Asian Pub. Corp.

www.asianpubs.org

ARTICLE

Synthesis, Spectral Analysis and Antibacterial Screening of Tetracyclic Thiazepine Based Pyrazole Derivatives

Jayanti B. Hirani[1,✉], Mayank Pandya[1] and Suresh B. Koradiya[2]

ABSTRACT

A series of tetracyclic thiazepine based pyrazoles (**6a-j**) have been synthesized and evaluated for antibacterial and antifungal activities. The newly synthesized compounds have been characterized by IR, ^{1}H & ^{13}C NMR, mass and elemental analyses. Compounds **6b** (2-OCH_3) and **6c** (4-OCH_3) have shown promising antibacterial, and **6g** (3-NO_2), **6f** (2-NO_2) and **6d** (3,4-diOCH_3) exhibited excellent an antifungal activity against standard drugs.

KEYWORDS

Thiazepine, Pyrazole, Cyclization, Antimicrobial activity.

Asian Journal of Organic & Medicinal Chemistry

Volume: 5 Year: 2020
Issue: 4 Month: October–December
pp: 283–288
DOI: https://doi.org/10.14233/ajomc.2020.AJOMC-P281

Received: 30 June 2020
Accepted: 11 September 2020
Published: 31 December 2020

Author affiliations:

[1]Department of Chemistry, School of Science, R K University, Rajkot-360020, India
[2]Department of Chemistry, Shree M. & N. Virani Science College, Rajkot-360005, India

✉To whom correspondence to be addressed:

E-mail: jayant.hirani@yahoo.co.in

Available online at: http://ajomc.asianpubs.org

INTRODUCTION

Assembly of pyrazole heterocycles based on thiazepine has received considerable attention. Thiazepine scaffolds are structural motifs that are useful for demonstrating the chemical functionality of biological active molecules. Several drugs having thiazepine functionality, such as antibacterial drug [1], anti-inflammatory and ulcerogenic agents [2], anticonvulsant agents [3], antimalarial agents [4], protease inhibitors [5] and cytotoxic agent [6] are used clinically. Moreover, these drugs present numerous anticancer agent applications [7]. Some thiazepines have also been verified as valuable herbicides [8]. Omapatrilat (Fig. 1a) is one of the example of the established drugs based on thiazepine and being investigated and inhibits both angiotensin-converting and neutral endopeptidase enzymes [9].

Furthermore, pyrazole derivatives have received substantial attention because this skeleton type exists in numerous compounds that contain different biological activates [10]. Developing an efficient method for pyrazole fabrication is crucial. A few derivatives having pyrazole ring systems exhibit useful pharmacological activities, including anti-inflammatory [11], antiviral [12], anticonvulsant [13], genotoxicity [14], anti-HIV [15] and antitubercular [16] activities. These derivatives also have antifungal, antitumor [17], antimicrobial, antibacterial, antitubercular [16], antimalarial, anti-inflammatory, anti-proliferative and ulcerogenicity activities [18]. Pyrazole based drugs are widely known as a chemotherapy agent *e.g.* lonazolac contains pyrazole core moiety (Fig. 1b) and is an excellent anti-inflammatory non-steroidal drug [19].

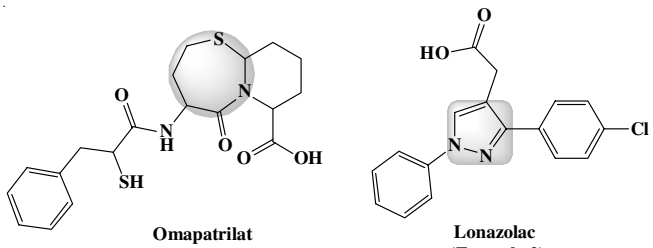


Fig. 1. Azepine and pyrazole based well-marketed drugs

In continuation of our current interest, a series of tetracyclic thiazepine based pyrazoles (**6a-j**) for developing potential antimicrobials. The structure of newly compounds were investigated using IR, ^{1}H & ^{13}C NMR and mass spectral analyses.

EXPERIMENTAL

The chemicals and solvents were procured from Merck Ltd., HIMEDIA, and SD fine chemicals. An open-end capillary was used to determine the melting points and are uncorrected. To monitor reactions, thin layer chromatography (TLC) was employed; ethyl acetate:*n*-hexane was used as the mobile phase and the reactions were visualized under UV light (254 and 365 nm). By using the ATR method, the IR spectra of each compound were obtained on a Shimadzu, Japan IR-435 Spectrophotometer. On a Bruker AVANCE II Spectrometer, the spectra of ^{13}C NMR (101 MHz) and ^{1}H NMR (400 MHz) were measured using DMSO-d_6 and TMS as the solvent and internal reference, respectively. On a Jeol-JMSD 300 mass spectrometer, mass spectra were measured at 70 eV. The elemental analysis was performed using a Perkin-Elmer 2400 CHN analyzer.

Synthesis of intermediates (5a-j): Intermediates were synthesized as according to reported work and characterized [20].

