Synthesis and pharmacological evaluation of heterocycles from benzocycloheptenones

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A new series of benzocyclohepten-5-one thiosemicarbazones 2a,b obtained by condensation of benzocyclohepten-5-ones 1a,b with thiosemicarbazide, are treated with monochloroacetic acid, 3-bromopropionic acid, chloroacetyl chloride, 1,3-dichloroacetone, phenacyl bromide and acetic anhydride, respectively to yield nitrogen and sulphur containing heterocycles. The structures of all these compounds have been determined by analytical and spectral methods. A few of them exhibit promising antibacterial activity.

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A literature survey reveals that thiosemicarbazones were active against various viruses. N-Methylisatin-β-thiosemicarbazone and isatin-β-thiosemicarbazone are active against poxviruses, including variola and vaccinia. 2-Hydroxy-1-naphthylaldehyde-4-methyl-3-thiosemicarbazone and 2-hydroxy-1-naphthylaldehyde-4,4-dimethyl-3-thiosemicarbazone showed high antiproliferative activity against SK-N-MC neuroepithelioma cells. 3-Aminopyridine-2-carboxaldehyde thiosemicarbazone has been described as a potent inhibitor of ribonucleotide reductase activity with antineoplastic activity and broad spectrum of antitumor activity. In view of these observations, we report herein the synthesis, structure determination and primary biological screening of new heterocycles derived from thiosemicarbazones.

3-Methyl-6,7,8,9-tetrahydrobenzocyclohepten-5-one 1a reacted with thiosemicarbazide in ethanol containing a catalytic amount of conc. HCl, to give the 3-methyl-6,7,8,9-tetrahydrobenzocyclohepten-5-one thiosemicarbazone 2a. IR spectra of 2a showed absorption peaks at 3419, 3245, 3142 and 1192 cm⁻¹ attributing to NH, NH₂ and C=S functional groups. The compound 2a was allowed to react with monochloroacetic acid and 3-bromopropionic acid in the presence of sodium acetate affording the compounds 3a and 4a, respectively. The IR spectra of 3a and 4a revealed the presence of amino group peaks at 3099 and 1689 cm⁻¹. The ¹H NMR spectra of 3a exhibited a two proton sharp singlet at δ 3.80 due to thiazolidine ring methylene protons suggesting the formation of the ring. In particular, ¹H NMR spectra of 4a showed two triplets at δ 2.85-2.95 and 3.00-3.15 attributable to 1,3-thiazine ring methylene protons. N,N-Disopropylethylamine catalyzed substitution of chloroacetyl chloride to compound 2a in dioxane gives 5a in 70% yield. The sharp singlet at δ 3.75 due to COCH₂ protons in ¹H NMR spectrum confirms the structure. Its IR spectrum exhibited three stretching bands in regions 3408 (NH), 1723 (C=O), and 1118 cm⁻¹ (C=S). Compound 2a on reaction with 1,3-dichloroacetone and phenacyl bromide give the corresponding thiazole derivatives 6a and 7a, respectively. The NH stretching band in the IR spectrum at 3405 cm⁻¹, a singlet at δ 4.50 assigned to Cl-CH₂ in ¹H NMR and molecular ion (M⁺) peak at 319 and (M⁺+2) peak at 321 in mass spectrum further confirm the structure of 6a. The ¹H NMR spectrum of 7a showed a one proton broad singlet at δ 12.80 (NH) and aromatic protons were seen at δ 6.90-7.80. The IR spectrum exhibited a band at 3045 cm⁻¹ (NH) further confirms the structure. The compound 2a underwent cyclization in acetic anhydride to give the thiadiazole derivative 8a. The ¹H NMR spectra of 8a, in particular, the methylene protons of 6th position split into two multiplets at δ 2.30-2.45 and 3.20-3.38 due to deshielding effect of sulphur atom in the thia-
diazole ring. The IR spectra of 8a showed the characteristic bands at 3154 (NH) and 1667 cm⁻¹ (CO) (Scheme I).

