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Short communication

Synthesis and biological evaluation of some 4-(1*H*-indol-3-yl)-6-phenyl-1,2,3,4-tetrahydropyrimidin--2-ones/thiones as potent anti-inflammatory agents*

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Twelve new 4-(1*H*-indol-3-yl)-6-phenyl-1,2,3,4-tetrahydropyrimidin-2-ones/thiones (**7-18**) have been synthesized by reacting 1-aryl-3-(1*H*-indol-3-yl)-2-propen-1-one with urea and thiourea in ethanolic potassium hydroxide. Their structures have been confirmed by IR, ^{1}H NMR and mass spectral data. The compounds were tested for their anti-inflammatory activity. Test results revealed that compounds showed 49.5 to 70.7% anti-inflammatory activity whereas the standard drug ibuprofen showed 86.4% activity at the same oral dose. Four compounds, 4-(1*H*-indol-3-yl)-6-(4-chlorophenyl)-1,2,3,4-tetrahydropyrimidin-2-one (**8**), 4-(1*H*-indol-3-yl)-6-(4-methylphenyl)-1,2,3,4-tetrahydropyrimidin-2-one (**10**), 4-(1*H*-indol-3-yl)-6-(4-chlorophenyl)-1,2,3,4-tetrahydropyrimidin-2-thione (**14**), 4-(1*H*-indol--3-yl)-6-(4-methylphenyl)-1,2,3,4-tetrahydropyrimidin-2-thione (**16**), that showed significant anti-inflammatory activity were selected to study their ulcerogenic and lipid peroxidation activities. All tested compounds showed significant reduction in the ulcerogenic potential and lipid peroxidation compared to the standard drug ibuprofen.

Keywords: pyrimidine derivatives, anti-inflammatory activity, ulcerogenicity, lipid peroxidation

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Among the wide range of heterocycles explored to develop pharmaceutically important molecules, pyrimidine has played an important role in medicinal chemistry. A survey of literature has shown that compounds having a pyrimidine nucleus possess a broad range of biological activities such as anticancer (1), antiviral (2), antibacterial (3), antimalarial (4), antihypertensive (5) and anti-inflammmatory activities (6, 7). Moreover, chemistry and synthesis of 1,2,3,4-tetrahydropyrimidin-2-ones/thiones have been attracting extensive attention. The importance of these tetrahydropyrimidines is mainly due to their close structural relationship to the clinically important dihydropyrimidine

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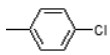
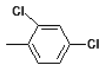
calcium channel blockers (8). As a result of the remarkable pharmacological efficiency of pyrimidine derivatives, intensive search has been focused on anti-inflammatory activity of the pyrimidine nucleus. Recently, two PCT international applications have been filed for 2-thiopyrimidine derivatives possessing potent activity against inflammations and immune disorders (9, 10). Furthermore, indoles and their derivatives have been found to be associated with various biological activities such as anticancer (11), antimicrobial (12) and anti-inflammatory (13, 14) activities. Encouraged by these observations and also in continuation of our search (15, 16) for potent anti-inflammatory molecules, we decided to synthesize indolyltetrahydropyrimidin-2-ones/thione derivatives in order to evaluate their anti-inflammatory activity.

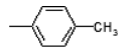
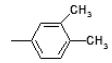
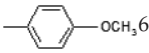
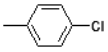
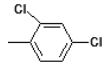
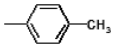
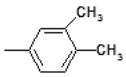
EXPERIMENTAL

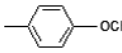
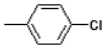
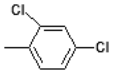
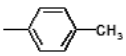
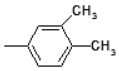
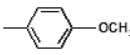
Melting points were measured in open capillary tubes and are uncorrected. IR (KBr) spectra were recorded on a Nicolet, 5PC FT-IR spectrometer (Browser Morner, USA) and ^{1}H NMR spectra on a Bruker DRX-300 FT NMR (Bruker, Germany) spectrophotometer using TMS as internal reference (chemical shift in δ ppm). Mass spectra were recorded on a Jeol-JMS-D-300 mass spectrometer (70 eV) (Jeol, Japan). Purity of the compounds was checked on silica gel G plates using iodine vapours as visualizing agents. All reagents used in the present work were of analytical grade.