Synthesis of 6-(5-(aryl)-1-aryl-4,5-dihydro-1*H*-pyrazol-3-yl)-9*H*-4,15-dithia-9,10-diazatribenzo[*b,ef,i*]heptalene (6a-j): Phenylhydrazine (1.1 mL) and the intermediates (**5a-j**) (0.01 mmol) were mixed in 5 mL of 1,4-dioxane. The reaction mixture was refluxed with stirring at 70 ºC for approximately 7 h. Reaction completion was monitored through TLC by using the mobile phase of acetone:*n*-hexane (4:6). The reaction mixture was cooled to room temperature and poured in ice water, the obtained crude solid was filtered, dried and purified through flash silica gel column chromatography.

6-(1,5-Diphenyl-4,5-dihydro-1*H*-pyrazol-3-yl)-9*H*-4,15-dithia-9,10-diazatribenzo[*b,ef,i*]heptalene (6a): Yield: 71%; m.p.: 198 ºC; IR (cm^{-1}): 3665 (N-H *str*. 2º amine), 3310 (C-H *str*. arom. ring), 1521 (C=C *str*. arom. ring), 1261 (C-N *str*. pyrazole ring), 1252 (C-S *str*. azepine ring); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.096 (2H, s, -CH_2), 5.285 (1H, s, -CH), 6.882-7.224 (4H, m, Ar-H), 7.236-7.003 (1H, t, Ar-H), 7.396-7.371 (2H, d, Ar-H), 7.521-7.628 (6H, m, Ar-H), 7.768-7.018 (5H, m, Ar-H), 8.232-8.213 (1H, d, Ar-H), 8.720 (1H, s, Ar-H), 9.542 (1H, s, -NH); ^{13}C NMR (101 MHz, DMSO-d_6, δ ppm): 161.12, 154.85, 154.85, 151.48, 148.65, 146.02, 141.85, 139.26, 138.41, 135.23, 133.50, 132.65, 132.50, 128.32, 128.32, 127.08, 127.08, 126.42, 124.53, 126.53, 125.77, 125.34, 124.89, 123.82, 122.90, 122.05, 121.58, 118.68, 115.20, 115.20, 67.50, 34.61; MS: *m/z* 552 (M^+); Elemental analysis calcd. (found) % for $C_{34}H_{24}N_4S_2$: C, 73.88 (73.82); H, 4.38 (4.41); N, 10.14 (10.17); S, 11.60 (11.62).

6-(5-(2-Methoxyphenyl)-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl)-9*H*-4,15-dithia-9,10-diazatribenzo[*b,ef,i*]-heptalene (6b): Yield: 80.55 %; m.p.: 191 ºC; IR (cm^{-1}): 3721 (N-H *str*. 2º amine), 3359 (C-H *str*. arom. ring), 1534 (C=C *str*. arom. ring), 1370 (C-N *str*. pyrazole ring), 1268 (C-S *str*. azepine ring); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.090 (2H, s, -CH_2), 3.736 (3H, s, -OCH_3), 5.343 (1H, s, -CH), 7.043-6.986 (2H, m, Ar-H), 7.175-7.157 (1H, d, Ar-H), 7.271-7.373 (4H, m, Ar-H), 7.636-7.529 (6H, m, Ar-H), 7.872-7.708 (4H, m, Ar-H), 8.245-8.226 (1H, d, Ar-H), 8.728 (1H, s, Ar-H), 9.656 (1H, s, -NH); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm: 166.21, 157.51, 149.84, 149.84, 148.25, 147.23, 145.45, 138.89, 137.02, 135.14, 134.56, 133.58, 133.58, 131.09, 130.58, 130.58, 129.15, 127.89, 126.54, 125.48, 125.01, 123.22, 122.48, 121.78, 121.14, 119.23, 118.85, 115.65, 115.65, 113.77, 61.45, 54.58, 33.85; MS: *m/z* 582 (M^+); Elemental analysis calcd. (found) % for $C_{35}H_{26}N_4OS_2$: C, 72.14 (72.11); H, 4.50 (4.46); N, 9.61 (9.64); S, 11.00 (11.05).

6-(5-(4-Methoxyphenyl)-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl)-9*H*-4,15-dithia-9,10-diazatribenzo[*b,ef,i*]-heptalene (6c): Yield: 83.45 %; m.p.: 187 ºC; IR (cm^{-1}): 3682 (N-H *str*. 2º amine), 3316 (C-H *str*. arom. ring), 1492 (C=C *str*. arom. ring), 1365 (C-N *str*. pyrazole ring), 1253 (C-S *str*. azepine ring); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.086 (2H, s, -CH_2), 3.784 (3H, s, -OCH_3), 5.350 (1H, s, -CH), 7.036-7.236 (3H, m, Ar-H), 7.381-7.362 (2H, dd, Ar-H), 7.641-7.535 (8H, m, Ar-H), 7.872-7.712 (4H, m, Ar-H), 8.255-8.236 (1H, d, Ar-H), 8.722 (1H, s, Ar-H), 9.429 (1H, s, -NH); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm: 163.45, 160.48, 158.32, 155.89, 154.58, 153.84, 151.36, 150.89, 148.45, 144.92, 145.85, 143.62, 139.51, 135.30, 134.58, 134.58, 131.58, 130.58, 130.58, 129.53, 127.29, 127.21, 126.08, 124.37, 123.22, 121.81, 116.34, 116.34, 113.09, 113.09, 81.54, 53..05, 36.51; MS: *m/z* = 582 (M^+); Elemental analysis calcd. (found) % for $C_{35}H_{26}N_4OS_2$: C, 72.14 (72.18); H, 4.50 (4.53); N, 9.61 (9.62); S, 11.00 (11.09).

