SYNTHESIS OF *trans*-2-[N-(2-HYDROXY-1,2,3,4-TETRAHYDRO-NAPHTHALENE-1-YL)]IMINOTHIAZOLIDINE AND RELATED COMPOUNDS — A NEW CLASS OF ANTIDEPRESSANTS*

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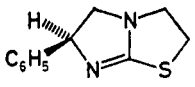
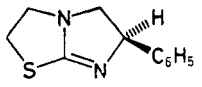
Dedicated to Dr Miroslav Protiva on the occasion of his 70th birthday.

Antiparasitic and antidepressant activities exhibited by tetramisole (*I*) and its enantiomers prompted the study of its structural analogs *trans*-2-[N-(2-hydroxy-1,2,3,4-tetrahydronaphthalene/indane-1-yl)]iminothiazolidine (*VIII*/*IX*) and 2,3,4a,5,6,10b-hexahydronaphtho[1′,2′ : 4,5]-imidazo[2,1-*b*]thiazole (*XII*), 2,3,4a,5-tetrahydro-9b*H*-indeno[1′,2′ : 4,5]imidazo[2,1-*b*]thiazole (*XIII*), and 2,3,4a,5-tetrahydro-9b*H*-indeno[1′,2′ : 4,5]imidazo[2,1-*b*]thiazole (*XVI*), and a homolog 3,4,6,7-tetrahydro-7-phenyl-2*H*-imidazo[2,1-*b*]-1,3-thiazine (*XX*). While none of these compounds showed any noteworthy antiparasitic activity, the *trans*-2-[N-(2-hydroxy-1,2,3,4-tetrahydronaphthalene-1-yl]iminothiazolidine (*VIII*) has shown marked antidepressant activity, better than imipramine in the tests used, and provides a new structural lead for antidepressants.

The 6-phenyl-2,3,5,6-tetrahydroimidazo[2,1-*b*]thiazole (*I*, tetramisole[1,2]) is known for its antiparasitic activity. The activity is mainly confined to its 6*S*-(−) enantiomer (levamisole) while the 6*R*-(+) enantiomer (dexamisole) has more positive ionotropic and chronotropic effects than levamisole on heart muscles in vitro and in vivo. It has antidepressant action and has shown mood elevating effects in men[3-9]. In search o



S(-)
Levamisole



R(+)
Dexamisole

Tetramisole
I

new structural leads for potential antidepressant and antiparasitic agents it ap-

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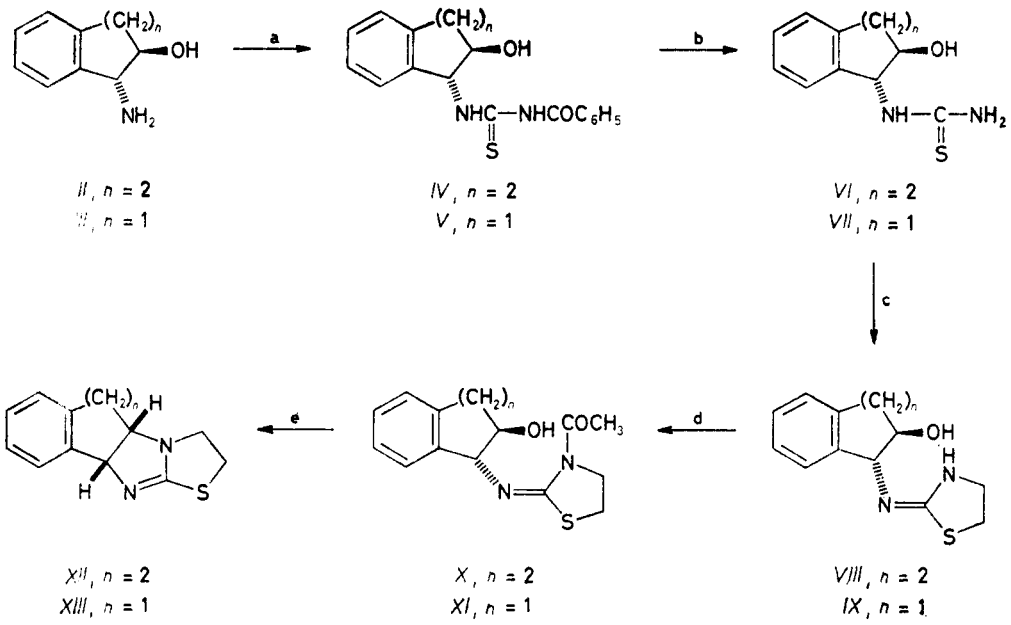
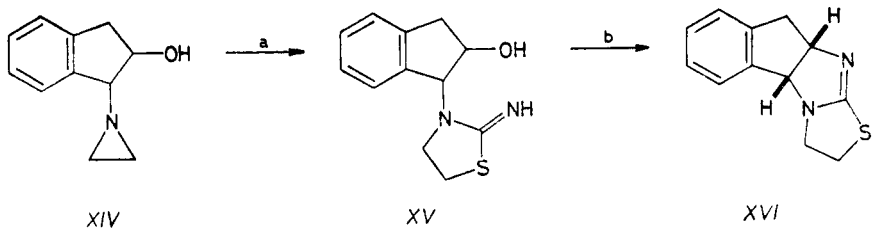
peared of interest to explore the title compounds and semirigid analogs of *I*: *XII*, *XIII*, *XVI*, and *XX* (see Schemes 1–3), for their CNS and antiparasitic activities.



