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Analgesic, Antiinflammatory and Antibacterial Activity of Some Novel 2-Phenyl-3-(substituted methyl amino) quinazolin-4(3*H*)-ones

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In view of the potent analgesic antiinflammatory and antimicrobial activities exhibited by quinazolin-4(3*H*)-ones, a series of novel 2-phenyl-3-(substitutedmethyl amino) quinazolin-4(3*H*)-ones have been synthesized. When these compounds were evaluated for analgesic, antiinflammatory and antibacterial activities, compounds I and II exhibited comparable analgesic activity, while the compounds II and III exhibited comparable antiinflammatory activity with the standard diclofenac sodium.

Bacterial infections often produce inflammation and pain. In normal practice, two groups of agents (chemotherapeutic, analgesic and antiinflammatory) are prescribed simultaneously. The compounds possessing all three activities are not common. Quinazolines and condensed quinazolines have received the attention of medicinal chemists due to their wide range of biological activities which include analgesic and antiinflammatory[1-3], antibacterial[4-7], antiviral[8-9], antihistaminic[10], antihypertensive[11] and anticancer[12] activities. Mannich bases of the above compounds were reported to possess potent antibacterial activity[13]. In the present study it was envisaged that a drug molecule possessing the above mentioned pharmacophore could be of advantage since it might possess analgesic, anti-inflammatory and antibacterial activities. The title compounds, 2-phenyl-3-(substitutedmethyl amino) quinazolin-4(3*H*)-ones [Mannich bases of 3-amino-2-phenylquinazolin-4(3*H*)-one] were synthesized by our earlier reported method[14], i.e. by condensing the active hydrogen atom of 3-amino of 3-amino-2-phenyl quinazolin-4-(3*H*)-one (3, Scheme I), with formaldehyde and the desired amines [Mannich reaction]. The starting material (3, Scheme I) was synthesized from anthranilic acid. The compounds were tested for analgesic, antiinflammatory and antibacterial activities.

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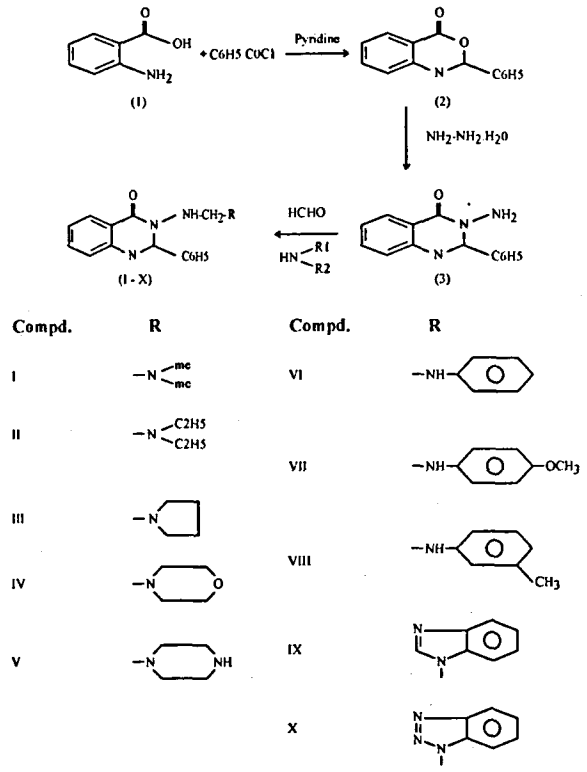

Scheme 1: Synthetic pathway of the title compounds (I-X).

The animals were maintained in colony cages at 25±2°, relative humidity of 45-55% maintained under12 h light and dark cycle and were fed with standard animal feed. All the animals were acclimatized for a week before use. Animal experimental protocols have been approved by an institutional animal ethics committee.

Test for analgesic activity was performed using the tail flick technique[15,16] in mice. Animals were divided into various group each consisting of six animals. Test compounds (I-X) and standard diclofenac sodium were administered orally at a dose of 20 mg/kg as an aqueous suspension in 1% sodium carboxymethyl cellulose (Na CMC), while the control group was fed with the same volume of 1% Na CMC suspension, the reaction time was recorded at 1, 2 and 3 h after the treatment. The percent analgesic activity (PAA) was calculated by the following formula, $PAA=(T_2/T_1)x100$, where, T_1 is the reaction time in s before treatment and T_2 is the reaction time in s after treatment. The results are presented in Table 1.

*Antiinflammatory activity was measured using the car*rageenan-induced paw oedema test in rats[17]. Animals were divided into different groups each consisting of six animals. Test compounds and standard diclofenac sodium were administered orally at a dose of 20 mg/kg as an aqueous sus-

TABLE 1: ANALGESIC AND ANTIINFLAMMATORY ACTIVITIES OF THE TEST COMPOUNDS I-X.

