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Venkateswarlu Peesapati [a] , Kancharla Anuradha [a] & Ponnuru Sreelakshmi [a]

[a] Centre for Environment, JNT University, Masabtank, Hyderabad, 500 028, India

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SYNTHETIC COMMUNICATIONS, 29(24), 4381–4395 (1999)

SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF NEW THIAZOLO/THIAZINOPYRIMIDINO[6,5-c]BENZOCYCLOHEPTENES

Venkateswarlu Peesapati*, Kancharla Anuradha and Ponnuru Sreelakshmi

Centre for Environment, JNT University, Masabtank, Hyderabad-500 028, India.

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Abstract : Synthesis of 2-methyl-8-phenyl-5,6,7,8,10,11-hexahydrobenzo[6,7]-cyclohepta[d][1,3]thiazolo[3,2-a]pyrimidin-10-ones (**4a-g**), 2-methyl-8-phenyl-5,6,7,8,11,12-hexahydro-10H-benzo[6',7']cyclohepta[4,5]pyrimido[2,1-b][1,3]-thiazin-10-ones (**6a-g**) and 2,11-dimethyl-8-phenyl-5,6,7,8,10,11-hexahydro-benzo[6,7]cyclohepta[d][1,3]thiazolo[3,2-a]pyrimidin-10-ones (**8a-g**) have been described. A number of compounds show promising antimicrobial acitity.

Polynuclear compounds incorporating fused pyrimidine rings are of considerable interest because of their synthetic and biological importance[1-3]. In continuation of our interest in the synthesis of biologically active fused heterocycles,[4-7] we have synthesised the hitherto unreported thiazolo/thiazino pyrimidines starting from 3-methyl-6,7,8,9-tetrahydro-5H-benzo[a]cyclohepten-5-one (**1**).

6-Arylidene-3-methyl-6,7,8,9-tetrahydro-5H-benzo[a]cyclohepten-5-ones (**2a-g**) obtained by the condensation of 3-methyl-6,7,8,9-tetrahydro-5H-benzo[a]cyclohepten-5-one (**1**) with appropriate aromatic aldehydes, on reaction

*To whom the correspondence should be addressed

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with thiourea in alkaline medium, yielded corresponding thioxo derivatives(3a-g) in good yield. The structures of **3a-g** were confirmed from their ^{1}H NMR spectra (experimental).

The thioxo derivatives being unsymmetrical, on reaction with chloroacetic acid and subsequent cyclisation of the intermediate in situ was likely to give **4** or **5** depending on the mode of cyclisation. The infrared and mass spectra were of no help in establishing either the structure **4** or **5**. However structure 4a-g in preference to the isomeric structures **5a-g** were finally assigned on the basis of ^{1}H NMR spectral data by comparing the chemical shifts of Ha in the thioxo derivatives with those of the corresponding protons in the cyclised products 4a-g or 5a-g respectively.

If the structures **4a-g** are correct, the Ha proton would be deshielded by the carbonyl group of the thiazolidine ring and as a result it would resonate at downfield as compared to the same proton (Ha) in **3a-g**. The protons Ha in **3a-g** resonate at δ 5.05, 4.98, 5.00, 5.00, 5.00, 5.04 & 5.05 respectively where as the signals assignable to Ha appeared at δ 5.52, 5.50, 5.62, 5.50, 5.60, 5.55, 5.54 in the ^{1}H NMR spectra of the cyclised products obtained from thioxo derivatives. This corroborated the structures **4a-g** (see experimental) and ruled out the alternative structures 5a-g which would not have shown such a downfield shift. The appearance of molecular ion peaks at m/z 360, 390, 394, 374, 438, 366 and 350 respectively further confirms the structures **4a-g**.

Further, thioxo derivatives **3a-g** on reaction with 3-bromopropionic acid afforded the hitherto unreported heterocyclic systems, thiazino pyrimidine benzocycloheptenones **6** or **7** depending upon the mode of cyclisation. The absorption bands 1691, 1691, 1693, 1691, 1692, 1693 & 1686 cm^{-1} in infrared spectra and appearance of molecular ion peaks at m/z 374, 404, 408, 388, 452,