In view of the potential biological activity of 1,2,5-thiadiazole⁹ and 1,2,3-selenadiazole¹⁰, it was thought worthwhile to prepare the title compounds with the hope that these ring systems may prove to be biologically active. The reaction of 3-methyl-6,7,8,9-tetrahydrobenzocyclohepten-5-one with semicarbazide hydrochloride afforded the 3-methyl-6,7,8,9-tetrahydrobenzocyclohepten-5-one semicarbazone 9a. IR spectrum of 9a exhibited bands in the region 3469, 3207 (NH and NH₂) and 1707 cm⁻¹ (C=O). Compound 9a upon oxidative cyclization using SOCl₂ and SeO₂ provides the compounds 10a and 11a, respectively. The formation of cyclized products is evident from the absence of signals at δ 2.45-2.55 due to methylene protons at 6th position in the ¹H NMR spectra of 10a and 11a. This is further confirmed by the absence of absorption bands due to NH, NH₂ and CO groups in the IR spectra of 10a and 11a (Scheme II).

Analogues 2b-11b were similarly obtained adopting the same procedure. The structures of the compounds were confirmed by analytical (CHN) and spectral (IR, ¹H NMR and mass spectra) data.
Biological Evaluation

Antibacterial Activity

All the compounds were screened for their antimicrobial activity at a concentration of 40 μg/well in agar media using Doxycyclin in antibacterial and Nalidixic acid in antifungal activity as reference compounds. Compounds 3a (20 mm), 3b (17 mm) and 6b (23 mm) showed maximum activity in terms of diameter of the zone of inhibition as compared with Doxycyclin (25 mm) against gram +ve bacterium *Bacillus subtilis*, while the other compounds 2a, 2b, 5a, 5b, 6a, 6b showed moderate activity (10 to 16 mm). Compounds 2a (17 mm) and 5a (17 mm) showed maximum activity as compared with Doxycyclin (16 mm) against gram –ve bacterium *E.coli*, while the other compounds 2a, 2b, 3a, 3b, 4a, 4b, 5a, 5b, 6a, 7a, 8a, and 8b showed moderate activity (10 to 16 mm). All the compounds are ineffective against the fungus *Trichoderma* species.

Analgesic and anti-inflammatory activities

Analgesic and anti-inflammatory activities of the compounds were determined by Turner, writhing test and rat - paw edema test. In the Turner method a positive analgesic response was recorded at ½ hr time intervals up to 4 hr. Percent of animals showing positive analgesic response was calculated by comparison with untreated mice (control mice). Whereas in the writhing test, thirty minutes after the drug administration, each mouse received 0.6% acetic acid i.p. and was placed in 1000 mL beaker. The number of stretching or writhing responses each animal showed in first 20 minutes after i.p. acetic acid were counted. Average writhing in control and compound treated groups was calculated by dividing the number of wriths by the number of animals per group. Test and standard compounds are given by oral route in rat-paw edema test. One hour after the administration of test and standard compounds, carrageenan (1%, 0.1 mL) was given to all rats at two subplantar region of left hind paw. A zero hour paw volume was measured before administration of carrageenan using a plethysmometer (UGO BASILE make). Paw volumes were again measured after 3 hr. The inhibition of edema was expressed as % inhibition of paw volume calculated with respect to control group. The results are given in Table I. Compounds 2a-11b showed 32-33% inhibition in rats while asprin and phenylbutazone at the same dose (100 mg/kg, P.O.) produced 17% and 39% inhibition of 1% carrageenan induced inflammation, respectively.

Compounds exhibited significant anti-inflammatory activity better than asprin but comparable with that of phenylbutazone. However, they were found to possess less analgesic with reference to asprin.

Experimental Section

Melting points were determined using Gallankamp apparatus and are uncorrected. IR Spectra are recorded on a FT-IR 1605 Perkin-Elmer; 1H NMR in CDCl3 on a Varian FT-80A spectrometer with TMS as internal standard; and mass spectra on a VG-Micromass 7070H mass spectrometer. TLC was run on Silica gel G coated plates and iodine vapour as visualizing agent.

