

## BIOLOGICAL PROFILE OF SOME THIODICARBONIMIDIC DIAMIDE DIHYDROCHLORIDES

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### ABSTRACT

Sixteen new thiodicarbonimidic diamide dihydrochlorides with morpholinyl piperidinyl and piperazinyl moieties have been synthesized by the interaction of  $\alpha$ -chloroamidine dihydrochlorides and corresponding thioureas at 0–5°C in acetone medium and screened for anticonvulsant, analgesic and local anaesthetic activities. Majority of the compounds exhibited protection (62–100%) from maximal electro shock seizures. In the analgesic test only compounds with *p*-chloro, *p*-ethoxy and *p*-methoxy substituents in benzene ring showed significant activity, while in the case of local anaesthetic activity piperidino and morpholino derivatives were more potent

### INTRODUCTION

SEVERAL thiourea derivatives containing piperazine and piperidine rings are known to exhibit anticonvulsant and analgesic actions. In analgesic test 1,4-bis-3-(3-allylthioureidopropyl piperazine)<sup>1</sup> (I) was highly active with low toxicity (LD<sub>50</sub> 160 mg/kg). Demerol (II) (a nitrogen heterocyclic) is a stronger pain reliever, analgesia lasts only about two hours at therapeutic doses. Several 1-aryl-3 (2-pyrimidyl/morpholinyl) thioureas<sup>2</sup> (III) showed anticonvulsant activity against pentylene tetrazole-induced convulsions and potentiated pentobarbital-induced hypnosis in mice. Some of the 1-(morpholino or piperidino) 2-propanol<sup>3</sup> (IV) derivatives were tested for local anaesthetic activity in toad sciatic nerve preparations.

#### Chemistry

The title compounds were synthesized by the interaction of  $\alpha$ -chloroarylformamidine hydrochlorides with N-alkyl/arylmorpholine/piperidine/piperazine carbothioamides in acetone at 0–5° to afford white crystalline solids (scheme 1).