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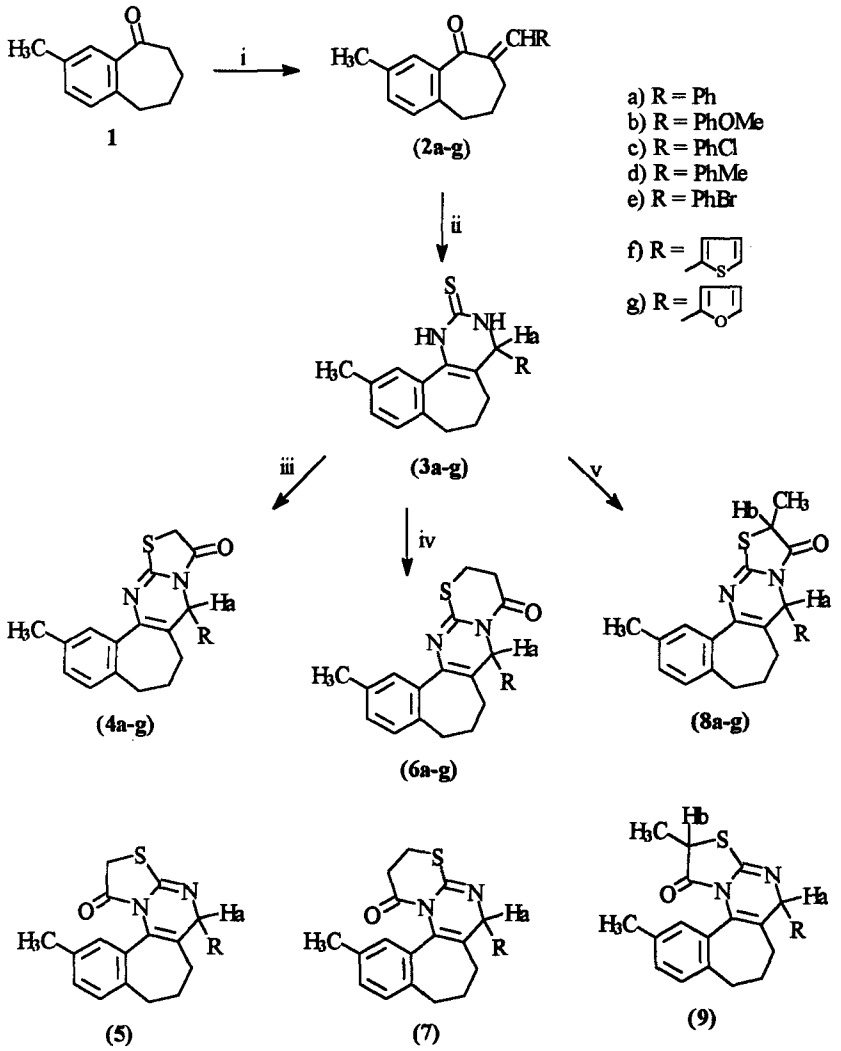

Reagents : i) alc. KOH, aromatic aldehyde; ii) alc. KOH, thiourea; iii) $ClCH_2COOH$, anhy. NaOAc, AcOH, Ac_2O; iv) $BrCH_2CH_2COOH$, Anhyd. NaOAc, AcOH, Ac_2O; v) $CH_3CH(Cl)COOH$, Anhyd. NaOAc, AcOH, Ac_2O.

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380 & 364 in the mass spectra of the products suggested that the cyclisation has occurred. The regiochemistry of the cyclised products was settled only on the basis of ^{1}H NMR spectral data which could distinguish the pairs of isomers **6** or **7**.

In ^{1}H NMR spectra the signals at δ 6.05, 6.05, 6.15, 6.05, 6.10, 6.05 & 6.10 were assigned to Ha proton in the cyclised products being downfield in comparision to the signals of Ha in thioxo derivatives **3a-g** which supported the structures **6a-g** and ruled out the possibility of structures **7a-g** respectively as no downfield shift is expected.

Reaction of **3a-g** with 2-chloropropionic acid afforded the unreported thiazolo pyrimidine derivative **8** or **9** depending upon the mode of cyclisation. Structures **8a-g** were similarly assigned on the basis of ^{1}H NMR spectra and ruled out the alternative structure **9**.

Biological Evaluation

All the compounds were screened for their antimicrobial activity at concentration 40 μg/disc in agar media[8] using streptomycin, ampicillin in antibacterial and nalidxic acid in antifungal activity as reference compounds. All the compounds showed activity against gram-positive bacterium *Staphylococcus aureus* and gram-negative bacterium *Escherichia coli*. Compounds **3f, 4e, 4f, 6e, 6f** and **8f** showed maximum zone of inhibition (26-30 mm) against *E. coli*, while **3f** and **6f** showed maximum zone of inhibition (20 and 25 mm) against *S. aureus*. Compounds **3f, 4f, 6f** and **8f** which was substituted with thiophene ring attached to the pyrimidine ring showed maximum activity (26-30 mm) as compared with ampicillin (22 mm) and streptomycin (30 mm) at the concentration of 10 μg/disc against *E. coli*.

