, P. aeruginosa, S. aureus and S. pyogenes and fungal strains like C. albicans, A. niger and A. clavatus using serial dilution method. The newly synthesized compounds 2i, 2j, 2k, 2l, 2m, 2q and 2t have shown significant activity against the above mentioned strains. The reported compounds in the present paper are supported by IR, 1H and 13C NMR, and LC-MS spectral analysis.

Keywords: One-pot synthesis, pyrazole, benzodiazepine, antimicrobial activity

Though many pharmaceutical drugs have been used on bacteria and fungi available in the market, microbial infection is a rising global problem due to the resistance of present antimicrobials1,2. We have observed the increasing level of microbial diseases in the surrounding geographical area too3,4. The only solution is to find new antimicrobials having zero resistance on microbes. Keeping this in mind, we have synthesized a new diverse structure of molecules for fighting against microbial infections based on heterocyclic chemistry. The literature review suggested that heterocyclic compounds have very good pharmacological effects5-8. Recently some review articles were published and on the basis of these articles, it is concluded that pyrazole9,11 and benzodiazepine12-15 showed notable pharmaceutical efficacy and therefore we have selected these versatile motifs in the present work. We have used a hybrid approach, using pyrazole and benzodiazepine in the same structure. Certain commercially available medicines are also having pyrazole and benzodiazepine motif. Some of them are shown in Figure 1 below.

Results and Discussion

Chemistry

The development of non-hazardous synthetic methodologies for organic reactions is one of the most complicated issues to the organic chemists now a days. In continuation to this, we synthesized 2-aryl-4-(1-phenyl-3-(p-tolyl)-1H-pyrazol-4-yl)-2,3-dihydro-1H-benzo[b][1,4]diazepines (2a-t) by a one-pot synthesis with the use of 1-phenyl-3-(1-phenyl-3-(p-tolyl)-1H-pyrazol-4-yl)prop-2-en-1-ones (1a-t) and benzene-1,2-diamine (Scheme I). This simple reaction was carried out in the presence of catalysts i.e. piperidine and acetic acid. 0.01 mol of chalcones (1a-t) was added to DMF, after the dissolution of (1a-t) benzene-1,2-diamine was added in the double ratio. The reaction was refluxed for 8-10 h for completion.

Antimicrobial Assay

“Antimicrobial activity was accomplished by Mueller Hinton Broth dilution method (Becton Dickinson, USA)16. The strains were acquired from the IMTECH, Chandigarh, India. Antibacterial activity was screened in triple sets at diverse concentrations of 1000, 500, 250 and 200 µg/mL. The compounds which were found to be active in primary analysis were further diluted and evaluated. 10 µg/mL suspensions were further injected on appropriate media and the growth was noted after one or two days. In antifungal evaluation, primary screening was carried out in six sets at different concentrations of 1000, 500, and 250 µg/mL. The compounds found
active were similarly diluted to 200, 125, 100, 62.5, 50, 25, and 12.5 µg/mL concentrations for a secondary screening. Minimum Inhibitory Concentration (MIC) is the lowest concentration which showed no growth of microbes after 78 h subculture for each compound. In this study, Ciprofloxacin and Nystatin were the standard drugs for evaluating the antibacterial activity and antifungal activity respectively. 16, 17

Discussion on antimicrobial activity

Antimicrobial activity data are as shown in Table I. A few compounds showed a minimum inhibitory concentration (MIC) value less than the standard drug, while some compounds showed values comparable to the standard drug. The most active compound among the twenty derivatives is 2q (-2,4-Cl₂) which showed 12.5 µg/mL MIC value against E.coli. Compounds 2m and 2j showed significant activity as compared to standard drug (Ciprofloxacin) for S. aureus and S. pyogenes strains respectively. Compounds 2l (-4-CH₃) and 2k (-4-OCH₃) showed very good activity against C. albicans. Compound 2t (-4-OH-3-OCH₃) showed prominent activity against A. niger while compound 2i exhibited similar potency to standard drug (Nystatin) for A. niger and A.
clavatus strains of fungi. The Standard drug used was Ciprofloxacin and Nystatin for antibacterial and antifungal activity respectively.

**Experimental Section**

Synthesis of 1-phenyl-3-(1-phenyl-3-(p-tolyl)-1H-pyrazol-4-yl)prop-2-en-1-one, 1a-t was achieved by the literature procedure.\(^1\)

Synthesis of 2-phenyl-4-(1-phenyl-3-(p-tolyl)-1H-pyrazol-4-yl)-2,3-dihydro-1H-benzo[b][1,4]diazepines, 2a-t

Compounds 1a-t (0.01 mol), benzene-1,2-diamine (0.02 mol) in DMF (10 mL) were taken in a round bottom flask and refluxed for 8-10 h. Piperidine and glacial acetic acid were used as catalysts in the reaction mixture. This reaction mixture was poured into crushed ice to give the product which was filtered and washed with ethyl acetate (to remove any traces of chalcone), followed by hot water (to remove an excess of OPD) and then recrystallization from ethanol (95%).