II, *n* = 2
III, *n* = 1
IV, *n* = 2
V, *n* = 1
VI, *n* = 2
VII, *n* = 1
VIII, *n* = 2
IX, *n* = 1
X, *n* = 2
XI, *n* = 1
XII, *n* = 2
XIII, *n* = 1

a) C_6H_5CONCS, Me_2CO; b) NaOH; c) $Br(CH_2)_2NH_2$, HBr, EtOH; d) $(CH_3CO)_2O$, MeOH; e) $SOCl_2$, C_6H_6

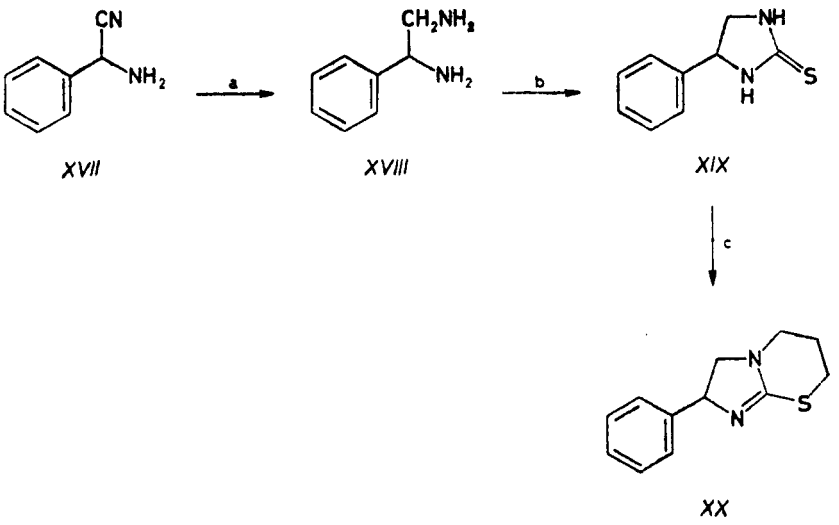
SCHEME 1



XIV *XV* *XVI*

a) NH_2CSNH_2, EtOH, HCl; b) $SOCl_2$, Na_2CO_3

SCHEME 2



XVII *XVIII* *XIX* *XX*

a) $LiAlH_4$, THF ; **b)** CS_2, EtOH ; **c)** $Cl(CH_2)_3Br$, $NaHCO_3$

SCHEME 3

EXPERIMENTAL

All melting points were taken on Towson and Mercer apparatus and are uncorrected. Each compound has been checked for its structure by IR (Perkin–Elmer 137, 337, 177 spectrometers, KBr technique, $\tilde{\nu}$ in cm^{-1}) and NMR (Varian A60D, R-32 spectrometers, $(CD_3)_2SO$ as a solvent, in ppm, δ scale) spectra. The compounds were analyzed for C, H, N and the values were within $\pm 0{\cdot}4\%$ of theoretical values. The purity of the compounds was monitored by thin-layer chromatography using silica gel or alumina (basic, neutral) plates.

