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Synthesis and Anti-ulcer Activity of Some Dihydropyrimidines

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ABSTRACT
Wide range of biological activities is associated with 1, 4-dihydropyridines/ pyrimidines, individually or in combination. In view of this, synthesis of various 6-methyl-4-substitutedphenyl-2-thioxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylic acid ethyl esters and 6-methyl-4-substituted phenyl-2-S-alkyl(benzyl)-1, 4-dihydropyrimidine-5-carboxylic acid ethyl esters were undertaken for synthesizing biologically active molecules with improved activity, lesser toxicity with undesirable side effects in clinical use. All the synthesized compounds have been characterized by using IR, Mass studies, ^{1}H NMR and elemental analysis. Further, some compounds were screened for anti-ulcer activity. Compound 4(r) has shown maximum anti-ulcer activity as compared to control group.

Keywords: Anti-ulcer Activity, Dihydropyrimidines, Thioethers, tetrahydropyrimidines.

INTRODUCTION

Among a wide variety of heterocylces that have been important
molecules, pyrimidines [1] have played an important role in medicinal chemistry. Some of them have received considerable attention as potential anti-hypertensive agents. Moreover, pyrimidines acquired a special place in heterocyclic field because of their diversified activities such as anti-virus, anti-tumor, anti-bacterial agents [2-5] etc. Further, dihydropyrimidines (DHPMs; popularly known as Biginelli's compounds) are associated with broad spectrum of biological activities ever since 4-Aryl-1, 4-dihydropyridines of nifedipine type were first introduced into clinical medicine in 1975. Even today they are the most potent calcium channel modulators available for the treatment of various cardiovascular diseases. [6] Several calcium channel blockers including nifedipine are reported with anti-ulcer activity. [7-8] It is thus envisaged that structural analogues of nifedipine may possess anti-ulcer potential. So, in view of these observations it was considered worthwhile to synthesize some dihydropyrimidines (4).

MATERIALS AND METHODS

Melting points are uncorrected and were recorded in liquid paraffin-bath using open end capillaries. Thin layer chromatography was performed on Silica gel G (Merck). ^{1}H NMR spectra were recorded on a Bruker 300 MHz NMR spectrometer (internal standard TMS). The mass spectra of all the compounds were obtained on a JEOL 5x102/DA-6000 Mass spectrometer. The IR spectra were obtained on a Perkin Elmer spectrometer. All the compounds gave satisfactory elemental analysis within $\pm$ 0.4% of the theoretical values. Characterization data of the compounds are given in Table II.

Step 1

6-methyl-4-(substituted phenyl)-2-thioxo -1, 2, 3, 4-tetrahydropyrimidin-5-carboxylic acid ethyl ester (3)

Two methods were used for the synthesis of these compounds. In both the methods acetoacetic ester (0.01 mole, 1.9 g), thiourea (0.01 mole, 0.9 g) and substituted aromatic aldehydes (0.01 mole) were used. In one method the reaction mixture was subjected to microwave heating [9] for five minutes use ethanol (5 ml) as a solvent and HCl (0.5 ml) as a catalyst and in most of the cases the reaction products separated out on long standing for 24 to 36 hr. The second method involves the use of piperdine (2 ml) as catalyst in the reaction mixture which on stirring for 4 hr and on standing for 24-36 hr afforded the products **3(a-t)**. **3a:** ^{1}H NMR (300 MHz $CDCl_3$ + DMSO) : δ. 10.1(s,1H,NH), 9.5(s,1H,NH), 8.2-7.5(m,4H,Ar-H), 5.4(s,1H,4-CH), 4.1 (q,2H,-$CH_2$$CH_3$), 2.4(s,3H,6-$CH_3$), 1.2(t,3H,-$OCH_2$ CH_3), Mass fragments m/z : 321 (60.6 $M^{+\cdot}$), 304 (37.2), 292 (34.6), 248 (31.6), 199 (100.0), 171 (35.2), IR (KBr) : cm^{-1} 3200(sec. NH str.), 3070(Aromatic C-H str.), 1680(C=O str. of ester), 1120(C=S str.), 1485(C=C str.), 1180(C-N vib.), 1080 (C-O str.).