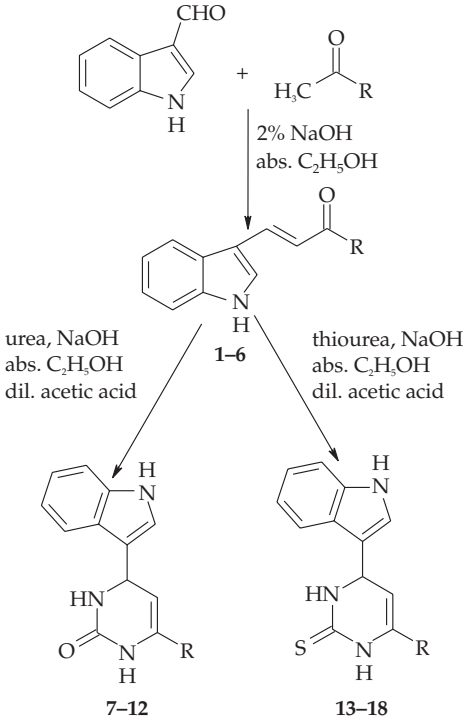
The synthetic pathway is given in Scheme 1 and characterization data of the compounds are given in Table I. Satisfactory analysis for C, H, N was obtained for all the compounds within ± 0.4% of the theoretical values.

Table I. Characterization data of newly synthesized compounds

Compd. No.	R	Yield (%)	M.p. (°C)	Molecular formula (M_r)	Spectral data		
					IR (KBr) (cm^{-1})	^{1}H NMR ($CDCl_3$/DMSO-d_6), δ (ppm)	Mass (*m/z*)
1		61	173–175	$C_{17}H_{13}NO$ (247.29)	3289 (NH) 3026 (C–H) 1690 (C=O) 1582 (C=C)	7.21 (d, 1H, –COCH=), 7.25 (d, 1H, =CHCOR), 7.37–9.96 (m, 9H, ArH), 11.12 (s, 1H, NH)	247 (M^+)
2		72	178–180	$C_{17}H_{12}ClNO$ (281.74)	3276 (NH) 2908 (C–H) 1696 (C=O) 1591 (C=C)	7.26 (d, 1H, –COCH=), 7.29 (d, 1H, =CHCOR), 7.43–8.10 (m, 9H, ArH), 11.16 (s, 1H, NH)	281 (M^+)
3		43	187–189	$C_{17}H_{11}Cl_2NO$ (316.18)	3306 (NH) 3051 (C–H) 1692 (C=O) 1601 (C=C)	7.32 (d, 1H, –COCH=), 7.38 (d, 1H, =CHCOR), 7.57–8.23(m, 9H, ArH), 11.27 (s, 1H, NH)	316 (M^+)

