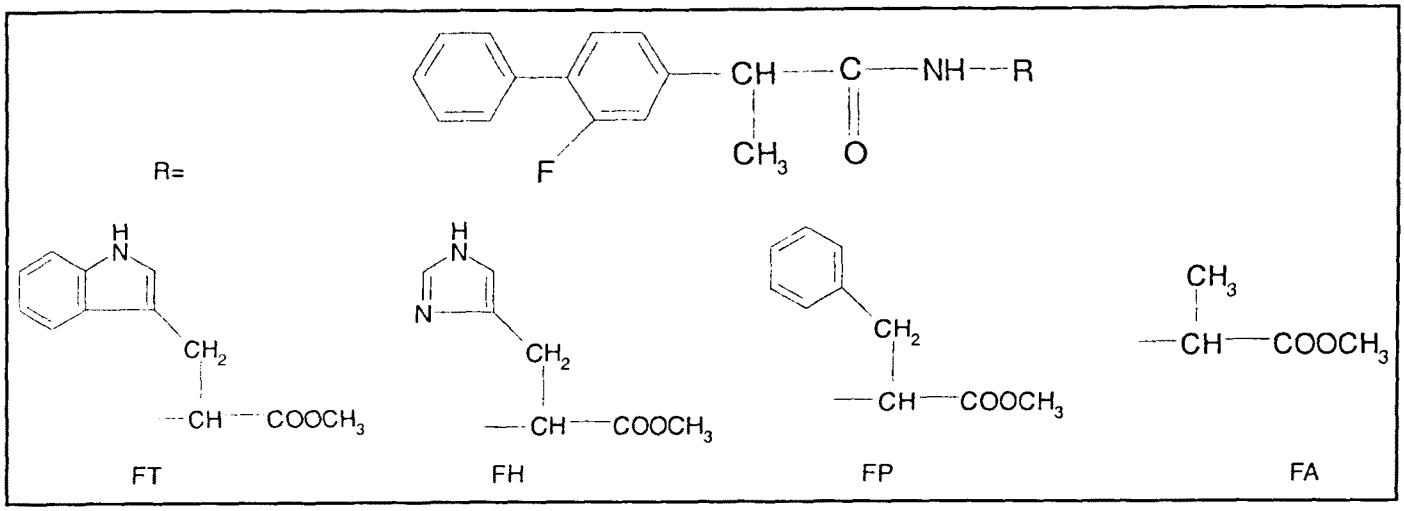

Fig. 1: Structures of prodrugs of flurbiprofen with amino acids.

tance to carry out this work.

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Pharmacological Evaluation of Synthetic Imidazolinones and their Schiff Bases

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Some imidazolines were synthesized from oxazolinones and upon treatment with benzaldehyde the Schiff's bases were synthesized from the respective imidazolinones. All these compounds

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were evaluated for analgesic, hypnotic and CNS depressant property and the LD_{50} of 4 compounds as representative of each series were determined. Some of the synthesized compounds were found to exhibit significant pharmacodynamic properties.

In recent years, several imidazolin-5(4H)-ones and their derivatives were found to have prominent pharmacological activities such as antiinflammatory, analgesic, cardiovascular, CNS stimultant, antithyperglycemic, anticonvulsant, MAO inhibitory, and α-2 adrenoreceptor blockade[1-6]. As a continuation of earlier reported work on imidazolones and Schiff's bases[6], a few more imidazolinone compounds (i) from respective oxazolinones have been synthesized along with their Schiff's bases (ii) and these compounds were characterized with spectral and analytical data as 1-aminoethyl/phenyl, 2-methyl/phenyl, 4-acetylidene/benzylidene-imidazolin-5(4H)ones (fig.1) (i: 1-8) and 1-phenylidene-amino-ethyl/phenyl-methyl/phenyl-4-acetylidene/benzylidene-imidazolin-5(4H)-ones (ii: 9-16). These compounds were evaluated to find out if they possessed any analgesic activity using acetic acid-induced writhing method[7] in mice, hypnotic activity by studying the effect on righting reflex[8] in mice and CNS depressant activity by studying the locomotor activity[8] of mice using an actophotometer.

For pharmacological evaluation adult Swiss mice of either sex (20-25 g) have been used. The experimental data obtained for the test compounds were compared with that obtained with standard such as aspirin in a dose of 100 mg/kg for analgesic activity, pentobarbitone at a dose of 50 mg/kg for hypnotic activity and chlorpromazine HCl at a dose of 5 mg/kg for CNS depressant property. Before the pharmacodynamic evaluation, LD_{50} values of four imidazolone derivatives (1, 5, 9 and 13) were determined using standard reported methods[9,10]. The intraperitoneal dose of each and every compound was fixed as 100 mg/kg. A control group was also taken and treated with the vehicle. No significant change was found with the vehicle treatment and thus the data associated with it were not taken into account for the evaluation.