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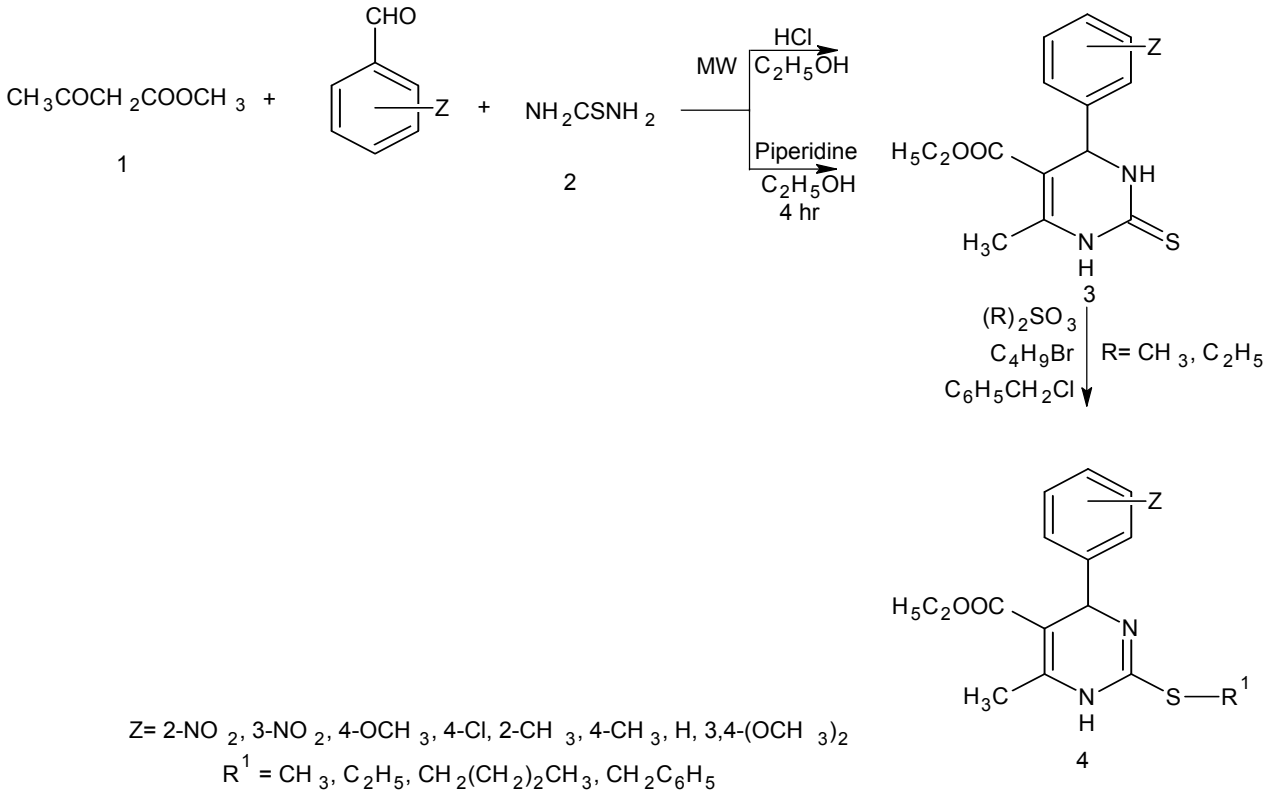

Scheme I

Scheme I

Step 2

(i) General procedure for synthesis of 6-methyl-4-substituted phenyl-2-S-alkyl-1, 4-dihydropyrimidin-5-carboxylic acid ethyl ester (4)

To tetrahydropyrimidine (0.004 mole) **3** dissolved in methanol was added NaOH solution which was prepared by dissolving NaOH (0.160 g) in water (2 ml). The mixture was cooled. To this mixture dimethyl sulphate (0.004 mole, 0.4 ml) or diethyl sulphate (0.004 mole, 0.6 ml) was added dropwise whilst stirring the mixture continuously. Then the mixture was refluxed for 3 hr. The mixture was cooled and poured over ice. Solid separated was filtered under reduced pressure, dried and recrystallised from methanol to give **4(a-l)**. Spectral data given in Table II.