trans-N-(2-Hydroxy-1,2,3,4-tetrahydronaphthalene-1-yl)-N′-benzoyl Thiourea (*IV*)

Benzoyl isothiocyanate (4·38 g, 27 mmol) in dry acetone (25 ml) was added dropwise to a stirred solution of *trans*-1-amino-1,2,3,4-tetrahydronaphthalene-2-ol (*II*; 4·35 g, 27 mmol) in dry acetone (50 ml) at room temperature. After complete addition, the reaction mixture was refluxed for 1 h, poured onto ice-water, the solid thus separated was filtered and dried to give *IV*, recrystallized from ethanol; yield 7·842 g (80%), m.p. 140–141°C. IR: 3 300, 1 672, 1 261, 1 179, 1 072. ^{1}H NMR: 1·90 m, 2 H (3-CH_2); 2·80 t, 2 H (4-CH_2, $J = 6$ Hz); 4·00 m, 1 H (2-CH); 5·50 d, 1 H (1-CH, $J = 7$ Hz); 6·90–7·60 m, 7 H (ArH); 7·85 m, 2 H (ArH adjacent to C=O). For $C_{18}H_{18}N_2O_2S$ (326·4) calculated: 66·27% C, 5·52% H, 8·59% N; found: 66·50% C, 5·74% H, 8·10% N.

trans-N-(2-Hydroxyindane-1-yl)-N′-benzoyl Thiourea (*V*)

It was prepared in 83% yield as described for *IV*, m.p. 185–187°C. IR: 3 300, 1 686, 1 645, 1 497, 1 180. For $C_{17}H_{16}N_2O_2S$ (312·3) calculated: 65·37% C, 3·24% H, 8·94% N; found: 65·80% C, 3·64% H, 9·10% N.

trans-N-(2-Hydroxy-1,2,3,4-tetrahydronaphthalene-1-yl) Thiourea (*VI*)

Compound *IV* (7·172 g, 22 mmol) was gradually added to a boiling solution of NaOH (5 g in 45 ml H_2O). The reaction mixture was heated and stirred for another 1 h. After cooling, the separated solid was filtered, washed with water and dried. The filtrate on acidification with concentrated HCl followed by basification (NH_4OH) gave additional small amount of solid product, crystallized from ethanol to give *VI*; yield 4·102 g (84%), m.p. 203–205°C. IR: 3 145, 1 631, 1 543, 1 060, 779. For $C_{11}H_{14}N_2OS$ (222·8) calculated: 59·46% C, 6·31% H, 12·61% N; found: 59·12% C, 6·54% H, 12·24% N.

trans-N-(2-Hydroxyindane-1-yl) Thiourea (*VII*)

It was obtained in 76% yield by the method as described for compound *VI*, crystallized from ethanol, m.p. 198–200°C. IR: 3 300, 1 640, 1 550, 1 070. For $C_{10}H_{12}N_2OS$ (208·2) calculated: 57·69% C, 5·76% H, 13·46% N; found: 57·55% C, 5·78% H, 13·58% N.

trans-2-[N-(2-Hydroxy-1,2,3,4-tetrahydro-1-naphthalene-1-yl)]iminothiazolidine (*VIII*)

A mixture of compound *VI* (2·22 g, 10 mmol) and β-bromoethylamine hydrobromide (30 g, 14 mmol) in ethanol (50 ml) was refluxed for 36 h under stirring, filtered and excess of ethanol was removed under reduced pressure. The residue was diluted with water, basified (NaOH) and the solid substance was filtered to give *VIII*, crystallized from ethanol, yield 1·314 g (53%), m.p. 169–170°C. ^{1}H NMR: 1·68 m, 2 H (3-CH_2); 2·65 t, 2 H (4-CH_2); 3·14 t, 2 H (N—CH_2); 3·76 t, 2 H (S—CH_2); 4·00 m, 1 H (CH—OH); 4·55 d, 1 H (=N=C—H), J = 7 Hz); 7·05 m, 4 H (ArH). For $C_{13}H_{16}N_2OS$ (248·5) calculated: 62·90% C, 6·45% H, 11·29% N; found: 62·54% C, 6·45% H, 11·08% N.

