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Synthesis and psychotropic evaluation of some new *N*-substitutedbenzothia/oxazepinylphenothiazines‡

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A number of *N*-[2-substitutedaryl-3-substitutedarylaminomethylene-2, 3-dihydro-1, 5-benzothia/oxazepin-4-yl]phenothiazines **4a-p** and **4a'-p'** have been synthesized from *N*-[2-substitutedaryl-2, 3-dihydro-1, 5-benzothia/oxazepin-4-yl]phenothiazines by Mannich reaction, on the 3rd position of benzothia/oxazepine ring . The structure of these compounds have been confirmed by IR, ^{1}H NMR and Mass analysis. The newly synthesized compounds have been evaluated for their psychotropic activities and acute toxicity studies. Compound **4i** is found to be most potent compound of this series.

Phenothiazines constitute one of the most active class of compounds possessing diversified biological applications[1, 2]. Literature survey reveals that various benzothiazepines[3, 4, 5] as well as benzoxazepines[6, 7] have attracted considerable attention as they also have wide range of biological activities. In light of these findings, synthesis of some novel phenothiazine derivatives by incorporating different benzothia/oxazepine have been undertaken in order to assess their psychotropic profile.

The synthetic route of compounds are shown in **Scheme I**. *N*-acetylphenothiazine **1** was prepared by the acetylation of 10*H*-phenothiazine. Compound **1** on refluxing with various aromatic aldehydes in the presence of 2% NaOH yielded *N*-substitutedbenzylideneacetylphenothiazines **2a-d**, which were cyclized with 2-amino-benzenethiol/2-aminophenol in the presence of few drops of glacial acetic acid to afford *N*-[2-substitutedaryl-2, 3-dihydro-1, 5-benzothiazepin-4-yl]phenothiazines **3a-d** and *N*-[2-substitutedaryl-2, 3-dihydro-1, 5-benzoxazepin-4-yl]phenothiazines **3a'-d'** respectively. These are subjected to Mannich's reaction with aromatic anilines to yield *N*-[2-substitutedaryl-3-substitutedarylaminomethylene-2, 3-dihydro-1, 5-benzothiazepin-4-yl]phenothiazines **4a-p** and *N*-[2-subtitutedaryl-3-substitutedarylaminomethylene-2, 3-dihydro-1, 5-benzoxazepin-4-yl]phenothiazines **4a'-p'** respectively.

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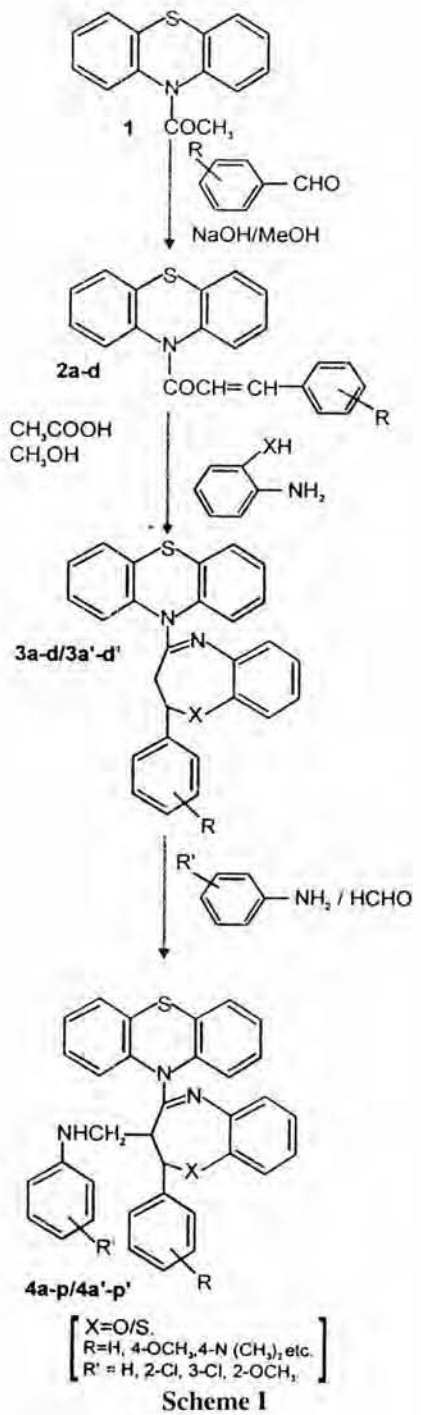
Experimental Section

