RESEARCH PAPER

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Synthesis and CNS Depressant of Newer Spirobarbiturates

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In an effort to search for more active CNS depressants, a series of spirobarbiturates incorporated with thiazolidinones and azetidinones were synthesized and evaluated for their sedative, hypnotic and anticonvulsant activities. Starting bis compounds (1a-d) were prepared from the reaction of acetone and substituted aldehydes. These bis compounds on Michael addition with barbituric acid give rises to triones (2a-d), which on condensation with $NH_2NH_2.H_2O$ afforded (3a-d) which on reaction with different aromatic aldehydes afforded and Schiff bases (4a-n). These on cyclocondensation with thiolactic acid and chloroacetyl chloride furnished the final products (5a-n) and (6a-n), respectively. Result of toxicity studies and central nervous system depressant activities of these compounds are reported. The structures of the products have been delineated by chemical reaction, elemental analysis and spectral studies.

A large number of 5-substituted barbituric acid derivatives have been synthesized, which have been reported to exhibit a broad spectrum of biological activities like anticonvulsant[1], antiparkinsonian[2], anaesthetic[3], sedative and hypnotic activities[4-6]. Recently certain spiroheterocycles have also been reported to possess diverse biological activities that include anticancer[7], antinflammatory[8], antibiotic[9], herbicides[10] and central nervous system (CNS) activities[11]. In addition to these, several thiazolidinone derivatives have considerable commercial importance as drugs[12,13] and spiroazetidinones were also reported as biological active agents[14]. These findings prompted our interest to incorporate spiro derivatives of barbiturates in to thiazolidinones and azetidinones in a single molecular frame with an aim to improve CNS depressant activity.

All the compounds were synthesized according to Scheme I. The key intermediate, 7,11-diaryl-3-oxo-2,4-diazaspiro-1,5,9-triones (2a-d) were prepared by Michael addition of 5-bis-(3-substitutedaryl)penta-1,4-dien-3-ones[14] (1a-d) with barbituric acid. The 7,11-diaryl-3-oxo-9-amino imino-[5.5]-undecane-2,4-diazaspiro-1,5-diones (3a-d) have been prepared by the condensation with hydrazine hydrate which on treatment with different aromatic aldehydes afforded their corresponding Schiff bases (4a-n). These Schiff bases on cyolocondensation with thioglycolic acid and chloroacetyl chloride furnished the final compound (5a-n) and (6a-n) respectively. The structural assignments of the products were based on elemental analysis (C, H and N), IR, and ^{1}H-NMR spectrometry. The spectral data of only representative compounds are given in experimental section.

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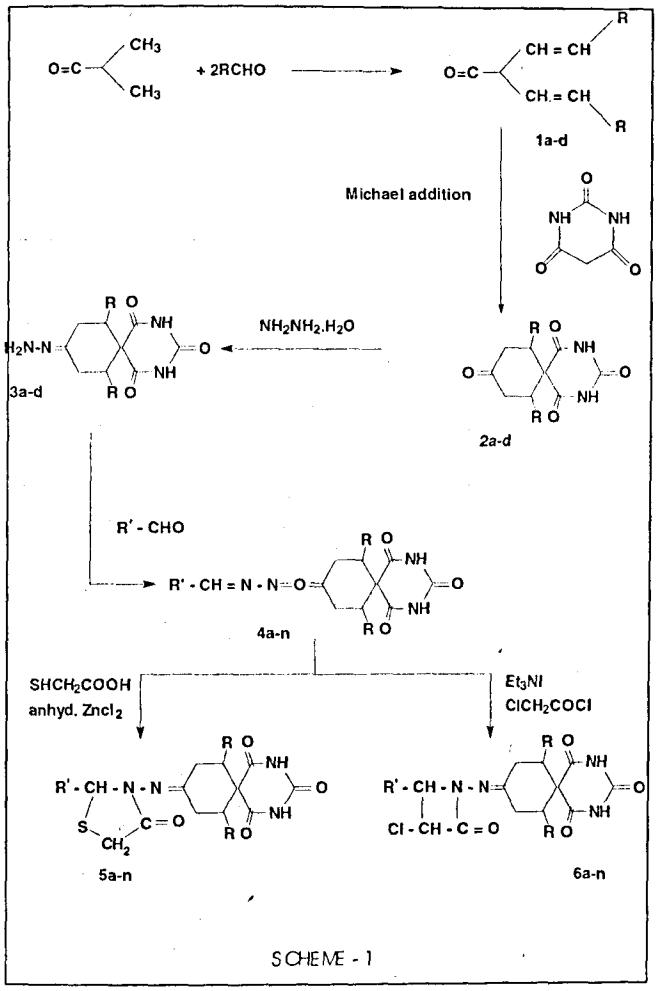
MATERIALS AND METHODS