General procedure for the synthesis of 2a. A mixture of 3-methyl-6,7,8,9-tetrahydrobenzocyclohepten-5-one 1a (1.0 mmole), thiosemicarbazide (1.0 mmole) and 0.4 mL of conc. HCl in absolute ethanol (10.0 mL) was stirred at room temperature for 3 hr. It was poured into ice-cooled water, the solid thus obtained was filtered, dried and recrystallized from ethanol to furnish 2a, yield 0.230g (93%), m.p. 200-
202°C; IR (KBr): 3419, 3245, 3142 (NH and NH₂), 1723 (C=O), 1659 (C=C) cm⁻¹; ¹H NMR (CDCl₃): δ 1.70-1.85 (4H, m, 7 and 8-CH₂), 2.40 (3H, s, 3-CH₃), 2.70-2.80 (4H, m, 6-CH₂), 2.85-3.20 (4H, m, 6 and 8-CH₂), 3.80 (2H, s, S-CH₂), 6.95-7.05 (1H, d, 1-CH), 7.05-7.15 (1H, d, 2-CH) and 7.30 (1H, s, 4-CH); MS: m/z 287 (M⁺). Anal. Found: C, 62.64; H, 5.87; N, 14.55. C₁₅H₁₉N₃OS requires C, 63.78; H, 6.31; N, 13.95%.

2b: Yield 93%, m.p. 206-08°C; IR (KBr): 3092 (NH), 1718 (C=O) cm⁻¹; ¹H NMR (CDCl₃): δ 1.62-1.80 (4H, m, 7- and 8-CH₂), 2.28 (6H, s, 2 and 3-CH₃), 2.70-2.80 (4H, m, 6- and 9-CH₂), 3.78 (2H, s, S-CH₂), 6.90 (1H, s, 1-CH) and 7.30 (1H, s, 4-CH); MS: m/z 301 (M⁺). Anal. Found: C, 63.62; H, 6.26; N, 13.83. C₁₆H₁₉N₃OS requires C, 63.78; H, 6.31; N, 13.95%.

General procedure for the synthesis of 4a. A mixture of 2a (0.5 mmole), 3-bromopropionic acid (0.5 mmole), anhyd. sodium acetate (0.700g), glacial acetic acid (1.0 mL) and acetic anhydride (0.1 mL) was heated under reflux for 8 hr. After the usual work-up, it was purified by PTLC using 30% ethyl acetate - hexane to afford 4a, yield 0.100g (66%), m.p. 156-58°C; IR (KBr): 3199 (NH), 1689 (C=O) cm⁻¹; ¹H NMR (CDCl₃): δ 1.60-1.80 (4H, m, 7- and 8-CH₂), 2.32 (3H, s, 3-CH₃), 2.68-2.80 (4H, m, 6- and 9-CH₂), 2.85-2.95 (2H, t, -COCH₂), 3.00-3.15 (2H, t, S-CH₂), 6.90-7.00 (1H, d, 1-CH), 7.00-7.10 (1H, d, 2-CH) and 7.25 (1H, s, 4-CH); MS: m/z 315 (M⁺). Anal. Found: C, 63.68; H, 6.25; N, 13.83. C₁₆H₁₉N₃OS requires C, 63.78; H, 6.31; N, 13.95%.

4b: Yield 68%, m.p.136-38°C; IR (KBr): 3153 (NH), 1676 (C=O) cm⁻¹; ¹H NMR (CDCl₃): δ 1.60-1.80 (4H, m, 7- and 8-CH₂), 2.30 (6H, s, 2- and 3-CH₃), 2.70-2.80 (4H, m, 6- and 9-CH₂), 2.90-3.00 (2H, t, -COCH₂), 3.05-3.20 (2H, t, S-CH₂), 6.90 (1H, s, 1-CH) and 7.28 (1H, s, 4-CH); MS: m/z 315 (M⁺). Anal. Found: C, 64.65; H, 6.53; N, 13.20. C₁₆H₁₉N₃OS requires C, 64.76; H, 6.66; N, 13.33%.