4		53	168–170	$C_{18}H_{15}NO$ (261.32)	3293 (NH) 3011 (C–H) 1679 (C=O) 1599 (C=C)	2.36 (s, 3H, CH_3), 7.12 (d, 1H, –COCH=), 7.27 (d, 1H, =CHCOR), 7.38–7.96 (m, 9H, ArH), 10.49 (s, 1H, NH)	261 (M^+)
5		85	160–162	$C_{19}H_{17}NO$ (275.35)	3283 (NH) 3050 (C–H) 1706 (C=O) 1609 (C=C)	2.34 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 7.08 (d, 1H, –COCH=), 7.23 (d, 1H, =CHCOR), 7.32–7.91 (m, 9H, ArH), 10.47 (s, 1H, NH)	275 (M^+)
6		64	155–157	$C_{18}H_{15}NO_2$ (277.32)	3306 (NH) 3028 (C–H) 1697 (C=O) 1570 (C=C)	3.91 (s, 3H, OCH_3), 7.34 (d, 1H, –COCH=), 7.38 (d, 1H, =CHCOR), 7.53–8.22 (m, 9H, ArH), 11.08 (s, 1H, NH)	277 (M^+)
7		53	153–156	$C_{18}H_{15}N_3O$ (289.33)	3382 (NH) 1703 (C=O) 1569 (C=C)	6.83 (d, 1H, methine), 7.04 (d, 1H, olefinic), 7.32–7.75 (m, 8H, ArH), 8.19 (s, 1H, NH), 9.75 (s, 1H, NH), 11.02 (bs, 1H, NH-indole)	289 (M^+)
8		46	210–213	$C_{18}H_{14}ClN_3O$ (323.78)	3389 (NH) 1692 (C=O) 1576 (C=C)	6.87 (d, 1H, methine), 7.13 (d, 1H, olefinic), 7.41–7.85 (m, 8H, ArH), 8.27 (s, 1H, NH), 9.81 (s, 1H, NH), 11.16 (bs, 1H, NH-indole)	323 (M^+)
9		48	181–183	$C_{18}H_{14}Cl_2N_3O$ (358.22)	3393 (NH) 1716 (C=O) 1581 (C=C)	6.98 (d, 1H, methine), 7.17 (d, 1H, olefinic), 7.53–7.94 (m, 8H, ArH), 8.31 (s, 1H, NH), 9.89 (s, 1H, NH), 11.22 (bs, 1H, NH-indole)	358 (M^+)
10		55	152–154	$C_{19}H_{17}N_3O$ (303.36)	3396 (NH) 1697 (C=O) 1587 (C=C)	2.39 (s, 3H, CH_3), 7.16 (d, 1H, methine), 7.29 (d, 1H, olefinic), 7.41–7.83 (m, 9H, ArH), 8.18 (bs, 1H, NH), 10.05 (bs, 1H, NH), 11.39 (bs, 1H, NH-indole)	303 (M^+)
11		56	195–198	$C_{20}H_{19}N_3O$ (317.39)	3389 (NH) 1701 (C=O) 1582 (C=C)	2.54 [s, 6H, $(CH_3)_2$], 7.26–8.15 (m, 11H, 9H–ArH + 1H–methine + 1H-olefinic), 8.34 (s, 1H, NH), 9.96 (s, 1H, NH), 12.17 (bs, 1H, NH-indole)	317 (M^+)

12		61	181–183	$C_{19}H_{17}N_3O_2$ (319.37)	3395 (NH) 1572 (C=C) 1694 (C=O)	3.89 (s, 3H, OCH_3), 7.12 (d, 1H, methine), 7.26 (d, 1H, olefinic), 7.25–7.86 (m, 9H, ArH), 8.25 (bs, 1H, NH), 10.01 (s, 1H, NH), 11.39 (bs, 1H, NH-indole)	319 (M^+)
13		68	161–164	$C_{18}H_{15}N_3S$ (305.39)	3411 (NH) 1576 (C=C) 1172 (C=S)	7.17–8.01 (m, 11H, ArH + 1H-methine + 1H-olefinic), 8.24 (s, 1H, NH), 9.87 (s, 1H, NH), 12.05 (bs, 1H, NH-indole)	305 (M^+)
14		57	179–182	$C_{18}H_{14}ClN_3S$ (339.84)	3397 (NH) 1592 (C=C) 1184 (C=S)	7.19–8.08 (m, 11H, ArH + 1H-methine + 1H-olefinic), 8.26 (s, 1H, NH), 9.91 (s, 1H, NH), 12.13 (bs, 1H, NH-indole)	339 (M^+)
15		62	203–205	$C_{18}H_{14}Cl_2N_3S$ (374.28)	3394 (NH) 1584 (C=C) 1169 (C=S)	7.23–8.17 (m, 11H, ArH + 1H-methine + 1H-olefinic), 8.29 (s, 1H, NH), 9.97 (s, 1H, NH), 12.16 (bs, 1H, NH-indole)	374 (M^+)
16		53	147–150	$C_{19}H_{17}N_3S$ (319.42)	3402 (NH) 1586 (C=C) 1173 (C=S)	2.42 (s, 3H, CH_3), 7.12 (d, 1H, methine), 7.23 (d, 1H, olefinic), 7.41–7.83 (m, 9H, ArH), 8.24 (bs, 1H, NH), 10.12 (bs, 1H, NH), 11.45 (bs, 1H, NH-indole)	319 (M^+)
17		67	187–189	$C_{20}H_{19}N_3S$ (333.45)	3398 (NH) 1590 (C=C) 1157 (C=S)	2.50 [s, 6H, $(CH_3)_2$], 7.19–8.10 (m, 11H, 9H–ArH + 1H–methine + 1H-olefinic), 8.28 (s, 1H, NH), 9.93 (s, 1H, NH), 12.14 (bs, 1H, NH-indole)	333 (M^+)
18		53	174–176	$C_{20}H_{19}N_3O$ (317.389)	3403 (NH) 1585 (C=C) 1166 (C=S)	3.87 (s, 3H, OCH_3), 7.21 (d, 1H, methine), 7.27 (d, 1H, olefinic), 7.51–7.97 (m, 9H, ArH), 8.29 (bs, 1H, NH), 10.08 (s, 1H, NH), 11.89 (bs, 1H, NH-indole)	317 (M^+)