(ii) General procedure for synthesis of 6-methyl-4-substituted phenyl-2-S-butyl-1, 4-dihydropyrimidin-5-carboxylic acid ethyl ester 4. A mixture of powdered tetrahydropyrimidine **3** (0.004 mole) butylbromide (0.8 ml, 0.004 mole) and absolute alcohol (5 ml) was refluxed for 5 hr. Then the product was allowed to separate at room temperature. The product was filtered under reduced pressure and crystallised from ethanol to give **4(m-q)**. Spectral data are given in Table II.

(iii) General procedure for synthesis of 6-methyl-4-substituted phenyl-2-S-benzyl-1, 4-dihydropyrimidin-5-carboxylic acid ethyl ester 4. To tetrahydropyrimidine **3**, (0.004 mole) dissolved in alcohol (2.5 ml) was added benzyl chloride (0.8 ml, 0.004 mole) and the mixture was refluxed for 4 hr. The mixture was cooled at room temperature. The solid separated was filtered and recrystallised from ethanol. Spectral data are given in Table II.

Anti-ulcer Activity Studies

Wistar rats (either sex) were bred at the Central Animal House, IIIM, Jammu. The animals were allowed a standard pellet diet and water *ad libitum*. Groups of five rats (150-200 g) were used in all sets of experiments. The animals were fasted for 18 hours before use. The approval from the Institutional Animal Ethical Committee of IIIM, Jammu was taken before carrying out biological studies.

Cold restraint stress induced ulcers

The ulcers were induced by subjecting the animals to cold restraint stress. Drugs or vehicle were administered 30 min prior to subjection of stress. The animals were placed in a restraint cage and the cage was placed at a temperature of 20°C for 3 h. After 3 h, the animals were sacrificed by over dose of ether anaesthesia and the stomach was isolated and cut opened along the greater curvature. The ulcer index was determined.

Aspirin-induced gastric ulcer

Aspirin was administered in a dose of 500 mg/kg body weight orally to all the animals. Food was withheld for duration of 5 more hours. Animals were then sacrificed by an overdose of anesthetic ether. The stomach was dissected out and a small opening was made along the greater curvature. All the gastric content was drained into a graduated centrifuge tube and used for biochemical estimations. The stomach was then cut open along the greater curvature and evenly spread out on a dissection board. A transparent film was placed over it and the boundary of the stomach and ulcerated area was traced on the film. The mucosal surface was then gently scraped with a blunt surface to collect the adherent mucus.

Pyloric ligation induced gastric ulcers

The animals were anaesthetized using anesthetic ether and a midline incision was made just below the xiphoid process. The stomach was lifted out and ligated at the level of the pylorus following which it was replaced and the abdomen wall was closed by interrupted sutures. The animals were then housed separately and food and water was withheld for duration of 4 h following which they were sacrificed by an overdose of anesthetic ether. The stomach was then dissected out, gastric contents were collected and the boundary and ulcerated area was traced as mentioned above.

Ethanol induced ulcers

All the animals were fasted for 36 h before administration of ethanol. The standard drug was administered 1 h before ethanol administration. Ethanol (90%) was administered to all the animals at a dose of 1 ml/200 g and after 1 h, the animals were sacrificed, stomachs were isolated and ulcer index was determined.

Table I : Synthesis of 6-methyl-4-substitutedphenyl-2-S-alkyl (Benzyl)-1, 4-dihydropyrimidin-5-carboxylic acid ethyl ester (4)

3(a-t)	m. p. (°C)	Z	4(a-t)	m. p. (°C)	R'
3a	215-16	2-NO_2	**4a**	205-06	Me
3b	195-96	3-NO_2	**4b**	220-21	Me
3c	140-41	4-OCH_3	**4c**	135-36	Me
3d	165-66	3,4-$(OCH_3)_2$	**4d**	110-11	Me
3e	200-01	H	**4e**	165-66	Me
3f	182-83	4-Cl	**4f**	170-71	Me
3g	185-86	4-CH_3	**4g**	175-76	Me
3b	195-96	3-NO_2	**4h**	108-09	Et
3g	185-86	4-CH_3	**4i**	120-21	Et
3d	165-66	3,4-(OCH_3)	**4j**	182-83	Et
3e	200-01	H	**4k**	175-76	Et
3f	182-83	4-Cl	**4l**	115-16	Et
3b	195-96	3-NO_2	**4m**	185-86	Bu
3c	140-41	4-OCH_3	**4n**	115-16	Bu
3d	165-66	3,4-(OCH_3)	**4o**	140-41	Bu
3e	200-01	H	**4p**	142-43	Bu
3f	182-83	4-Cl	**4q**	140-41	Bu
3d	165-66	3,4-$(OCH_3)_2$	**4r**	153-	Bu
3e	200-01	H	**4s**	170-71	Bz
3f	182-83	4-Cl	**4t**	192-93	Bz