Compd. No.	Percent Analgesic Activity			Percent protection		
	1st h	2nd h	3rd h	1st h	2nd h	3rd h
I	297±3.1*	233±2.2*	201±4.4*	29.1±3.5*	28.4±3.3*	25.9±1.5*
II	236±4.6*	201±6.3*	151±5.5*	38.4±3.3*	39.2±4.0*	36.0±2.4*
III	324±4.4*	225±3.3*	198±2.2*	36.1±4.2*	40.2±4.3*	37.0±3.6*
IV	220±5.6*	206±5.4*	191±5.5*	27.5±6.6**	25.2±4.4*	21.0±3.3*
V	209±6.6*	202±5.5*	190±6.5*	25.3±2.2*	25.0±4.5*	20.0±4.5*
VI	199±6.8*	197±4.3*	197±1.4*	24.4±2.3*	19.6±4.1*	18.2±1.2*
VII	207±4.3*	189±2.3*	175±1.4*	22.1±4.5*	21.3±1.2*	15.9±2.8*
VIII	223±4.6*	203±5.4*	151±6.4*	24.0±2.4*	20.4±1.6*	22.0±2.3*
IX	260±1.5*	201±2.4*	180±6.5*	30.1±5.5*	26.3±4.4*	20.0±4.4*
X	245±2.3*	205±4.2*	129±5.2*	27.2±2.2*	25.4±3.1*	21.0±1.2*
Control	2.6±1.2	4.2±2.6	2.4±1.6	1.2±2.5	2.8±1.2	2.2±1.6
Standard	356±1.9*	269±5.4*	206±2.6*	40.4±3.3*	45.2±5.6*	39.9±6.4*

* denotes significant differences from control at $P \leq 0.05$. Standard used was diclofenac sodium.

TABLE 2: ANTIBACTERIAL ACTIVITY OF THE TEST COMPOUNDS I - X.

Compd. No.	Zone of Inhibition (mm)				
	B. subtilis	*K. pneumoniae*	*S. aureus*	*E. coli*	*V. cholerae*
I	19	20	18	19	19
II	19	23	20	19	21
III	20	22	21	20	22
IV	25	32	27	26	25
V	25	26	27	24	24
VI	20	21	22	20	20
VII	21	23	18	18	18
VIII	21	24	20	19	19
IX	25	27	29	25	24
X	22	22	24	21	20
Control	Nil	Nil	Nil	Nil	Nil
Standard	22	26	23	25	24

Standard used was ciprofloxacin at 10 μg/ml.

pension in 1% Na CMC, while the control group was fed with the same volume of 1% Na CMC suspension. The paw volume were measured using the mercury displacement technique with the help of a plethysmometer immediately before and 1, 2 and 3 h after the carrageenan injection. The percent inhibition of paw volume was calculated by using the formula, Percent inhibition I=100[1- (a-x)/ (b-y)], where x is the mean paw volume of rats before the administration of carrageenan and test compounds or standard compound (test group), a is the mean paw volume of rats after the administration of carrageenan in the test group (drug treated), b is the mean paw volume of rats after the administration of carrageenan in the control group, y is the mean paw volume of rats before the administration of carrageenan in the control group.

All the compounds synthesized (I-X), were screened for their antibacterial activity by agar cup-plate method[18] at a concentration of 100 μg/ml using DMF as a solvent against the following organisms. *Bacillus subtilis, Escherichia coli. Vibrio cholerae, Staph. aureus* and *Klebsiella pneumoniae.* The zone of inhibition of each strain was recorded (Table 2). The activity has been compared with known standard drug ciprofloxacin at 10 μg/ml concentration. The biological results were analysed statistically by student 't' test.

While all the compounds exhibited analgesic activity (Table 1) the compounds I and II shown analgesic activity comparable to standard diclofenac sodium and the activities were found to be significant when compared to control group. However none of the compounds found to be equipotent to diclofenac sodium. All the test compounds exhibited good antiinflammatory activity and compounds II and III exhibited potency comparable to the standard, diclofenac sodium. All the test compounds inhibited the bacterial growth to varying extents. However, the compounds IV, V and IX showed similar zones of inhibition (at 100 μg/ml) as observed with the standard, ciprofloxacin (at 10 μg/ml)

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Hypocholesterolemic and Antihypercholesterolemic Activity of Extracts of *Trichila Connaroids* on Rats

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Hypocholesterolemic activity was studied on normal rats for hexane, chloroform and methanol extracts of *Trichilia connaroides* (W. & A.) Bentilezen. The parameters studied include free cholesterol, triglycerides and high density lipoprotein levels in blood. Only hexane and methanol extracts produced a rise in high density lipoprotein level ($p<0.05$ at 90 mg/kg) and did not show any fall in cholesterol and triglyceride levels when compared to control group. On Triton-induced hypercholesterolemia, only cholesterol and triglyceride levels were studied for all the three extracts. Chloroform and methanol extracts produced a significant fall in cholesterol level ($p<0.05$) within 24 h of induction when compared to control group.

Trichilia connaroides (W. & A.) Bentilezen (Meliaceae) is known as *Karai* or *Karaivilangu* in Tamil. It is found in moist forests throughout the greater part of India. The bark and leaves possess bitter and tonic properties[1]. The isolation of tri and tetranortriterpenoids from chloroform extract of the leaves has been reported[2-4]. Preliminary pharmacological screening of the chloroform extract of the leaves of *T. connaroides* revealed significant hypotensive activity in rats (unpublished data). In the present work, an attempt has been made to investigate the possible effect of the extracts of *T. connaroides* on normal and Triton-induced cholesterol levels in rats. The parameters recorded were free cholesterol, triglycerides and high density lipoprotein (HDL) levels in mg/dl.

The leaves of *T. connaroides* (2 kg) were collected from Salem, Tamil Nadu, shade dried and coarsely powdered. The powder was first defatted with n-hexane at room temperature. The powder was then extracted with chloroform, distilled and last traces of solvent were removed by vacuum. The marc was then extracted with methanol twice. Chloroform and methanol used were of AR grade. AR grade Triton

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