Melting points were taken in open capillaries and are uncorrected. All the compounds were routinely checked for their purity by TLC on silica gel-G plates using benzene and methanol as eluent in different proportions, and spots were located by iodine. IR spectra were recorded in KBr on a Beckmann Acculab-1-spectrophotometer and Perkin-Elmer 157 spectrophotometer (ν_{max} in cm^{-1}), and ^{1}H-NMR spectra in $CDCl_3$/$DMSOd_6$ on a Bruker WM 400-FT, Em-360,



SCHEME - 1

Varian 190D using TMS as internal standard, chemical shift in (δ), are reported in ppm. The C, H, N analysis was performed on a Carlo Erba-1108 instrument.

Synthesis of 5-bis-(3-substitutedaryl)-penta-1,4-dien-3-ones (1a-d):

These were synthesized according to the method of Bayer *et al.*[14]. According to this method, aldehyde (0.22 mol) in methanol (20 ml) was added during 1 h at room temp with stirring to a solution of NaOH in acetone (0.14 mol), methanol and water. Crystals were separated out which were filtered and recrystallised from suitable solvents . Compound 1a: IR (KBr): 1680 (C=O streching), 1650 (-CH=CH- streching) cm^{-1}: ^{1}H-NMR ($CDCl_3$): δ 8.8 (d, 2H, 2×Ar-C<u>H</u>=), 8.20-7.50 (m, 10H, Ar-<u>H</u>), 5.9 (d, 2H, $O=C(CH)_2$. ppm)

Synthesis of 7, 11-diaryl-3-oxo-2,4-diazaspiro [5.5] undecane-1,5,9-trione (2a-d):

These were synthesized according to the method of Osman *et al.*[15]. A mixture of equimolar amount (0.005 mol) of barbituric acid in dioxane (15 ml) on Michael addition with solution of 5-bis-3-aryl-penta-1, 4-dien-3-one in ethanol (20 ml) with few drops of triethanolamine (as base) was refluxed for 7h with constant stirring on mechanical stirrer. The reaction mixture was filtered, cooled and poured on to ice cold water. The solid product was crystallized from different recrystallisation solvents . Compound 2a (7,11-Diphenyl-3-oxo-2,4-diazaspiro[5.5] undecane 1,5,9-trione): IR (KBr): 3200-3100 (NH, streching), 1750, 1720, 1700, 1680 cm^{-1} (C=O streching); ^{1}H-NMR ($CDCl_3$): δ 9.25 (ss, 2H, 2N<u>H</u>CO), 7.56-6.70 (m, 10H, Ar-<u>H</u>), 4.40 (dd, 2H, 7H and 11H, J_{XA}=7.5 Hz, J_{XM}=2.5 Hz, <u>H</u>$_X$), 6.45 (dd, 2H, 8H_{ax} and 10 H_{ax} J_{MA}=12.5 Hz, J_{mx}=2.5 Hz, <u>H</u>m), 2.80 (dd, 2H, 8H_{eq},10H_{eq} J_{AM}=12.5 Hz, J_{AX}=<u>H</u>$_A$) (ppm).

Synthesis of 7,11-Diaryl-3-oxo-9-aminoimino-2,4-diazosphio[5.5]undecane-1,5-diones: (3a-d):