RESULTS AND DISCUSSION

Table I shows the melting points of different synthesized dihydropyrimidines in reference to the substitution at R' position as per the Scheme I.

Table II Shows the characterization data of different synthesized dihydropyrimidines in reference to the substitution at R' position as per the Scheme I.

Table III Shows the anti-ulcer activity studies of different synthesized dihydropyrimidines in reference to the substitution at R' position as per the Scheme I.

The synthesis of the compounds (DHPMs) was performed using the route shown in Scheme I. In step 1 {6-methyl-4-(substituted phenyl)-2-thioxo-1, 2, 3, 4-tetrahydropyrimidin-5-carboxylic acid ethyl ester} (3a-t) were synthesized by condensation of acetoacetic ester, thiourea and substituted aromatic aldehydes by stirring for 4 h using piperidine as catalyst. These were also synthesized under microwave heating for five minutes using ethanol as a solvent and HCl as a catalyst. Compounds were confirmed by IR and PMR spectral data. These compounds showed band at 1080 cm^{-1} indicating the presence of C=S (Streching) group and secondary N-H showed band at 3190-3200 cm^{-1} besides ester carbonyl function at 1650 cm^{-1}. The PMR spectra using $CdCl_3$ as solvent showed two D_2O exchangeable N-H protons at δ 10.1 and δ 9.5 as sharp singlets. In addition to this, multiplet for aromatic protons at δ 8.2- 7.5 and sharp singlet at δ 5.4 for C-4 proton were observed.

In step 2, these compounds (3a-t) were converted to their thioethers (DHPMs; 4a-t) as given in scheme 1, where R= Methyl, ethyl, butyl and benzyl by simply refluxing the tetrahydropyrimidine with dimethyl sulphate and diethyl sulphate in case of methyl and ethyl thioethers respectively and with butyl bromide and benzyl chloride in case of butyl and benzyl thioethers. These were confirmed through PMR, IR and Mass spectral studies. Here, only one D_2O exchangeable N-H is present at δ 9.5 besides aromatic protons in the region δ 8.6-7.0. It is interesting to note that benzylic CH_2 (4r-t) attached to sulphur shows non-equivalence of two hydrogens (δ 4.9 and δ 4.2).This is a phenomenon in which slow rotation around C-S single bond being responsible for the non-equivalence of the protons.