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Compounds **2a-d, 3b, 3d, 4c, 6b, 8a** and **8b** showed moderate antifungal activity with inhibition area (50-60 mm) against fungi saccharomyces when compared with nalidixic acid (resistant).

Anti-inflammatory activity : Anti-inflammatory activity of the compounds was conducted by the reported method.[9] All the compounds were screened at a dose of 100 mg/kg in 5% gum acacia suspension. The result showed that all the compounds **2a-d, 3a-d, 4a-d, 6a-c, 8a-b** exhibited greater degree (31-33%) of inhibition of oedema as compared with a standard drug asprin (17%) at a dose of 100 mg/kg.

Invitro Evaluation of Anti-tuberculosis activity

Primary screening of the compounds for anti-tubercular activity have been conducted as 12.5 μg/ml against *Mycobacterium tuberculosis* H 37 Rv in BACTEC 12B medium using the BACTEC 460 radiometric system.

Most of the derivatives exhibited various degree of activity but **2a** and **2d** showed 82-85% and **2b, 3a, 3c, 4a** and **6c** showed 25-50% inhibition against *Mycobacterium tuberculosis* H 37 Rv. The antimycobacterial activity data were compared with standard drug Rifampin as 0.25 to 0.031 μg/ml concentration. Compounds **2a** & **2d** exhibited high antitubercular activity and **3b, 3c, 4a, 4d, 6a** and **6c** showed moderate antitubercular activity.

EXPERIMENTAL

M.Ps were determined using Gallankamp apparatus and are uncorrected. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Varian FT 80A spectrometer with TMS as an internal standard. Infrared spectra were recorded using Shimadzu 470

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spectrometer. Mass spectra were taken on a VG high resolution 7070 H and Finnigan Met 1020 B spectrometers.

6-Arylidene-3-methyl-6,7,8,9-tetrahydro-5H-benzo[a]cyclohepten-5-ones (2a-g):

General procedure: A mixture of 3-methyl-6,7,8,9-tetrahydro-5H-benzo[a]-cycloheptene-5-one[10] (1) (0.35g, 2 mmole), benzaldehyde (0.22g, 2 mmole) in 4% of ethanolic potassium hydroxide (0.08 g in 2 ml) was stirred at room temperature for ½ hr. The reaction mixture was neutralised with dilute acetic acid. The solid thus obtained was filtered and washed thoroughly with water and dried. Recrystallised from methanol gave the product **2a** (0.5g, 94%) as colourless crystals, mp 112-113°C. IR υ_{max} (KBr) : 1661 (CO, chelated) and 1601 (C=C) cm^{-1} . ^1H NMR : δ 2.00-2.10 (2H, m, 8-CH_2), 2.40 (3H, s, -CH_3), 2.60 (2H, t, 7-CH_2), 2.85 (2H, t, 9-CH_2), 7.80 (1H, S, C=CH), 7.00-7.75 (8H, m, aromatic). Anal. Calcd. for $C_{19}H_{18}O$: C, 87.02; H, 6.87. Found : C, 87.00; H, 6.80.

2b : yield 97%, colourless crystals, mp 110-112°C, IR υ_{max} (KBr) : 1663 (CO), 1588 (C=C) cm^{-1}. Anal. Calcd. for $C_{20}H_{20}O_2$: C, 82.19; H, 6.85. Found : C, 82.00; H, 6.87.

2c : yield 90%, colourless crystals, mp 120-121°C, IR υ_{max} (KBr) : 1663 (CO), 1601 (C=C) cm^{-1}. Anal. Calcd. for $C_{19}H_{17}ClO$: C, 77.02; H, 5.74. Found : C, 76.94; H, 5.70.

2d : yield 95%, colourless crystals, mp 90-92°C, IR υ_{max} (KBr): 1657 (CO), 1593 (C=C) cm^{-1}. Anal. Calcd. for $C_{20}H_{20}O$: C, 86.95; H, 7.24. Found : C, 86.90; H, 7.20.

2e : yield 90%, colourless crystals, mp 124-125°C. IR υ_{max} (KBr) : 1657 (CO),

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1585 (C=C) cm^{-1}. Anal. Calcd. for $C_{19}H_{17}BrO$: C, 67.05; H, 5.00. Found : C, 67.00; H, 4.96.

2f : yield 75%, colourless crystals, mp 135-137°C. IR υ_{max} (KBr) : 1653 (CO), 1580 (C=C)cm^{-1}. Anal. Calcd. for $C_{17}H_{16}OS$: C, 76.12; H, 5.97. Found : C, 76.11; H, 5.98.