After primary screening, finally ten groups consisting of 10 mice in one group for 8 groups and 12 mice per group for other 2 groups for each compound were taken in acute toxicity test. In the interpretation of LD_{50}, the observed % mortality was converted into probit by referring to the appropriate table. The values thus obtained were plotted against the corresponding log dose. Results were fitted with straight line after regression analysis of probits. The dose corresponding to probit 5 was found as LD_{50} of compound.

Analgesic activity was observed as the % protection to the produced writhings by 3% aqueous acetic acid of 2 ml/kg dose in comparison to control. To observe the hypnotic activity, pentobarbitone, at first, was administered and then after 5 min interval the test compounds were also injected. The onset of action on mice was recorded by noting the time when the animal lost its righting reflex. The time of recovery from sleep was also noted down by recording the time when the animal recovers its normal posture. The average onset and duration of action were calculated. For CNS depressant activity of the synthesized compounds, individually each mouse of each group was kept in an INCO photoactometer for 5 min before treating with drugs. The drugs were administered later and then retested individually. The average percent decrease of movement (scores) i.e. locomotor activity values were calculated, which indicates CNS depressant property. The results are presented in Table 1.

After intraperitoneal administration of the test compounds to the experimental animals and subsequent determination of the corresponding LD_{50} values, it was found that compound 5 was most toxic. It was further noted that the compound-treated animals exhibited impaired spontaneous motor activity and exploratory behavior. The compounds produced muscle relaxation also in animals. So far as the anal-

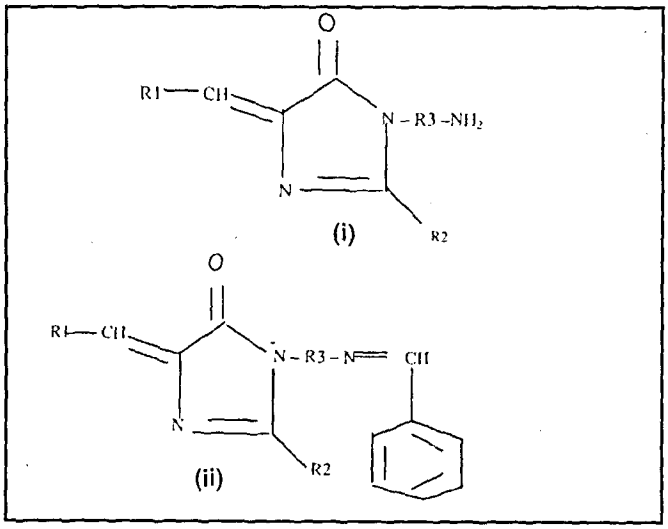

Fig. 1: General structures of compounds

General structure of i. imidazolin-5(4H)-ones and ii. Schiff's bases from i

TABLE 1: PHARMACODYNAMIC DATA OF COMPOUNDS 1-16

Com.	substituents			LD_{50} (mg/kg bw)	Analgesic %Protection to writhing	Hypnotic activity		
	R1	R2	R3			Duration of sleep (min)	Pentobarbitone[a]	CNS Activity[b]
1	CH_3	CH_3	CH_2CH_2	719.66	44.18	38.2	14.0	52.09
2	CH_3	C_6H_5	CH_2CH_2	—	35.96	29.2	11.8	39.48
3	C_6H_5	CH_3	CH_2CH_2	—	65.75	39.0	11.2	42.43
4	C_6H_5	C_6H_5	CH_2CH_2	—	39.73	31.0	11.2	38.60
5	CH_3	CH_3	$*C_6H_4$	360.27	34.25	36.5	11.5	56.29
6	CH_3	C_6H_5	$*C_6H_4$	—	19.86	27.5	12.3	55.85
7	C_6H_5	CH_3	$*C_6H_4$	—	56.16	37.4	11.6	56.15
8	C_6H_5	C_6H_5	$*C_6H_4$	—	22.26	28.4	13.4	52.37
9	CH_3	CH_3	CH_2CH_2	540.44	48.29	38.8	11.2	53.92
10	CH_3	C_6H_5	CH_2CH_2	—	41.10	32.4	11.4	51.32
11	C_6H_5	CH_3	CH_2CH_2	—	69.52	40.5	10.7	52.38
12	C_6H_5	C_6H_5	CH_2CH_2	—	42.47	34.6	12.8	50.77
13	CH_3	CH_3	$*C_6H_4$	730.51	26.03	30.8	12.6	52.03
14	CH_3	C_6H_5	$*C_6H_4$	—	12.67	21.6	10.8	41.96
15	C_6H_5	CH_3	$*C_6H_4$	—	47.60	31.6	11.6	42.24
16	C_6H_5	C_6H_5	$*C_6H_4$	—	18.49	22.8	11.6	40.04
Std 1	—	—	—	—	78.42	—	—	—
Std 2	—	—	—	—	—	42.0	6.8	—
Std 3	—	—	—	—	—	—	—	57.93

