Synthesis and antimicrobial activity of new triazolo / tetrazolo-pyridazine [6,7] benzocycloheptenes

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Synthesis of 2-methyl-6,7-dihydro-5H-benza[6,7)cyclohepta[1,2,4] triazolo[4,3-b]pyridazinc (8a,b) 2-methyl-6,7-dihydro-5H-benza[6,7)cyclohepta[1,2,3,4] tetrazolo[1,5-b]pyridazinc (10a,b) and their precursors has been described. A few of them show promising antibacterial activity.

Polynuclear compounds incorporating fused pyridazine ring systems are of considerable interest because of their antihypertensive, antithrombotic, and as selective aldose reductase inhibitors. In continuation of our earlier work, on the synthesis of fused heterocyclic systems, herein we report, the hitherto unreported, the synthesis of new fused triazolo, tetrazolo and pyridazinone derivatives starting from 3-methyl-6,7,8,9-tetrahydro-5H-benza[c]cyclohepten-5-one 1a,b.

3-Methyl-5-benzosuberone 1a,b was condensed with glyoxylic acid to give unsaturated acid 2a,b which was reduced with zinc in acetic acid to give the substituted acetic acid 3a,b (Scheme 1). The reaction of 3a,b with hydrazine hydrate in refluxing ethanol led to 4a,b in a 75% yield. This method markedly improved the overall yield compared to 22% yield reported earlier.

Oxidation of 4a,b to 10-methyl-3,5,6,7-tetrahydro-2H-benza[6,7) cyclohepta[c]pyridazin-3-one 5a,b was accomplished in an 84% yield using sodium metanitrobenzene sulfonate in sodium hydroxide solution. The 1H NMR spectra of 5a,b displayed a multiplet at δ 6.75-7.20 corresponding to aromatic protons. The 4-CH proton signal at δ 7.60 showed that oxidation has taken place. The broad singlet at δ 12.50 was due to ring -NH proton.

Reagents: (a) Glyoxylic acid /OH/Δ, (b) Zn / CH3COOH/Δ, (c) NH2-NH2/H2O EtOH, (d) sodium metanitro-benzene sulfonate / OH-, (e) POCl3 / NaOH.

Scheme 1
10-Methyl-6, 7-dihydro-5H-benzo[6, 7]cyclohepta[\text{-l}]pyridazin-3-yl)hydrazine 7a, b were obtained via nucleophilic displacement of the 3-chlorine atom of the corresponding pyridazinyl chlorides 6a, b, which in turn were prepared by the chlorination of the appropriate pyridazines with phosphorus oxychloride. The aromatic protons resonated at 8 7.10-7.50 producing a multiplet and the hydrazine protons signal appeared in the form of singlets at 8 4.00-4.30 and 8 8.20-8.50 integrating for two and one protons respectively.

Compounds 7a, b when treated with triethyl orthoformate in ethanol afforded fused triazolo compounds 8a, b. In the same manner, when 7a, b are treated with p-bromo benzaldehyde in glacial acetic acid, substituted triazolo pyridazine compounds 9a, b are obtained as shown in Scheme II. The signal at 8 9.10 in the 1H NMR was assigned to 12-H proton in the cyclized products 8a, b. The aromatic protons of 9a, b resonated as a multiplet at 8 7.10-8.50. Further, the absence of bands in the region 3460-3210 cm\(^{-1}\) thus in the solid state, 10a, b have the tetrazole structure. The same 10a, b have the tetrazole structure. The same compounds 10a, b were formed. The IR spectra of these compounds do not show any characteristic band for the azido group at 2000 - 2200 cm\(^{-1}\) thus in the solid state, 10a, b have the tetrazole structure. The same compounds 10a, b were obtained by direct condensation of 6a, b with sodium azide in the presence of ammonium chloride in which in situ generation of ammonium azide facilitated the reaction (Method-B). The method B gave slightly better yields (40%) compared to method A (32%) (Scheme II).