<table>
<thead>
<tr>
<th>Compd</th>
<th>-R</th>
<th>Minimum bactericidal concentrations (MICB) in µg/mL</th>
<th>Minimum fungicidal concentrations (MICF) in µg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>-H</td>
<td>100</td>
<td>125</td>
</tr>
<tr>
<td>2b</td>
<td>-3-NO₂</td>
<td>125</td>
<td>50</td>
</tr>
<tr>
<td>2c</td>
<td>-4-NO₂</td>
<td>62.5</td>
<td>100</td>
</tr>
<tr>
<td>2d</td>
<td>-3-Br</td>
<td>100</td>
<td>250</td>
</tr>
<tr>
<td>2e</td>
<td>-4-Br</td>
<td>250</td>
<td>125</td>
</tr>
<tr>
<td>2f</td>
<td>-2-OH</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>2g</td>
<td>-3-OH</td>
<td>250</td>
<td>250</td>
</tr>
<tr>
<td>2h</td>
<td>-4-OH</td>
<td>62.5</td>
<td>100</td>
</tr>
<tr>
<td>2i</td>
<td>-2-OCH₃</td>
<td>50</td>
<td>250</td>
</tr>
<tr>
<td>2j</td>
<td>-3-OCH₃</td>
<td>100</td>
<td>200</td>
</tr>
<tr>
<td>2k</td>
<td>-4-OCH₃</td>
<td>200</td>
<td>250</td>
</tr>
<tr>
<td>2l</td>
<td>-4-CH₃</td>
<td>250</td>
<td>200</td>
</tr>
<tr>
<td>2m</td>
<td>-2-Cl</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>2n</td>
<td>-4-Cl</td>
<td>125</td>
<td>62.5</td>
</tr>
<tr>
<td>2o</td>
<td>-4-F</td>
<td>100</td>
<td>250</td>
</tr>
<tr>
<td>2p</td>
<td>-2,4-F₂</td>
<td>200</td>
<td>250</td>
</tr>
<tr>
<td>2q</td>
<td>-2,4-Cl₂</td>
<td>12.5</td>
<td>200</td>
</tr>
<tr>
<td>2r</td>
<td>-3,4-Cl₂</td>
<td>250</td>
<td>100</td>
</tr>
<tr>
<td>2s</td>
<td>-2-Br-4-Cl</td>
<td>62.5</td>
<td>200</td>
</tr>
<tr>
<td>2t</td>
<td>-4-OH-3-OCH₃</td>
<td>125</td>
<td>100</td>
</tr>
</tbody>
</table>

Ciprofloxacin 25 25 50 50 – – –
Nystatin – – – – – – –

Escherichia coli (E.c.) MTCC-442; Pseudomonas aeruginosa (P.a.) MTCC-441; Staphylococcus aureus (S.a.) MTCC-96; Streptococcus pyogenes (S.p.) MTCC-443; Candida albicans (C.a.) MTCC-227; Aspergillus niger (A.n.) MTCC-282; Aspergillus clavatus (A.c.) MTCC-1323.

Physical constants and characterization of 2-phenyl-4-(1-phenyl-3-(p-tolyl)-1H-pyrazol-4-yl)-2,3-dihydro-1H-benzo[b][1,4]diazepine, 2a: IR (KBr): 680 (-C-H bending, aromatic ring), 740, 752 (-C-H bending, 1,2-substituted ring (benzodiazepine)), 811 (-C-H bending, 1,4-substituted benzene ring), 962 (-C-H bending, aromatic ring), 1294 (-C-N stretching, pyrazole ring (>N-H)), 1396 (-C-H bending, -CH₃ group), 1474 (-C-H bending, aromatic ring), 1516, 1574 (-N-H bending, benzodiazepine ring (>N-H)) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.32 (s, 3H, -CH₃), 2.52 (dd, J = 5.7, 1.9 Hz, 1H, H-C-H of benzodiazepine), 2.78 (dd, J = 5.7, 2.1 Hz, 1H, H-C-H of benzodiazepine), 3.91 (s, 1H, -CH of benzodiazepine), 5.86 (s, 1H, -NH of benzodiazepine), 6.86-7.67 (m, 18H, Ar-H), 8.43 (s, 1H, -CH of pyrazole); ¹³C NMR (100 MHz, CDCl₃): δ 21.4, 39.5, 64.4, 112.9, 114.5, 119.7 (2), 121.8, 126.3, 126.7, 126.8, 127.0 (2), 128.2, 128.5 (2), 128.8 (2), 129.4 (2), 129.6 (2), 130.2, 130.5, 131.8, 137.4, 139.8, 140.5, 145.6, 150.2, 162.8; LC-
Physical constants and characterization of 2-(3-nitrophenyl)-4-(1-phenyl-3-(p-toly1)-1H-pyrazol-4-yl)-2,3-dihydro-1H-benzo[b][1,4]diazepine, 2b: IR (KBr): 678 (-C-H bending, aromatic ring), 754 (-C-H bending, 1,2-substituted ring (benzodiazepine)), 825 (-C-H bending, 1,4-substituted benzene ring), 974 (-C-H bending, aromatic ring), 1305 (-C-N stretching, pyrazole ring (>N-H)), 1378 (-C-H bending, -CH group), 1456 (-C-H bending, aromatic ring), 1347, 1512 (-N=O stretching, -NO₂ group), 1524, 1582 (-N-H bending, benzodiazepine ring (>N-H)) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.35 (s, 3H, -CH₃), 2.55 (dd, J = 5.7, 1.1 Hz, 1H, H-C-H of benzodiazepine), 2.78 (dd, J = 5.3, 1.8 Hz, 1H, H-C-H of benzodiazepine), 3.93 (s, 1H, -CH of benzodiazepine), 5.89 (s, 1H, -NH of benzodiazepine), 6.90-8.24 (m, 17H, Ar- of benzodiazepine), 3.92 (s, 1H, -CH of benzodiazepine), 2.74 (dd, J = 7.2, 5.9 Hz, 1H, H-C-H of benzodiazepine), 6.85-7.88 (m, 17H, Ar- of benzodiazepine), 5.89 (s, 1H, -NH of benzodiazepine), 6.90-7.64 (m, 1H, Ar-H), 8.45 (s, 1H, -CH of pyrazole); ¹³C NMR (100 MHz, CDCl₃): δ 21.3, 39.1, 62.3, 113.2, 114.7, 119.8 (2), 120.4, 121.7, 121.9, 126.2, 126.7, 128.3, 128.6 (2), 129.2, 129.5 (2), 129.6 (2), 130.1, 130.6, 131.6, 133.2, 137.5, 139.9, 144.2, 145.3, 147.5, 150.3, 162.7; LC-MS: m/z 532.14 [M⁺]. Anal. Calcd for: C₂₂H₂₃N₂O₂: C, 74.53; H, 5.04; N, 14.02. Found: C, 74.54; H, 5.05; N, 14.03%.