6-(5-(3,4-Dimethoxyphenyl)-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl)-9*H*-4,15-dithia-9,10-diazatribenzo[*b,ef,i*]-heptalene (6d): Yield: 79.88%; m.p.: 205 ºC; IR (cm^{-1}): 3671 (N-H *str*. 2º amine), 3348 (C-H *str*. arom. ring), 1418 (C=C *str*. arom. ring), 1381 (C-N *str*. pyrazole ring), 1189 (C-S *str*. azepine ring); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.081 (2H, s, -CH_2), 3.825-3.841 (6H, s, -OCH_3), 5.343 (1H, s, -CH), 7.043-6.986 (2H, m, Ar-H), 7.175-7.157 (1H, d, Ar-H), 7.273-7.236 (1H, t, Ar-H), 7.397-7.373 (2H, d, Ar-H), 7.636-7.529 (6H, m, Ar-H), 7.872-7.700 (4H, m, Ar-H), 8.245-8.226 (1H, d, Ar-H), 8.728 (1H, s, Ar-H), 9.656 (1H, s, -NH); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm: 162.15, 159.48, 158.36, 156.09, 154.78, 151.02, 149.52, 146.47, 145.65, 142.59, 139.48, 138.32, 136.59, 136.59, 134.98, 123.89, 123.89, 122.58, 121.61, 121.05, 120.95, 118.88, 117.65, 116.45, 115.54, 114.73, 113.95, 111.99, 111.35, 109.35, 83.58, 59.21, 55.30, 34.30; MS: *m/z* = 612 (M^+); Elemental analysis calcd. (found) % for $C_{36}H_{28}N_4O_2S_2$: C, 70.56 (70.54); H, 4.61 (4.59); N, 9.14 (9.17); S, 10.47 (10.42).

6-(1-Phenyl-5-(3,4,5-trimethoxyphenyl)-4,5-dihydro-1*H*-pyrazol-3-yl)-9*H*-4,15-dithia-9,10-diazatribenzo[*b,ef,i*]-heptalene (6e): Yield: 77.60%; m.p.: 218 ºC; IR (cm^{-1}): 3739

(N-H *str*. 2º amine), 3361 (C-H *str*. arom. ring), 1457 (C=C *str*. arom. ring), 1360 (C-N *str*. pyrazole ring), 1225 (C-S *str*. azepine ring); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.073 (2H, s, -CH_2), 3.782 (9H, s, -OCH_3), 5.298 (1H, s, -CH), 7.116-7.058 (2H, m, Ar-H), 7.265-7.373 (4H, m, Ar-H), 7.640-7.438 (6H, m, Ar-H), 7.770-8.40 (4H, m, Ar-H), 8.736 (1H, s, Ar-H), 9.644 (1H, s, -NH); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm: 165.74, 160.41, 159.12, 157.36, 146.15, 144.85, 143.22, 142.74, 141.62, 137.62, 135.02, 133.95, 132.32, 131.43, 130.35, 130.35, 128.51, 128.51, 127.26, 125.19, 124.06, 123.98, 122.26, 121.25, 120.12, 118.46, 116.61, 116.61, 107.32, 107.32, 85.36, 65.02, 59.31, 54.31, 35.78; MS: *m/z* = 642 (M^+); Elemental analysis of $C_{37}H_{30}N_4O_3S_2$: C, 69.14 (69.17); H, 4.70 (4.68); N, 8.72 (8.75); S, 9.98 (9.95).

6-(5-(2-Nitrophenyl)-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl)-9*H*-4,15-dithia-9,10-diazatri benzo[*b,ef,i*]heptalene (6f): Yield: 81.45 %; m.p.: 235 ºC; IR (cm^{-1}): 3741 (N-H stretching Sec. amine), 3269 (C-H stretching aromatic ring), 1470 (C=C stretching aromatic ring), 1362 (C-N stretching pyrazole ring), 1481, 1320 (-NO_2 group), 1289 (C-S stretching azepine ring); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.235 (2H, s, -CH_2), 5.258 (1H, s, -CH), 7.354-6.584 (2H, m, Ar-H), 7.685-7.425 (1H, d, Ar-H), 7.358-7.258 (4H, m, Ar-H), 7.568-7.213 (6H, m, Ar-H), 7.845-7.736 (4H, m, Ar-H), 8.285-8.225 (1H, d, Ar-H), 8.841 (1H, s, Ar-H), 9.771 (1H, s, -NH); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm: 164.45, 163.15, 161.23, 157.56, 155.89, 154.20, 151.98, 146.20, 142.38, 139.51, 138.98, 137.02, 136.68, 134.55, 134.55, 131.58, 131.58, 130.25, 129.18, 128.36, 127.97, 127.25, 125.08, 124.77, 123.45, 122.20, 121.54, 119.65, 116.32, 114.33, 67.87, 36.81; MS: *m/z* = 572 (M^+); Elemental analysis of $C_{34}H_{23}N_5O_2S_2$: C, 68.32 (68.27); H, 3.88 (3.91); N, 11.72 (11.69); S, 10.73 (10.75).