A mixture of equimolar amount (0.01 mol) of triones (2a-d) in methanol (50 ml) and hydrazine hydrate (99%) with 30 ml methanol was heated and refluxed for 12 h. The solution was stripped of solvent *in vacuo* and to it was added water. The resultant precipitate was filtered, washed and recrystallised from different recrystallisation solvents. Compound 3a (7,11-Diphenyl-3-oxo-9-aminoimino-2,4-diazasphiro [5.5] undecane-1,5-diene): 3280 (NH_2 streching), 3050 (NH, streching), 1730, 1720, 1690 (C=O, streching), 1250 (N-N, streching) cm^{-1} ^{1}H-NMR ($CDCl_3$) δ : 9.30 (ss, 2H, 2N<u>H</u>CO), 7.25-6.25 (m, 10H, Ar-H), 5.50 (bs, 2H, N<u>H</u>$_2$), 4.55 (dd, 2H, 7H and 11H, J_{XA}=7Hz, J_{XM}= 2.5 Hz, Hx), 3.88 (dd, 2H, 8H_{ax} and 10H_{ax} J_{MA}=12 Hz, J_{MX}= 2.5 Hz, <u>H</u>$_M$) 2.74 (dd, 2H, 8H_{eq} and 10H_{eq}, J_{AM}=12 Hz, J_{AX}= 7Hz, <u>H</u>$_A$) (ppm).

Synthesis of 7,11-diphenyl-3-oxo-9-(substituted arylidene)imino-2,4-diazospiro[5.5]undecane-1,5-diones(4a-n):

An equimolar mixture (0.01 mol) of 7,11-diaryl-3-oxo-9-aminoimino-2,4-diazospiro [5.5] undecane-1,5-diene (3a-d) on condensation with substituted aldehydes (0.01 mol) in presence of glacial acetic acid was refluxed in ethanol for 4h. Excess of ethanol was distilled off and separated solid filtered and recrystallised from appropriate solvents to give compound 4a-n. Compound 4a (7, 11-Diphenyl-3-oxo-9-benzylidene imino-2,4-diazosphiro [5.5] undecane-1,5-diene) IR (KBr): 3330 (NH), 1730, 1715, 1680 (C=O, streching), 1660-1640 (-N=C, streching), 1270 (N-N streching) cm^{-1}, ^{1}H-NMR ($CDCl_3$) δ 9.65 (ss, 2H, 2N<u>H</u>CO), 8.80 (s, 1H-CH=N moiety), 7.7-6.4 (m, 15H, Ar-H), 4.28 (dd,

TABLE1: PHYSICAL AND BIOLOGICAL DATA OF COMPOUNDS 1A-D, 2A-D, 3A-D, 4A-N, 5A-N, 6A-N.