R: phenyl, 4-chlorophenyl, 2,4-dichlorophenyl,
4-methylphenyl, 3,4-dimethylphenyl, 4-methoxyphenyl

Scheme I

Syntheses

*1-Aryl-3-(*1H-*indol-3-yl)-2-propen-1-ones (**1-6**)*. – To a solution of indole-3-carboxaldehyde (0.01 mol) in absolute ethanol (50 mL), different substituted acetophenones (0.01 mol) were added in the presence of 2% NaOH solution (5 mL). The reaction mixtures were stirred for 10–12 h at room temperature and then refluxed for 4–6 h. Excess solvent was distilled off and the crude product was poured into ice water. The resulting solid thus separated was filtered, washed with water and recystallized from ethanol.

*4-(*1H-i*ndol-3-yl)-6-phenyl-1,2,3,4-tetrahydropyrimidin-2-ones (**7-12**)* and *4-(*1H-i*ndol-3--yl)-6-phenyl-1,2,3,4-tetrahydropyrimidin-2-thiones (**13-18**)*. – A mixture of **1-6** (0.01 mol) and urea or thiourea (0.01 mol) in ethanolic potassium hydroxide (1 g in 10 mL) was refluxed for 4–7 h. The volume of the reaction mixture was reduced to half of its original volume, diluted with ice-cold water, then acidified with dilute acetic acid and kept overnight. The solid thus obtained was filtered, washed with water and recrystallized from ethanol.

Pharmacology

Wistar rats used in the present study were housed and cared in accordance with the Hamdard University Animal Care Unit, which applies the guidelines and rules laid down by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Social Justice and Empowerment, Government of India. Jamia Hamdard Animal Ethics Committee (JHAEC) approved the use of rats for biological studies reported in this paper. Wistar rats of either sex, weighing 180–200 g (12 weeks) were used. The animals were housed in groups of six and were acclimatized to room conditions for at least 2 days before the experiment. Food and water were freely available up to the time of experiments. The food was withdrawn on the day before the experiment, but free access to water was allowed.

All the compounds (70 mg kg^{-1} body mass) and the reference NSAID ibuprofen (70 mg kg^{-1} body mass) were suspended in 1% carboxymethyl cellulose (CMC) and administered orally with an animal feeding needle. The control groups received appropriate volumes of vehicle (1% CMC, oral) only.

Anti-inflammatory activity. – This activity was performed by the procedure of Winter *et al*. (17) on groups of six animals each. A freshly prepared suspension of carragenean (1.0% *m/V*, 0.1 mL) was injected in the plantar region of the right hind paw of each rat. One group was kept as control and the animals of the other group were pretreated with the test drugs (70 mg kg^{-1} body mass) suspended in 1.0% CMC given orally 1 h before carragenean treatment. The volume was measured before and after 3 and 4 h of carragenean treatment using a pleythysmometer.