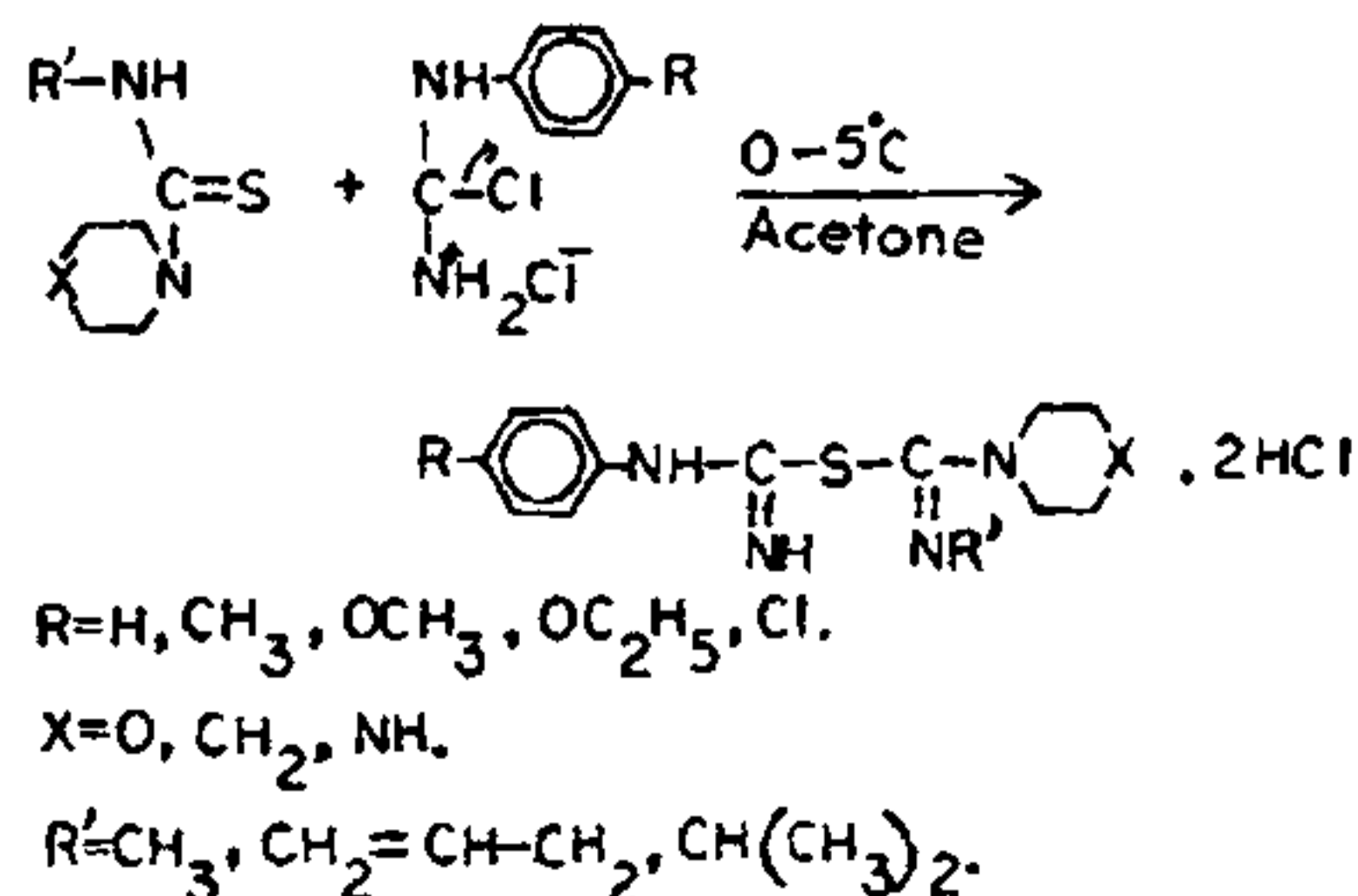
Structural evaluation was done on the basis of IR spectra, elemental analysis and reaction with water. All melting points were determined by open capillary method and are uncorrected. IR spectra with characteristic group frequencies were obtained on Perkin-Elmer 720 grating spectrophotometer by preparing nujol mull. The IR spectra showed important peaks: 3620–3150 cm<sup>-1</sup> (NH and NH<sub>2</sub><sup>+</sup>); 1620 cm<sup>-1</sup> (C=N) and) 1320 cm<sup>-1</sup> (>C-S-C<).

The results of elemental analysis were within  $\pm 0.4\%$  of the calculated values.

N-alkyl/aryl-morpholino/piperidino/piperazino carbothioamide were prepared by condensation of appropriate alkyl/aryl isothiocyanates with the cyclcamines in ethanol.  $\alpha$ -Chloroaryl formamidine hydrochlorides were obtained by passing dry hydrogen chloride gas into ethereal solution of arylcyanamides, which were in turn prepared by complete desulphurization of arylthioureas with alkaline lead acetate solution.

#### *N*-(alkyl/arylthiocarbamoyl) derivatives of cyclic amines<sup>4</sup> 1-(Methylthiocarbamoyl) piperazine

Piperazine hexahydrate (19.6 g, 0.10 M) was dissolved in absolute ethanol, (50 ml) and methylisothiocyanate (7.3 g, 0.10 M) in ethanol (25 ml) was added slowly. Reaction mixture was refluxed for 2 hr and the colourless solid which was separated out on cooling was filtered, washed with aq. NH<sub>3</sub> and ether, to remove unreacted materials and crystallized from a mixture of dimethylformamide and methanol (50:50) yield 8 g (50%): m.p., 226°C.



Scheme 1.