Melting points were recorded in open capillaries on Thermonic melting point apparatus. Formation of the compounds was routinely checked by TLC on silica gel-G plates of 0.5 mm. thickness and spots were located by iodine. ^{1}H NMR were determined as $CDCl_3$/DMSO-d_6 solution at 300 MHz on Bruker DRX-300 spectrometer. IR spectra were recorded on Perkin-Elmer 881 spectrophotometer in KBr/Nujol (ν_{max} in cm^{-1}). Elemental analysis of the newly synthesized compounds was carried out on Carlo Erba 1108 analyzer and are found within the range of ± 0.04% of theoretical value. Physical and analytical data of all the compounds i.e. **2a-d, 3a-d, 3a'-d', 4a-p** and **4a'-p'** are given in **Table 1**.

***N*-Acetylphenothiazine 1.** To the solution of 10H-phenothiazine (0.01 mole) in dry benzene (50 mL), acetyl chloride (0.01 mole) was added dropwise at 0-5°C. The reaction mixture was stirred for 3-4 hr. at room temperature. After being stirred, the reaction mixture was kept overnight. The resulting mixture was distilled off and poured onto ice. The solid thus obtained was recrystallized from ethanol/water to afford **1**: yield 72%, m.p. 196°(reported[8] mp 198°). (Anal. calcd for $C_{14}H_{11}NOS$: C, 69.71; H, 4.56; N, 5.81. Found: C, 69.75; N, 4.52; N, 5.85%). IR (KBr): 1650 (CO), 1450(C-N), 1580 (C ⎓ C of aromatic ring) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.00-7.48 (m, 8H, Ar-*H*), 2.60 (s, 3H, $COCH_3$); MS: m/z (%): 241 (6.3) M^+, 266 (75), 198 (100), 166 (65), 153 (35).

***N*-Benzylideneacetylphenothiazine 2a.** To the solution of *N*-acetylphenothiazine (0.01 mole) in absolute methanol (50 mL), benzaldehyde



Scheme I

(0.01 mole) was added in the presence of 2% NaOH (2 mL) and refluxed for 10-12 hr. After refluxing, the reaction mixture was concentrated to half of its volume and poured onto ice, extracted with benzene and solvent was removed to get residue, which was washed several times with water and finally recrystallized from ethanol to give **2a:** yield 70%, m.p. 168°; IR (KBr): 1656 (CO), 1620 (CH=CH), 1575 (C ═ C of aromatic ring) cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.67 (d, 1H, =C*H*-Ar), 7.00-7.67 (m, 13H, Ar-*H*), 6.70 (d, 1H, COC*H*=); MS: m/z (%): 329 (8.5) M^+, 266(70), 198 (100), 166 (62), 153 (30), 103 (65), 90 (72), 77 (75).