Physical constants and characterization of 2-(4-bromophenyl)-4-(1-phenyl-3-(p-toly1)-1H-pyrazol-4-yl)-2,3-dihydro-1H-benzo[b][1,4]diazepine, 2c: IR (KBr): 684 (-C-H bending, aromatic ring), 742, 757 (-C-H bending, aromatic ring), 1347, 1344 (-C-N stretching, pyrazole ring (>N-H)), 1378 (-C-H bending, -CH group), 1526, 1574 (-N-H bending, benzodiazepine ring (>N-H)) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.36 (s, 3H, -CH₃), 2.55 (dd, J = 7.2, 5.9 Hz, 1H, H-C-H of benzodiazepine), 2.79 (dd, J = 17.0, 2.1 Hz, 1H, H-C-H of benzodiazepine), 3.94 (s, 1H, -CH of benzodiazepine), 5.86 (s, 1H, -NH of benzodiazepine), 6.90-7.64 (m, 1H, Ar-H), 8.45 (s, 1H, -CH of pyrazole); ¹³C NMR (100 MHz, CDCl₃): δ 21.2, 39.3, 62.5, 113.1, 114.5, 119.6 (2), 121.5, 122.4, 125.6, 126.3, 126.8, 128.4, 128.7 (2), 129.2, 129.4 (2), 129.7, 129.8 (2), 130.3, 130.7, 131.5, 131.6, 137.6, 139.7, 142.5, 145.4, 150.5, 162.6; LC-MS: m/z 532.14 [M⁺]. Anal. Calcd for: C₂₂H₂₂BrN₂: C, 69.80; H, 4.72; N, 10.50. Found: C, 69.81; H, 4.70; N, 10.53%.

Physical constants and characterization of 2-(4-nitrophenyl)-4-(1-phenyl-3-(p-toly1)-1H-pyrazol-4-yl)-2,3-dihydro-1H-benzo[b][1,4]diazepine, 2d: IR (KBr): 678 (-C-H bending, aromatic ring), 754 (-C-H bending, 1,2-substituted ring (benzodiazepine)), 825 (-C-H bending, 1,4-substituted benzene ring), 974 (-C-H bending, aromatic ring), 1305 (-C-N stretching, pyrazole ring (>N-H)), 1378 (-C-H bending, -CH group), 1456 (-C-H bending, aromatic ring), 1347, 1512 (-N=O stretching, -NO₂ group), 1524, 1582 (-N-H bending, benzodiazepine ring (>N-H)) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.36 (s, 3H, -CH₃), 2.55 (dd, J = 8.8, 2.4 Hz, 1H, H-C-H of benzodiazepine), 2.74 (dd, J = 9.3, 2.4 Hz, 1H, H-C-H of benzodiazepine), 3.88 (s, 1H, -CH of benzodiazepine), 5.89 (s, 1H, -NH of benzodiazepine), 6.85-7.88 (m, 17H, Ar-H), 8.41 (s, 1H, -CH of pyrazole); ¹³C NMR (100 MHz, CDCl₃): δ 21.5, 39.0, 62.9, 113.3, 114.8, 119.7 (2), 121.3, 121.5, 123.9 (2), 126.3, 126.6, 128.2, 128.5 (2), 129.5 (2), 129.7 (2), 130.2, 130.4, 131.5, 131.7 (2), 137.7, 139.4, 143.2, 150.2, 162.6; LC-MS: m/z 532.16 [M⁺]. Anal. Calcd for: C₂₂H₂₂BrN₂:
Physical constants and characterization of 2-(2-hydroxyphenyl)-4-(1-phenyl-3-(p-toly)-1H-pyrazol-4-yl)-2,3-dihydro-1H-benzo[b][1,4]diazepine, 2f: IR (KBr): 687 (-C-H bending, aromatic ring), 748, 762 (-C-H bending, 1,2-substituted ring (benzodiazepine)), 823 (-C-H bending, 1,4-substituted benzene ring), 982 (-C-H bending, aromatic ring), 1316 (-C-N stretching, pyrazole ring (>N-H)), 1326 (-C-O-H bending, -OH group), 1391 (-C-H bending, -CH3 group), 1471 (-C-H bending, aromatic ring), 1522, 1535 (-N-H bending, benzodiazepine ring (>N-H)) cm⁻¹; 1H NMR (400 MHz, CDCl3): δ 2.33 (s, 3H, -CH3), 2.50 (dd, J = 8.1, 5.4 Hz, 1H, H-C-H of benzodiazepine), 2.76 (dd, J = 17.0, 10.1 Hz, 1H, H-C-H of benzodiazepine), 3.92 (s, 1H, -CH of benzodiazepine), 5.89 (s, 1H, -NH of benzodiazepine), 6.85-7.71 (m, 17H, Ar-H); 13C NMR (100 MHz, CDCl3): δ 21.0, 39.4, 56.7, 113.4, 114.6, 115.8, 119.7 (2), 121.4, 121.5, 126.2, 126.3, 126.7, 128.0, 128.4, 128.5 (2), 129.7 (2), 129.8 (2), 130.3, 130.5, 130.7, 131.8, 137.4, 145.7, 152.0, 154.2, 162.6; LC-MS: m/z 470.20 [M⁺]. Anal. Caled for: C31H26N4O: C, 79.12; H, 5.57; N, 11.91. Found: C, 79.10; H, 5.56; N, 11.88%.