trans-2-[N-(2-Hydroxyindane-1-yl)]iminothiazolidine (*IX*)

It was obtained in 56% yield, as described above for compound *VIII*, crystallized from ethanol, m.p. 180–181°C. IR: 3 250, 3 010, 1 610, 1 540, 1 240, 1 080. For $C_{12}H_{14}N_2OS$ (234·3) calculated: 61·55% C, 5·98% H, 11·96% N; found: 62·00% C, 5·74% H, 11·46% N.

trans-2-[(2-Hydroxy-1,2,3,4-tetrahydronaphthalene-1-yl)] imino-3-acetyl Thiazolidine (*X*)

A mixture of compound *VIII* (1·736 g, 7 mmol), acetic anhydride (820 mg, 8 mmol) and methanol (20 ml) was refluxed for 7 h on a steam bath. After removing the solvent under reduced pressure, the residue was taken in ether, washed with H_2O, dried over Na_2SO_4 and concentrated to give *X* as a white solid which was crystallized from ethanol, yield 1·989 g (98%), m.p. 180–182°C. IR: 3 190, 1 670, 1 080, 770. ^{1}H NMR: 1·80 m, 5 H (N—$COCH_3$ and 3-CH_2); 2·75 t, 2 H (4-CH_2); 3·24 t, 2 H (N—CH_2); 3·85 t, 2 H (S—CH_2); 4·45 b, 2 H (CH—OH); 4·68 d, 1 H (=N—CH, J = 6 Hz); 7·15 m, 4 H (ArH). For $C_{15}H_{18}N_2O_2S$ (290·1) calculated: 62·07% C, 6·25% H, 9·65% N; found: 62·47% C, 6·52% H, 10·01% N.

trans-2-[N-(2-Hydroxyindane-1-yl)]imino-3-acetylthiazolidine (*XI*)

It was synthesized similarly by acetylation of compound *VIII* in 98% yield, crystallized from ethanol, m.p. 145–147°C. IR: 3 150, 1 675, 1 095, 760. For $C_{14}H_{16}N_2O_2S$ (276·4) calculated: 60·87% C, 5·80% H, 10·14% N; found: 61·00% C, 5·90% H, 9·98% N.

trans-4a-10b-*cis*-2,3,4a,6,6,10b-Hexahydronaphtho(1′,2′ : 4,5)- imidazo[2,1-*b*]thiazole (*XII*)

The compound *X* (2·610 g, 9 mmol) was added portionwise to a stirred solution of $SOCl_2$ (5 ml) at 0°C. The resulting mixture was stirred for 24 h at room temperature, concentrated under reduced pressure and residue was refluxed in dry benzene (20 ml) for 6 h. The hydrochloride of compound *XII* thus formed, was filtered and washed with dry ether, yield 99·4 mg (48%), m.p. 202–204°C; free base crystallized from ethanol, m.p. 95°C. IR: 2 900, 1 630, 1 030, 750. ^{1}H-NMR ($CDCl_3$): 2·3 m, 2 H (5-CH_2); 2·9 m, 2 H (6-CH_2); 3·35 t, 2 H (3-CH_2); 4·05 t, 2 H (2-CH_2); 4·85 q, 1 H (4a-CH, J = 8·0 and 4·0 Hz); 5·35 d, 1 H (10b-CH, J = 4·0 Hz); 7·30 m, 4 H (ArH). For $C_{13}H_{14}N_2S$ (230·6) calculated: 67·82% C, 6·08% H, 12·17% N; found: 68·04% C, 6·20% H, 12·04% N. MS: M^+ 230.