2g : yield 73%, colourless crystals, mp 108-110°C. IR υ_{max} (KBr) : 1657 (CO), 1593 (C=C)cm^{-1}. Anal. Calcd. for $C_{17}H_{16}O_2$: C, 80.95; H, 6.35. Found : C, 80.92; H, 6.37.

10-Methyl-4-phenyl-2,3,4,5,6,7-hexahydro-1H-benzo[6,7]cyclohepta[d]-pyrimidine-2-thiones (3a-g):

General Procedure : A mixture of 6-arylidenebenzocyclohepten-5-one (**2a**) (0.524 g, 2 mmole) and thiourea (0.15 g, 2 mmole) in 4% ethanolic potassium hydroxide (0.08g in 2 ml) was heated under reflux for 1½ hr. At the end of the reaction, excess ethanol was removed under reduced pressure and kept aside overnight. The solid thus seperated from the solution was filtered and recrystallised from ethanol gave the product **3a** (0.58 g, 90%) as colourless crystals, mp 226-227°C. IR υ_{max} (KBr) : 3405 (NH) cm^{-1}. ^1H NMR : δ 1.65-1.90 (4H, m, 6-CH_2 & 5-CH_2), 2.34 (3H, s, -CH_3), 2.45 (2H, t, 7-CH_2), 5.05 (1H, s, Ha), 7.05-7.45 (8H, m, aromatic). Anal. Calcd. for $C_{20}H_{20}N_2S$: C, 75.00; H, 6.25; N, 8.75. Found : C, 74.89; H, 6.13; N, 8.77.

3b : yield 80%, colourless crystals, mp 168-170°C. IR υ_{max} (KBr) : 3401 (NH) cm^{-1}. ^1H NMR : δ 1.60-1.95 (4H, m, 6-CH_2 & 5-CH_2), 2.32 (3H, s, -CH_3), 2.45 (2H, t, 7-CH_2), 3.80 (3H, s, -OCH_3), 4.98 (1H, s, Ha), 6.80-7.35 (7H, m, aromatic). Anal. Calcd. for $C_{21}H_{22}N_2OS$: C, 72.00; H, 6.28; N, 8.00. Found : C, 71.88; H, 6.20; N, 8.03.

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3c : Yield 90%, colourless crystals, mp 160-162°C. IR υ_{max} (KBr) : 3406 (NH) cm^{-1}. ^1H NMR : δ 1.60-1.95 (4H, m, 6-CH_2 & 5-CH_2), 2.30 (3H, s, -CH_3), 2.44 (2H, t, 7-CH_2), 5.00 (1H, s, Ha), 7.00-7.48 (7H, m, aromatic). Anal. Calcd. for $C_{20}H_{19}N_2ClS$: C, 67.79; H, 5.36; N, 7.90. Found : C, 67.70; H, 5.29; N, 7.81.

3d : Yield 84%, colourless crystals, mp 190-192°C. IR υ_{max} (KBr) : 3401 (NH) cm^{-1} . ^1H NMR : δ 1.65-2.05 (4H, m, 6-CH_2 & 5-CH_2), 2.30 (3H, s, -CH_3), 2.46 (2H, t, 7-CH_2), 5.00 (1H, s, Ha), 7.00-7.45 (7H, m, aromatic). Anal. Calcd. for $C_{21}H_{22}N_2S$: C, 75.44; H, 6.58; N, 8.38. Found : C, 75.40; H, 6.51; N, 8.30.

3e : Yield 80%, colourless crystals, mp 154-155°C. IR υ_{max} (KBr) : 3405 (NH) cm^{-1}. ^1H NMR : δ 1.65-2.05 (4H, m, 6-CH_2 & 5-CH_2), 2.30 (3H, s, -CH_3), 2.46 (2H, t, 7-CH_2), 5.00 (1H, s, Ha), 7.00-7.55 (7H, m, aromatic). Anal. Calcd. for $C_{20}H_{19}N_2BrS$: C, 60.30; H, 4.77; N, 7.03. Found : C, 60.32; H, 4.75; N, 7.00.

3f : Yield 70%, colourless crystals, mp 108-110°C. IR υ_{max} (KBr) : 3405 (NH) cm^{-1}. ^1H NMR : δ 1.65-2.10 (4H, m, 6-CH_2 & 5-CH_2), 2.45 (3H, s, -CH_3), 2.50 (2H, t, 7-CH_2), 5.10 (1H, s, Ha), 6.95-7.50 (6H, m, aromatic). Anal. Calcd. for $C_{18}H_{18}N_2S_2$: C, 66.25; H, 5.52; N, 8.58. Found : C, 66.27; H, 5.53; N, 8.57.