Physical constants and characterization of 2-(3-hydroxyphenyl)-4-(1-phenyl-3-(p-toly)-1H-pyrazol-4-yl)-2,3-dihydro-1H-benzo[b][1,4]diazepine, 2g: IR (KBr): 690 (-C-H bending, aromatic ring), 746, 753 (-C-H bending, 1,2-substituted ring (benzodiazepine)), 817 (-C-H bending, 1,4-substituted benzene ring), 959 (-C-H bending, aromatic ring), 1316 (-C-O-H bending, -OH group), 1327 (-C-N stretching, pyrazole ring (>N-H)), 1364 (-C-H bending, -CH3 group), 1485 (-C-H bending, aromatic ring), 1513, 1575 (-N-H bending, benzodiazepine ring (>N-H)) cm⁻¹; 1H NMR (400 MHz, CDCl3): δ 2.32 (s, 3H, -CH3), 2.56 (dd, J = 5.3, 1.9 Hz, 1H, H-C-H of benzodiazepine), 2.78 (dd, J = 8.7, 5.7 Hz, 1H, H-C-H of benzodiazepine), 3.87 (s, 1H, -CH of benzodiazepine), 5.84 (s, 1H, -NH of benzodiazepine), 6.80-7.70 (m, 17H, Ar-H); 13C NMR (100 MHz, CDCl3): δ 21.2, 39.4, 63.4, 112.4, 112.8, 113.7, 114.6, 119.4, 119.7 (2), 121.5, 126.3, 126.5, 128.4, 128.7 (2), 129.3 (2), 129.9 (2), 130.9, 130.4, 131.8, 137.4, 139.7, 144.8, 145.2, 150.6, 156.6, 162.8; LC-MS: m/z 470.24 [M⁺]. Anal. Caled for: C31H26N4O: C, 79.12; H, 5.57; N, 11.91. Found: C, 79.13; H, 5.55; N, 11.90%.

Physical constants and characterization of 2-(4-hydroxyphenyl)-4-(1-phenyl-3-(p-toly)-1H-pyrazol-4-yl)-2,3-dihydro-1H-benzo[b][1,4]diazepine, 2h: IR (KBr): 684 (-C-H bending, aromatic ring), 743, 754 (-C-H bending, 1,2-substituted ring (benzodiazepine)), 820 (-C-H bending, 1,4-substituted benzene ring), 965 (-C-H bending, aromatic ring), 1323 (-C-O-H bending, -OH group), 1345 (-C-N stretching, pyrazole ring (>N-H)), 1387 (-C-H bending, -CH3 group), 1473 (-C-H bending, aromatic ring), 1527, 1563 (-N-H bending, benzodiazepine ring (>N-H)) cm⁻¹; 1H NMR (400 MHz, CDCl3): δ 2.35 (s, 3H, -CH3), 2.55 (dd, J = 5.3, 1.9 Hz, 1H, H-C-H of benzodiazepine), 2.76 (dd, J = 8.7, 5.2 Hz, 1H, H-C-H of benzodiazepine), 3.92 (s, 1H, -CH of benzodiazepine), 5.89 (s, 1H, -NH of benzodiazepine), 6.68-7.63 (m, 17H, Ar-H); 8.43 (s, 1H, -CH of pyrazole), 9.08 (s, 1H, -OH); 13C NMR (100 MHz, CDCl3): δ 21.1, 39.3, 63.4, 113.3, 114.6, 115.8 (2), 121.5, 126.3, 126.5, 127.2 (2), 128.4, 128.7 (2), 129.4 (2), 129.5 (2), 130.2, 130.7, 131.8, 133.2, 137.4, 139.8, 145.2, 150.1, 156.4, 162.8; LC-MS: m/z 470.20 [M⁺]. Anal. Caled for: C31H26N4O: C, 79.12; H, 5.57; N, 11.91. Found: C, 79.12; H, 5.59; N, 11.90%.

