# 1-(4-Anilino) Morpholines/Piperidine and related compounds as CNS active agents.

RAJENDRA S.VARMA, RAM PRAKASH
AND C.R.PARSAD
*Chemistry Department, Lucknow University,*
*Lucknow - 226 007, India*
*Division of Pharmacology,*
*Central Drug Research Institute,*
*Lucknow-226001, India*

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**Summary:** "The reaction of 1-(4-anilino) morpholine/piperidine (I) with carbon disulfide, chloroacetic acid and hydrazine hydrate in ethanol yielded 4-(N-morpholino/piperidino)- phenylthiosemicarbazide (II) which on condensation with carbonyl compounds such as benzaldehyde, isatin, N-methylisatin furnished (VI),(VII) and (VIII) respectively. Treatment of (II) with sodium nitrite and hydrochloric acid afforded 5- 4-(N-morpholino) -anilino- 1,2,3,4 thiatriazole (IX). (I )on condensation with ethyl chloroacetate followed by reaction with hydrazine hydrate afforded (III) which when treated with isatin, and N-methyl isatin, yielded (IV) & (V) respectively. 2-Methyl-3-(4-N-morpholino/piperidino)phenyl-4-quinazolinones (X) and 2-styryl-3-[4-N-morpholiinolpiperledinol] Phenyl-4- quinazolinones (XI) were also designed using I."

## Introduction

Substituted morpholines as well as piperidines exhibit antihypertensive, antiarrhythmic, anti- depressant, anticonvulsant and anxiolytic activities, [1-4]. In view of these wide ranging CNS responses it was considered of interest to incorporate 1-(4-anilino) morpholine/piperidine into various pharmacologically active moieties such as quinazolinones [5,6] and isatins [7,8].

The starting materials 1-(4-anilino) morpholine/piperidine (I) [9,10] were prepared by the condensation of p-chloronitrobenzene with morpholine and piperidine followed by reduction with Raney Ni/hydrazine hydrate [11].

(I) on treatment with ammonia and carbon disulfide followed by sodium salt of monochloroacetic acid and hydrazine hydrate yielded (II) [12]. Condensation of (II) with benzaldehyde, isatin, N-methyl isatin in methanol afforded (VI), (VII) & (VIII). (II) on cyclisation [13] with sodium nitrite and hydrochloric acid in water yielded IX.

Further condensation of (I) with ethyl chloroacetate in dry acetone and pot.carbonate followed by treatment with hydrazine hydrate yielded (III). Condensation of (III) with isatin, obtained in good yields by the Sandmeyer isonitrososynthesis [14] furnished (IV) & (V).

Part XLIV of the series Potential Biologically Active Agent.

Acetanthranil obtained from anthranilic acid and acetic anhydride when allowed to react with (I) yielded (X) which underwent smooth condensation with benzaldehyde yielding (XI).

The compounds have been characterized by I.R. NMR mass spectral data and correct elemental analysis.

The NMR ($\delta$ -scale) spectrum of XIb showed signals at 1.48 ($-(CH_2)_3$) and 3.2 $-N(CH_2)_2$. The signals due to vinylic protons centred at 6.43 (-N=C-CH=) and 7.86 (PhCH=) having a coupling constant J = 16 Hz indicated their trans geometry [15]. The aromatic protons were observed at 7 - 8.2.

*CNS activity*

Compounds of the series were screened for acute toxicity and CNS activity. The $ALD_{50}$ values of various compounds were determined in albino mice of either sex bred at CDRI Lucknow. Groups of 4 mice were taken for testing whereas one group of 4 mice served as control. Graded doses of the compounds were administered to test animals intraperitoneally using 2% gum acacia suspension as vehicle. The gross effects were obsrved for 3 hours and mortality was noted after 24 hours. The controls were given 2% gum acacia suspension only. The $ALD_{50}$ and confidence limits were calculated according to the method as described by H.J.Horn [16].

For their effect on the CNS, they were finally introduced in albino mice by the similar aforementioned procedure at 1/5 of their $ALD_{50}$ and changes in their spontaneous motor activity (SMA) and reaction to sound, touch and body temperature was recorded.