3g : Yield 70%, colourless crystals, mp 90°C (decomp). IR υ_{max} (KBr); 3402 (NH) cm^{-1}. ^1H NMR : δ 1.65-2.05 (4H, m, 6-CH_2 & 5-CH_2), 2.40 (3H, s, CH_3), 2.40 (2H, t, 7-CH_2), 5.10 (1H, s, Ha), 7.00-7.55 (6H, m, aromatic). Anal. Calcd. for $C_{18}H_{18}N_2OS$: C, 69.67; H, 5.80; N, 9.03. Found : C, 69.68; H, 5.82; N, 9.05.

2-Methyl-8-phenyl-5,6,7,8,10,11-hexahydrobenzo[6,7]cyclohepta[d][1,3]-thiazolo[3,2-a]pyrimidin-10-ones (4a-g) :

General Procedure : Amixture of thione **3a** (0.48 g, 1.5 mmole), chloroacetic acid (0.14 g, 1.5 mmole), anhydrous sodium acetate (0.13 g), glacial acetic acid (2

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ml) and acetic anhydride (0.5 ml) was heated under reflux for 3 hr. The reaction mixture was cooled to room temperature and then poured into icewater. The solid thus seperated from solution was filtered, washed with water and finally crystallized from ethanol to give **4a** (0.48 g, 90%) as crystals, mp 185-187°C. IR υ_{max} (KBr) : 1723 (CO) cm^{-1}. ^1H NMR : 1.60-2.05 (4H, m, 6-CH_2 & 7-CH_2), 2.34 (3H, s, -CH_3), 2.45 (2H, t, 5-CH_2), 3.60-3.85 (2H, m, S-CH_2), 5.52 (1H, s, Ha), 7.00-7.50 (8H, m, aromatic). MS : 360 (M^+). Anal. Calcd. for $C_{22}H_{20}N_2OS$: C, 73.33; H, 5.55; N, 7.77. Found: C, 73.29; H, 5.50; N, 7.69.

4b : Yield 89%, crystals, mp 82-85°C. IR υ_{max} (KBr) : 1725 (CO) cm^{-1}. ^1H NMR: 1.70-2.10 (4H, m, 6-CH_2 & 7-CH_2), 2.35 (3H, s, -CH_3), 2.50 (2H, t, 5-CH_2), 3.65-3.85 (2 H, m, S-CH_2), 3.80 (3H, s, OCH_3), 5.50 (1H, s, Ha) 6.85-7.40 (7H, m, aromatic). MS : 390 (M^+). Anal. Calcd. for $C_{23}H_{22}N_2O_2S$: C, 70.76; H, 5.64; N, 7.17. Found : C, 70.69; H, 5.59; N, 7.10.

4c : Yield 81%, colourless crystals, mp 108-110°C. IR υ_{max} (KBr) : 1726 (CO) cm^{-1}. ^1H NMR : δ 1.70-2.10 (4H, m, 6-CH_2 & 7-CH_2), 2.20 (3H, s, -CH_3), 2.55 (2H, t, 5-CH_2), 3.80-4.00 (2H, m, S-CH_2), 5.62 (1H, s, Ha), 7.05-7.50 (7H, m, aromatic). MS : 394 (M^+). Anal. Calcd. for $C_{22}H_{19}N_2ClOS$: C, 67.00; H, 4.82; N, 7.10. Found : C, 66.89; H, 4.77; N, 7.00.

4d : Yield 80%, colourless crystals, mp 120-122°C. IR υ_{max} (KBr) : 1724 (CO) cm^{-1}. ^1H NMR : δ 1.60-2.10 (4H, m, 6-CH_2 & 7-CH_2), 2.30 (3H, s, -CH_3), 2.35 (3H, s, CH_3), 2.45 (2H, t, 5-CH_2), 3.62-3.85 (2H, m, S-CH_2), 5.50 (1H, s, Ha), 6.85-7.65 (7H, m, aromatic). MS : 374 (M^+). Anal. Calcd. for $C_{23}H_{22}N_2OS$: C, 73.79; H, 5.88; N, 7.48. Found : C, 73.75; H, 5.85; N, 7.44.