Physical constants and characterization of 2-(2-methoxyphenyl)-4-(1-phenyl-3-(p-toly)-1H-pyrazol-4-yl)-2,3-dihydro-1H-benzo[b][1,4]diazepine, 2i: IR (KBr): 686 (-C-H bending, aromatic ring), 752, 760 (-C-H bending, 1,2-substituted ring (benzodiazepine)), 814 (-C-H bending, 1,4-substituted benzene ring), 969 (-C-H bending, aromatic ring), 1308 (-C-N stretching, pyrazole ring (>N-H)), 1365 (-C-H bending, -CH3 group), 1459 (-C-H bending, aromatic ring), 1534, 1574 (-N-H bending, benzodiazepine ring (>N-H)), 2823 (-C-H stretching, -OCH3 group) cm⁻¹; 1H NMR (400 MHz, CDCl3): δ 2.36 (s, 3H, -CH3), 2.50 (dd, J = 5.4, 51.7 Hz, 1H, H-C-H of benzodiazepine), 2.78 (dd, J = 9.7, 7.6 Hz, 1H, H-C-H of benzodiazepine), 3.74 (s, 3H, -OCH3), 3.89 (s, 1H, -CH of benzodiazepine), 5.85 (s, 1H, -NH of benzodiazepine), 6.87-7.72 (m, 17H, Ar-H); 8.41 (s, 1H, -CH of pyrazole); 13C NMR (100 MHz, CDCl3): δ 21.4, 39.5, 56.2, 57.3, 112.3, 113.4, 114.6, 119.9 (2), 120.7, 121.5, 126.1, 126.3, 126.4, 127.5, 128.6, 128.8 (2), 129.2, 129.4 (2), 129.7 (2), 130.2, 130.7, 131.8, 137.3, 139.6, 145.5, 150.2, 156.4, 162.8;
Physical constants and characterization of 2-(3-methoxyphenyl)-4-(1-phenyl-3-(p-toly)-1H-pyrazol-4-yl)-2,3-dihydro-1H-benzol[b][1,4]diazepine, 2j: IR (KBr): 696 (-C-H bending, aromatic ring), 741, 752 (-C-H bending, 1,2-substituted ring (benzodiazepine)), 825 (-C-H bending, 1,4-substituted benzene ring), 973 (-C-H bending, aromatic ring), 1336 (-C-N stretching, pyrazole ring (>N-H)), 1382 (-C-H bending, -CH$_3$ group), 1474 (-C-H bending, aromatic ring), 1518, 1553 (-N-H bending, benzodiazepine ring (>N-H)), 2819 (-C-H stretching, -OCH$_3$ group) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 2.31 (s, 3H, -CH$_3$), 2.54 (dd, $J = 5.3$, 1.8 Hz, 1H, H-C-H of benzodiazepine), 2.77 (dd, $J = 8.5$, 5.2 Hz, 1H, H-C-H of benzodiazepine), 3.68 (s, 3H, -OCH$_3$), 3.92 (s, 1H, -CH of benzodiazepine), 5.86 (s, 1H, -NH of benzodiazepine), 6.86-7.69 (m, 17H, Ar-$H$), 8.43 (s, 1H, -CH of pyrazole); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 21.3, 39.4, 55.6, 63.3, 112.1, 112.5, 113.1, 114.8, 119.3, 119.9 (2), 121.6, 126.3, 126.8, 128.4, 128.7 (2), 129.6, 129.6 (2), 129.7 (2), 130.0, 130.7, 131.7, 137.6, 140.0, 144.3, 145.4, 150.5, 160.5, 162.8; LC-MS: $m/z$ 484.24 [M$^+$]. Anal. Calcd for: C$_{29}$H$_{32}$N$_{2}$O: C, 79.31; H, 5.82; N, 11.56. Found: C, 79.33; H, 5.80; N, 11.53%.

Physical constants and characterization of 2-(4-methoxyphenyl)-4-(1-phenyl-3-(p-toly)-1H-pyrazol-4-yl)-2,3-dihydro-1H-benzol[b][1,4]diazepine, 2k: IR (KBr): 687 (-C-H bending, aromatic ring), 750, 758 (-C-H bending, 1,2-substituted ring (benzodiazepine)), 822 (-C-H bending, 1,4-substituted benzene ring), 964 (-C-H bending, aromatic ring), 1286 (-C-N stretching, pyrazole ring (>N-H)), 1390 (-C-H bending, -CH$_3$ group), 1474 (-C-H bending, aromatic ring), 1541, 1571 (-N-H bending, benzodiazepine ring (>N-H)), 2831 (-C-H stretching, -OCH$_3$ group) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 2.32 (s, 3H, -CH$_3$), 2.50 (dd, $J = 5.4$, 1.7 Hz, 1H, H-C-H of benzodiazepine), 2.76 (dd, $J = 16.9$, 10.1 Hz, 1H, H-C-H of benzodiazepine), 3.82 (s, 3H, -OCH$_3$), 3.93 (s, 1H, -CH of benzodiazepine), 5.89 (s, 1H, -NH of benzodiazepine), 6.85-7.63 (m, 17H, Ar-$H$), 8.45 (s, 1H, -CH of pyrazole); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 21.0, 39.4, 55.7, 62.9, 113.4, 114.3 (2), 114.9, 119.6 (2), 121.9, 126.4, 126.6 (2), 126.9, 128.5, 128.8 (2), 129.7 (2), 129.8 (2), 130.3, 130.7, 131.8, 132.8, 137.7, 139.6, 145.5, 150.4, 158.4, 162.6; LC-MS: $m/z$ 484.22 [M$^+$]. Anal. Calcd for: C$_{29}$H$_{32}$N$_{2}$O: C, 79.31; H, 5.82; N, 11.55. Found: C, 79.29; H, 5.83; N, 11.55%.