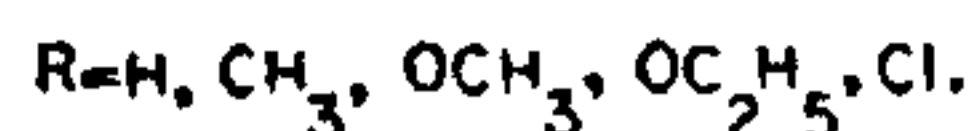
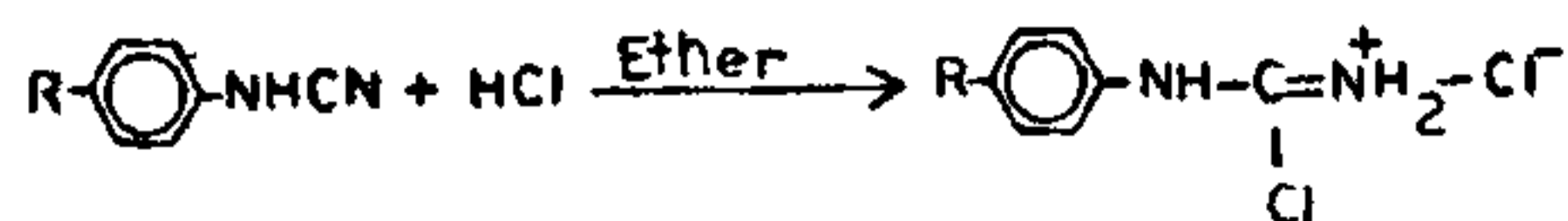
\* For correspondence.

*Aryl cyanamide*<sup>5</sup>  
*Phenylcyanamide*

Phenylthiourea (5.0 g, 0.03 M) was dissolved in hot water, a mixture of sodium hydroxide (5.0 g, 0.12 M) and lead acetate (11.4 g, 0.03 M) was added to the hot solution of phenylthiourea. The whole content was heated on a water bath for 1 hr. The lead sulphide was filtered and the filtrate was acidified with cold acetic acid. This precipitated phenyl-cyanamide was extracted with ether and dried over anhydrous sodium sulphate. Other aryl cyanamides were prepared similarly.

*α-Chloroarylformamidinium hydrochloride*<sup>6</sup>  
*α-Chlorophenylformamidinium hydrochloride*

Dry hydrogen chloride gas was passed into the ethereal solution of phenyl cyanamide (5 g, 0.04 M) giving rise to a pale-yellow viscous liquid. The liquid was identified as α-chlorophenylformamidinium hydrochloride. It was soluble in acetone (scheme 2).



Scheme 2.

## RESULTS AND DISCUSSION

The results are summarized in table 1. The general observation is that compounds possessing morpholino ring are most potent as compared to piperidino and piperazino derivatives as local anaesthetic, anticonvulsant and analgesics. Among the substituents, chlorine in the para position of the phenyl ring was found to be most effective. In the local anaesthetic activity morpholino derivatives were more potent than the standard drug lidocaine requiring less time for onset of anaesthesia, this was also the case with piperidino compounds. The piperizino derivatives took more time for onset of anaesthesia than the standard drug. The compound