**Results and Discussion**

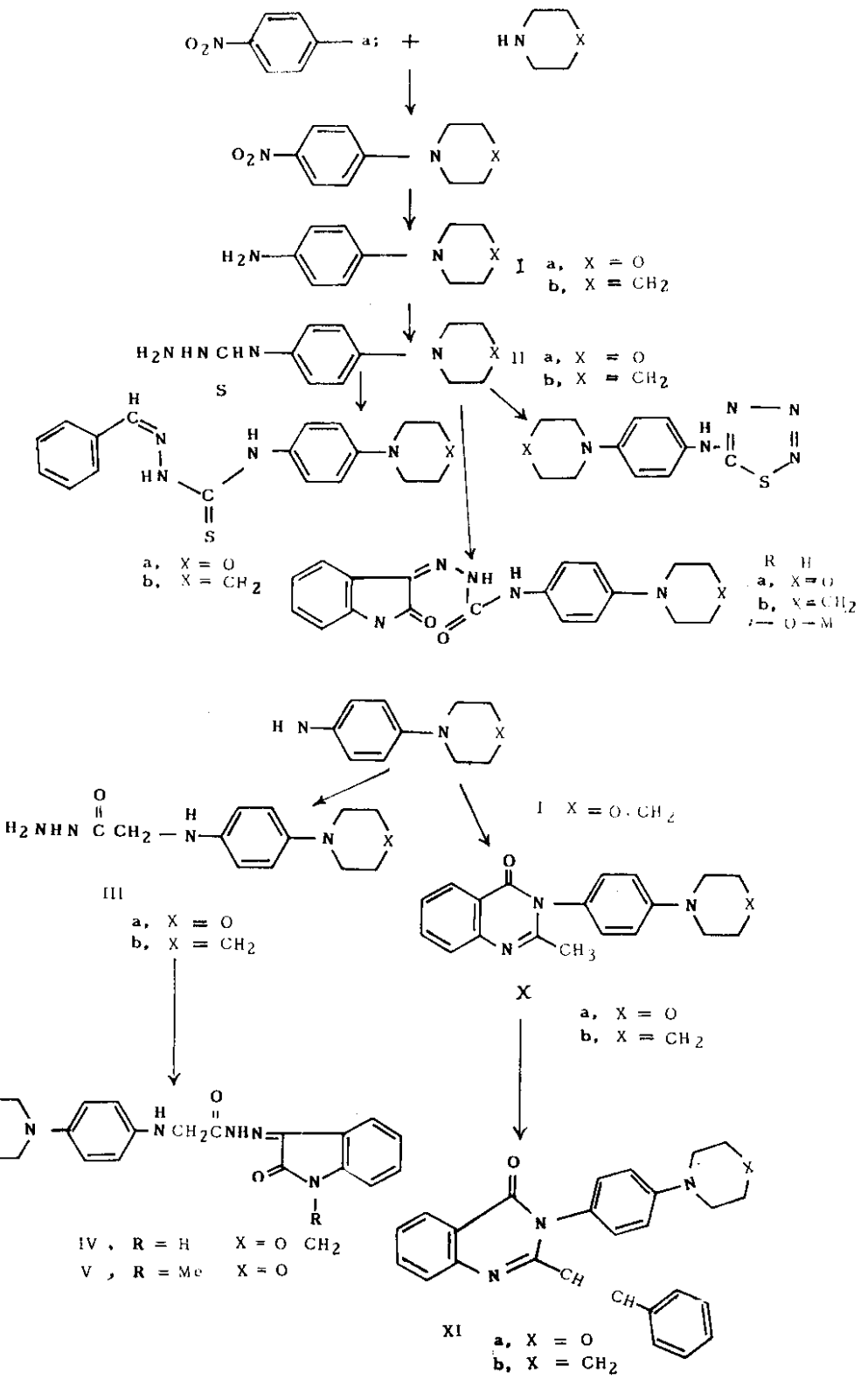
The results of the toxicity test and gross CNS observations are recorded in Table-1. All the compounds screened were found to be nontoxic ($ALD_{50}$ : 1000 mg/kg). It was observed that the compounds (VIa), (VIIa), (Xa) and (Xb) were stimulants while (VIII) was depressant, as they increased or decreased, the SMA and reactivity respectively. Few of the compounds induced writhing (twisting of belly) indicating their muscle relaxant behaviour. The compounds have also shown effect on the body temperature.

**Experimental**

Melting points were taken in a sulphuric acid bath and are uncorrected. Compounds were routinely checked for their homogeneity on silica gel.G TLC plates. IR spectra were recorded on Perkin-Elmer 157 spectrophotometer ( $\nu_{max}$ in $cm^{-1}$) in KBr. PMR spectra were taken in $CDCl_3$ on a varian A-600 at 60 MHz instrument using TMS as internal reference and mass spectra were obtained on a Jeol-JMS D 300 mass spectrometer at 70 eV.