Synthesis of 3-substituted derivatives 11a, b and 12a, b having sulphur functional group at the 3-position are outlined in Scheme II. Heating of 6a, b with excess thiourea in methyl cellosolve afforded the 3-thioxo derivatives 11a, b. Further methylation of 11a, b by treating with excess methyl iodide and sodium methoxide afforded the 3-methylthio derivatives 12a, b.

Finally, 3-substituted derivatives having oxygen functional group at 3-position 13a, b were synthesized in good yields from reaction of 6a, b with excess of ethanol in the presence of sodium at room temperature.

**Antibacterial activity**

All the compounds were screened for the antibacterial activity at conc. 80\(\mu\)g/disc in aga agar media using Doxycyclin as reference compound. Most of the compounds showed maximum moderate activity against gram positive bacteria Staphylococcus aureus and gram negative bacteria Escherichia coli. Compounds 2a, 5a, 6a, 10a showed maximum zone of inhibition (20 mm) against E. coli as compared with Doxycyclin (30 mm), while the other compounds 11a, 12a and 13b showed moderate activity (10-15 mm) against E. coli and S. aureus.

**Experimental Section**

Commercially available solvents were distilled or purified by recommended procedures prior to use. Melting points were determined using Gallenkamp apparatus and are uncorrected. IR spectra were recorded on a FT-IR 1605 Perkin Elmer. 1H NM spectra were recorded in CDC\textsubscript{3} on a Varian FT-80 spectrometer with TMS as internal standard and mass spectra were taken on a VG micromass 7070H mass spectrometer.

2-(3-Methyl-5-oxo-6,7,8,9-tetrahydro-5H-benzo[a]cyclohepten-6-ylidene) acetic acid 2a. Sulphur acid (0.22 mL) was added to an ice-cold solution of sodium meta periodate (2.34 g, 11 mmole) in water (15 mL) followed by a solution of tartaric acid (1.6 g, 11 mmole) in water (5 mL) over 15 min. The solution was stirred at room temperature for 30 min and the 3-methyl benzocycloheptene-5-one (2.0 g, 1 mmole) was added followed by a solution of Na\textsubscript{2}O\textsubscript{2} (1.68 g, 0.42 mmole) in 30 mL of water and finally 10 mL of ethanol. The reaction mixture was stirred at room temperature overnight, heated on a steam bath for 30 min, cooled, and diluted with water. The mixture was extracted with CHCl\textsubscript{3} (2x25 mL) an then the aqueous portion was acidified with dil. HCl. The solid thus obtained was filtered and dried. Recrystallization from ethyl acetate afforded 2a (2 g, 90%), m.p. 174-176°C; IR (KBr) : 2875-309 (OH), 1695 (CO), 1670 (CO) cm\(^{-1}\). Anal. Found: C 73.02; H, 6.00. C\textsubscript{12}H\textsubscript{16}O\textsubscript{3} requires C, 73.04; H, 6.08%.

**2b** : Yield 84%, m.p. 184-86°C; IR (KBr) : 2875-3095 (OH), 1690 (CO), 1670 (CO) cm\(^{-1}\). Anal. Found: C, 73.71; H, 6.50. C\textsubscript{13}H\textsubscript{16}O\textsubscript{3} requires C, 73.77; H, 6.55%.

2-(3-Methyl-5-oxo-6,7,8,9-tetrahydro-5H-benzo[a]cyclohepten-6-yl)acetic acid 3a. A mixture of keto acid 2a (2.2 g, 9.5 mmole), glacial acetic acid (10 mL), water (5 mL) and zinc dust (1.0 g) was
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Reagents: (f) anhydrous hydrazine / EtOH, (g) triethyl orthoformate / EtOH, (h) p-Bromobenzaldehyde / glacial acetic acid (i) NH₄Cl / NaNO₂, (j) Sodium nitrite / glacial acetic acid / H₂O (k) Thiourea, methylcellosolve, (l) Sodium methoxide, Methyliodide, methanol, (m) Sodiumethoxide, ethanol.