6-(5-(3-Nitrophenyl)-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl)-9*H*-4,15-dithia-9,10-diazatribenzo[*b,ef,i*]heptalene (6g): Yield: 83.57 %; m.p.: 240 ºC; IR (cm^{-1}) 3640 (N-H *str*. 2º amine), 3281 (C-H *str*. arom. ring), 1437 (C=C *str*. arom. ring), 1468, 1380 (-NO_2 group), 1298 (C-N *str*. pyrazole ring), 1254 (C-S *str*. azepine ring); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.514 (2H, s,-CH_2), 5.652 (1H, s,-CH), 7.956-6.145 (2H, m, Ar-H), 7.852-7.485 (1H, d, Ar-H), 7.583-7.521 (4H, m, Ar-H), 7.756-7.265 (5H, m, Ar-H), 7.465-7.242 (4H, m, Ar-H), 8.325-8.254 (2H, d, Ar-H), 8.652 (1H, s, Ar-H), 9.512 (1H, s, -NH); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm: 162.45, 160.48, 157.81, 157.81, 156.15, 155.36, 151.85, 147.29, 141.86, 138.20, 137.03, 135.59, 134.98, 133.69, 133.69, 131.85, 130.53, 130.53, 129.56, 128.65, 127.65, 125.41, 124.82, 124.01, 122.36, 121.52, 120.69, 118.21, 115.95, 114.62, 79.22, 33.21; MS: *m/z* = 572 (M^+); Elemental analysis calcd. (found) % for $C_{34}H_{23}N_5O_2S_2$: C, 68.32 (68.35); H, 3.88 (3.84); N, 11.72 (11.77); S, 10.73 (10.68).

6-(5-(4-Nitrophenyl)-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl)-9*H*-4,15-dithia-9,10-diazatribenzo[*b,ef,i*]heptalene (6h): Yield: 84.61 %; m.p.: 256 ºC; IR (cm^{-1}): 3766 (N-H *str*. 2º amine), 3319 (C-H *str*. arom. ring), 1548 (C=C *str*. arom. ring), 1451, 1386 (-NO_2 group), 1366 (C-N *str*. pyrazole ring), 1285 (C-S *str*. azepine ring); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 3.124 (2H, s, -CH_2), 5.840 (1H, s, -CH), 7.812-7.562 (3H, m, Ar-H), 7.628-7.485 (2H, d, Ar-H), 7.652-7.412 (8H, m, Ar-H), 7.548-7.215 (4H, m, Ar-H), 8.586-8.452 (1H, d, Ar-H), 8.658 (1H, s, Ar-H), 9.125 (1H, s, -NH); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm: 164.25, 163.58, 159.41, 159.41, 156.02, 153.19, 149.65, 148.26, 146.12, 144.65, 138.32, 137.02, 136.65, 136.65, 133.47, 133.47, 130.23, 128.29, 128.29, 126.88, 125.36, 124.10, 124.95, 123.25, 122.86, 121.65, 121.08, 119.65, 118.36, 116.06, 80.56, 34.59; MS: *m/z* = 572 (M^+); Elemental analysis calcd. (found) % for $C_{34}H_{23}N_5O_2S_2$: C, 68.32 (68.26); H, 3.88 (3.81); N, 11.72 (11.78); S, 10.73 (10.74).

4-(3-(9*H*-4,15-Dithia-9,10-diazatribenzo[*b,ef,i*]-heptalen-6-yl)-1-phenyl-4,5-dihydro-1*H*-pyrazol-5-yl)aniline (6i): Yield: 80.55 %; m.p.: 188 ºC; IR (cm^{-1}): 3691 (N-H *str*. 2º amine), 3297 (C-H *str*. arom. ring), 1518 (C=C *str*. arom. ring), 1327 (C-N *str*. pyrazole ring), 1290 (C-S *str*. azepine ring); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.852 (2H, s, -CH_2), 4.582-4.362 (2H, s, -N$\underline{H}_2$), 5.681 (1H, s, -CH), 7.652-7.215 (3H, m, Ar-H), 7.568-7.358 (2H, d, Ar-H), 7.458-7.365 (8H, m, Ar-H), 7.356-7.265 (4H, m, Ar-H), 8.285-8.235 (1H, d, Ar-H), 8.589 (1H, s, Ar-H), 9.895 (1H, s, -NH); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm: 162.21, 158.56, 155.32, 155.32, 154.12, 152.02, 151.58, 147.36, 146.85, 138.36, 135.98, 134.54, 134.54, 131.84, 131.84, 130.58, 129.96, 129.96, 127.02, 126.43, 125.35, 124.82, 122.98, 121.08, 119.51, 118.62, 115.98, 114.30, 112.91, 110.85, 84.03, 35.51; MS: *m/z* = 567 (M^+); Elemental analysis calcd. (found) % for $C_{34}H_{25}N_5S_2$: C, 71.93 (71.91); H, 4.44 (4.48); N, 12.34 (12.37); S, 11.30 (11.35).