Table 1 Biological activity of thiodicarbonimidic diamide dihydrochlorides

Compound No.*	Anticonvulsant activity		Analgesic activity** Latent period of tail-flick response (sec) Mean ± S.E.			Local anaesthetic activity*** onset of anaesthesia (min)
	% Protection	p value	Control	30 minutes	60 minutes	
Va	37.5	0.20	3.2 ± 0.53	6.6 ± 0.46	4.5 ± 0.61	12.0 ± 0.4
Vb	87.5	0.01	4.0 ± 0.41	5.4 ± 0.41	5.4 ± 0.65	11.0 ± 0.4
Vc	100.0	0.001	4.5 ± 0.38	7.5 ± 0.38 <sup>a</sup>	6.8 ± 0.53 <sup>b</sup>	11.0 ± 1.08
Vd	75.0	0.01	3.6 ± 0.46	5.8 ± 0.65	5.8 ± 0.60	11.0 ± 0.8
Ve	75.0	0.01	4.6 ± 0.64	5.0 ± 0.90	6.5 ± 0.42	10.0 ± 0.4
Vf	100.0	0.001	5.4 ± 0.33	5.9 ± 0.62	7.8 ± 1.18	9.0 ± 0.5
Vg	62.5	0.05	4.9 ± 0.47	7.3 ± 0.93	9.3 ± 0.49 <sup>a</sup>	9.0 ± 0.4
Vh	50.0	0.10	9.3 ± 1.43	12.5 ± 3.07	9.0 ± 0.98	11.0 ± 1.5
Vi	75.0	0.01	6.3 ± 0.96	8.8 ± 1.8	15.0 ± 2.06 <sup>b</sup>	8.0 ± 0.71
Vj	37.5	0.20	5.8 ± 0.61	5.6 ± 0.70	4.8 ± 0.19	9.0 ± 0.7
Vk	62.5	0.05	6.08 ± 0.43	9.0 ± 0.84	8.0 ± 0.86	10.0 ± 1.08
Vi	62.5	0.05	2.6 ± 0.35	5.6 ± 0.38 <sup>a</sup>	4.9 ± 0.40 <sup>b</sup>	16.0 ± 1.08
Vm	37.5	0.20	6.1 ± 0.22	9.5 ± 1.36	6.0 ± 0.68	18.0 ± 1.15
Vn	75.0	0.01	4.2 ± 0.26	7.7 ± 0.83 <sup>b</sup>	7.8 ± 0.34 <sup>a</sup>	22.0 ± 1.15
Vo	50.0	0.10	5.1 ± 0.31	7.3 ± 0.80	8.3 ± 0.90	14.0 ± 1.63
Vp	62.5	0.05	8.5 ± 1.40	15.5 ± 3.0	16.7 ± 4.12	26.0 ± 1.47
Phenobarbitone	100.0	0.001	—	—	—	—
Acetyl salicylic acid	—	—	6.7 ± 1.41	13.64 ± 3.03	19.2 ± 2.60	—
Lidocaine hydrochloride	—	—	—	—	—	12.0 ± 1.78

\* Dose 50 mg/kg i.p. (n = 8); \*\* Dose 50 mg/kg i.p. (n = 5); \*\*\* Conc = 1% aq. solution (n = 4). Acute toxicity = 100 mg/kg; <sup>a</sup> P < 0.001; <sup>b</sup> P < 0.001; <sup>c</sup> P < 0.01.

Vi was the most potent, which required only 8 min to produce anaesthesia.

All the compounds demonstrated anticonvulsant action. Most of the morpholino derivatives were active with 60–100% protection (except Va). The compounds Vc and Vf gave 100% protection against the maximal electroshock seizure like phenobarbitone (50 mg/kg i.p.) at 50 mg/kg. Both compounds possessed chlorine in the para position of the phenyl ring.

In the analgesic test, the compounds were devoid of any appreciable activity except Vc, Vi and Vn. The compounds Vc and Vi gave significant ( $P < 0.001$ ) analgesic effect after 30 min and their activity prolonged ever after 1 hr. The activity of compound Vn gradually increased and showed most significant results ( $P < 0.001$ ) after 1 hr. Although compound Vi was not active initially it produced significant ( $P < 0.01$ ) analgesia after 1 hr.

No correlation among three activities could be established. However compound Vc was active in all the three tests. This may be due to chlorine being resistant to biological oxidation in the ring, thereby decreasing the loss of activity.