Physical constants and characterization of 2-(4-methylphenyl)-4-(1-phenyl-3-(p-toly)-1H-pyrazol-4-yl)-2,3-dihydro-1H-benzol[b][1,4]diazepine, 2l: IR (KBr): 674 (-C-H bending, aromatic ring), 747, 759 (-C-H bending, 1,2-substituted ring (benzodiazepine)), 827 (-C-H bending, 1,4-substituted benzene ring), 980 (-C-H bending, aromatic ring), 1314 (-C-N stretching, pyrazole ring (>N-H)), 1328 (-C-H bending, -CH$_3$ group), 1378 (-C-H bending, -CH$_2$ group), 1460 (-C-H bending, aromatic ring), 1526, 1579 (-N-H bending, benzodiazepine ring (>N-H)) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 2.17 (s, 3H, -CH$_3$), 2.33 (s, 3H, -CH$_3$), 2.53 (dd, $J = 17.0$, 2.0 Hz, 1H, H-C-H of benzodiazepine), 2.78 (dd, $J = 10.1$, 2.0 Hz, 1H, H-C-H of benzodiazepine), 3.92 (s, 1H, -CH of benzodiazepine), 5.89 (s, 1H, -NH of benzodiazepine), 6.90-7.68 (m, 17H, Ar-$H$), 8.45 (s, 1H, -CH of pyrazole); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 21.4 (2), 39.3, 63.1, 113.4, 114.5, 119.7 (2), 121.6, 125.6, 126.4, 126.5, 128.2, 128.7 (2), 129.2, 129.6 (2), 129.8 (2), 130.3, 130.5, 131.7, 136.2, 137.4, 137.9, 139.8, 145.2, 150.1, 162.8; LC-MS: $m/z$ 468.20 [M$^+$]. Anal. Calcd for: C$_{32}$H$_{36}$N$_{2}$: C, 82.02; H, 6.02; N, 11.96. Found: C, 82.01; H, 6.03; N, 11.97%.

Physical constants and characterization of 2-(2-chlorophenyl)-4-(1-phenyl-3-(p-toly)-1H-pyrazol-4-yl)-2,3-dihydro-1H-benzol[b][1,4]diazepine, 2m: IR (KBr): 692 (-C-H bending, aromatic ring), 714 (-C-Cl stretching, -Cl group), 742, 762 (-C-H bending, 1,2-substituted ring (benzodiazepine)), 819 (-C-H bending, 1,4-substituted benzene ring), 969 (-C-H bending, aromatic ring), 1306 (-C-N stretching, pyrazole ring (>N-H)), 1369 (-C-H bending, -CH$_3$ group), 1452 (-C-H bending, aromatic ring), 1537, 1570 (-N-H bending, benzodiazepine ring (>N-H)) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 2.37 (s, 3H, -CH$_3$), 2.50 (dd, $J = 8.5$, 5.3 Hz, 1H, H-C-H of benzodiazepine), 2.74 (dd, $J = 5.4$, 1.8 Hz, 1H, H-C-H of benzodiazepine), 3.92 (s, 1H, -CH of benzodiazepine), 5.84 (s, 1H, -NH of benzodiazepine), 6.85-7.64 (m, 17H, Ar-$H$), 8.42 (s, 1H, -CH of pyrazole); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 21.2, 38.6, 57.8, 113.3, 114.5, 119.6 (2), 121.8, 126.4, 126.7, 126.9, 127.9, 128.1, 128.2, 128.5 (2), 128.7, 129.7 (2), 129.8 (2), 130.2, 130.5, 131.7.
132.4, 137.4, 140.1, 143.3, 145.4, 150.1, 162.6; LC-MS: m/z 488.20 [M⁺]. Anal. Calcd for: C₃₁H₳₄FN₄: C, 76.14; H, 5.15; N, 11.46. Found: C, 76.15; H, 5.18; N, 11.45%.

Physical constants and characterization of 2-(4-chlorophenyl)-4-(1-phenyl-3-(p-tolyl)-1H-pyrazol-4-yl)-2,3-dihydro-1H-benzo[b][1,4]diazepine, 2n: IR (KBr): 698 (-C-H bending, aromatic ring), 743, 757 (-C-H bending, 1,2-substituted ring (benzodiazepine)), 778 (-C-Cl stretching, -Cl group), 816 (-C-H bending, 1,4-substituted benzene ring), 972 (-C-H bending, aromatic ring), 1319 (-C-N stretching, pyrazole ring (N=N-H)), 1378 (-C-H bending, -CH₃ group), 1475 (-C-H bending, aromatic ring), 1551, 1579 (-N-H bending, benzodiazepine ring (N=N-H)) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.32 (s, 3H, -CH₃), 2.52 (dd, J = 9.8, 1.6 Hz, 1H, H-C-H of benzodiazepine), 2.76 (dd, J = 8.7, 5.3 Hz, 1H, H-C-H of benzodiazepine), 3.88 (s, 1H, -CH of benzodiazepine), 5.90 (s, 1H, -NH of benzodiazepine), 6.87-7.65 (m, 17H, Ar-H), 8.45 (s, 1H, -CH of pyrazole); ¹³C NMR (100 MHz, CDCl₃): δ 21.0, 39.3, 63.2, 112.8, 114.6, 119.8 (2), 121.6, 123.5 (2), 124.6, 126.8, 128.5, 128.7 (2), 128.9 (2), 129.8 (2), 129.9 (2), 130.2, 130.4, 131.9, 132.4, 132.6, 133.9, 145.2, 150.1, 162.6; LC-MS: m/z 488.15 [M⁺]. Anal. Calcd for: C₃₁H₳₄FN₄: C, 76.14; H, 5.15; N, 11.46. Found: C, 76.15; H, 5.17; N, 11.44%.