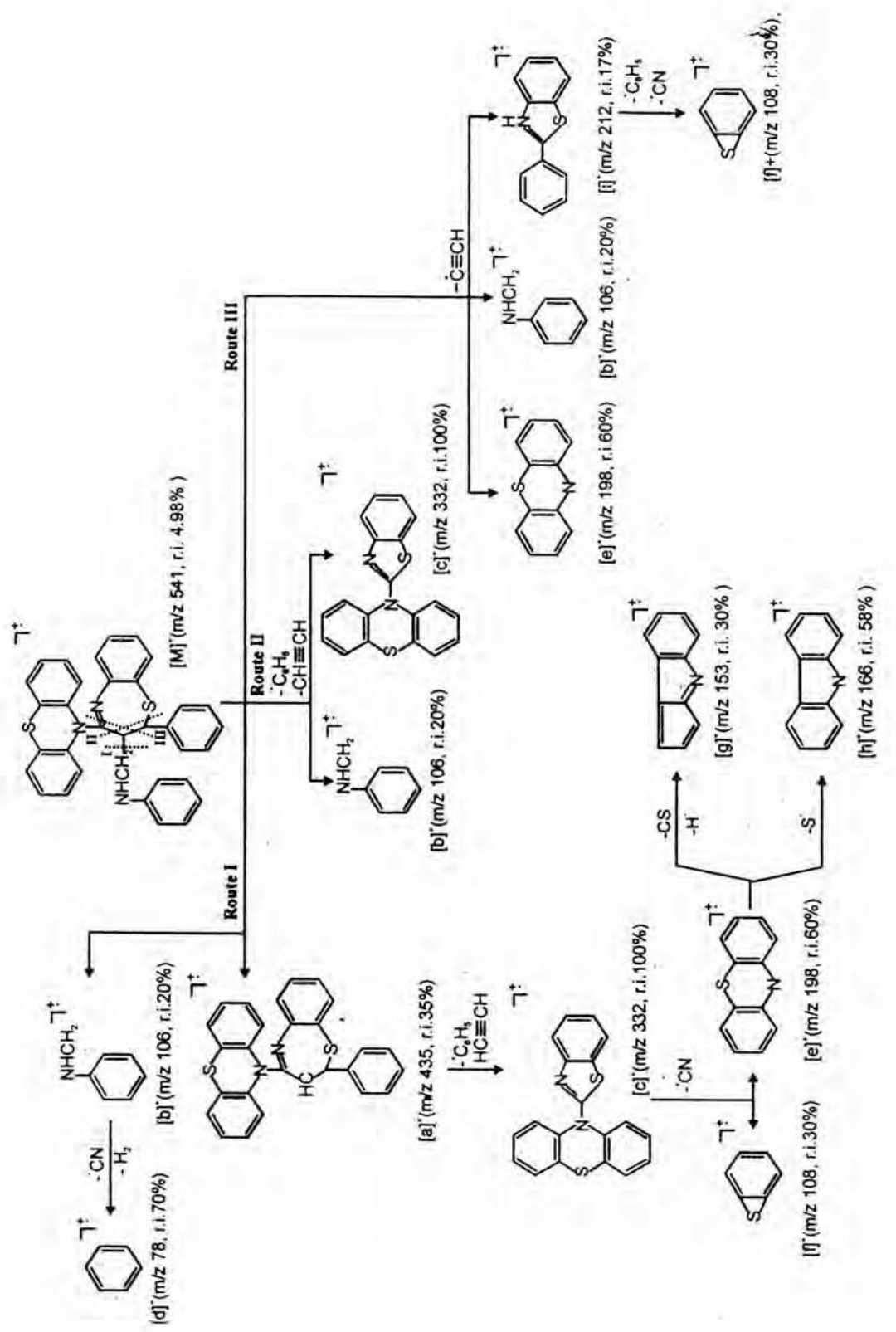
***N*-[2-aryl-2, 3-dihydro-1, 5-benzothiazepin-4-yl]phenothiazine 3a.** To the solution of compound **2a** (0.02 mole) in methanol, 2-aminobenzenethiol (0.02 mole) and few drops of glacial acetic acid were added. The reaction mixture was refluxed for 3-4 hr, distilled under reduced pressure and cooled. The separated solid was recrystallized with MeOH/Water to give **3a:** yield 65%, m.p. 204°; IR (Nujol): 1665 (C=N), 1565 (C ═ C of aromatic ring), 1462 (C-N), 700 (C-S-C) cm^{-1};[1] H NMR ($CDCl_3$): δ 7.70 (d, 2H, C_3-H_2 of thiazepine ring), 7.50-6.70 (m, 17H, Ar-*H*), 6.40 (t, 1H, C_2-*H* of thiazepine ring). MS: m/z (%): 436 (4.5) M^+, 332 (100), 225 (65), 212 (20), 198 (81), 166 (60), 153 (38), 108 (35), 104 (55), 78 (68).

***N*-[2-aryl-3-arylaminomethylene-2, 3-dihydro-1, 5-benzothiazepin-4-yl]phenothiazine 4a.** To the solution of compound **3a** (0.01 mole) in methanol (50 mL), formaldehyde (0.02 mole) and aniline (0.02 mole) were added and refluxed for 4-6 hr, distilled and poured onto ice. The solid thus obtained was washed with petroleum ether (40°-60°) and recrystallized with DMF/water to give **4a:** yield 73%, m.p. 198°; IR(KBr): 1690 (C=N), 1510 ((C ═ C of aromatic ring), 1465 (C-N), 741 (C-S-C) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.70 (dd, 1H, C_3-*H* of thiazepine ring), 6.48 (d, 1H, C_2-*H* of thiazepine ring), 6.60-7.00 (m, 22H, Ar-*H*), 3.08 (bs, 1H, N*H*CH_2), 1.65 (m, 2H, NHCH_2). MS: m/z (%): 541 (6.8) M^+, 435 (35), 332 (100), 212 (17), 198 (60), 166 (58), 153 (30), 108 (30), 106 (20), 78 (70). The mass spectral fragmentation pattern of this compound is given in **Scheme II**.