## EXPERIMENTAL

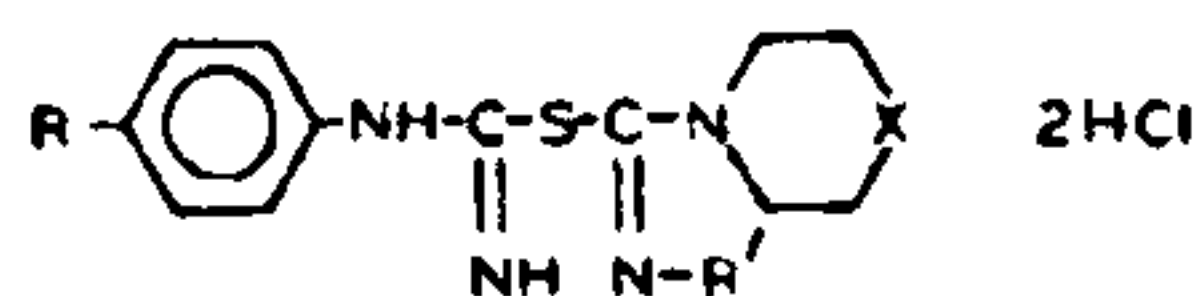
### Synthesis of *N*-methyl-4-morpholinecarboximidothioic acids anhydrosulfide with *p*-arylcarbamiidothioic acid

An acetone solution of *N*-methyl-4-morpholine carbothioamide (3.2 g, 0.02 mol) was mixed with an equivalent molar quantity of  $\alpha$ -chloro-*p*-tolylformamide hydrochloride (4.1 g, 0.02 mol). The reaction temperature was maintained at 0–5°. After 30 min a microcrystalline solid precipitated out, which was filtered and washed several times with acetone and ether. Yield, 61% m.p., 141°C; Calcd. for  $C_{14}H_{22}Cl_2N_4OS$ ; C, 56.03; H, 6.03; N, 15.34%. Found: C, 56.18; H, 6.23; N, 15.29. Other derivatives of this series were similarly prepared and are shown in table 2.

### Action of water

The compound was boiled with water for 10 min and filtered hot. The filtrate on cooling gave a crystalline product which was identified as *p*-anisylthio-urea m.p., 204°C undepressed mixed melting point with an authentic sample.

Table 2 Physical properties of *N*-alkyl-(4-morpholine/1-piperidine/1-piperazine) carboximidothioic acid, anhydrosulfide with aryl carbamimidothioic acid, dihydrochlorides



Compd. No.	R	R'	m.p. (°C)	Molecular formula
		X=O		
Va	CH <sub>3</sub>	CH <sub>3</sub>	141	C <sub>14</sub> H <sub>22</sub> Cl <sub>2</sub> N <sub>4</sub> OS
Vb	CH <sub>3</sub>	CH <sub>2</sub> =CH-CH <sub>2</sub>	147	C <sub>16</sub> H <sub>24</sub> Cl <sub>2</sub> N <sub>4</sub> OS
Vc	Cl	CH <sub>3</sub>	160	C <sub>13</sub> H <sub>19</sub> Cl <sub>3</sub> N <sub>4</sub> OS
Vd	Cl	C <sub>2</sub> H <sub>5</sub>	141	C <sub>14</sub> H <sub>21</sub> Cl <sub>3</sub> N <sub>4</sub> OS
Ve	Cl	CH <sub>2</sub> =CH-CH <sub>2</sub>	146	C <sub>15</sub> H <sub>24</sub> Cl <sub>3</sub> N <sub>4</sub> OS
Vf	Cl	4-ClC <sub>6</sub> H <sub>4</sub>	142	C <sub>18</sub> H <sub>20</sub> Cl <sub>4</sub> N <sub>4</sub> OS
Vg	OCH <sub>3</sub>	CH(CH <sub>3</sub> ) <sub>2</sub>	139	C <sub>16</sub> H <sub>26</sub> Cl <sub>2</sub> N <sub>4</sub> O <sub>2</sub> S
		X=CH <sub>2</sub>		
Vh	CH <sub>3</sub>	CH(CH <sub>3</sub> ) <sub>2</sub>	110	C <sub>17</sub> H <sub>28</sub> Cl <sub>2</sub> N <sub>4</sub> S
Vi	Cl	CH(CH <sub>3</sub> ) <sub>2</sub>	149	C <sub>16</sub> H <sub>25</sub> Cl <sub>3</sub> N <sub>4</sub> S
Vj	Cl	4-OCH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	157	C <sub>20</sub> H <sub>25</sub> Cl <sub>3</sub> N <sub>4</sub> OS
		X=NH		
Vk	OCH <sub>3</sub>	CH <sub>3</sub>	140	C <sub>14</sub> H <sub>23</sub> Cl <sub>2</sub> N <sub>5</sub> OS
VI	OCH <sub>3</sub>	<i>n</i> -C <sub>4</sub> H <sub>9</sub>	240	C <sub>17</sub> H <sub>29</sub> Cl <sub>2</sub> N <sub>5</sub> OS
Vm	OCH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	140	C <sub>19</sub> H <sub>31</sub> Cl <sub>2</sub> N <sub>5</sub> OS
Vn	OC <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub>	195	C <sub>15</sub> H <sub>25</sub> Cl <sub>2</sub> N <sub>5</sub> OS
Vo	OC <sub>2</sub> H <sub>5</sub>	<i>n</i> -C <sub>4</sub> H <sub>9</sub>	185	C <sub>18</sub> H <sub>31</sub> Cl <sub>2</sub> N <sub>5</sub> OS
Vp	Cl	CH <sub>3</sub>	145	C <sub>13</sub> H <sub>20</sub> Cl <sub>3</sub> N <sub>5</sub> S