6-(1-Phenyl-5-(*p*-tolyl)-4,5-dihydro-1*H*-pyrazol-3-yl)-9*H*-4,15-dithia-9,10-diazatribenzo[*b,ef,i*]heptalene (6j): Yield: 77.34 %; m.p.: 201 ºC; IR (cm^{-1}): 3687 (N-H *str*. 2º amine), 3289 (C-H *str*. arom. ring), 1521 (C=C str. arom. ring), 1381 (C-N *str*. pyrazole ring), 1286 (C-S *str*. azepine ring); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.568 (3H, s, -C$\underline{H}_3$), 2.485 (2H, s,-CH_2), 5.856 (1H, s,-CH), 7.856-7.745 (3H, m, Ar-H), 7.759-7.652 (2H, d, Ar-H), 7.695-7.584 (8H, m, Ar-H), 7.584-7.365 (4H, m, Ar-H), 8.456-8.365 (1H, d, Ar-H), 8.725 (1H, s, Ar-H), 9.526 (1H, s, -NH); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm: 161.58, 159.45, 158.42, 154.98, 151.80, 149.12, 147.65, 145.85, 143.51, 142.65, 139.41, 135.30, 133.95, 133.95, 131.25, 131.25, 128.52, 127.65, 126.12, 125.41, 124.65, 123.41, 122.30, 120.49, 118.65, 117.62, 116.82, 116.21, 114.59, 113.23, 83.52, 36.41, 17.21; MS: *m/z* 566 (M^+); Elemental analysis calcd. (found) % for $C_{35}H_{26}N_4S_2$: C, 74.17 (74.20); H, 4.62 (4.58); N, 9.89 (9.77); S, 11.32 (11.36).

RESULTS AND DISCUSSION

New thiazepine derivatives **(6a-j)** were synthesized in five steps procedure in an atom economy way. Synthetic pathway and progress of reaction for the compounds were sketched in **Scheme-I**. The obtained IR spectral data confirmed that the targeted compounds were successfully synthesized. The broad stretching band appearing at 3766-3640 cm^{-1} corresponded to secondary amines present in compounds **6a-j**. Moreover, the stretching vibration bands appearing at 3361-3281 cm^{-1} indicated that in the C–H bond was present in aromatic nucleus. A band appearing at 1548–1418 cm^{-1} confirmed the existence of C=C in the aromatic ring of compounds. A stretching band observed at 1381-1261 cm^{-1} proved the presence of C–N linked in the pyrazole ring of molecules **6a-j**. The existence of C–S linked was confirmed by the absorption band that appeared at