Biological evaluation

The compounds **2a-d**, **3a-d**, **3a'-d'**, **4a-p** and **4a'-p'** were screened for their psychotropic activities by induction of catalepsy[10], amphetamine antagonism[10], seizure protection test[11] and for their acute toxicity[9]. Compounds were administered interaperitoneally (i.p.) as solution in propylene glycol (0.5 mL) at 40 mg/kg dose. Whereas compound **4i**, being the most potent compound of this series, was tested at 20, 40 and 80 mg/kg.

The experiments were performed on albino rats of either sex weighing 100-120 g in the group of 5 animals each for amphetamine antagonism, induction of catalepsy and group of 10 animals for seizure protection test. Haloperidol was used as reference drug for


Route I
Route II
Route III
[M]+(m/z 541, r.i. 4.98%)
[a]+(m/z 435, r.i.35%)
[b]+(m/z 106, r.i.20%)
[c]+(m/z 332, r.i.100%)
[d]+(m/z 78, r.i.70%)
[e]+(m/z 198, r.i.60%)
[f]+(m/z 108, r.i.30%)
[g]+(m/z 153, r.i. 30%)
[h]+(m/z 166, r.i. 58%)
[i]+(m/z 212, r.i.17%)
-·CN
-H·
-CS
-S·
-·C6H5
HC≡CH
-·C6H4
-CH≡CH
-·C≡CH
-·C2H3

Scheme II

Table I—Physicochemical properties and psychotropic activities of compound **2a-d, 3a-d, 3a´-d´, 4a-p** and **4a´-p´**

Compd	R	R'	X	m.p. (°C)	Yield (%)	Recrystallization. solvent	Cataleptic behaviour mean score±S.E.	Amphetamine induced SB mean score±S.E.	MES % seizure protection
							60	0-60	
2a	H	-		168	70	Ethanol	0.4 ± 0.24	2.6 ± 1.00	20
2b	4-OCH_3	-		188	72	Methanol	0	2.8 ± 0.98	0
2c	4-$N(CH_3)_2$	-		166	75	Ethanol	0	2.0 ± 0.75	0
2d	4-OH, 3-OCH_3	-		180	70	Methanol	0	2.2 ± 1.65	20
3a	H	-	S	204	65	Methanol/water	1.0 ± 0.20*	1.0 ± 0.98	40
3b	4-OCH_3	-	S	210	70	Ethanol	1.0 ± .40	1.6 ± 0.71	20
3c	4-$N(CH_3)_2$	-	S	206	68	DMF/Water	1.2 ± 0.24*	1.0 ± 1.03	60*
3d	4-OH, 3-OCH_3	-	S	222	72	Benzene	1.0 ± 0.24*	1.2 ± 0.24**	60*
3a'	H	-	O	214	72	Ethanol/water	0.8 ± 0.20	1.6 ± 0.51*	20
3b'	4-OCH_3	-	O	226	70	Ethanol	0.4 ± 0.51	1.8 ± 0.20*	20
3c'	4-$N(CH_3)_2$	-	O	190	68	Benzene	0	1.4 ± 1.24	40
3d'	4-OH, 3-OCH_3	-	O	238	60	Benzene	0	1.6 ± 1.30	20
4a	H	H	S	198	73	DMF/water	1.2 ± 0.24*	0.0	40
4b	H	2-Cl	S	196	68	Methanol	1.0 ± 0.40	0.4 ± 0.28**	50*
4c	H	3-Cl	S	204	68	Benzene	0.8 ±0.56	0.2 ± 1.00*	40
4d	H	2-OCH_3	S	192	65	Benzene/pet. ether	1.0 ± 0.86*	0.2 ± 1.16	70**
4e	4-OCH_3	H	S	214	72	Ethanol/water	1.2 ± 1.00*	0.0	20
4f	4-OCH_3	2-Cl	S	210	70	Methanol	0.4 ± 0.28	0.0	50
4g	4-OCH_3	3- Cl	S	220	74	DMF/water	0.8 ± 0.40*	0.2 ± 0.86*	20
4h	4-OCH_3	2-OCH_3	S	218	70	Benzene	1.0 ± 0.20	0.2±1.16	70**
4i	4-$N(CH_3)_2$	H	S	216	74	Ethanol	0.6±0.20	1.2±0.24**	70**
							1.0±0.40*	0.0	80**
							1.4±0.24**	0.0	80**
4j	4-$N(CH_3)_2$	2-Cl	S	219	67	Benzene/pet. ether	1.6 ± 0.71*	0.4 ± 0.66*	60*
4k	4-$N(CH_3)_2$	3-Cl	S	222	65	DMF/water	1.6 ± 0.20*	0.4 ± 1.03	50*
4l	4 -$N(CH_3)_2$	2-OCH_3	S	228	60	Benzene	1.4 ± 0.24**	0.0	70**
4m	4-OH, 3-OCH_3	H	S	224	70	Ethanol	1.0 ± 0.40*	0.0	40
4n	4-OH, 3-OCH_3	2-Cl	S	214	68	Methanol/water	1.2 ± 0.24*	0.4 ± 0.51**	60*
4o	4-OH, 3-OCH_3	3-Cl	S	212	65	Benzene/pet. ether	1.0 ± 0.40*	0.6 ± 0.28**	40
4p	4-OH, 3-OCH_3	2-OCH_3	S	215	68	Ethanol/water	1.0 ± 0.24*	0.4 ± 0.24**	60*
4a'	H	H	O	230	70	DMF/water	1.2 ± 0.71*	0.0	40
4b'	H	2-Cl	O	226	72	Ethanol/water	1.2 ± 0.28*	0.8 ± 0.37**	40
4c'	H	3-Cl	O	228	65	Methanol	0.8 ± 0.37	0.2 ± 0.71*	30
4d'	H	2-OCH_3	O	232	60	Ethanol/water	0.8 ± 0.24	0.2 ± 1.00*	60*
4e'	4-OCH_3	H	O	224	70	Ethanol/water	1.2 ± 0.20**	0.2 ± 0.56**	40
4f'	4-OCH_3	2-Cl	O	213	70	Methanol/water	1.2 ± 0.40**	0.4 ± 1.00	50*
4g'	4-OCH_3	3-Cl	O	221	68	Methanol	1.0 ± 0.28*	0.4 ± 1.03	20
4h'	4-OCH_3	2-OCH_3	O	225	65	Benzene	0.8 ± 0.37	0.2 ± 0.56**	40
4i'	4-$N(CH_3)_2$	H	O	202	62	Chloroform	1.8 ± 0.20	0.0	70**