*4-(N-Morpholino/piperidino)phenyl-thiosemicarbazide (II)*

To a solution of (I) (1.76 g, 0.01 mol) in ethanol was added ammonium hydroxide (2.8 ml sp.gr.0.88). The reaction mixture was cooled below 30°. Carbon disulfide (2 ml) was added during 15 minutes with shak-


I a, X = O
b, X = CH2
II a, X = O
b, X = CH2
a, X = O
b, X = CH2
III
a, X = O
b, X = CH2
I X = O, CH2
X
a, X = O
b, X = CH2
IV, R = H X = O CH2
V, R = Me X = O
XI
a, X = O
b, X = CH2

ing. After the dissolution of $CS_2$, it was allowed to stand for 1 hour and then an aqueous solution of sodium salt of monochloroacetic acid (0.94 g) was added. Hydrazine hydrate 99% (2 ml) was added with shaking. The reaction mixture was cooled and the product, that separated was filtered and recrystallized from chloroform.

(IIa) Yield 61% m.p. 167-68°
IR (KBr) [15]: 3100 ($NHNH_2$), 1100 (C-O-C), 1220 (C=S) (Found: C, 51.83: H, 6.06 $C_{11}H_{16}N_4OS$ requires C, 52.38; H, 6.34%).

(IIb): Yield 63%; m.p. 158-60° (Found: C, 58.0; H, 6.95 $C_{12}H_{18}N_2S$ requires C, 57.6; H, 7.2%)..

*4-(N-Morpholino/Piperidino phenyl)-glycyl hydrazide (III)*

(I) (1.76g 0.01 mole) and ethyl chloroacetate (1.5 ml;0.01 mol) were refluxed in dry acetone (10 ml) and anhydrous potassium carbonate (1.4 g) for 4 hours. At the end of the period $K_2CO_3$ was filtered off and the acetone was removed. The remaining ester was dissolved in 20 ml of methanol and refluxed with hydrazine hydrate (4 ml) for 2-3 hours. Solid that separated on cooling was filtered and recrystallized from methanol.

(IIIa): yield 58% m.p. 158-59° (Found: C, 57.3; H, 7.09; $C_{12}H_{18}N_4O_2$ requires C, 57.60; H, 7.20%).

Table-1: CNS Activity at 1/5 of $ALD_{50}$ dose

| Compd. No. | $ALD_{50}$ mg/kg(i.p) | SMA | Reactivity | Writhing | Hypothermia |
|---|---|---|---|---|---|
| (VIa) | >1000 | ↑ | ↑ | - | 0.5° |
| (VIIa) | >1000 | ↑ | ↑ | - | 0.8° |
| (VIII) | >1000 | ↓ | ↓ | + | 0.5° |
| (Xa) | >1000 | ↑ | ↑ | + | 0.4° |
| (Xb) | >1000 | ↑ | ↑ | + | 0.6° |

$ALD_{50}$ = Approximate lethal doses in 50% of animals tested.
SMA = Spontaneous motor activity
↑ = Increased
↓ = Decreased
- = No effect
+ = Present

(IIIb): yield 55%; m.p. 160-61° (Found C, 60.8; H, 8.08; N, 22.10; $C_{13}H_{20}N_4O_2.1/2\ H_2O$ requires C, 60.70; H, 8.17; N. 21.70)

*3-[4-(N-Morpholino/Piperidinophenyl)glycylhydrazono]-2-indolinone (IV)*

4-(N-Morpholino/Piperidinophenyl) glycyl hydrazide (2.32 g, 0.01 mol. and isatin (1.47 g, 0.01 mol) were refluxed in methanol (10 ml) containing 2-3 drops of gl. acetic acid for 4-5 hours. The solid which separated on cooling was filtered and recrystallised from methanol.

(IVa):yield 63%, m.p. 185-87° (Found: C, 63.5; H, 5.83 $C_{20}H_{21}N_5O_3$ requires C, 63.32; H, 5.54%).
(IVb): yield 60% m.p. 115-16° (Found: C, 66.70; H, 5.60 $C_{21}H_{23}N_5O_2$ requires C, 66.84%; H, 6.10%).

*1-Methyl 3-[4-(N-morpholino phenyl) glycyl hydrazono]-2-indolinone (V)*

It was prepared by the procedure described for (IV) using N-methylisatin in place of isatin. The product was recrystallised from chloroform-pet. ether (60-80°).

yield 58% m.p. 185-87° IR (KBr) [15], 3320 (NH), 1680 (C=O), 1100 (C-O-C) (Found: C, 64.0, H, 5.96, $C_{21}H_{23}N_5O_3$ requires C, 64.12; H, 5.85%).