4e : Yield 90%, colourless crystals, mp 103-105°C. IR υ_{max} (KBr) : 1725 (CO)

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cm^{-1}. ^1H NMR : δ 1.75-2.00 (4H, m, 6-CH_2 & 7-CH_2), 2.40 (3H, s, -CH_3), 2.45 (2H, t, 5-CH_2), 3.70-3.90 (2H, m, S-CH_2), 5.55 (1H, s, Ha), 7.00-7.50 (7H, m, aromatic). MS: 438 (M^+). Anal. Calcd. for $C_{22}H_{19}N_2BrOS$: C, 60.27; H, 4.33; N, 6.39. Found: C, 60.25; H, 4.35; N, 6.39.

4f : Yield : 85%, colourless crystals, mp 148-150°C. IR υ_{max} (KBr) : 1724 (CO) cm^{-1}. ^1H NMR : δ 1.70-2.05 (4H, m, 6-CH_2 & 7-CH_2), 2.45 (3H, s, -CH_3), 2.40 (2H, t, 5-CH_2), 3.65-3.90 (2H, m, S-CH_2), 5.45 (1H, s, Ha), 6.95-7.45 (6H, m, aromatic). MS : 366 (M^+). Anal. Calcd. for $C_{20}H_{18}N_2OS_2$: C, 65.57; H, 4.92; N, 7.65. Found : C, 65.53; H, 4.90; N, 7.61.

4g : Yield: 60%, colourless crystals, mp 103-105°C. IR υ_{max} (KBr) : 1723 (CO) cm^{-1}. ^1H NMR : δ 1.65-1.95 (4H, m, 6-CH_2 & 7-CH_2), 2.40 (3H, s, -CH_3), 2.45 (2H, t, 5-CH_2), 3.60-3.90 (2H, m, S-CH_2), 5.50 (1H, s, Ha), 7.00-7.50 (6H, m, aromatic). MS : 350 (M^+) Anal. Calcd. for $C_{20}H_{18}N_2O_2S$: C, 68.57; H, 5.14; N, 8.00. Found : C, 68.56; H, 5.10; N, 8.10.

2-Methyl-8-phenyl-5,6,7,8,11,12-hexahydro-10H-benzo[6',7']cyclohepta-[4,5]pyrimido[2,1-b][1,3]thiazin-10-ones (6a-g) :

General procedure : A mixture of thione **3a** (0.16 g, 0.5 mmole), 3-bromo propionic acid (0.08 g, 0.05 mmole), anhydrous sodium acetate (0.07 g), glacial acetic acid (1 ml) and acetic anhydride (0.2 ml) was heated under reflux for 2hr and worked up in the usual way gave the product **6a** (0.165 g, 89%), as crystals, mp 145-147°C. IR υ_{max} (KBr) : 1691 (CO) cm^{-1}. ^1H NMR : δ 1.70-2.12 (4H, m, 6-CH_2 & 7-CH_2), 2.32 (3H, s, -CH_3), 2.50 (2H, t, 5-CH_2), 2.68-3.10 (4H, m, S-CH_2-CH_2), 6.05 (1H, s, Ha), 6.90-7.50 (8H, m, aromatic). MS : 374 (M^+).

Anal. Calcd. for $C_{23}H_{22}N_2OS$: C, 73.79; H, 5.88; N, 7.48. Found : C, 73.70; H, 5.83; N, 7.39.

6b : Yield 88%, colourless crystals, mp 112-115°C. IR υ_{max} (KBr) : 1691 (CO) cm^{-1}. ^1H NMR : δ 1.70-2.10 (4H, m, 6-CH_2 & 7-CH_2), 2.30 (3H, s, -CH_3), 2.50 (2H, t, 5-CH_2), 2.65-3.10 (4H, m, S-CH_2-CH_2), 3.75 (3H, s, -OCH_3), 6.05 (1H, s, Ha), 6.80-7.40 (7H, m, aromatic). MS : 404 (M^+). Anal. Calcd. for $C_{24}H_{24}N_2O_2S$: C, 71.28; H, 5.94; N, 6.93. Found : C, 71.25; H, 5.94; N, 6.90.

6c : Yield: 74%, colourless crystals, mp 115-118°C. IR υ_{max} (KBr) : 1693 (CO) cm^{-1}. ^1H NMR : δ 1.60-2.00 (4H, m, 6-CH_2 & 7-CH_2), 2.40 (3H, s, -CH_3), 2.55 (2H, t, 5-CH_2), 2.74-3.10 (4H, m, S-CH_2-CH_2), 6.15 (1H, s, Ha), 7.00-7.45 (7H, m, aromatic). MS : 408 (M^+). Anal. Calcd. for $C_{23}H_{21}N_2ClOS$: C, 67.64; H, 5.14; N, 6.86. Found : C, 67.62; H, 5.10; N, 6.82.