Scheme II

heated on a steam bath for 1 hr and worked-up in the usual way to get the product 3a which was recrystallized from ethanol-water (9:1) as a crystalline solid (2.0 g, 90%), m.p. 140-42°C; IR (KBr) : 2870-3133 (OH), 1710 (CO), 1667 (CO) cm⁻¹. Anal. Found: C, 72.39; H, 6.87. C₁₄H₁₃O₂ requires C, 72.41; H, 6.89%.

3b : Yield 89%, m.p. 146-48°C; IR (KBr) : 2870-3150 (OH), 1710 (CO) cm⁻¹. Anal. Found: C, 73.11; H, 7.27. C₁₄H₁₃O₂ requires C, 73.17; H, 7.31%.

10-Methyl-3,4,4a,5,6,7-tetrahydro-2H-benzo[6,7]-cyclohepta[c]pyrazin-3-one 4a. A mixture of 3a (1.95 g, 8.4 mmole) and hydrazine hydrate (0.49 mL, 10.2 mmole) in 10 mL of ethanol was refluxed for 1-1½ hr, cooled, filtered and recrystallized from benzene-ethanol to give 4a as white solid (1.6 g, 84%), m.p. 138-40°C; IR (KBr) : 3250 (NH), 1680 (CO) cm⁻¹; ¹H NMR (CDCl₃) : δ 1.60-2.00 (5H, m, 5- & 6-CH₂, 4a-H), 2.35 (3H, s, 10-CH₃), 2.65-3.00 (4H,
4h : Yield 80%, m.p. 160-64°C; IR (KBr) : 3250 (NH), 1675 (CO) cm⁻¹; ¹H NMR (CDCl₃) : δ 1.55-2.00 (5H, m, 5 & 6-CH₃, 6a-H), 2.40 (6H, s, 9, 10-CH₃), 2.65-3.00 (4H, m, 4 & 7-CH₂), 6.85 & 7.05 (2H, aromatic) and 8.75 (1H, brs, NH₂, D₂O exchangeable). Anal. Found: C, 73.68; H, 7.01; N, 12.28%.

4b : Yield 80%, m.p. 160-64°C; IR (KBr) : 3250 (NH), 1675 (CO) cm⁻¹; ¹H NMR (CDCl₃) : δ 2.15-2.30 (2H, m, 6-CH₂), 2.40 (6H, s, 9, 10-CH₃), 2.55-2.65 (4H, t, 5,7-CH₂), 6.70 & 6.95 (2H, aromatic), 7.50 (1H, s, 4-CH) and 12.60 (1H, brs, NH, D₂O exchangeable). Anal. Found: C, 74.30; H, 6.00; N, 11.66%. C₆H₄N₂O requires C, 72.70; H, 5.60; N, 11.66%.

10-Methyl-3,5,6,7-tetrahydro-2H-benzo[6,7]cyclohept[a]pyrazin-3-one 5a. A mixture of 4a (1.5 g, 6.6 mmole), sodium meta-nitrobenzene sulfonate (1.5g, 6.75 mmole) and sodium hydroxide (1.14 g, 28.5 mmole) in water (40 mL) was heated on steam bath for 1.5 hr. After cooling, the reaction mixture was neutralised with conc. hydrochloric acid, filtered, dried and recrystallized from ace ethanol to afford 5a (1.25 g, 84%), m.p 200-202°C; IR (KBr) : 3464 (NH), 1647 (CO) cm⁻¹; ¹H NMR (DMSO-d₆) : δ 7.02-7.10 (3H, m, aromatic), 7.50 (1H, s, 4-CH) and 12.50 (1H, brs, NH, D₂O exchangeable). Anal. Found: C, 74.70; H, 6.14; N, 12.35. C₆H₄N₂O requires C, 74.30; H, 6.00; N, 11.66%.