General procedure for the synthesis of 5a. To a solution of 2a (1.0 mmole) and N,N-diisopropylethylamine (2.0 mmoles) in dry dioxane (2.0 mL) was added dropwise chloroacetyl chloride (1 mmole) in dry dioxane (1.0 mL). The solution was stirred at room temperature for 8 hr and monitored by TLC. N,N-Diisopropylethylamine hydrochloride was filtered off. The solvent was evaporated in vacuo and the residue was poured into ice-cooled water. The solid thus separated was filtered, washed with water, dried and recrystallized from 5% ethyl acetate - hexane to give the product 5a, yield 0.200g (70%), m.p.148-50°C; IR (KBr): 3408 (NH), 1723 (C=O), 1118 (C=S) cm⁻¹; ¹H NMR (CDCl₃): δ 1.60-1.80 (4H, m, 7- and 8-CH₂), 2.35 (3H, s, 3-CH₃), 2.70-2.80 (4H, 3a: Anal. Found: C, 64.26; H, 7.03; N, 15.98. C₁₃H₁₇N₃S requires C, 63.15; H, 6.88; N, 17.00%.

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m, 6- and 9-CH₂), 3.75 (2H, s, COCH₂), 6.95-7.05 (1H, d, 1-CH), 7.05-7.15 (1H, d, 2-CH), 7.20 (1H, s, 4-CH); MS: m/z 301 (M⁺).

5b: Yield 72%, m.p. 150-52°C; IR (KBr): 3448 (NH), 1735 (C=O), 1128 (C=S) cm⁻¹; ¹H NMR (CDCl₃): δ 1.68-1.80 (4H, m, 7- and 8-CH₂), 2.25 (6H, s, 2- and 3-CH₃), 2.45-2.55 (2H, t, 6-CH₂), 2.80-2.90 (2H, t, 9-CH₂), 3.20-3.40 (1H, m, 6-CH), 3.60 (1H, s, thiazole proton), 6.90-7.00 (1H, d, 1-CH), 7.05-7.15 (1H, d, 2-CH) and 7.20 (1H, s, 4-CH). Anal. Found: C, 70.39; H, 5.81; N, 11.50. C₁₇H₂₁N₃S requires C, 70.00; H, 5.57; N, 11.25%.

General procedure for the synthesis of 6a. To a solution of 2a (1.0 mmole) and N,N-diisopropyl-ethylamine (2.0 mmoles) in dry dioxane (2.0 mL) was added dropwise 1,3-dichloroacetone (1.0 mmole) in dry dioxane (2.0 mL). The solution was stirred at room temperature for 12 hr and monitored by TLC. After the usual work-up the crude product was recrystallized from 5% ethyl acetate - hexane to afford the product 6a, yield 0.250g (78%), m.p. 84-86°C; IR (KBr): 3405 (NH) cm⁻¹; ¹H NMR (CDCl₃): δ 1.65 - 1.82 (4H, m, 7- and 8-CH₂), 2.18 (3H, s, 3-CH₃), 2.50-2.60 (2H, t, 6-CH₂), 2.70 - 2.80 (2H, t, 9-CH₂), 4.50 (2H, s, Cl-CH₂), 6.60 (1H, s, thiazole proton), 6.90-7.05 (1H, d, 1-CH), 7.05-7.15 (1H, d, 2-CH) and 7.30 (1H, s, 4-CH); MS: m/z 319 (M⁺), 321 (M⁺+2). Anal. Found: C, 63.62; H, 6.25; N, 13.77. C₁₃H₁₇N₃OS requires C, 63.62; H, 6.25; N, 13.77%.

6b: Yield 79%, m.p. 88-90°C; IR (KBr): 3433 (NH) cm⁻¹; ¹H NMR (CDCl₃): δ 1.68-1.80 (4H, m, 7- and 8-CH₂), 2.25 (6H, s, 2- and 3-CH₃), 2.45-2.50 (2H, t, 6-CH₂), 2.60-2.70 (2H, t, 9-CH₂), 4.45 (2H, s, Cl-CH₂), 6.60 (1H, s, thiazole proton), 6.80 (1H, s, 1-CH) and 7.20 (1H, s, 4-CH); MS: m/z 333 (M⁺), 335 (M⁺+2). Anal. Found: C, 61.10; H, 5.93; N, 12.54. C₁₇H₂₀N₃S requires C, 61.26; H, 6.00; N, 12.61%.