Table II: Characterization data of the synthesized compounds

Compd.	Yield (%)	^{1}H NMR (δ, ppm), Mass
4a	33	9.1(s,1H,NH), 7.9-7.5(m,4H,Ar-H), 5.8(s,1H,4-CH), 4.1(q,2H, -O*CH*$_2$CH$_3$), 2.4(s,3H,6-CH$_3$), 1.0(t,3H,-OCH$_2$*CH*$_3$), 2.9(s,3H, S-CH$_3$); m/z 335 M^+
4b	59	9.1(s,1H,NH), 8.4-7.6(m,4H,Ar-H), 5.4(s,1H, 4-CH), 4.1(q,2H -O*CH*$_2$CH$_3$), 2.4(s,3H,6-CH$_3$), 3.1 (s,3H-S-CH$_3$); m/z 335 M^+
4c	35	7.3-6.8(m,4H,Ar-H), 6.2(s,1H,NH), 5.7(s,1H, 4-CH), 4.1(q,2H, -O*CH*$_2$CH$_3$), 3.8(s,3H-OCH$_3$), 2.4(s,3H,S-CH$_3$), 2.3(s,3H,6 -CH$_3$), 1.2(t,3H,-OCH$_2$*CH*$_3$); m/z 321(5.0), 320(29.7), 291(100.0), 247(49.5), 213(82.0), 185(37.9), 140(11.0)
4d	80	7.8(s,1H,NH), 6.7(m,3H,Ar-H), 5.4(s,1H,4-CH), 4.1(q,2H, O*CH*$_2$CH$_3$), 3.8(s,6H,-OCH$_3$), 2.4(s,3H,S-CH$_3$), 2.3(s,3H,6-CH$_3$), 1.1(t,3H,-OCH$_2$*CH*$_3$), m/z 349 M^+
4e	70	7.3(s,5H,Ar-H), 6.2(s,1H,NH), 5.8(s,1H,4-CH), 4.1(q,2H,-O*CH*$_2$CH$_3$), 2.4(s,3H,S-CH$_3$), 2.3(s,3H,6-CH$_3$), 1.2(t,3H,-OCH$_2$*CH*$_3$), m/z 290 M^+
4f	72	7.4-6.8(m, 4H,Ar-H), 6.2(s,1H,NH), 5.6(s,1H,4-CH), 4.1(q,2H, -O*CH*$_2$CH$_3$), 2.4(s,3H,S-CH$_3$), 2.3(s,3H,6-CH$_3$), 1.2(t,3H, -OCH$_2$*CH*$_3$), m/z 303 M^+
4g	78	7.2-7.0(m,4H,Ar-H), 6.0(s,1H,NH), 5.3(s,1H,4-CH), 4.1(q,2H, -O*CH*$_2$CH$_3$), 2.4(s,3H,6-CH$_3$), 2.3(s,3H,Ar-CH$_3$), 2.1(s,3H,S-CH$_3$), 1.1(t,3H,-OCH$_2$*CH*$_3$), m/z 325 M^+
4h	35	7.3-7.1(m,5H,Ar-H), 5.6(s,1H,4-CH), 4.1(q,2H,-O*CH*$_2$CH$_3$), 3.1(m,1H,S-CH$_2$), 2.9(m,1H,S-CH$_2$), 2.3(s,3H,6-CH$_3$), 1.3-1.1(m,6H,S-CH$_2$*CH*$_3$ & OCH$_2$*CH*$_3$); m/z 304(7.8), 275(40.5), 255(38.8), 226(70.3), 198(25.6), 169(100.0), 128(25.6), 111(30.4), 83(30.0), 71(60.8)
4i	52	8.2-7.4(m,4H,Ar-H), 5.5(s,1H,4-CH), 4.1(q,2H,-O*CH*$_2$CH$_3$), 3.3(m,1H,S-CH$_2$), 3.1(m,1H,S-CH$_2$), 2.3(s,3H,6-CH$_3$), 1.3-1.1(m,6H,S-CH$_2$*CH*$_3$ & OCH$_2$*CH*$_3$); m/z 349 M^+
4j	60	7.3-6.8(m,4H,Ar-H), 6.3(s,1H,NH), 5.5(s,1H,4-CH), 4.1(q,2H -O*CH*$_2$CH$_3$), 3.7(s,3H,-OCH$_3$), 3.1(m,1H,S-CH$_2$), 2.9(m,1H, S-CH$_2$), 2.4(s,3H,6-CH$_3$), 1.1-1.2(m,6H,S-CH$_2$*CH*$_3$ & OCH$_2$*CH*$_3$), m/z 319 M^+
4k	72	7.3-6.8(m,3H,Ar-H), 6.3(s,1H,NH), 5.5(s,1H,4-CH), 4.1(q,2H, -O*CH*$_2$CH$_3$), 3.7(s,6H,-OCH$_3$), 3.1(m,1H,S-CH$_2$), 2.9(m,1H, S-CH$_2$), 2.3(s,3H,6-CH$_3$), 1.1-1.2(m, 6H,S-CH$_2$*CH*$_3$ & OCH$_2$*CH*$_3$); m/z 365 M^+
4l	40	7.1(d,2H,Ar-H), 6.8(d,2H,Ar-H), 5.5(s,1H,4-CH), 4.1(q,2H, -O*CH*$_2$CH$_3$), 3.1(m,1H,S-CH$_2$), 2.9(m,1H,S-CH$_2$), 2.3(s,3H, 6-CH$_3$), 1.3-1.1(m,6H,S-CH$_2$*CH*$_3$ & OCH$_2$*CH*$_3$), m/z 339 M^+
4m	77	7.4(d,2H,Ar-H), 6.8(d,2H,Ar-H), 5.8(s,1H,4-CH), 4.1(q,2H, -O*CH*$_2$CH$_3$), 3.8(s,3H,-OCH$_3$), 3.6(m,1H of S-CH$_2$), 3.2(m,1H of S-CH$_2$), 2.6(s,3H,6-CH$_3$),