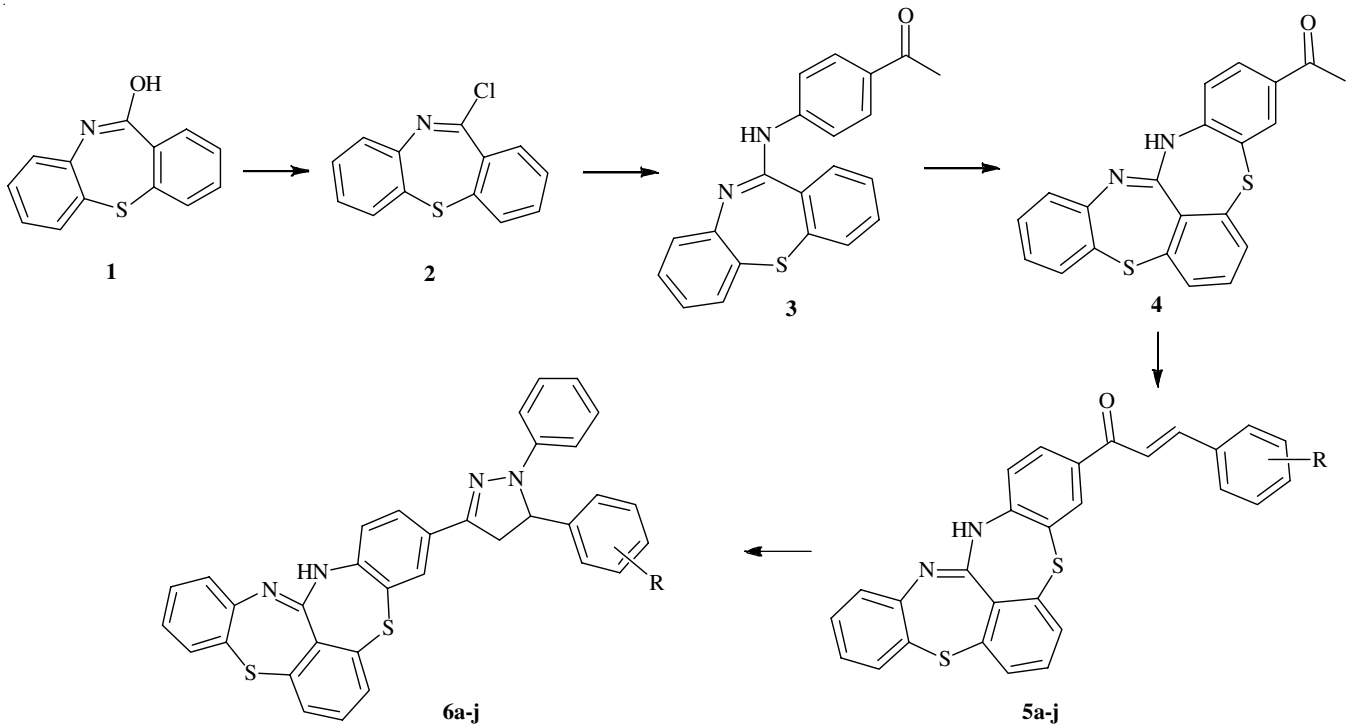
1290-1226 cm^{-1} for the azepine ring. The interpretation of the absorption peaks acquired in the proton spectral data confirmed the generation of the targeted compounds. For the molecules having pyrazole ring, the existence of two protons of the methylene group was confirmed through a sharp peak observed at δ ppm = 3.124-2.073. The absorption peak observed at δ ppm = 9.895-9.125 indicated that a proton belonging to secondary amine existed in the structure. The absorption peak appearing at δ ppm = 8.254-6.986 corresponded to the protons of the aromatic nucleus. The ^{13}C NMR further confirmed the generation of target motifs. The signal observed at δ ppm = 36.81-33.85 corresponded to the methylene carbon present in pyrazole. For methoxy group, the chemical shift for carbon was observed at δ ppm = 60.65-53.05. Mass spectra revealed that a molecular ion peak was observed for the compounds **6a-j** at *m/z* = 552-624. The elemental analysis results and proposed molecular weight were is in well agreement with the molecular ion peak.

Antimicrobial activity: Initially, *in vitro* antibacterial activity of each newly synthesized compound (**6a-j**) was evaluated against Gram-negative bacteria [*Escherichia coli* (ATCC 25922), *Enterobacter aerogenes* (ATCC 13048)] and Gram-positive bacteria [*Bacillus megaterium* (ATCC 14581), *Bacillus subtilis* (ATCC 23857)] by using the cup plate method [21]. Table-1 presents the values of individual minimal inhibition concentration (MIC) of the test compounds and reference compounds, including chloramphenicol, ampicillin and norfloxacin. The screening results indicated that the final compound **6g** (3-NO_2) has an excellent activity against all the strains. Compound **6f** (2-NO_2) exhibits good activity against *B. subtilis*, *B. megaterium* and *E. coli*. Compound **6e** (3,4,5-triOCH_3) has a good activity against *E. coli*, *B. megaterium* and *E. aerogenes*. Compounds **6c** (4-OCH_3) and **6b** (2-OCH_3) possess good activity against *E. coli* and *B. subtilis*, respectively. The rest of the compounds have a moderate antibacterial activity.

Furthermore, *in vitro* antifungal activity of compounds (**6a-j**) against the strain [*Aspergillus awamori* (ATCC 22342)] was studied in the potato-dextrose-agar (PDA) medium by employing the same cup plate method [22]. The antifungal activities of these compounds are comparable to those of the standard drug named griseofulvin. Compounds **6f** (2-NO_2), **6g** (3-NO_2) and **6d** (3,4-diOCH_3) exhibited excellent antifungal activity against *A. awamori*, however, rest of the compounds have a weak antifungal activity.

Conclusion

A series of tetracyclic thiazepine based pyrazole derivatives were successfully synthesized, characterized and tested for their antimicrobial activity. The presence of the pyrazole moiety is also in contributing the net biological activity. Herein, two different thiazepine and pyrazole nuclei were incorporated in one structure and also studied the biological behaviour of the resultant systems. Hence, it is concluded that thiazepine linked pyrazoles are more active and thus, there is enough scope for further study in developing such compounds as a good lead molecule. The synthesized compounds were shown promising activity as compared to the standard drug for all representative panel of bacterial and fungal strains.