6d : The usual work up gave material which was chromatographed on silica gel elution with benzene gave two bands. The first band on further purfication from preparative tlc (silicagel, 5% ethyl acetate-benzene) yielded the title compound (15%) as colourless crystals, mp 100-102°C. IR υ_{max} (KBr) : 1691 (CO) cm^{-1}. ^1H NMR : δ 1.70-2.05 (4H, m, 6-CH_2 & 7-CH_2), 2.32 (6H, s, 2 x -CH_3), 2.50 (2H, t, 5-CH_2), 2.63-3.11 (4H, m, S-CH_2-CH_2), 6.05 (1H, s, Ha), 6.80-7.40 (7H, m, aromatic). MS : 388 (M^+). Anal. Calcd. for $C_{24}H_{24}N_2OS$: C, 74.22; H, 6.18; N, 7.21. Found : C, 74.20; H, 6.19, N, 7.20.

The second major fraction (65%) was the unreacted starting material, m.p. 190-192°C.

6e : Yield 75%, colourless crystals, mp : 104-106°C. IR υ_{max} (KBr) : 1692 (CO) cm^{-1}. ^1H NMR : δ 1.65-2.10 (4H, m, 6-CH_2 & 7-CH_2), 2.40 (3H, s, -CH_3), 2.45

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(2H, t, 5-CH_2), 2.65-3.10 (4H, m, S-CH_2-CH_2), 6.10 (1H, s, Ha), 7.05-7.65 (7H, m, aromatic). MS : 452 (M^+). Anal.Calcd. for : $C_{23}H_{21}N_2BrOS$: C, 61.06; H, 4.65; N, 6.19. Found : C, 61.05; H, 4.63; N, 6.17.

6f : Yield: 50%, colourless crystals, mp 98-100°C. IR υ_{max} (KBr) : 1693 (CO) cm^{-1}. ^1H NMR : δ 1.55-2.05 (4H, m, 6-CH_2 & 7-CH_2), 2.45 (3H, s, -CH_3), 2.45 (2H, t, 5-CH_2), 2.55-3.05 (4H, m, S-CH_2-CH_2), 6.05 (1H, s, Ha), 7.00-7.55 (6H, m, aromatic). MS : 380 (M^+). Anal. Calcd. for $C_{21}H_{20}N_2OS_2$: C, 66.31; H, 5.26; N, 7.37. Found : C, 66.29; H, 5.25; N, 7.34.

6g : Yield 63%, colourless crystals, mp 100°C (decomp). IR υ_{max} (KBr):1686 cm^{-1}. ^1H NMR : δ 1.60-2.10 (4H, m, 6-CH_2 & 7-CH_2), 2.40 (3H, s, -CH_3), 2.45 (2H, t, 5-CH_2), 2.60-3.10 (4H, m, S-CH_2-CH_2), 6.10 (1H, s, Ha), 7.05-7.60 (6H, m, aromatic). MS : 364 (M^+). Anal. Calcd. for $C_{21}H_{20}N_2O_2S$: C, 69.23; H, 5.49; N, 7.69. Found : C, 69.21; H, 5.47; N, 7.71.

2,11-Dimethyl-8-phenyl-5,6,7,8,10,11-hexahydrobenzo[6,7]cyclohepta[d]-[1,3]thiazolo[3,2-a]pyrimidin-10-ones (8a-g) :

General Procedure : A mixture of thione **3a** (0.24 g, 0.75 mmole), 2-chloro-propionic acid (0.082 g, 0.75 mmole), anhydrous sodium acetate (0.08 g) in glacial acetic acid (2 ml) and acetic anhydride (0.25 ml) was heated under reflux for 6 hr and worked up in the usual way to give a mixture of two products (TLC). These were separated by preparative tlc on silica gel using 5% ethylacetate benzene. The first band yielded the desired product **8a** (0.035 g, 12%) as colourless crystals, mp 128-130°C. IR υ_{max} (KBr) : 1732 (CO) cm^{-1}. ^1H NMR : δ 1.78-2.05 (4H, m, 6-CH_2 & 7-CH_2), 1.38 (3H, d, 11-CH_3), 2.38 (3H, s, 2-CH_3), 2.45 (2H, t, 5-CH_2), 4.00-4.15 (1H, q, Hb), 5.50 (1H, s, Ha), 7.00-7.60 (8H, m,

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aromatic). MS : 374 (M^+). Anal. Calcd. for $C_{23}H_{22}N_2OS$: C, 73.79; H, 5.88; N, 7.48. Found : C, 73.70; H, 5.82; N, 7.48.