		2.0(s,1H,NH), 1.5(m,2H,-CH_2 $CH_2$$CH_3$ of S-butyl), 1.3(m,2H,-$CH_2CH_2CH_3$ of S-butyl), 1.1(t,3H,-OCH_2 CH_3), 0.8(t,3H,CH_3 of S-butyl); m/z 363(8.1), 362(6.6), 334(24.2), 333(100.0), 305(25.7), 289(33.4), 277(48.1), 255(89.8), 233(36.2), 199(40.0), 171(20.6), 82(36.8), 80(37.6)
4n	42	8.6-7.0(m,5H,4Ar-H & one NH), 5.4(s,1H,4-CH), 4.1(q,2H, -OCH_2CH_3), 3.6(m,1H of S-CH_2), 3.2(m,1H, of S-CH_2), 2.6(s,3H,6-CH_3), 1.5-1.3(m,4H,-CH_2CH_2-CH_3 of S-butyl), 1.1(t,3H,-OCH_2CH_3), 0.8(t,3H,-CH_3 of S-butyl), m/z 378 M^+
4n	42	8.6-7.0(m,5H,4Ar-H & one NH), 5.4(s,1H,4-CH), 4.1(q,2H, -OCH_2CH_3), 3.6(m,1H of S-CH_2), 3.2(m,1H, of S-CH_2), 2.6(s,3H,6-CH_3), 1.5-1.3(m,4H,-CH_2CH_2-CH_3 of S-butyl), 1.1(t,3H,-OCH_2CH_3), 0.8(t,3H,-CH_3 of S-butyl), m/z 378 M^+
4o	72	7.3-6.8(m,3H,Ar-H), 5.8(s,1H,4-CH), 4.1(q,2H,-OCH_2 CH_3), 3.7-3.6(d,6H,$(O\text{-}CH_3)_2$), 3.6(m,1H, of S-CH_2), 3.2(m,1H, of S-CH_2), 2.6(s,3H,6-CH_3), 1.5-1.3(m,4H,-CH_2CH_2-CH_3 of S-butyl), 1.1(t,3H,O-CH_2CH_3), 0.8(t,3H,-CH_3 of S-butyl); m/z 393 M^+
4p	70	7.6(s,1H,NH), 7.3(m,5H,Ar-H), 5.8(s,1H,4-CH), 4.1(q,2H,-OCH_2 CH_3), 3.6(m,1H of S-CH_2), 3.2(m,1H of S-CH_2), 2.6(s,3H,6-CH_3), 1.5-1.3(m,4H,-$CH_2CH_2CH_3$ of S-butyl), 1.1(t,3H,OCH_2 CH_3), 0.8(t,3H,-CH_3 of S-butyl); m/z 332(30.6), 255(24.3), 198(18.3), 169(100.00), 128(15.8), 111(30.6), 71(89.0)
4q	62	8.2(s,1H,NH), 7.3(d,2H,Ar-H), 7.2(d,2H,Ar-H), 5.8(s, 1H,4-CH), 4.1(q,2H,OCH_2CH_3), 3.6(m,1H of S-CH_2), 3.2(m,1H of S-CH_2), 2.6(s,3H,6-CH_3), 1.5-1.3(m,4H,-$CH_2CH_2CH_3$ of S-butyl), 1.1(t,3H,OCH_2CH_3), 0.8(t, 3H,-CH_3 of S-butyl); m/z 368 M^+
4r	40	12.0(s,1H,NH), 7.3-6.6(m,3H,Ar-H); 5.8(s,1H,4-CH), 4.9(d,1H, of S-CH_2), 4.2(d,1H, of S-CH_2), 4.1(q,2H, -OCH_2CH_3), 3.9(d,6H,t-OCH_3), 2.5(s,3H,6-CH_3), 1.1(t,3H,-OCH_2CH_3); m/z 427(16.3), 398(7.8), 353(5.2), 335(16.8), 289(18.2), 91(100.00), 65.0(10.0), 58.0(15.2), 56(11.0)
4s	76	12.0(s,1H,NH), 7.2-7.0(m,5H,Ar-H), 5.8(s,1H,4-CH), 5.0(d,1H of S-CH_2), 4.5(d,1H of S-CH_2), 4.1(q,2H, -OCH_2CH_3), 2.5(s,3H,6-CH_3), 1.1(t,3H,-OCH_2CH_3); m/z 367(17.9), 338(4.6), 289(19.3), 276(5.2), 144(2.3), 91.0(100.0), 77.0(6.0), 65.0(9.5), 58.0(14.4)
4t	65	10.0(s,1H,NH), 7.3(d,2H,Ar-H), 7.2(d,2H, AR-H), 5.8(s,1H,4-CH), 4.9(d,1H, of S-CH_2), 4.3(d,1H, of S-CH_2), 4.1(q,2H,-OCH_2CH_3), 2.5(s,3H,6-CH_3), 1.1(t, 3H,-OCH_2CH_3)