Where,

R= **6a** = -H **6b** = -2-OCH_3 **6c** = -4-OCH_3 **6d** = -3,4-$(OCH_3)_2$ **6e** = -3,4,5-$(OCH_3)_3$ **6f** = -2-NO_2 **6g** = -3-NO_2 **6h** = -4-NO_2 **6i** = -4-NH_2 **6j** = -4-CH_3

Reaction conditions: (a) $POCl_3$, 70 °C, 3.0 h, (b) 4-amino acetophenone, pyridine, 116 °C, 4.0 h, (c) S, I_2, 161 °C, 30 min, (d) various aromatic aldehyde, methanol, 20% NaOH, RT, 24-26 h, (e) phenyl hydrazine, 1,4-dioxane, 70 °C, 7.0 h

Scheme-I: Synthetic route for the synthesis of title compounds **(6a-j)**

TABLE-1
in vitro RESULTS OF ANTIBACTERIAL SCREENING OF COMPOUNDS **6a-j**

No.	R	Gram-positive bacteria		Gram-negative bacteria		Fungi
		Bacillus megaterium ATCC 14581	*Bacillus subtilis* ATCC 23857	*Escherichia coli* ATCC 25922	*Enterobacter aerogenes* ATCC 13048	*Aspergillus awamori* ATCC 22342
6a	H	13	17	16	13	19
6b	2-OCH_3	14	18	14	12	18
6c	4-OCH_3	13	14	18	20	17
6d	3,4-$(OCH_3)_2$	12	13	15	14	21
6e	3,4,5-$(OCH_3)_3$	21	15	20	21	20
6f	2-NO_2	22	19	18	15	22
6g	3-NO_2	20	18	19	19	22
6h	4-NO_2	16	15	14	12	18
6i	4-NH_2	19	13	16	14	16
6j	4-CH_3	12	16	11	13	15
	Ampicillin	23	18	18	20	–
	Chloramphenicol	22	20	21	19	–
	Norfloxacin	20	19	22	21	–
	Gliseafulvin	–	–	–	–	21

ACKNOWLEDGEMENTS

The authors are grateful to The Director, Crest Life Sciences, Ahmedabad, India for providing the necessary research work facilities. Thanks are also due to H_2O Scientific, Rajkot, India for antimicrobial activity analysis.