Acute ulcerogenesis. – Acute ulcerogenesis test was done according to Cioli *et al*. (18). Wistar rats were divided into different groups of six animals each. Ulcerogenic activity was evaluated after *p.o*. administration of test compounds or ibuprofen at a dose of 200 mg kg^{-1} body mass. Control rats received a suspension of 1% carboxymethyl cellulose per os. Food, but not water, was removed 24 h before administration of the test compounds. After the drug treatment, the rats were fed a normal diet for 17 h and were then sacrificed. The stomach was removed and opened along the greater curvature, washed with distilled water and cleaned gently by dipping in saline. The mucosal damage was examined by means of a magnifying glass. For each stomach, the mucosal damage was assessed according to the following scoring system: 0.5 – redness; 1.0 – spot ulcers; 1.5 – hemorrhagic streaks; 2.0 – 3 < ulcers ≤ 5; 3.0 – ulcers >5.

The mean score of each treated group minus the mean score of the control group was regarded as the severity index of gastric mucosal damage.

Lipid peroxidation. – Lipid peroxidation in the gastric mucosa was determined according to the method of Ohkawa *et al*. (19). After screening for ulcerogenic activity, the gastric mucosa was scrapped with two glass slides, weighed (100 mg) and homogenized in 1.8 mL of 1.15% ice-cold KCl solution. The homogenate was supplemented with 0.2 mL of 8.1% sodium dodecyl sulfate (SDS), 1.5 mL of acetate buffer (pH = 3.5) and 1.5 mL of 0.8% thiobarbituric acid (TBA). The mixture was heated at 95 °C for 60 min. After cooling, the reactants were supplemented with 5 mL of the *n*-butanol/pyridine mixture (15:1, *V/V*), shaken vigorously for 1 minute and centrifuged for 10 min at 4000 rpm. The supernatant organic layer was taken out and absorbance was measured at λ = 532 nm on a

UV-Vis spectrophotometer. The results were expressed as nmol malondialdehyde per 100 mg tissue, using the molar absorption coefficient of 1.56×10^5 mol^{-1} cm^{-1} (20).

All the pharmacological data are expressed as mean ± SEM; Student's *t*-test was applied to determine the significance of the difference between the standard group and the animals treated with the test compounds.

RESULTS AND DISCUSSION

1-Aryl-3-(1*H*-indol-3yl)-2-propen-1-ones (**1-6**) were prepared by treating indol-3--carboxaldehyde with substituted acetophenone in the presence of ethanol and 2% NaOH. The IR spectra of compounds **1-6** revealed the presence of absorption bands from 3276 to 3306 cm^{-1} for the NH group and from 1679 to 1706 cm^{-1} due to C=O stretching vibrations. The ^{1}H NMR spectrum of compounds **1-6** showed two doublets from δ 7.08 to 7.38 ppm and from δ 7.23 to 7.38 ppm for COCH= and =CHCOR protons confirming the formation of compounds **1–6**. The mass spectrum of compounds **1-6** showed molecular ion peaks M$^+$ at *m/z* corresponding to their respective molecular masses, which is in consistency with their respective molecular formulas (Table I). Treatment of compounds **1-6** with urea in ethanolic potassium hydroxide solution afforded 4-(1*H*-indol-3-yl)-6-phenyl--1,2,3,4-tetrahydropyrimidin-2-ones (**7-12**). The IR spectra of compounds **7-12** showed the presence of absorption bands from 3382 to 3396 cm^{-1} for the NH group and from 1692 to 1716 cm^{-1} for C=O stretching vibrations. The structure of the pyrimidin-2-ones (**7-12**) was further supported by their ^{1}H NMR spectral data, which showed two doublets from δ 6.83 to 7.26 ppm and from δ 7.04 to 7.29 ppm, respectively, due to methene and olefinic protons of the pyrimidine ring. The two NH protons of the pyrimidine ring were seen as two broad singlets from δ 8.18 to 8.34 ppm and from δ 9.75 to 10.05 ppm, respectively. The aromatic protons resonated as a complex multiplet in the region from δ 7.32 to 8.15 ppm, integrating for 9 protons. The mass spectra of compounds **7-12** showed molecular ion peaks M$^+$ at *m/z* corresponding to their respective molecular mass, which is in consistency with their respective molecular formulas (Table I). 4-(1*H*-indolyl-3yl)-6-phenyl--1,2,3,4-tetrahydropyrimidin-2-thiones (**13-18**) were synthesized by treatment of 1-aryl--3-(1*H*-indol-3-yl)-2-propen-1-one (**1-6**) with thiourea in the presence of ethanolic KOH solution. IR spectra of compounds **13-18** showed absorption bands from 3394 to 3411 cm^{-1} for NH and from 1157 to 1184 cm^{-1} for C=S groups. The ^{1}H NMR spectra of compounds **13-18** showed two doublets from δ 7.12 to 7.21 ppm and from δ 7.23 to 7.27 ppm, respectively, due to methene and olefinic protons of the pyrimidine ring. The two NH protons of the pyrimidine ring were seen as two broad singlets from δ 8.24 to 8.29 ppm and from δ 9.97 to 10.12 ppm, respectively. The aromatic protons resonated as a complex multiplet in the region from δ 7.23 to 8.17 ppm, integrating for 9 protons. The mass spectra of compounds **12-18** showed molecular ion peaks M$^+$ at *m/z* corresponding to their respective molecular mass, which is consistent with their respective molecular formulas (Table I).