Compd	R	R'	Mp (°)	% yield	Gross CNS behaviour	Pentobarbitone-induced sleeping (min±SEM) time		% seizure protection[d]
						Before drug Treatment	After drug Treatment	
1a	$-C_6H_5$	-	112	80		-	-	0
1b	$4\text{-}OCH_3C_6H_4$	-	132	70	No effect	-	-	0
1c	$4\text{-}N(CH_3)_2C_6H_4$	-	80	85	-do-	-	-	0
1d	C_4H_3O	-	28	65	-do-	-	-	0
2a	$-C_6H_5$	-	292	75	-do-	23.0±2.1	31.3±4.2	0
2b	$-4\text{-}OCH_3C_6H_4$	-	232	80	Deprsnt[c]	27.5±2.6	38.4±4.5	50*
2c	$4\text{-}N(CH_3)_2C_6H_4$	-	218	77	-do-	26.0±2.1	40.3±4.7*	40*
2d	C_4H_3O	-	289	77	-do-	23.5±2.6	29.3±4.4	60*
3a	$-C_6H_5$	-	220	70	No effect	26.5±2.9	42.5±4.9*	0
3b	$4\text{-}OCH_3C_6H_4$	-	200	72	Deprsnt[c]	29.0±2.8	50.2±5.0*	60*
3c	$4\text{-}N(CH_3)_2C_6H_4$	-	245	65	-do-	27.5±2.4	79.5±6.3*	50*
3d	C_4H_3O	-	212	66	-do-	24.5±2.6	39.9±4.1*	70*
4a	C_6H_5	-	180	60	-do-	23.6±2.3	37.5±4.2*	10
4b	C_6H_5	-	198	55	No effect	28.0±0.01	34.6±4.4	30
4c	$4\text{-}N(NH_3)_2C_6H_4$	$-C_6H_5$	182	62	-do-	26.5±2.8	40.3±4.7*	20
4d	$4\text{-}N(CH_3)_2C_6H_4$	$4\text{-}OCH_3C_6H_4$	215	60	Deprsnt[c]	26.5±2.9	42.8±4.8*	30
4e	$4\text{-}N(CH_3)_2C_6H_4$	$4\text{-}N(CH_3)_2C_6H_4$	260	55	-do-	25.5±2.3	51.3±5.0*	40*
4f	$4\text{-}N(CH_3)_2C_6H_4$	$2\text{-}OCH_3C_6H_4$	168	54	-do-	28.5±2.4	48.4±4.7*	60*
4g	$4\text{-}N(CH_3)_2C_6H_4$	$-C_4H_3O$	158	50	-do-	26.5±2.6	40.5±4.1*	50*
4h	$4\text{-}OCH_3C_6H_4$	$-C_6H_5$	165	55	-do-	22.5±2.8	37.6±4.3*	20
4i	$4\text{-}OCH_3C_6H_4$	$4\text{-}N(CH_3)_2C_6H_4$	177	50	-do-	25.5±2.6	44.9±5.2*	30
4j	$-C_4H_3O$	$-C_6H_5$	184	58	Deprsnt[c]	26.0±2.8	32.3±4.7	40*
4k	$-C_4H_3O$	$4\text{-}OCH_3C_6H_4$	154	60	No effect	24.5±2.4	36.2±4.8	20
4l	$-C_4H_3O$	$-NH(CH_3)_2C_6H_4$	210	55	Deprsnt[c]	25.5±2.7	42.4±5.0*	30
4m	$-C_4H_3O$	$2\text{-}OCH_3C_6H_4$	176	60	-do-	23.0±2.6	43.7±4.6*	40*
4n	$-C_4H_3O$	$-C_4H_3O$	169	55	-do-	27.5±2.6	30.8±4.9	40*
5a	$-C_6H_5$	$-C_6H_5$	215	45	-do-	28.5±2.4	43.8±4.2*	0
5b	$-C_6H_5$	$-C_4H_3O$	170	45	-do-	26.5±2.6	39.9±4.4*	40*
5c	$4\text{-}N(CH_3)_2C_6H_4$	$-C_6H_5$	190	40	-do-	22.5±2.8	48.3±4.9*	30
5d	$4\text{-}N(CH_3)_2C_6H_4$	$4\text{-}OCH_3C_6H_4$	222	42	-do-	25.5±2.6	54.6±5.3*	50*
5e	$4\text{-}N(CH_3)_2C_6H_4$	$4\text{-}N(CH_3)_2C_6H_4$	258	45	-do-	23.0±2.6	110±7.8*	70*
5f	$4\text{-}N(CH_3)_2C_6H_4$	$2\text{-}OCH_3C_6H_4$	206	40	-do-	27.4±2.6	88.3±6.2*	90*
5g	$4\text{-}N(CH_3)_2C_6H_4$	$-C_6H_3O$	240	42	-do-	29.0±3.0	49.2±4.4*	80*

5h	4-$OCH_3C_6H_4$	-C_6H_5	149	38	-do-	26.0±2.1	45.4±4.1*	30
5i	4-$OCH_3C_6H_4$	4-$N(CH_3)_2C_6H_4$	188	45	-do-	23.5±2.3	45.4±4.1*	40*
5j	-C_4H_3O	-C_6H_5	233	40	-do-	26.0±2.8	53.2±5.4*	60*
5k	-C_4H_3O	4-$OCH_3C_6H_4$	228	49	-do-	22.5±2.1	40.3±4.4*	20
5l	-C_4H_3O	4-$N(CH_3)_2C_6H_4$	239	42	-do-	28.0±3.0	43.8±4.6*	40*
5m	-C_4H_3O	-$OCH_3C_6H_4$	210	45	Deprsnt[c]	23.5±3.3	47.4±4.9*	50*
5n	-C_4H_3O	-C_4H_3O	240	40	-do-	26.5±2.9	39.9±4.7*	60*
6a	-C_6H_5	-C_6H_5	226	48	-do-	27.5±2.6	39.6±4.2*	20
6b	-C_6H_5	-C_4H_3O	205	49	-do-	26.0±2.1	35.4±4.9	40*
6c	4-$N(CH_3)_2C_6H_4$	-C_6H_5	193	45	No effect	23.5±2.6	41.7±4.8*	30
6d	4-$N(CH_3)_2C_6H_4$	-$OCH_3C_6H_4$	208	50	-do-	28.0±2.3	45.8±4.6*	40*
6e	4-$N(CH_3)_2C_6H_4$	-	292	48	Deprsnt[c]	26.5±2.6	53.0±5.0*	60*
6f	4-$N(CH_3)_2C_6H_4$	4-$N(CH_3)_3C_6H_4$	730	45	-do-	25.0±2.8	50.7±5.1*	70*
6g	4-$N(CH_3)_2C_6H_4$	-C_4H_3O	260	49	-do-	29.0±3.0	42.3±4.2*	60*
6h	4-$OCH_3C_6H_4$	-C_6H_5	217	50	-do-	25.5±2.7	41.8±4.7*	20
6i	4-$OCH_3C_6H_4$	4-$N(CH_3)_2C_6H_4$	195	45	No effect	27.5±2.6	47.7±4.9*	30
6j	-C_4H_3O	-C_6H_5	209	42	Deprsnt[c]	23.0±2.6	34.2±4.1	50*
6k	-C_4H_3O	4-$OCH_3C_6H_4$	220	44	-do-	22.5±2.1	39.8±4.7*	20
6l	-C_4H_3O	4-$N(CH_3)_2C_6H_4$	239	48	-do-	24.5±2.4	48.6±5.02*	40*
6m	-C_4H_3O	2-$OCH_3C_6H_4$	226	45	-do-	29.0±2.9	49.4±4.2*	60*
6n	-C_4H_3O	-C_4H_3O	180	40	-do-	23.0±2.5	31.0±4.3	50*
pg[a]					No effect		26.0±2.9	0
ps[b]					No effect		-	80*