Physical constants and characterization of 2-(4-fluorophenyl)-4-(1-phenyl-3-(p-tolyl)-1H-pyrazol-4-yl)-2,3-dihydro-1H-benzo[b][1,4]diazepine, 2o: IR (KBr): 683 (-C-H bending, aromatic ring), 747, 750 (-C-H bending, 1,2-substituted ring (benzodiazepine)), 827 (-C-H bending, 1,4-substituted benzene ring), 975 (-C-H bending, aromatic ring), 1017 (-C-F stretching, -F group), 1328 (-C-N stretching, pyrazole ring (N=N-H)), 1358 (-C-H bending, -CH₃ group), 1451 (-C-H bending, aromatic ring), 1536, 1578 (-N-H bending, benzodiazepine ring (N=N-H)) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.35 (s, 3H, -CH₃), 2.56 (dd, J = 16.8, 8.2 Hz, 1H, H-C-H of benzodiazepine), 2.77 (dd, J = 5.4, 1.7 Hz, 1H, H-C-H of benzodiazepine), 3.91 (s, 1H, -CH of benzodiazepine), 5.89 (s, 1H, -NH of benzodiazepine), 6.85-7.64 (m, 17H, Ar-H), 8.43 (s, 1H, -CH of pyrazole); ¹³C NMR (100 MHz, CDCl₃): δ 21.4, 39.0, 63.3, 113.3, 114.5, 115.4 (2), 119.8 (2), 121.6, 126.3, 126.6, 128.4, 128.5 (2), 128.7 (2), 129.4 (2), 129.5 (2), 130.2, 130.7, 131.8, 136.4, 137.4, 139.8, 145.1, 150.4, 160.7, 162.5; LC-MS: m/z 472.23 [M⁺]. Anal. Calcd for: C₃₁H₂₃FN₄: C, 78.79; H, 5.33; N, 11.86. Found: C, 78.80; H, 5.35; N, 11.84%.

Physical constants and characterization of 2-(2,4-difluorophenyl)-4-(1-phenyl-3-(p-tolyl)-1H-pyrazol-4-yl)-2,3-dihydro-1H-benzo[b][1,4]diazepine, 2p: IR (KBr): 685 (-C-H bending, aromatic ring), 742, 758 (-C-H bending, 1,2-substituted ring (benzodiazepine)), 815 (-C-H bending, 1,4-substituted benzene ring), 967 (-C-H bending, aromatic ring), 1104 (-C-F stretching, -F group), 1323 (-C-N stretching, pyrazole ring (N=N-H)), 1394 (-C-H bending, -CH₃ group), 1484 (-C-H bending, aromatic ring), 1517, 1576 (-N-H bending, benzodiazepine ring (N=N-H)) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.35 (s, 3H, -CH₃), 2.55 (dd, J = 10.0, 1.5 Hz, 1H, H-C-H of benzodiazepine), 2.76 (dd, J = 5.9, 1.7 Hz, 1H, H-C-H of benzodiazepine), 3.90 (s, 1H, -CH of benzodiazepine), 5.84 (s, 1H, -NH of benzodiazepine), 6.69-7.62 (m, 16H, Ar-H), 8.45 (s, 1H, -CH of pyrazole); ¹³C NMR (100 MHz, CDCl₃): δ 21.4, 39.2, 56.3, 104.2, 104.6, 110.7, 113.2, 114.7, 120.1 (2), 121.7, 126.3, 126.7, 128.2, 128.5 (2), 129.4 (2), 129.7 (2), 129.9, 130.2, 130.5, 131.8, 137.4, 139.5, 145.2, 150.2, 159.3, 161.1, 162.7; LC-MS: m/z 490.22 [M⁺]. Anal. Calcd for: C₃₁H₂₃FN₄: C, 75.90; H, 4.93; N, 11.42. Found: C, 75.92; H, 4.92; N, 11.42%.