The anti-inflammatory activity of the synthesized compounds **7-10** and **13-16** were evaluated by the carragenean induced paw edema method. The compounds were tested at an oral dose of 70 mg kg^{-1} body mass, and were compared with the standard drug ibuprofen at the same oral dose, first after 3 and then after 4 h of carragenean treatment.

Both readings are reported in Table II, but since % inhibition was found to be more significant after 4 h, the discussion is based on this reading. Test compounds **7-10** and **13-16** showed anti-inflammatory activity ranging from 49.5 to 70.7%, and the standard drug ibuprofen showed 86.4% inhibition after 4 h. Pyrimidin-2-one derivatives (**7-10**) showed anti-inflammatory activity ranging from 55.6 to 70.7%. Compound **8**, having 4-chlorophenyl group at the 6th position of pyrimidine nucleus, showed maximum inhibition (70.7%), whereas replacement of the 4-chlorophenyl group with 4-methylphenyl group (**10**) resulted in a slight decrease of activity (68.7%). The pyrimidin-2-one derivative, having a phenyl group at the 6th position, showed minimum activity. The pyrimidin-2-thione derivatives (**13-16**) showed anti-inflammatory activity ranging from 49.5 to 68.7%. Compound **14**, having 4-chlorophenyl group at the 6th position of pyrimidine nucleus, showed maximum activity (68.7%); a slight decrease in activity was observed when the 4-chlorophenyl group was replaced with 4-methyl phenyl group (**16**, 65.7%). Compound **13**, having a phenyl group at the 6th position, showed minimum activity. Thus, it was noted that pyrimidin-3-one derivatives had shown a slightly improved anti-inflammatory activity compared to pyrimidin-2-thione derivatives. It was also observed that in both derivatives, compounds having the 4-chlorophenyl and 4-methyl phenyl group at the 6th position of pyrimidine nucleus showed significant anti-inflammatory activity.

Compounds **8**, **10**, **14**, **16** that showed more than 65% activity were further tested for ulcerogenic activity. All the compounds were tested at an oral dose of 200 mg kg^{-1} body mass. The standard drug ibuprofen showed a high severity index of 2.0 ± 0.12. Maximum reduction in ulcerogenic activity (mean severity index ± SEM, n = 6) was 0.33 ± 0.10, found in pyrimidin-2-one derivative (**10**) having the 4-chlorophenyl group at the

Table II. Biological data of synthesized compounds

Compd. No.	Dose (mg kg^{-1})	Anti-inflammatory activity (% inhibition)[a]		Dose (mg kg^{-1})	Ulcerogenic activity (severity index)[a]	MDA (nmol per 100 mg tissue)[a]
		After 3 h	After 4 h			
7	70	50.0 ± 2.5	55.6 ± 1.3[b]	200	–	–
8	70	56.9 ± 2.5	70.7 ± 1.9[c]	200	0.33 ± 0.10[b]	4.20 ± 0.15[b]
9	70	50.0 ± 1.3	57.6 ± 2.2[b]	200	–	–
10	70	62.7 ± 2.0	68.7 ± 1.8[b]	200	0.75 ± 0.25[d]	4.34 ± 0.12[b]
13	70	40.2 ± 2.8	49.5 ± 2.0[b]	200	–	–
14	70	55.9 ± 2.5	68.7 ± 1.9[b]	200	0.41 ± 0.08[b]	4.21 ± 0.13[b]
15	70	47.0 ± 2.6	56.6 ± 1.9[b]	200	–	–
16	70	54.9 ± 2.5	65.7 ± 1.3[b]	200	0.58 ± 0.08[b]	4.36 ± 0.07[b]
Ibuprofen	70	83.3 ± 2.8	86.4 ± 2.0	200	2.00 ± 0.12	6.15 ± 0.18
Control	1 mL 1% CMC	–	–	1 mL 1% CMC	–	3.26 ± 0.05[b]