pg[a]=Propylene glycol (control group), ps[b] is the phenytoin sodium reference standard for anticonvulsant activity, [c]Depressant implies statistically significant reduction in spontaneous activity, loss of sound reflex, pinna reflex and righting reflex, [d] anticonvulsant activity measured using the supra maximal electro shock seizure pattern test. * indicates statistical significance at $p>0.05$

2H, 7H and 11H, J_{XA}=7Hz, J_{XB}=2.5 z, $\underline{H}_X$), 3.25 (dd, 2H, $8H_{ax}$ and $10H_{ax}$, J_{MA}=12.5Hz, J_{MX}=2.5 Hz, $\underline{H}_M$), 2.88 (dd, 2H, $8H_{eq}$ and $10H_{eq}$. J_{AM}=12.5Hz, J_{AX}=7Hz, $\underline{H}_A$) (ppm).

Synthesis of 7,11-Diaryl-3-oxo-9-[4-oxo-2-substitutedt - hiazolidinyl)imino] 2,4-diazospiro [5.5] undecane-1,5-diones (5a-n):

To a solution of 4a-n, (0.01 mol) in absolute methanol (50ml) containing a pinch of $ZnCl_2$ was added thioglycolic acid (0.02 mol) and the mixture was kept for three days at room temperature and refluxed for 8 h on water bath. The separated solid was filtered, washed with petroleum ether (40°) and recrystallised from different recrystallisation solvents. Compound 5a: IR (KBr) 3300 (NH, stretching), 1720 (thialactam moiety, stretching), 1700, 1690, 1680 (C=O of amido form stretching), 1590 (C=N, stretching) cm^{-1}, ^{1}H-NMR ($CDCl_3$) δ : 9.55 (ss, 2H, 2N$\underline{H}$CO), 7.7-6.4 (m, 15H; Ar-$\underline{H}$), 5.95 (s, 1H, -S-C$\underline{H}$-Ar), 4.20 (dd, 2H, 7H and 11H, J_{XA}=7.5 Hz, J_{XB} 2.5 Hz, $\underline{H}$x), 3.85 (s, 2H,-C$\underline{H}_2$), 3.20 (dd, 2H, $8H_{ax}$ and 10 H_{AX}, J_{MA}=12 Hz, J_{MX}=2.5 Hz, H_M), 2.60 (dd, 2H, $8H_{eq}$ and $10H_{eq}$ J_{AM}=12 Hz, J_{AX}=7.5 Hz, $\underline{H}_A$) (ppm).