Anti-ulcer Activity studies

20 compounds were synthesized as substituted DHPMs. Four differently substituted compounds were selected as 4d, 4i, 4o and 4r for screening of anti-ulcer activity in four different animal models viz. Cold restraint stress (CRS), pylorus ligation (PL), aspirin (ASP) and ethanol (EtOH) induced gastric ulceration in rats. Omeprazole, a standard agent and proved proton pump inhibitor has been used in the present investigation and showed significant anti-ulcer activity as compared to control group. Test compound 4r which was benzyl substituted DHPMs, has shown most potent anti-ulcer activity and compound 4i and 4o showed moderate activity as compared to control group. Moreover, compound 4d was found to be devoid of anti-ulcer activity.

Thus, it may be concluded that benzyl substitution of DHPMs may have significant anti-ulcer activity. Further studies are needed to find out its mechanism of action and to synthesize more substituted DHPMs for characterization of a lead compound.

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Table III : Anti-ulcer Activity Studies of test compounds

Treatment Group	Dose	CRS RUI (mm^2/rat)	PL RUI (mm^2/rat)	ASP RUI (mm^2/rat)	EtOH RUI (mm^2/rat)
Group 1: Control	saline	31.2±2.71	10.8±1.31	13.3±2.12	17.9±1.83
Group 2:Omeprazole	10mg	7.2± 0.93*	2.8± 0.05*	6.5± 0.25*	3.4± 0.35*
Group 3:Omeprazole	20mg	4.7± 0.39*	1.2± 0.02*	3.6± 0.12*	1.0± 0.21*
Group 4 and 5: Methyl substituted DHPMs (4d)	10mg	29.8±2.87	11.0±1.63	12.6±2.8	17.1±2.64
	20mg	26.6± 0.02	10.8± 0.12	8.6± 0.12	14.6±0.24
Group 6 and 7: Ethyl substituted DHPMs (4i)	10mg	24.8 ±0.12	9.6± 0.21	10.5±0.34	16.6±0.54
	20mg	20.6± 0.18[a]	7.6 ± 0.23[a]	6.6 ± 0.44[a]	6.2 ± 0.32[a]
Group 8 and 9: Butyl substituted DHPMs (4o)	10mg	14.6± 0.65[a]	5.6± 0.11[a]	9.6± 0.55[a]	11.6±0.72[a]
	20mg	11.6± 0.34[a]	3.7± 0.35[a]	5.4±0.012[a]	4.6± 0.01[a]
Group 10 and 11: Benzyl substituted DHPMs (4r)	10mg	7.6± 0.62[a]	3.4± 0.01[a]	7.6 ± 0.32[a]	6.6± 0.22[a]
	20mg	5.6± 0.05[a]	1.6± 0.23[a]	4.6± 0.07[a]	1.6± 0.84[a]

n=5; Data is expressed as Mean±S.E.M. ; *P≤0.05 Vs Control; [a]P≤0.05 Vs Standard

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