

Pharmacological Evaluation of 1-(N,N-Disubstituted aminomethyl)-3-imino-(2-phenyl-3,4-dihydro-4-oxo-quinazolin-3-yl) indolin-2-ones

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Eleven new Mannich bases of isatins were screened for potentiation of pentobarbitone-induced narcosis, analgesic, antidepressant, anticonvulsant and H₁-antihistaminic activities. The test compounds were found to exhibit a moderate analgesic activity and also to potentiate the pentobarbitone-induced narcosis. However, these compounds were found to be devoid of antidepressant, anticonvulsant and antihistaminic activities.

LITERATURE reveals that the Mannich bases of isatins possess antiviral^{1,2} antimicrobial³, CNS⁴, and antiinflammatory,⁵ activities. A number of 3-imino derivatives in the form of schiff bases were prepared from isatin and a majority of them were converted into their Mannich bases in search of biologically potent compounds. Though extensive work is reported on isatin Mannich bases, relatively very little is known, so far, about the Mannich bases of isatin containing heteryl group at 3-position. It is well known that the quinazolinone system is also associated with a variety of pharmacological activities.

This enthused us to synthesize some new Mannich bases of isatin containing Quinazolinone system, with a view to evaluate them for antimicrobial, analgesic, anticonvulsant and antihistaminic activities and for their effect on pentobarbitone-induced narcosis. The latter has been chosen as a method to know whether these new synthetic compounds have any effect on sleep time; if so whether they could be tested for Tricyclic-type antidepressant activity. The synthesis and antimicrobial activity of the title compounds were previously reported⁶ and the present investigation deals with the different pharmacological activities exhibited by the title compounds.

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EXPERIMENTAL

Analgesic Activity (Writhing method)⁷:

Overnight fasted healthy and adult male albino swiss mice weighing 20-30 g in groups of six each were used in this investigation. Sodium carboxymethyl cellulose suspensions (0.8%) of the test compounds were administered, intraperitoneally at a dose of 100 mg/kg. The control group of animals was given only sodium CMC suspension and one group of animals was administered with aspirin as a standard, intraperitoneally at a dose of 8 mg/kg. After 30 min. of the administration of the test compounds or standard drug, all the groups of the mice were given the writhing agent, 3% aqueous acetic acid, in a dose of 2 ml/kg, intraperitoneally. The writhings produced

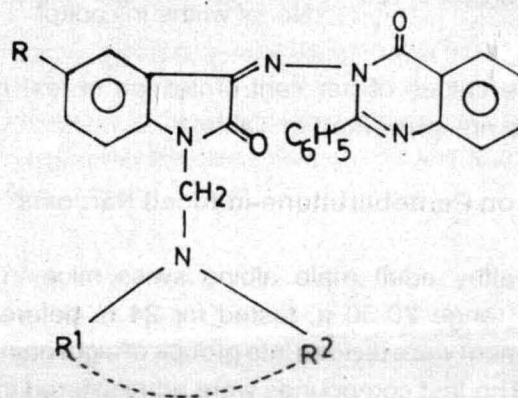


Table 1 : Pharmacological Activities of 1-(N,N-Disubstituted aminomethyl)-3-imino-(2-phenyl-3,4-dihydro-4-oxo-quinazolin-3-yl)indolin-2-ones

Compound	Substituents		Analgesic activity (% protection)	Effect on pentobarbitone induced narcosis (% potentiation)
	R	NR ¹ R ²		
a	H	morpholino	46.56	131.53
b	H	Piperidino	53.45	121.02
c	H	dicyclohexylamino	39.66	156.41
d	H	bis-β-hydroxyethyl amino	48.28	107.69
e	5-CH ₃	morpholino	43.11	133.84
f	5-CH ₃	piperidino	48.28	124.10
g	5-CH ₃	dicyclohexylamino	23.42	144.35
h	5-CH ₃	bis-β-hydroxyethyl	17.25	105.12
i	5-Br	morpholino	51.73	150.76
j	5-Br	piperidino	56.90	136.41
k	5-Br	bis-β-hydroxyethyl	37.94	139.24
l	Aspirin (8 mg/kg)		55.94	—
m	Imipramine HCl (5 mg/kg)		—	123.70
n	control			100

in these animals were counted for 30 min. and compared with those in the control group. The per cent protection for each compound was calculated using the following formula.

$$\% \text{ Protection} = 100 - \frac{\text{No. of wriths in test}}{\text{No. of wriths in control}} \times 100$$

The values of per cent protection of test compounds are presented in Table 1.

Effect on Pentobarbitone-induced Narcosis^{8,9}

Healthy adult male albino swiss mice in the weight range 20-30 g, fasted for 24 h. before the experiment were divided into groups of eight animals, each. The test compounds were administered in the

form of 0.8% sodium carboxymethyl cellulose suspension, intraperitoneally at a dose of 100 mg/kg. After 30 min pentobarbitone sodium was administered, intraperitoneally to all the groups at a dose of 30 mg/kg. The average duration of loss of righting reflex was noted and the percentage potentiation of pentobarbitone induced narcosis by the test compounds was calculated using the formula given below.

$$\% \text{ Effect} = \frac{\text{Average duration of loss of righting reflex in test group}}{\text{Average duration of loss of righting reflex in control}} \times 100$$

The results are presented in Table 1.

The test compounds were also screened for their anticonvulsant and H₁ - antihistaminic activities by standard methods^{10,11} and found to be inactive.

RESULTS AND DISCUSSION

All the compounds tested found to exhibit some degree of analgesic activity. Perusal of the **Table 1** indicates that out of eleven compounds of the series, compound **j** with 1- piperidinomethyl and 5-bromo substituents in indolinone system has been found to be relatively more potent analgesic with a percentage protection of 56.9 while **p** with same 1-substituent but unsubstituted at 5 position has been found to be next in the order of analgesic activity with 53.45 percent protection. Compound **i** with a 1-morpholinomethyl and 5-bromo substituents in indolinone system with 51.73 percent protection could be noticed as the third effective analgesic of the series. Except compounds **h**, **g**, **k** and **c** rest were found to exhibit a moderate analgesic activity.

The results of potentiation of pentobarbitone-induced narcosis indicate that compound **c** with dicyclohexylaminomethyl group as 1- substituent in indolinone system, is the most potent of all the compounds with a potentiation of narcosis to a tune of over 156 percent. Next effective compound was found to be **j** with a 1- morpholinomethyl ad 5-bromo substituents exhibiting the potentiation of narcosis over 150 per cent. Compound **g** with a dicyclohexylaminomethyl as 1-substituent and a 5-methyl substituent in indolinone was found to be next in the order of potentiation with over 144 per cent effect.

These three compounds (**c**, **g**, and **f**) were thus assayed for the antidepressant activity (Tricyclic type)¹² and found to be insignificant.

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