The second major band (0.196 g, 70%) was the unreacted starting material along with other impurities. The same phenomena was observed with other compounds also.

8b : Yield 10%, colourless crystals, mp 136-138°C. IR υ_{max} (KBr) : 1731 (CO) cm^{-1}. ^1H NMR : δ 1.65-1.96 (4H, m, 6-CH_2 & 7-CH_2), 1.30 (3H, d, 11-CH_3), 2.30 (3H, s, 2-CH_3), 2.60 (2H, t, 5-CH_2), 4.05-4.15 (1H, q, Hb), 5.40 (1H, s, Ha), 6.70-7.50 (7H, m, aromatic). MS : 404 (M^+). Anal. Calcd. for $C_{24}H_{24}N_2O_2S$: C, 71.28; H, 5.94; N, 6.93. Found : C, 71.20; H, 5.90; N, 6.90.

8c : Yield 20%, colourless crystals, mp. 110-112°C. IR υ_{max} (KBr) : 1728 (CO) cm^{-1}. ^1H NMR : δ 1.60-1.95 (4H, m, 6-CH_2 & 7-CH_2), 1.50 (3H, d, 11-CH_3), 2.45 (3H, s, 2-CH_3), 2.50 (2H, t, 5-CH_2), 4.00-4.18 (1H, q, Hb), 5.55 (1H, s, Ha), 7.00-7.65 (7H, m, aromatic). MS : 408 (M^+). Anal. Calcd. for $C_{23}H_{21}N_2ClOS$: C, 67.64; H, 5.14; N, 6.86. Found : 67.62; H, 5.12; N, 6.88.

8d : Yield 20%, colourless crystals, mp. 120-124°C. IR υ_{max} (KBr) : 1725 cm^{-1}. ^1H NMR : δ 1.60-1.90 (4H, m, 6-CH_2 & 7-CH_2), 1.52 (3H, d, 11-CH_3), 2.45 (6H, s, 2 x CH_3), 2.52 (2H, t, 5-CH_2), 4.05-4.18 (1H, q, Hb), 5.52 (1H, s, Ha), 7.00-7.50 (7H, m, aromatic). MS : 388 (M^+). Anal. Calcd. for $C_{24}H_{24}N_2OS$: C, 74.22; H, 6.18; N, 7.21. Found : C, 74.24; H, 6.20; N, 7.20.

8e : Yield 60%, colourless crystals, mp 105-107°C. IR υ_{max} (KBr) : 1722 (CO) cm^{-1}. ^1H NMR : 1.60-1.95 (4H, m, 6-CH_2 & 7-CH_2), 1.50 (3H, d, 11-CH_3), 2.45 (3H, s, 2-CH_3), 2.50 (2H, t, 5-CH_2), 4.00-4.18 (1H, q, Hb), 5.55 (1H, s, Ha),

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7.00-7.65 (7H, m, aromatic). MS : 452 (M^+). Anal. Calcd. for $C_{23}H_{21}N_2BrOS$: C, 61.06; H, 4.64; N, 6.19. Found : C, 61.08; H, 4.66; N, 6.18.

8f : Yield 30%, colourless crystals, mp 90°C (decomp). IR υ_{max} (KBr) : 1724 (CO) cm^{-1}. ^1H NMR : δ 1.78-2.00 (4H, m, 6-CH_2 & 7-CH_2), 1.50 (3H, d, 11-CH_3), 2.35 (3H, s, 2-CH_3), 2.50 (2H, t, 5-CH_2), 4.00-4.15 (1H, q, Hb), 5.45 (1H, s, Ha), 7.00-7.60 (6H, m, aromatic). MS : 380 (M^+). Anal. Calcd. for $C_{21}H_{20}N_2OS_2$: C, 66.32; H, 5.26; N, 7.36. Found : C, 66.35; H, 5.25; N, 7.35.

8g : Yield 35%, colourless crystals, mp: 136-138°C. IR υ_{max} (KBr) : 1726 (CO) cm^{-1}. ^1H NMR : δ 1.76-1.98 (4H, m, 6-CH_2 & 7-CH_2), 1.38 (3H, d, 11-CH_3), 2.40 (3H, s, 2-CH_3), 2.50 (2H, t, 5-CH_2), 4.02-4.18 (1H, q, Hb), 5.40 (1H, s, Ha), 6.90-7.50 (6H, m, aromatic). MS : 364 (M^+). Anal. Calcd. for $C_{21}H_{20}N_2O_2S$: C, 69.23, H, 5.49; N, 7.69. Found : C, 69.25; H, 5.50; N, 7.70.

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