Analytical values were within the range of  $\pm 0.4\%$ ; Yield 40 to 80%.

### Pharmacological testing methods

The local anaesthetic activity was performed on frog *Rana tigrina* using its partially de-sheathed sciatic nerve-trunk<sup>7</sup>. The time when the muscle failed to respond to the stimulation was recorded (table 1).

The anticonvulsant activity was tested by the method of Swinyard<sup>8</sup>. Synthesized compounds were tested at a dose of 50 mg/kg i.p. on albino rats of either sex weighing 150–200 g. Anticonvulsant activity in the maximal electroshock seizure (MES) test is defined as abolition of the hind limbs tonic extensor component of the maximal electroshock seizure elicited in rats with a 60-Hz alternating current of 50 mA delivered for 0.2 s via corneal electrodes. Phenobarbitone was used as the standard drug. The statistical significance of the results was calculated using  $\chi^2$  test<sup>9</sup>.

The analgesic activity was performed on a techno analgesiometer using rat-tail hot wire technique, as

described by Davis *et al*<sup>10</sup>. Albino rats of either sex weighing 150–200 g were administered with the synthesized drugs at a dose of 50 mg/kg body weight i.p. The tail-flick response was noted after 30 and 60 m of drug administration. Student's *t* test was applied for the determination of statistical significance of results (table 1).

### ACKNOWLEDGEMENTS

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## NEWS

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### JAWAHARLAL NEHRU FELLOWSHIP

The Jawaharlal Nehru Memorial Fund has awarded Fellowships to Prof. N. Mukunda of the Indian Institute of Science, Bangalore and Prof. S. K. Kacker of the All India Institute of Medical Sciences, New Delhi. The Fellowships are tenable for two years and were announced on 26 May 1987, the eve of Jawaharlal Nehru's death anniversary.

Prof. Mukunda has been given the award to pursue research on "The roles and importance of geometry, group theory and topology in problems of optics, mechanics, field theory and extended relativistic systems; and on the foundations of quantum mechanics". He has published over 100 papers in various journals, in the areas of group representation theory relevant for physical problems, classical and quantum dynamics, field theory and theoretical optics. He received the C.S. Bhatnagar Prize for

Physical Sciences in 1980 and is a Fellow of the Indian Academy of Sciences, Bangalore and the Indian National Science Academy, New Delhi. He is also a member of the Editorial Board of *Current Science*.

Prof. Kacker has been given the award to work on the project "Prevention of hearing impairment in rural areas of the country with special reference to prevention of deafness in infants and children". He received the Padmashri in 1986, and earlier the B.C. Roy Award in 1981. He is a Fellow of the National Academy of Medical Sciences. Prof. Kacker, who has been doing research on the problem of deafness for the past 15 years has identified several villages around Delhi and in Haryana for initial study which if it proves effective, will lead to a rational policy on prevention of deafness.

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