4,4a-*trans*-4a,9b-*cis*-2,3,4a,5-Tetrahydro-9b*H*-indeno[1′,2′ : 4,5]imidazo[2,1-*b*]thiazole (*XIII*)

This compound was synthesized according to the procedure described for hydrochloride of *XII* crystallized from absolute ethanol–ether, yield 63%, m.p. 210°C; free base crystallized from ethanol, m.p. 85°C. IR: 2 830, 1 640, 1 340, 1 025, 760. ^{1}H NMR ($CDCl_3$): 3·40 m, 4 H (5-CH_2 and 3-CH_2); 4·10 t, 2 H (2-CH_2); 5·10 dt, 1 H (4a-H, J = 5·5 and 2·0 Hz); 5·50 d, 1 H (9b-H, J = 5·5 Hz); 7·28 s, 4 H (ArH). For $C_{12}H_{12}N_2S$ (216·2) calculated: 66·67% C, 5·56% H, 12·96% N; found: 66·40% C, 5·68% H, 13·00% N. MS: M^+ 216.

2-Imino-3-(2-hydroxyindane-1-yl)thiazolidine (*XV*)

A solution of 1-(1-aziridinyl)-2-indanol[10] (*XIV*; 2·5 g, 14 mmol) in ethanol was added dropwise to a stirred solution of thiourea (1·1 g, 14 mmol) in ethanol (10 ml) containing concentrated HCl (0·3 ml) at room temperature. After the addition, the reaction mixture was refluxed for 18 h, cooled, filtered, excess of ethanol was removed under reduced pressure, diluted with water, basified with 5% NaOH and reaction mixture worked up in the usual manner. The residue was crystallized from ethanol, yield 2·5 g (76%), m.p. 160°C. IR: 3 150, 1 590, 1 260, 1 095, 758. ^{1}H NMR ($CDCl_3$): 2·66–3·66 m, 6 H (3-CH_2, N—CH_2 and S—CH_2); 4·40–4·80 d, 1 H (1-CH, J = 6 Hz); 7·20 s, 4 H (ArH). For $C_{12}H_{14}N_2OS$ (234·4) calculated: 61·53% C, 5·98% H, 11·96% N; found: 61·45% C, 6·24% H, 11·79% N.

4,4a-*trans*-4a,9b-*cis*-2,3,4a,5-Tetrahydro-9b*H*-indeno[1′,2′ : 4,5]imidazo[2,1-*b*]thiazole (*XVI*)

Thionyl chloride (0·6 g, 5 mmol) in dry $CHCl_3$ (5 ml) was added dropwise to a stirred solution of compound *XV* (1 g, 4 mmol) in dry $CHCl_3$ (10 ml) at room temperature. After stirring for 24 h at room temperature, the reaction mixture was refluxed for 2 h, solvent was removed under reduced pressure and the residue was washed with dry ether. The residue was suspended in 1M-Na_2CO_3 solution (10 ml), heated on steam bath and worked up in usual manner. The oily substance thus obtained was purified by column chromatography using basic alumina column and benzene as eluant; yield 400 mg (44%), m.p. 112–114°C. ^{1}H NMR ($CDCl_3$): 2·9 m, 4 H (3,9-CH_2); 3·2 m, 2 H (2-CH_2); 4·30 d, 1 H (4a-CH, J = 5·0 Hz); 4·90 q, 1 H (9a-H, J = 8·0 and 4·0 Hz); 7·30 m, 4 H (ArH). For $C_{12}H_{12}N_2S$ (248·2) calculated: 66·67% C, 5·56% H, 12·96% N; found: 67·00% C, 5·40% H, 12·50% N.

4-Phenyl-4,5-dihydro-1*H*-imidazol-2-thione (*XIX*)

Carbon disulfide (2·1 g, 27 mmol) was added to a solution of 1-phenylethylenediamine (*XVIII*; 3·7 g, 27 mmol) in 80% aqueous ethanol (40 ml) in one lot. The reaction mixture was refluxed

for 1 h and concentrated HCl (0·5 ml) was added. The reaction mixture was further refluxed for 7 h, it was cooled to 30°C and left for 15 h. The separated solid was filtered, washed with water, dried and crystallized from ethanol, yield 2·8 g (60%), m.p. 191–193°C (ref.[11], m.p. 191 to 193·5°C).