Physical constants and characterization of 2-(2,4-dichlorophenyl)-4-(1-phenyl-3-(p-tolyl)-1H-pyrazol-4-yl)-2,3-dihydro-1H-benzo[b][1,4]diazepine, 2q: IR (KBr): 686 (-C-H bending, aromatic ring), 731 (-C-Cl stretching), 744 (-C-H bending, 1,2-substituted ring (benzodiazepine)), 821 (-C-H bending, 1,4-substituted benzene ring), 956 (-C-H bending, aromatic ring), 1276 (-C-N stretching, pyrazole ring (N=N-H)), 1409 (-C-H bending, -CH₃ group), 1452 (-C-H bending, aromatic ring), 1504, 1587 (-N-H bending, benzodiazepine ring (N=N-H)) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.33 (s, 3H, -CH₃), 2.52 (dd, J = 5.3, 1.8 Hz, 1H, H-C-H of benzodiazepine), 2.76 (dd, J = 5.4, 2.9 Hz, 1H, H-C-H of benzodiazepine), 3.93 (s, 1H, -CH of benzodiazepine), 5.86 (s, 1H, -NH of benzodiazepine), 6.84-7.66 (m, 16H, Ar-H), 8.45 (s, 1H, -CH of pyrazole); ¹³C NMR (100 MHz, CDCl₃): δ 21.1, 38.4, 57.8, 113.2, 114.7, 119.6, 119.8 (2), 121.7, 126.3, 126.6, 126.9, 128.1, 128.5 (2), 129.4 (2), 129.7 (2), 130.1, 130.4, 131.2, 133.8, 137.4, 139.9, 141.4, 145.2, 150.6, 151.3, 162.8; LC-
Physical constants and characterization of 2-(3,4-dichlorophenyl)-4-(1-phenyl-3-(p-tolyl))-1H-pyrazol-4-yl)-2,3-dihydro-1H-benzo[b][1,4]diazepine, 2r: IR (KBr): 688 (-C-H bending, aromatic ring), 744, 754 (-C-H bending, 1,2-substituted ring (benzodiazepine)), 821 (-C-H bending, 1,4-substituted benzene ring), 950 (-C-H bending, aromatic ring), 1060, 1220 (-C-O-C stretching, -OCH₃ group), 1276 (-C-N stretching, pyrazole ring (>N-H)), 1386 (-C-O-H bending, -OH group), 1409 (-C-H bending, -CH₃ group), 1456 (-C-H bending, aromatic ring), 1506, 1589 (-N-H bending, benzodiazepine ring (>N-H)) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.34 (s, 3H, -CH₃), 2.54 (dd, J = 8.7, 3.6 Hz, 1H, H-C-H of benzodiazepine), 2.77 (dd, J = 9.3, 5.5 Hz, 1H, H-C-H of benzodiazepine), 3.89 (s, 1H, -CH of benzodiazepine), 5.91 (s, 1H, -NH of benzodiazepine), 6.82-7.64 (m, 16H, Ar-H), 8.46 (s, 1H, -CH of pyrazole); ¹³C NMR (100 MHz, CDCl₃): δ 21.2, 38.7, 56.4, 59.3, 113.1, 114.7, 120.0 (2), 121.8, 125.4, 126.3, 126.7, 128.2, 128.4, 128.6 (2), 129.4 (2), 129.7 (2), 130.2 (2), 130.5, 131.6, 131.8, 131.9, 137.1, 139.4, 143.2, 145.3, 150.2, 162.5; LC-MS: m/z 522.12 [M⁺]. Anal. Calcld for: C₂₃H₂₄BrClN₄; C, 65.56; H, 4.26; N, 9.87. Found: C, 65.55; H, 4.27; N, 9.86%.  

Physical constants and characterization of 2-methoxy-4-(4-(1-phenyl-3-(p-tolyl))-1H-pyrazol-4-yl)-2,3-dihydro-1H-benzo[b][1,4]diazepin-2-yl)phenol, 2t: IR (KBr): 688 (-C-H bending, aromatic ring), 744, 754 (-C-H bending, 1,2-substituted ring (benzodiazepine)), 821 (-C-H bending, 1,4-substituted benzene ring), 950 (-C-H bending, aromatic ring), 1060, 1220 (-C-O-C stretching, -OCH₃ group), 1276 (-C-N stretching, pyrazole ring (>N-H)), 1386 (-C-O-H bending, -OH group), 1409 (-C-H bending, -CH₃ group), 1456 (-C-H bending, aromatic ring), 1506, 1589 (-N-H bending, benzodiazepine ring (>N-H)) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.34 (s, 3H, -CH₃), 2.53 (dd, J = 7.2, 6.0 Hz, 1H, H-C-H of benzodiazepine), 2.75 (dd, J = 8.8, 3.4 Hz, 1H, H-C-H of benzodiazepine), 3.74 (s, 3H, -CH₃), 3.90 (s, 1H, -CH of benzodiazepine), 5.87 (s, 1H, -NH of benzodiazepine), 6.70-7.67 (m, 16H, Ar-H), 8.47 (s, 1H, -CH of pyrazole), 9.98 (s, 1H, -OH); ¹³C NMR (100 MHz, CDCl₃): δ 21.2, 38.7, 56.4, 63.5, 110.3, 113.4, 114.7, 115.2, 119.2, 119.7 (2), 121.7, 126.3, 126.8, 128.2, 128.5 (2), 129.4 (2), 129.8 (2), 130.1, 130.4, 131.5, 137.2, 139.9, 145.3, 146.8, 147.5, 150.2, 162.7; LC-MS: m/z 500.23 [M⁺]. Anal. Calcld for: C₁₉H₂₄N₂O₂; C, 76.78; H, 5.64; N, 11.19. Found: C, 76.80; H, 5.66; N, 11.20%.  

Conclusion  
In conclusion, new hybrids of pyrazole and benzodiazepine have been synthesized and characterized by different spectral techniques. All newly synthesized compounds were evaluated for their antibacterial and antifungal activity against different strains of bacteria and fungi using serial dilution method. On the basis of above mentioned data of biological activity, it may be concluded that synthesized novel series of compounds exhibited good to excellent activity against different bacterial and fungal strains. Evaluation of compounds 2j, 2m and 2q exhibited excellent activity against bacterial strains while compounds 2i, 2k, 2l and 2t showed prominent activity against fungal strains. Results of biological activity conclude that electron withdrawing and electron donating groups were much effective for bacterial and fungal strains respectively.
Supplementary Information

Supplementary information is available in the website http://nopr.niscair.res.in/handle/123456789/60.

Acknowledgement

Authors are grateful to the UGC, New Delhi and Department of Science and Technology, New Delhi (DST-FIST-SR/FST/CSI-212/2010) for financial support under the NON-SAP and DST-FIST programs respectively.

References