REFERENCES

1. A.K. Singh, Synthesis and Antimicrobial Activity of Azepine Analogue of Lignan, *J. Nep. Chem. Soc.*, **29**, 44 (2013); https://doi.org/10.3126/jncs.v29i0.9236
2. N.A. El-Sayed, F.M. Awadallah, N.A. Ibrahim and M.T. El-Saadi, Synthesis, Anti-inflammatory and Ulcerogenicity Studies of Some Substituted Pyrimido[1,6-*a*]azepine Derivatives, *Eur. J. Med. Chem.*, **45**, 3147 (2010); https://doi.org/10.1016/j.ejmech.2010.04.005
3. W.B. Zhang, R.B. Han, W. Zhang, R.S. Jiang and F.Y. Piao, Synthesis and Anticonvulsant Activity of 8-Alkoxy-5,6-dihydro-4*H*-benzo[*f*]-[1,2,4]triazolo[4,3-*a*]azepine Derivatives, *Med. Chem. Res.*, **21**, 2587 (2012); https://doi.org/10.1007/s00044-011-9771-5
4. H. Turner, Spiroindolone NITD609 is a Novel Antimalarial Drug that Targets the P-type ATPase PfATP4, *Future Med. Chem.*, **8**, 227 (2016); https://doi.org/10.4155/fmc.15.177
5. A.K. Ghosh and D.D. Anderson, Tetrahydrofuran, Tetrahydropyran, Triazoles and Related Heterocyclic Derivatives as HIV-Protease Inhibitors, *Future Med. Chem.*, **3**, 1181 (2011); https://doi.org/10.4155/fmc.11.68
6. X. Pan, L. Tao, M. Ji, X. Chen and Z. Liu, Synthesis and SAR of Novel Capsazepine Analogs with Significant Anti-cancer Effects in Multiple Cancer Types, *Bioorg. Med. Chem. Lett.*, **28**, 866 (2018); https://doi.org/10.1016/j.bmcl.2018.02.004
7. J. De La Chapa, M. Valdez, F. Ruiz III, K. Gonzales, W. Mitchell, S.F. McHardy, M. Hart, S.R. Polusani and C.B. Gonzales, *Bioorg. Med. Chem.*, **27**, 208 (2019); https://doi.org/10.1016/j.bmc.2018.11.040
8. N. Kaur, N. Ahlawat, P. Bhardwaj, Y. Verma, P. Grewal and N.K. Jangid, Synthesis of Five-Membered *N*-Heterocycles using Rh Based Metal Catalysts, *Synth. Commun.*, **50**, 137 (2020); https://doi.org/10.1080/00397911.2019.1689271
9. U. Sharma, G.E. Cozier, E.D. Sturrock and K.R. Acharya, Molecular Basis for Omapatrilat and Sampatrilat Binding to Neprilysin-Implications for Dual Inhibitor Design with Angiotensin-Converting Enzyme, *J. Med. Chem.*, **63**, 5488 (2020); https://doi.org/10.1021/acs.jmedchem.0c00441
10. S. Kiyonaka, K. Kato, M. Nishida, K. Mio, T. Numaga, Y. Sawaguchi, T. Yoshida, M. Wakamori, E. Mori, T. Numata, M. Ishii, H. Takemoto, A. Ojida, K. Watanabe, A. Uemura, H. Kurose, T. Morii, T. Kobayashi, Y. Sato, C. Sato, I. Hamachi and Y. Mori, Selective and Direct Inhibition of TRPC3 Channels Underlies Biological Activities of a Pyrazole Compound, *Proc. Natl. Acad. Sci. USA*, **106**, 5400 (2009); https://doi.org/10.1073/pnas.0808793106
11. M. Song, B. Liu, S. Yu, S. He, Y. Liang, S. Li, Q. Chen and X. Deng, New Hydrazone Derivatives of Pyrazole-4-carboxaldehydes Exhibited Anti-inflammatory Properties, *Lett. Drug Des. Discov.*, **17**, 502 (2020); https://doi.org/10.2174/1570180816666190731113441
12. Z. Yang, P. Li and X. Gan, Novel Pyrazole-Hydrazone Derivatives Containing an Isoxazole Moiety: Design, Synthesis, and Antiviral Activity, *Molecules*, **23**, 1798 (2018); https://doi.org/10.3390/molecules23071798
13. V. Alagarsamy and G. Saravanan, Synthesis and Anticonvulsant Activity of Novel Quinazolin-4(3*H*)-one Derived Pyrazole Analogs, *Med. Chem. Res.*, **22**, 1711 (2013); https://doi.org/10.1007/s00044-012-0169-9
14. S.A. Galal, A.S. Abdelsamie, S.A. Shouman, Y.M. Attia, H.I. Ali, A. Tabll, R. El-Shenawy, Y.S. El Abd, M.M. Ali, A.E. Mahmoud, A.H. Abdel-Halim, A.A. Fyiad, A.S. Girgis and H.I. El-Diwani, Part I: Design, Synthesis and Biological Evaluation of Novel Pyrazole-Benzimidazole Conjugates as Checkpoint Kinase 2 (Chk2) Inhibitors with Studying their Activities alone and in Combination with Genotoxic Drugs, *Eur. J. Med. Chem.*, **134**, 392 (2017); https://doi.org/10.1016/j.ejmech.2017.03.090
15. A. Messore, A. Corona, V.N. Madia, F. Saccoliti, V. Tudino, A. De Leo, L. Scipione, D. De Vita, G. Amendola, S. Di Maro, E. Novellino, S. Cosconati, M. Métifiot, M.-L. Andreola, P. Valenti, F. Esposito, N. Grandi, E. Tramontano, R. Costi and R. Di Santo, Pyrrolyl Pyrazoles as Non-Diketo Acid Inhibitors of the HIV-1 Ribonuclease H Function of Reverse Transcriptase, *ACS Med. Chem. Lett.*, **11**, 798 (2020); https://doi.org/10.1021/acsmedchemlett.9b00617
16. K.M. Pandya, A.H. Patel and P.S. Desai, Development of Antimicrobial, Antimalarial and Antitubercular Compounds Based on a Quinoline-Pyrazole Clubbed Scaffold Derived *via* Doebner Reaction, *Chem. Afr.*, **3**, 89 (2020); https://doi.org/10.1007/s42250-019-00096-5
17. A. Titi, M. Messali, B.A. Alqurashy, R. Touzani, T. Shiga, H. Oshio, M. Fettouhi, M. Rajabi, F.A. Almalki and T. Ben Hadda, Synthesis, Characterization, X-Ray Crystal Study and Bioctivities of Pyrazole Derivatives: Identification of Antitumor, Antifungal and Antibacterial Pharmacophore Sites, *J. Mol. Struct.*, **1205**, 127625 (2020); https://doi.org/10.1016/j.molstruc.2019.127625
18. W.A. Fadaly, Y.A. Elshaier, E.H. Hassanein and K.R. Abdellatif, New 1,2,4-Triazole/Pyrazole Hybrids Linked to Oxime Moiety as Nitric Oxide Donor Celecoxib Analogs: Synthesis, Cyclooxygenase Inhibition Anti-Inflammatory, Ulcerogenicity, Anti-proliferative Activities, Apoptosis, Molecular Modeling and Nitric Oxide Release Studies, *Bioorg. Chem.*, **98**, 103752 (2020); https://doi.org/10.1016/j.bioorg.2020.103752

19. K.R. Abdellatif, W.A. Fadaly, Y.A. Elshaier, W.A. Ali and G.M. Kamel, Non-Acidic 1,3,4-Trisubstituted-Pyrazole Derivatives as Lonazolac Analogs with Promising COX-2 Selectivity, Anti-inflammatory Activity and Gastric Safety Profile, *Bioorg. Chem.*, **77**, 568 (2018); https://doi.org/10.1016/j.bioorg.2018.02.018
20. J.B. Hirani, M.K. Pandya and S.B. Koradiya, Synthesis of Diverse Fused Tetracyclic Thiazepine-Chalcone Derivatives by Claisen-Schmidt Condensation Reaction and their Antimicrobial Activity, *Asian J. Chem.*, **32**, 2860 (2020: https://doi.org/10.14233/ajchem.2020.22867
21. A.L. Banty, The Antimicrobial Susceptibility test. Illus lea and Febiger, Philadelphia, USA, p. 180 (1976).
22. H.W. Seeley, P.J. Vandemark and P.J. van Demark, Microbes in Action: A Laboratory Manual of Microbiology (1970).