7-Phenyl-3,4,6,7-tetrahydro-2*H*-imidazo[2,1-*b*]-(1,3)-thiazine (*XX*)

A mixture of compound *XIX* (1 g, 5 mmol), aqueous KOH (2·5 ml, 20%), 1-chloro-3-bromopropane (2·5 ml), isopropyl alcohol (30 ml) and $NaHCO_3$ (2–3 g) was refluxed for 3 h. The reaction mixture was concentrated and the residue was treated with 15% KOH to give *XX*, crystallized from ethanol, yield 600 mg (50%), m.p. 103–104°C. IR: 2 900, 1 600, 1 410, 1 240, 780. ^{1}H NMR ($CDCl_3$): 1·10–1·30 m, 2 H (3-CH_2); 1·75–2·30 m, 4 H (4,6-CH_2); 2·78–3·35 m, 3 H (2-CH_2 and 7-CH); 7·15 s, 5 H (ArH). For $C_{12}H_{14}N_2S$ (218·2) calculated: 66·04% C, 6·42% H, 12·84% N; found: 66·00% C, 6·50% H, 12·30% N.

RESULTS AND DISCUSSION

The thiazoles *XII* and *XIII* were synthesized as described in Scheme 1. The stereochemistry of key intermediates *II* and *III* was assigned according to refs[12–15]. In ^{1}H NMR spectrum of compound *XII*, 4a-H appeared as a quartet at 4·85 (J = 8·0 and 4·0 Hz) and 10b-H appeared as a doublet at 5·35 (J = 4·0 Hz). Compound *XII* showed bands in the region of 2 700–2 900 cm^{-1} (Bohlmann band[16–18]) in the IR spectrum which is indicative of relative *trans* arrangement of unpaired electron pair of the bridgehead nitrogen at position 4 and hydrogen of the bridgehead carbon at position 4a. These values corresponded with the theoretical J values obtained from Karplus equation in case of 4a,10b-*cis* arrangement with half-boat conformation, suggesting 4,4a-*trans*-4a,10b-*cis* stereochemistry with half-boat conformation for compound *XII*. In the ^{1}H NMR spectrum of compound *XIII*, 9b-H appeared as a doublet at 5·5 (J = 5·5 Hz) and 4a-H appeared as a sextet at 5·1 (J = 5·5, 5·5, and 2·0 Hz). The coupling constant of 5·5 Hz between 4a-H and 9b-H favours *cis* arrangement at these ring junction. The IR spectrum of compound *XIII* showed Bohlmann bands in the region 2 700–2 900 cm^{-1} which is indicative of *trans* arrangement between unshared electron pair of the bridgehead nitrogen at position 4 and the hydrogen of bridgehead carbon at position 4a. In view of these observed values compound *XIII* has been assigned 4,4a-*trans*-4a,9b-*cis* geometry.

The synthesis of thiazole *XVI* was carried out according to the method outlined in Scheme 2. The 1-aziridinyl-indan-2-ol (*XIV*), required as starting material, was obtained by treatment of 2-bromoindan-1-ol with KOH in dioxane[19] followed by the reaction with aziridine as reported in literature[10]. In the ^{1}H NMR spectrum of compound *XVI*, the proton at position 4a appeared as a doublet at 4·3 (J = = 5·0 Hz) whereas proton at position 9a appeared as a quartet at 4·9 (J = 8·0 and 4·0 Hz). In the IR spectrum compound *XVI* showed Bohlmann bands in the region

2 700–2 900 cm^{-1} and thus, like compound *XIII*, compound *XVI* has been assigned 4,4a-*trans* and 4a,9a-*cis* arrangement.

The synthesis of a homolog of tetramisole *XX* is outlined in Scheme 3. Starting compound *XVII* was obtained by the method of Matier[11,20].

Biological Activity

Gross behavioral effects and toxicity (ALD_{50}) of the compounds were studied in albino mice by intraperitoneal administration of the compounds suspended in gum