*4-(N-Morpholino/Piperidino)phenyl benzaldehyde thiosemicarbazone (VI)*

4-(N-Morpholino/Piperidino) phenyl thiosemicarbazide (2.5 g, 0.01 mole) and benzaldehyde (1.2 ml) were refluxed in isopropyl alcohol (15 ml) with 2-3 drops of acetic acid for 3-4 hours. Solid product, separated on cooling was filtered and recrystallised from methanol.

(VIa): yield 56%; m.p. 165-66° (Found: C, 63.20; H, 5.88; $C_{18}H_{20}N_4OS$ requires C, 63.53; H, 5.88).

(VIb): yield 52%, m.p. 190° (Found: C, 67.81; H, 6.09: $C_{19}H_{22}N_4S$ requires C, 67.45; N, 6.50)

*3-[4-(N-Morpholino/Piperidino)phenyl thiosemicarbazono]-2-indolinone (VII)*

Isatin (1.479, 0.01 mole) and (II) (2.5 g, 0.01 mole) were refluxed in methanol (15 ml) for 2-3 hours. The solid product obtained on cooling was filtered and recrystallised from methanol.

(VIIa): yield 61% m.p. 200°d. (Found: C, 59.40: H, 4.80 $C_{19}H_{19}N_5O_2S$ requires C, 59.85; H, 4.98)

(VIIb): yield 60%; m.p. 215°d, IR (KBr) [15]; 3325 (NH), 1625 (C=O), 1240 (C=S) (Found: C, 63.70; H, 5.85, $C_{20}H_{21}N_5OS$ requires C, 63.32; H, 5.54).

*1-Methyl-3-[4-(-N-piperidino)phenyl thiosemicarbazono]-2-indolinone (VIII)*

(VIII) was prepared by the procedure described for (VII), using N-methyl isatin in place of isatin.

The product was recrystallised from chloroform pet.ether (60-80°), yield 55%; m.p. 200° (Found C, 64.4; H,

5.46; N, 17.34; $C_{21}H_{23}N_5OS$ requires C, 64,12: H, 5.85; N, 17.81).

*5-[4-(N-Morpholino)anilino]-1,2,3, 4-thiatriazole (IX)*

To the sitrred and cooled mixture of (IIa) (2.5g, 0.01 mol), hydrochloric acid (20 ml) and sodium nitrite (1 g) were added at 10-15° over 40 minutes. The solid turned rapidly reddish brown. It was filtered and recrystallised from methanol, yield 52%; m.p. 104-5°, IR(KBr) [15]; 3325 (NH), 1095 (C-O-C) (Found: C, 49.52; H, 4.56 $C_{11}H_{13}N_5OS$ requires C, 50.19; H, 4.94).

*2-Methyl-3-[4-(N-morpholino/Piperidino)Phenyl]-4-quinazolinone(X)*

Anthranilic acid (1.37 g; 0.01 mol) and acetic anhydride (8 ml) were refluxed for 2 hours. Excess of acetic anhydride was distilled off and to the resulting acetanthranil, (I) (1.6 g, 0.01 mol) was added. The reaction mixture was heated on a flame. The viscous mass was cooled and treated with methanol (10 ml). It was then filtered and recrystallised from methanol.

(Xa):yield 63% m.p. 168-70° (Found: C, 71.62; H, 6.10) $C_{19}H_{19}N_3O_2$ requires C, 71.02; H, 5.91).

(Xb): yield 60%; m.p. 260°d, MS; m/z 319 ($M^+$), 318, 218, 177,118. (Found: C, 74.83; H, 6.62, $C_{20}H_{21}N_3O$ requires C, 75.23; H, 6.58).

*2-Styryl-3-[4-(N-Morpholino/Piperidino)phenyl]-4-quinazolinone (XI)*

(X) (3.2 g, 0.01 mol) and benzaldehyde (2 ml) were refluxed in methanol (10 ml) for 2-3 hours. Solid separated on cooling was filtered and recrystallised from methanol.

(XIa): yield 45%, m.p. 233°,IR [15] KBr 1120 (C-O-C) 1685 (CO) (Found: C, 76.5; H, 5.8, $C_{26}H_{23}N_3O_2$ requires C, 76.28, H, 5.62)

(XIb): yield 48%; m.p. 273°, NMR (δ scale), 1.48 ($-CH_2-CH_2-CH_2$), 3.2 [$N(CH_2)_2$], 6.43 -N=C(-N-)-CH= J= 16 Hz), 7.86 (PhCh=, J = 16 Hz), 7-8.2 (Ar-H). (Found: C, 78.34; H, 6.24 $C_{27}H_{25}N_3O.1/2\ H_2O$ requires C, 77.88; H, 6.25).

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