General procedure for the synthesis of 7a. A mixture of 2a (0.5 mmole) and phenacyl bromide (0.5 mmole) in absolute ethanol (5.0 mL) was stirred at room temperature for 15 min. The solid thus separated was filtered and washed with ethanol. It was recrystallized from ethanol to furnish the product 7a, yield 0.160g (92%), m.p. 206-08°C; IR (KBr): 3045 (NH) cm⁻¹; ¹H NMR (CDCl₃): δ 1.75 - 1.90 (4H, m, 7- and 8-CH₂), 2.38 (3H, s, 3-CH₃), 2.70 - 2.78 (2H, t, 6-CH₂), 2.82-2.90 (2H, t, 9-CH₂), 6.70-7.80 (9H, m, ArH) and 12.80 (1H, s, NH); MS: m/z 347 (M⁺).

7b: Yield 94%, m.p. 210-12°C; IR (KBr): 3036 (NH) cm⁻¹; ¹H NMR (CDCl₃): δ 1.75-1.90 (4H, m, 7- and 8-CH₂), 2.30 (6H, s, 2- and 3-CH₃), 2.65-2.75 (2H, t, 6-CH₂), 2.80-2.90 (2H, t, 9-CH₂), 6.70-7.80 (8H, m, ArH) and 12.85 (1H, s, NH); MS: m/z 361 (M⁺).

General procedure for the synthesis of 1N-[3'-acetyl-3-methylspiro[6,7,8,9-tetrahydro-5H-benzo[a]cyclohepten-5,2'-[2',3'-dihydro[1,3,4(thiadiazole)-5-yl]]acetamide 8a. Compound 2a (0.5 mmole) was treated with freshly distilled acetic anhydride (7.0 mL) and the mixture was refluxed for 1 hr on a water-bath. The solid thus separated was filtered and dried. It was recrystallized from ethanol to give the product 8a, yield 0.155g (94%), m.p.178-80°C; IR (KBr): 3154 (NH), 1667 (C=O) cm⁻¹; ¹H NMR (CDCl₃): δ 1.80-2.05 (7H, m, NCOCH₃, 7- and 8-CH₂), 2.25 (3H, s, 3-CH₃), 2.30-2.45 (4H, m, NHCOC₂H₃ and 6-CH₂), 2.82-2.95 (2H, t, 9-CH₂), 3.20-3.38 (1H, m, 6-CH), 6.70 (1H, s, 4-CH), 6.85-7.00 (2H, m, 1- and 2-CH) and 9.20 (1H, s, NH); MS: m/z 331 (M⁺).

General procedure for the synthesis of 9a. A mixture of 1a (1.0 mmole), semicarbazide hydrochloride (1.0 mmole) and sodium acetate (0.200g) in ethanol (8.0 mL) was refluxed for 4 hr. The contents were cooled and poured into ice-cooled water. The precipitated semicarbazone was filtered and dried. It was recrystallized from ethanol to furnish 9a, yield 0.210g (91%), m.p. 180-82°C; IR (KBr): 3469, 3207 (NH and NH₂), 1707 (C=O) cm⁻¹; ¹H NMR (CDCl₃): δ 1.80-2.10 (7H, m, NCOCH₃, 7 and 8-CH₂), 2.25(6H, s, 2- and 3-CH₃), 2.30-2.50 (4H, m, NHCOC₂H₃ and 6-CH₂), 2.85-2.95 (2H, t, 9-CH₂), 3.20-3.40 (1H, m, 6-CH), 6.60 (1H, s, 4-CH), 6.90 (1H, s, 1-CH) and 8.00 (1H, s, NH); MS: m/z 345 (M⁺). Anal. Found: C, 62.52; H, 6.57; N, 12.09. C₁₅H₂₁N₃O₂S requires C, 62.60; H, 6.66; N, 12.17%.

General procedure for the synthesis of 9b. A mixture of 1b (1.0 mmole), semicarbazide hydrochloride (1.0 mmole) and sodium acetate (0.200g) in ethanol (8.0 mL) was refluxed for 4 hr. The contents were cooled and poured into ice-cooled water. The precipitated semicarbazone was filtered and dried. It was recrystallized from ethanol to furnish 9b, yield 0.210g (91%), m.p. 180-82°C; IR (KBr): 3469, 3211 (NH and NH₂), 1702 (C=O) cm⁻¹; ¹H NMR
(CDCl₃): δ 1.65-1.90 (4H, m, 7 and 8-CH₂), 2.30 (6H, s, 2 and 3-CH₃), 2.45 – 2.55 (2H, t, 6-CH₂), 2.68-2.78 (2H, t, 9-CH₂), 6.90 (1H, s, 1-CH) and 7.20 (1H, s, 4-CH). Anal. Found: C, 68.53; H, 7.66; N, 17.05. C₁₄H₁₉N₃O requires C, 68.57; H, 7.75; N, 17.14%.