[a] Mean ± SEM, n = 6.
Significant difference in respect to ibuprofen: [b] $p < 0.0001$, [c] $p < 0.001$, [d] $p < 0.005$.

6th position and showing the highest anti-inflammatory activity. The pyrimidin-2-thione derivative (**14**), having the 4-chlorophenyl group at the 6th position, also showed reduction in the severity index (0.41 ± 0.08). The other two compounds (**8** and **16**) showed moderate severity indices.

It has been reported in the literature that lower ulcerogenic activity of compounds is combined with reduced malondialdehyde content in the affected area of the gastrointestinal tract, an end product of lipid peroxidation. Therefore, an attempt was made to correlate the decrease in ulcerogenic activity of the compounds with that of lipid peroxidation. All the compounds screened for ulcerogenic activity were also analyzed for lipid peroxidation. Lipid peroxidation is measured as nmol of MDA per 100 mg of gastric mucosa tissue. Ibuprofen (standard drug) showed the maximum lipid peroxidation (6.15 ± 0.18 nmol MDA per 100 mg tissue), whereas the control group receiving the vehicle (suspension of 1% CMC) per os and showed 3.26 ± 0.05 nmol MDA per 100 mg tissue. It was found that compounds showing lower ulcerogenic activity also showed a reduction in lipid peroxidation (Table II). Thus, these studies show that synthesized compounds have inhibited induction of gastric mucosal lesions and the results further suggest that their protective effect might be related to the inhibition of lipid peroxidation in the gastric mucosa.

CONCLUSIONS

Various 1,2,3,4-tetrahydropyrimidine derivatives were prepared with the objective of developing better anti-inflammatory molecules with minimum ulcerogenic potential. Among these derivatives, pyrimidin-2-ones were found to have slightly improved activity compared to pyrimidin-2-thiones. The presence of a 4-chlorophenyl group at the 6th position in both pyrimidine derivatives showed high activity. Compound **8**, 4-(1*H*-indol-3-yl)-6-(4-chlorophenyl)-1,2,3,4-tetrahydropyrimidin-2-one, showed maximum anti-inflammatory activity with maximum reduction of the severity index and minimum lipid peroxdation.

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S A Ž E T A K

Sinteza i biološko vrednovanje 4-(1*H*-indol-3-il)-6-fenil--1,2,3,4-tetrahidropirimidin-2-ona/tiona kao jakih protuuplanih tvari

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Dvanaest novih 4-(1*H*-indol-3-il)-6-fenil-1,2,3,4-tetrahidropirimidin-2-ona/tiona (**7–18**) sintetizirano je reakcijom 1-aril-3-(1*H*-indol-3-il)-2-propen-1-ona s ureom i tioureom u etanolnoj otopini kalijeva hidroksida. Njihove strukture potvrđene su IR, ^{1}H NMR i masenom spektrometrijom. Farmakološko vrednovanje pokazalo je da ti spojevi imaju od 49,5 do 70,7% protuupalnog djelovanja, dok je standardni lijek ibuprofen pokazao 86,4% djelovanja uz istu peroralno uzetu dozu. Spojevi koji pokazuju značajno protuupalno djelovanje (**8**, **10**, **14**, **16**) ispitani su na ulcerogenost i djelovanje na lipidnu peroksidaciju. Svi testirani spojevi su značajno manje ulcerogeni i manje djeluju na lipidnu peroksidaciju od ibuprofena.

Ključne riječi: derivati pirimidina, protuupalno djelovanje, ulcerogenost, lipidna peroksidacija

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