Synthesis of 7,11-diphenyl-3-oxo-9-[3-chloro-2-substituted-4-oxo-1-azetidinyl) amino]2,4-diazospiro[5.5] undecane-1,5-diones (6a-n):

To the stirred solution of 4a-n (0.02 mol) in absolute ethanol (50 ml) chloroacetyl chloride was added (0.02 mol) with few drops of triethylamine at 0.5°. The reaction mixture

was left at room temperature for 6 h. and then refluxed for 8 h. and distilled off. Residue was poured on to crushed ice. The resultant precipitate was filtered and washed with petroleum ether (40°) and recrystallised from different solvents. Compound 6a: IR 3280 (NH, stretching), 1710, 1700, 1680 (C=O of NHCO streching), 790 (C-Cl, stretching), 1760 (lactum moiety C=O, streching) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 9.80 (ss, 2H, 2XN$\underline{H}$CO), 7.45-6.80 (m, 15H, Ar-$\underline{H}$), 6.40 (d, 1H,-C-C$\underline{H}$-Cl), 4.18 (dd, 2H, 7H and 11H, J_{XA} = 7.5 Hz, J_{XM}=2.5 Hz, $\underline{H}_X$), 4.50 (d, 1H,-N-C$\underline{H}$), 3.28 (dd, 2H, 8$\underline{H}_{AX}$ and 10H_{AX} J_{MA}=12.5 Hz, J_{MX}=- 2.45 Hz, $\underline{H}_M$), 2.68 (dd, 2H, 8$\underline{H}_{eq}$ and 10$\underline{H}_{eq}$ J_{AM}=12.5 Hz, J_{AX}=7.5 $\underline{H}_A$) (ppm).

Pharmacological evaluation:

All newly synthesized compounds were screened for their sedative and hypnotic activity viz. spontaneous behavioural activity[17], loss of righting reflex[18], potentiation of pentobarbitone sodium-induced sleeping time[19], anticonvulsant activity[20] and for acute toxicity studies[21]. Compounds were administrated intraperitoneally to Charles Fisher rats of either sex (120-180 g) at the dose of 100 mg/kg. The rats were divided into three groups (control, drug-reated and standard) of six animals each. Propylene glycol (0.5 ml)-reated rats were served as control group, and phenytoin sodium (30 mg/kg) was used as a reference drug for anticonvulsant activity. The experimental protocols have been approved by L. L. R. M. Medical College, Meerut animal ethics committe. All the compounds were screened for their CNS depressant viz. hypnotic, sedative and anticonvulsant activities in albino rats.

Sedative and hypnotic activity:

Spontaneous behavior activity, loss of sound reflex and pinna reflex were studied according to the method of Borsy *et al.*[17]

Loss of righting reflex:

It was done as per the method of Janscen *et al.*[18]. Rats of either sex were taken in six groups of six animals each. Selection of animals was done by placing each animal gently on its back on an undulated surface and observing that it quickly comes to its normal posture within 15 s. The animals exhibiting delayed action were discarded. After administration of the drug the time taken to loss of righting reflex was noted for each animal.

Potentiation of pentobarbitone sodium-induced sleeping time:

It was done according to the procedure of Suinyard[19]. Six groups f six rats of either sex weighing between 100-150 g exhibiting sleeping time (the interval between the loss of righting reflex and the time of regaining it) between 15-50 min with pentobarbitone sodium (30 mg/kg) were selected out, two days prior to the experiment. Test drugs were administered one hour prior to pentobarbitone sodium treatment and sleeping time was noted.

Anticonvulsant activity:

It was performed according to the method of Tomen *et al.*[20]. Ten groups of six rats of either sex in each group weighing between 100-150 g were treated with different doses of test drugs or phenytoin sodium 30.0 mg/kg orally. After one hour they were subjected to a shock of 150 mA by convulsiometer through ear electrodes for 0.2 s and the presence or absence of extensor response was noted. Animals in which extensor response was abolished were taken as protected rats.

RESULTS AND DISCUSSION

Majority of compounds exhibited CNS depressant action, as they produced reduction in spontaneous behavioural activity, loss of sound reflex, loss of pinna reflex and loss of righting reflex. The observation of potentiation of pentobarbitone sodium-induced hypnosis also reflects the CNS depressant nature of these compounds (Table 1). The most potent compound of this series was compound 5e, interestingly this compound showed anticonvulsant action (maximum 90% protection) and prolongation in pentobarbitone induced sleeping time (0.69±7.82). Compounds 1a-d did not show any marked effect of CNS activities.