General procedure for the synthesis of 9-methyl-5,6-dihydro-4H-benzo[6,7]cyclohepta[d][1,2,3]thiadiazole 10a. Compound 9a (0.5 mmole) was added in portionwise to a solution of thionyl chloride (0.4 mL) in CH₂Cl₂ cooled at –10°C for a period of 30 min. After complete addition, the contents were allowed to attain room temperature. To it CH₂Cl₂ was added and the excess thionyl chloride was decomposed with saturated Na₂CO₃ solution. The organic layer was separated, washed with water, dried and removal of solvent in vacuo afforded the crude product which was purified by PTLC using 20% ethyl acetate - hexane to give the product 10a, yield 0.090g (83%), liquid, ¹H NMR (CDCl₃): δ 2.20 – 2.30 (2H, m, 5-CH₂), 2.45 (3H, s, 9-CH₃), 2.75 - 2.82 (2H, t, 6-CH₂), 3.12-3.20 (2H, t, 4-CH₂), 7.00-7.10 (2H, m, 1- and 2-CH) and 8.00 (1H, s, 4-CH); MS: m/z 216 (M⁺). Anal. Found: C, 66.53; H, 5.40; N, 12.85. C₁₂H₁₂N₂S requires C, 66.66; H, 5.55; N, 12.96%.

11a: Yield 86%, m.p. 54-56°C; ¹H NMR (CDCl₃): δ 2.20-2.38 (8H, m, 8, 9-CH₃ and 5-CH₂), 6.22-2.75 (2H, t, 6-CH₂), 3.05-3.15 (2H, t, 4-CH₂), 7.00 (1H, s, 1-CH) and 7.85 (1H, s, 4-CH); MS: m/z 277 (M⁺). Anal. Found: C, 56.20; H, 4.95; N, 10.03. C₁₃H₁₄N₂Se requires C, 56.31; H. 5.05; N, 10.10%.

General procedure for the synthesis of 9-methyl-5,6-dihydro-4H-benzo[6,7]cyclohepta[d][1,2,3]sele nadiazole 11a. Compound 9a (0.5 mmole) in glacial acetic acid (2.5 mL) was heated (60-70°C) while stirring until the solid gets dissolved completely. To this, selenium dioxide powder (1.0 mmole) was added portionwise and heating was continued until the evolution of gas ceases. Then, the reaction mixture was cooled to room temperature and filtered to remove the deposited selenium. The filtrate was poured into crushed ice and extracted with chloroform. It was purified by PTLC using 20% ethyl acetate - hexane to give the 11a, yield 0.110g (84%), liquid, ¹H NMR (CDCl₃): δ 2.20 - 2.35 (2H, m, 5-CH₂), 2.42 (3H, s, 9-CH₃), 2.65-2.72 (2H, t, 6-CH₂), 3.08-3.15 (2H, t, 4-CH₂), 7.10-7.20 (2H, m, 1- and 2-CH) and 7.90 (1H, s, 4-CH); MS: m/z 263 (M⁺). Anal. Found: C, 54.63; H, 4.47; N, 10.55. C₁₂H₁₂N₂Se requires C, 54.75; H, 4.56; N, 10.64%.

11b: Yield 86%, m.p. 54-56°C; ¹H NMR (CDCl₃): δ 2.20-2.38 (8H, m, 8, 9-CH₃ and 5-CH₂), 2.62-2.75 (2H, t, 6-CH₂), 3.05-3.15 (2H, t, 4-CH₂), 7.00 (1H, s, 1-CH) and 7.85 (1H, s, 4-CH); MS: m/z 277 (M⁺). Anal. Found: C, 56.20; H, 4.95; N, 10.03. C₁₃H₁₄N₂Se requires C, 56.31; H. 5.05; N, 10.10%.

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References