10-Methyl-6,7-dihydro-5H-benzo[6,7]cyclohepta[c]pyrazin-3-yl-hydrazine 7a. A mixture of 6a (0.13 g, 22%) as needles, m.p. 124-26°C; IR (KBr) : 3235 (NH) cm⁻¹; ¹H NMR (CDCl₃) : δ 2.01-2.20 (2H, m, 6-CH₂), 2.35 (3H, s, 1O-CH₃), 2.48-2.55 (4H, t, 5,7-CH₂), 6.70-6.95 (2H, aromatic), 7.60 (1H, s, 4-CH) and 12.60 (1H, brs, NH, D₂O exchangeable). Anal. Found: C, 79.85; H, 6.58; N, 23.30. C₆H₆N₄ requires C, 79.80; H, 6.66; N, 23.33%.
dazin e 9a. A mixture of 7a (0.14 g, 0.58 mmole) and p-bromobenzaldehyde (0.10 g, 0.58 mmole) in glacial acetic acid (5 mL) was refluxed in an oil bath for 17 hr. After the usual work up, the resulting residue was purified by preparative tlc on silicagel (benzene-ethylacetate 7:3) and recrystallized from benzene to afford 9a (0.09 g, 38%). m.p. 220-222°C; 1H NMR (CDCl₃) : δ 2.12-2.25 (2H, m, 6-CH₂), 2.45 (3H, s, 2-CH₃), 2.55-2.70 (4H, t, 5,7-CH₂) and 7.10-8.50 (8H, m, aromatic & 4-CH); MS. m/z 404 (M⁺). Anal. Found: C, 63.15; H, 4.54; N, 13.39 %.

C, 63.11; H, 4.32%; m.p. 216-18 °C; 10-Methyl-3-methylsulfanyl-6,7-dihydro-SH-benzo[6,7]cyclohepta-[1,2,3,4]tetrazolo[1,5-b]pyridazine 10a: Method A. To a stirred solution of 7a (0.12 g, 0.5 mmole) in glacial acetic acid (1 mL) was added aq. sodium nitrite (0.02 g, 2 mL) by small portions at 0-5°C and the stirring was continued for 4 hr. The mixture was poured into cold water and the solid that separated was filtered, washed with water, dried and recrystallized from benzene to afford 10a (0.04 g, 32%), m.p. 216-18°C; MS : m/z 251 (M⁺). Anal. Found: C, 66.98; H, 5.12; N, 27.94. C₂₇H₁₂N₄S requires C, 66.93; H, 4.54; N, 27.88%.

Method-B: To a well stirred solution of ammonium chloride (0.025 g, 0.49 mmole) and sodiumazide (0.031 g, 0.49 mmole) in dimethyl sulphoxide (1 mL) was added 6a (0.12 g, 0.49 mmole) in portions and the mixture was stirred at 70°C for 2.5 hr and for 1 hr at room temperature. After the usual work-up, the residue was recrystallized from benzene-cyclohexane to afford 10a (0.05 g, 40%) identical in all respects with the compound prepared by method A.

10-Methyl-3,5,6,7-tetrahydro-2H-benzo[6,7]cyclohepta[c]pyridazin-3-thione 11a. A mixture of 6a (0.24 g, 0.98 mmole) and thiourea (0.36 g, 4.8 mmole) in methyl cellosolve (10 mL) was refluxed with stirring for 7 hr. The reaction mixture was concentrated to dryness in vacuo, dissolved in 2N sodium hydroxide solution (10 mL) and stirred at room temperature for 2 hr. The mixture was acidified with acetic acid. The solid thus obtained was filtered, dried and recrystallized from benzene-ethanol to give 11a (0.2 g, 84%), m.p. >300°C; IR (KBr) : 3464 (NH), 1104 (C=S) cm⁻¹; 1H NMR (CDCl₃) : δ 2.10-2.25 (2H, m, 6-CH₂), 2.45 (3H, s, 10-CH₂), 2.50-2.70 (4H, t, 5,7-CH₂), 7.10-7.40 (3H, m, aromatic), 7.55 (1H, s, 4-CH) and 12.20 (1H, brs, NH, D₂O exchangeable). Anal. Found: C, 69.38; H, 5.75; N, 11.52. C₂₉H₁₉N₅S requires C, 69.42; H, 5.78; N, 11.57%.