TABLE I
Pharmacological activity of the compounds

Compd.	ALD_{50} mg/kg, i.p. (mice)	Gross effects (mice)	Effect on blood pressure, change in mm Hg (min)	Special test
IV	>1 000	D	60[a] (30)	inhibited the response of acetylcholine, adrenaline, histamine and isoprenaline on cat blood pressure (25–50%); at 200 mg/kg showed 60% diuretic activity in rat
V	>1 000	D	–[b]	
VI	680	–[b]	20[c] (10)	
VII	680	–[b]	–[b]	
VIII	110	A	40[c] (30)	details given in Table II
IX	>1 000	–[b]	–[b]	
X	178	–[b]	–[b]	
XI	316	–[b]	–[b]	at 63 mg/kg antagonized reserpine induced ptosis and sedation in mice
XII	316	A	–[b]	at 63 mg/kg potentiated barbiturate hypnosis (100%) and antagonized reserpine induced ptosis and sedation (50%)
XIII	147	A	–[b]	at 30 mg/kg potentiated barbiturate hypnosis (100%) and antagonized reserpine induced ptosis and sedation (75%)
XV	316	–[b]	–[b]	at 63 mg/kg antagonized reserpine induced ptosis and sedation in mice

A antidepressant, D depressant. [a] Fall in blood pressure; [b] no effect; [c] rise in blood pressure.

accacia using five animals per dose. Effects on blood pressure and interaction with histamine, adrenaline, isoprenaline, and acetylcholine were studied in anaesthetized (pentabarbitone 35 mg/kg, *i.v.*) cats using 5 mg/kg of each compound.

Compounds showing promising CNS activity were further screened at 1/5 LD_{50} dose in mice against certain special CNS tests which includes pentobarbitone (40 mg/kg) hypnosis, antireserpine (2·5 mg/kg) anticonvulsant, antiamphetamine (5 mg/kg) conditioned avoidance response (rat) and anorexigenic activity. Compounds showing promising activity in these tests are indicated in Table I.

TABLE II

Activity of compound *VIII* in comparison to imipramine as given by various tests

Test mice	ED_{50}, mg/kg, i.p.	
	VIII	Imipramine
1. Toxicity test	110·90 ± 6·5	110·0
2. Reversal of reserpine syndrome	1·39 ± 0·002	4·0 ± 0·002
3. Reversal of tetrabenzene induced ptosis	1·87 ± 0·03	5·22 ± 0·002
4. Potentiation of spontaneous motor activity	2·15 ± 0·01	3·10 ± 0·003
5. Antagonism to reserpine induced emesis in pigeons	5·63 ± 0·005	5·68 ± 0·01
6. Antagonism to amphetamine induced toxicity in aggregoted mice	87·50 ± 2·83	174·0
7. Potentiation of yohimbine toxicity	1·32 ± 0·05	3·26 ± 0·08
8. Immobility test[a]	9·00 ± 1·79	8·80 ± 1·61
9. Antagonism to physostigmine induced lethality	>50·0	—
10. Antagonism to pilocarpine induced salivation	>50·0	—
11. Antagonism to tremarine induced hypothelmia, tremor and lacrimation	42·6 ± 2·63	—
12. Antagonism to nicotine induced	17·6 ± 1·83	—

[a] Indicated in min at a dose of 5·0 mg/kg, i.p.

In gross observations, compounds *IV* and *V* showed CNS depressant activity and compounds *XII* and *XIII* showed mild antidepressant activity while compound *VIII* exhibited significant antidepressant activity in comparison with standard drug imipramine. So it was evaluated in detail and compared with imipramine in reversal of reserpine syndrome, tetrabenzene induced ptosis and in potentiation of yohimbine toxicity (Table II). In each of these tests compound *VIII* showed a better profile of antidepressant activity than imipramine. The antidepressant activity was further confirmed by the immobility test[21] (Table II). Apart from these activities compound *VIII* showed weaker anticholinergic activity than imipramine. It exhibited α-adrenergic blocking activity on cat blood pressure which lasted for 3 h. In this preparation, a small dose (1 mg/kg) of the compound lowered the blood pressure whereas at high dose (2–5 mg/kg) it produced a biphasic response. Like imipramine it causes cardiac depression. The tyramine induced (50 μg/kg, *i.v.*) pressor response was more effectively blocked by compound *VIII* than by imipramine.

All the compounds were tested for their in vivo antifilarial activity against *Litomosoides carinii* infection in cotton rats. The compounds were administered intraperitonially daily for 6 days to infected animals and blood samples were examined for microfilarial count and compared with the microfilarial count before start of treatment. The animals were sacrificed on the 7th day post-treatment to find out any effect of the adult worms. None of the compounds showed microfilaricidal activity.

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