SAR of these compounds (1-6) reveals that structural changes of triones (2a-d) into there corresponding iminoamino compounds 3a-d markedly enhanced CNS depressant activities. Compound 3c (substituted with N,N-dimethyl amino phenyl moiety) exhibited highly significant result ($p<0.001$) of potentiation of sleeping time. While a notable decrease in activity was seen in Schiff bases (4a-n) derived from compounds (3a-d). It was observed that substitution with 2-OCH_3-C_6H_4 (5f) was found to be more potent than its para isomer (4d) and variable degree of (20-60%) anticonvulsant action has been shown by these Schiff bases. Cyclisation of compounds (4a-n) into there corresponding thiazolidinones (5a-n) and azitidinones (6a-n) enhances hypnotic, sedative and anticonvulsant activities. Moreover thiazolidinone were found to be more potent than azetidinones.

From the analysis of pharmacological data it seems

that the CNS depressant activity is greatly influence by the nature of substitutent at 7th and 11th position of the cyclohexyl moiety which decreased in the order of $N(CH_3)_2$>C_6H_4>4-OCH_3>C_6H_4>C_6H_5>C_4H_3O. It may be concluded that compound 5e is the most potent compound while 3c and 5f revealed more potent anticonvulsant action than that of standard drug. However, further studies on these compounds may lead to the development of better CNS depressant agents.

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REFERENCES

1. Gupta, K.P., Gupta, R.C., Bhargava, K.P. and Ali, B., **Eur. J. Med. Chem. Chim. Ther.**, 1982, 17, 448.
2. Kumar, P., Nath, C., Agarwal, J.C., Bhargava, K.P. and Shanker, K., **Indian J. Chem.**, 1983, 22B, 955.
3. Andres, G., In: Medical Pharmacology, The CV Mosby Company., St. Louis, 1976, 243.
4. Abdul-Hamide, S.G., El Hakin, A.E. and El Helby, A.A., **Chem. Abstr.**, 1997, 126, 2252699.
5. Fraser, W., Suckling, C.J. and Wood, H.C.S., **J. Chem. Soc., Perkin. Trans.**, I, 1990, 11, 3137.
6. Srivastava, A.and Kumar, V.K., **Arzneim-Forsch-Drug. Res.**, 2002, 52, 787.
7. Shalmashi, A., Palit, G., Srivastava, V.K. and Shanker, K., **Indian J. Chem.**, 1994, 33B, 597.
8. Friebe, W., Scheuler, W. and Tibes, V., **Chem. Abstr.**, 1994, 120, 164007e.
9. Mckillop, A., Melaren, L., Watson, R.J., Taylor, R.J.K. and Lewis, N., **Tetrahedron lett.**, 1993, 34, 5519.
10. Fisher, R., Bretsehneider, T., Krueger, B.W., Sanlet, H.J., Dallinger, M., Erdelen, E. and Wachendroff, N.U., **Chem. Abstr.**, 1994, 121, 300756y.
11. Guillaume, G., Podona, T., Adan, G., Guardiola, B. and Renard, P., **Chem. Abstr.**, 1994, 120, 164006d.
12. Singh, S.P., Parmar, S.S., Roman, K. and Stenbereg, V.I., **Chem. Rev.**, 1981, 81, 175.
13. Goel, B., Tilak, R., Tyagi, R., Bansal, E., Kumar, A., Mukherjee, D. and Sinha, J.N., **Eur. J. Med. Chem.**, 1999, 34, 265.
14. Marzoog, S.A.T. and Maher, F.E.Z., **Indian J. Chem.**, 1998, 37B, 804.
15. Baeyer, A. and Villiger, V., **Chem. Ber.**, 1902, 35, 3023a.
16. Osman, A.N., Kandeel, M.M., Said, M.M. and Ahmed, E.M., **Indian J. Chem.**, 1996, 35B, 107.
17. Borsy, J., Csanyi, E. and Hazar, I, **Arch. Int. Pharmacology**, 1960, 124, 180.
18. Janseen, P.A.J., Vande, W.C., Jageneau, A.D., Hermans, B.K.F., Va Dacle, G.H.P., Schelickens, K.H.L., Vader Eycken, C.A.N. and Niemegere, C.J.E., **J. Med. Pharm. Chem.**, 1959, 1, 289.
19. Swinyard, E.A. and Costellion, A.W., **J. Pharmacol. Exp. Ther.**, 1966, 161, 369.
20. Tomer, J.E.P., Swinyard, E.A. and Goodman, L.S., **J. Neuro. Physiol.**, 1946, 9, 23.
21. Smith, Q.E., In; Tests Progress In Medicinal Chemistry, Brtterworth, London, 1960, 1.