Std 1 is aspirin; Std 2 is pentobarbitone and Std 3 is chlorpromazine HCl. $*C_6H_4$ stands for phenyl. [a]Onset of action in min after pentobarbitone injection and [b]CNS depressant activity (%change of decrease in movement)

gesic activity was concerned, none of the compounds had activity equal to or more than that of the standard drug- aspirin. However, compounds 3,7 and 11 had significant activity. It was noted that the Schiff's bases (13-16) did not show activity better than that of their respective imidazolinones (5-8). Compound 11 showed highest activity in this series. It was also noted that in all imidazole derivatives the activity was maximum in compounds having R1=C_6H_5 and R2=CH_3.Thus, R2=CH_3 might be an essential factor for increase or decrease in analgesic activity. The hypnotic activity of all imidazole derivatives were recorded by measuring the onset and duration of sleep in mice in minutes. It has been found that no synthesized imidazole derivative either potentiate the duration of sleep or promote the onset of sleep which might be due to many factors like the antagonistic activity to pentobarbitone. The delaying effect on the onset of sleep by all the imidazole derivatives was noteworthy. Tendency to reduce the duration of sleep was found maximum in compound 14 and minimum in compound 11. Again, the activity to reduce the duration of sleep was found less in compounds (1-4) than their corresponding Schiff's bases (9-12) whereas it was reverse in case of aminophenyl imidazolinones (5-8) where their Schiff's bases (13-16) showed less and furthermore, the aminophenyl derivatives showed more activity in this regard than the corresponding aminoethyl imidazolinones. Thus the substitution of C_6H_4 (phenyl) in position R2 and R3 played a significant role in the reduction of sleeping time. In detailed study of individual series i.e. 1-4, 5-8, 9-12 and 13-16, it has been observed that in reducing the duration of sleep the substitution of C_6H_5

at position R2 potentiated and at R1 depressed the effect. With regard to the CNS depressant activity, it has been found that all compounds have different degrees of CNS depressant property and among them a few (compounds 1, 8, 9, 10, 11, 12 and 13) were found to have significant activity in comparison to the standard drug while a few had shown comparable effect (compounds 5, 6 and 7); but all were less active than the standard. Compound 5 showed CNS depressant activity having a score of 56.3, the highest among the compounds, where as in case of chlorpromazine HCl, it was 57.9. Among the aminoethyl and aminophenyl imidazolinones, compounds 5-8 were found to show more activity than compounds 1-4, while compounds 13-16 were found to be less active than compounds 5-8. The observations of the CNS depressant property exhibited by individual series of compounds i.e. 1-4, 5-8, 9-12 and 13-16 indicate that the activity was highest in case of CH_3 substitution in position R1 and R2 and it gradually decreased upon substitution with C_6H_5 on those positions. It was observed that in case of Schiff's bases, the activity was more, when R3 = CH_2CH_2, and in case of imidazolinones the amino phenyl ($R3=C_6H_4$) showed more activity than aminoethyl ($R3=CH_2CH_2$) derivatives.

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Spectrophotometric Analysis of Amlodipine Besylate in Bulk and in Tablet Dosage Forms

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A reproducible and sensitive method for estimation of amlodipine besylate in bulk drug and in its tablet formulations has been developed. The method is based on formation of a yellow colored ion pair with methyl orange in acidic medium. This method follows Beer's law and has a range of 1 to 10µg/ml.

Amlodipine besylate is a calcium channel blocker used as antihypertensive and antianginal drug[1]. A survey of literature revealed that a direct spectrophotometric method[2], difference spectrophotometric methods[3], HPLC[4-9], GC[10] and HPTLC[11-12] have been reported for the analysis of amlodipine besylate. In the reported difference spectroscopy method[3]

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