11b : Yield 84%, m.p >300°C; 1H NMR (CDCl₃) : δ 2.00-2.25 (2H, m, 6-CH₂), 2.40 (6H, s, 9,10-CH₂), 2.60-2.68 (4H, t, 5,7-CH₂), 6.80 & 7.10 (1H, s, aromatic), 7.60 (1H, s, 4-CH) and 12.20 (1H, brs, NH, D₂O exchangeable). Anal. Found: C, 70.27; H, 6.21; N, 10.89. C₂₉H₂₅N₅S requires C, 70.31; H, 6.25; N, 10.93%.

10-Methyl-3-methylsulfanyl-6,7-dihydro-5H-benzo[6,7]cyclohepta[c]pyridazine 12a. To a stirred solution of 11a (0.1 g, 0.41 mmole) in dry methanol (5 mL), sodium methoxide (0.02 g, 0.41 mmole) was added and the mixture was heated under reflux for 2 hr. After cooling, methyl iodide (0.12 mL, 2.0 mmole) was added and the resultant solution was stirred at room temperature for 2 hr. Finally, the solvent was removed under vacuum and the crude product was recrystallized from benzene-ethanol (3:1) to give 12a (0.03 g, 28%), m.p. 96-98°C; 1H NMR (CDCl₃) : δ 2.15 - 2.30 (2H, m, 6-CH₂), 2.45 (3H, s, 10-CH₂), 2.50-2.60 (4H, t, 5,7-CH₂), 2.30 (3H, s, S-CH₃), 7.10-7.30 (3H, m, aromatic) and 7.65 (1H, s, 4-CH). Anal. Found: C, 70.27; H, 6.20; N, 10.89. C₂₉H₂₅N₅S requires C, 70.31; H, 6.25; N, 10.93%.

12b : Yield 30%, m.p. 107-109°C; 1H NMR (CDCl₃) : δ 2.15-2.30 (2H, m, 6-CH₂), 2.40 (6H, s, 9,10-CH₂), 2.60-2.78 (4H, t, 5,7-CH₂), 2.30 (3H, s, S-CH₃), 7.00 & 7.15 (2H, aromatic), 7.50 (1H, s, 4-CH). Anal. Found: C, 71.08; H, 6.62; N, 10.33 C₂₉H₂₅N₅S requires C, 71.11; H, 6.66; N, 10.37%.

3-Ethoxy-10-methyl-6,7-dihydro-5H-benzo[6,7]cyclohepta[c]pyridazine 13a. To a stirred solution of sodium (0.015 g) in dry ethanol (5.0 mL) was added the ethanolic solution (5 mL) of 6a (0.1 g, 0.4 mmole) by portions at room temperature and stirring was continued for 12 hr. The solution was concentrated to the 1/3 volume in vacuo, diluted with water (20 mL) and the resulting solution was extracted with chloroform. After the usual work-up, the residue was purified by preparative TLC using (benzene – ethyl acetate 9:1) and recrystallized from benzene to afford 13a (0.05 g, 48%), m.p 82-84°C; 1H NMR (CDCl₃):
δ 1.45-1.60 (3H, t, CH₃CH₂), 2.10-2.25 (2H, m, 6-CH₂), 2.30 (3H, s, 10-CH₃), 2.45-2.60 (4H, t, 5,7-CH₂), 4.55-4.70 (2H, m, -OCH₂), 6.75-7.20 (3H, m, aromatic) and 7.60 (1H, s, 4-CH); MS: m/z 254 (M⁺). Anal. Found: C, 75.54; H, 7.03; N, 11.08. C₁₆H₁₅N₂O requires C, 75.59; H, 7.08; N, 11.02%.

13b: Yield 55%, m.p. 92°C; ¹H NMR (CDCl₃): δ 1.45-1.60 (3H, t, CH₃CH₂), 2.10-2.25 (2H, m, 6-CH₂), 2.30 (6H, s, 9,10-CH₃), 2.40-2.50 (4H, t, 5,7-CH₂), 4.55-4.68 (2H, m, -OCH₂), 6.80 & 7.00 (2H, aromatic) and 7.60 (1H, s, 4-CH). Anal. Found: C, 76.08; H, 7.41; N, 10.40. C₁₇H₂₀N₂O requires C, 76.11; H, 7.46; N, 10.44%.

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