—Contd

Table I—Physicochemical properties and psychotropic activities of compound **2a-d, 3a-d, 3a´-d´, 4a-p** and **4a´-p´**—*Contd*

Compd	R	R'	X	m.p. (°C)	Yield (%)	Recrystallization. solvent	Cataleptic behaviour mean score±S.E.	Amphetamine induced SB mean score±S.E.	MES % seizure protection
4j'	4-$N(CH_3)_2$	2-Cl	O	200	68	DMF/water	1.2 ± 0.20	0.2 ± 0.56**	80**
4k'	4-$N(CH_3)_2$	3-Cl	O	207	72	Benzene/pet. ether	1.0 ± 0.24*	0.4 ± 1.03	50
4l'	4 -$N(CH_3)_2$	2-OCH_3	O	215	70	Benzene	1.2 ± 0.40*	0.2 ± 0.56**	80**
4m'	4-OH, 3-OCH_3	H	O	235	68	Methanol/water	1.0 ± 0.26*	0.8 ± 0.51*	40
4n'	4-OH, 3-OCH_3	2-Cl	O	232	65	DMF/water	0.8 ± 0.20*	0.6 ± 0.98	60*
4o'	4-OH, 3-OCH_3	3-Cl	O	238	62	Benzene	0.4 ± 0.28	0.2 ± 1.03	60*
4p'	4-OH, 3-OCH_3	2-OCH_3	O	242	70	Methanol	0.8 ± 0.28	0.4 ± 1.00	60*
Propylene glycol	-	-	-	-	-	-	0.0	3.8 ± 0.37	0
Haloperidol	-	-	-	-	-	-	2.0±0.20**	-	-
Chlorpromazine	-	-	-	-	-	-	-	0	-
Phenytoin Sodium	-	-	-	-	-	-	-	-	80**

induction of catalepsy, Chlorpromazine was used as reference drug for amphetamine antagonism and Phenytoin sodium was used as reference drug for seizure protection test.

As shown in the results (**Table I**), the compounds **2a-d** did not show any marked response towards cataleptic behaviour and seizure protection test but showed good reduction in amphetamine induced stereotyped behaviour. It was noted by the next step compounds that benzothiazepine series has better enhancement in psychotropic properties than the benzoxazepine analogues. The Mannich products **4a-p/4a´-p´** showed potent results towards amphetamine antagonism and anticonvulsant activities. The compound **4i,** being most potent, compound of this series, was found to be equipotent with the reference drugs except for cataleptic behaviour. ALD_{50} of all the compounds is >1000 mg/kg p.o., except for compound **4i**. Where its value is >1600 mg/kg p.o.

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