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Synthesis, Characterization and Biological Evaluation of Some Dihydropyrimidinones

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An efficient and facile one pot synthesis of 3,4-dihydropyrimidinones (Biginelli compounds) from divergent aldehydes, β-keto esters and urea or thiourea under solvent free conditions was performed using citric acid as catalyst, resulted in promising yields. These compounds were subjected for anticancer and antiinflammatory activities which showed significant activities.

Key Words: Biginelli compounds, Citric acid, Anticancer activity, Antiinflammatory activity.

INTRODUCTION

Being important building blocks and versatile synthons, 3,4-dihydropyrimidinones are highly featured in medicinal chemistry due to their attractive pharmacological properties, including calcium channel blockers, antihypertensive agents, α-1a-antagonists, HIV gp-120-CD4 inhibitors (crambine and betzellidine alkaloids), antiviral, antitumour, antibacterial activities and neuropeptide Y(NPY) antagonists[1-4]. Therefore, the discovery of milder and practical routes for the synthesis of dihydropyrimidin-2(1*H*)-ones continues to attract the attention of researchers[5-8]. In the present study, a series of dihydropyrimidinone derivatives were prepared and evaluated for anticancer and antiinflammatory studies.

EXPERIMENTAL

Melting points were recorded on SD fine 9100 electrothermal melting point apparatus and are uncorrected. Infrared spectra were recorded on Perkin-Elmer model 683 or 1310 spectrometers. ^{1}H NMR spectra were recorded as solutions in $CDCl_3$ or DMSO(d_6) and chemical shifts reported in parts per million (ppm) on a Varian Gemini 200 MHz or AV 300 MHz, instrument using tetramethylsilane (TMS) as an internal standard. Low-resolution mass spectra were recorded on VG 7070H micromass mass spectrometers. Analytical TLC of all reactions was performed on Merck prepared plates (silica gel 60F-254 on glass).

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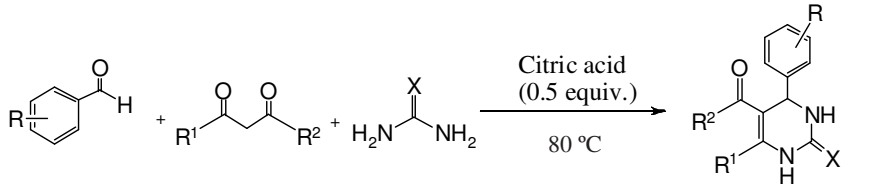
General procedure for the synthesis of 3,4-dihydropyrimidinones: In the experimental procedure, a mixture of aldehyde (1.0 mmol), β-keto ester (1.1 mmol), urea or thiourea (1.3 mmol) and citric acid (0.5 mmol) were taken into a round bottom flask under stirring and the reaction mixture heated at 80 ºC for appropriate time (Table-1, **Scheme-I**). After completion of the reaction as monitored by TLC, cold water was added to the reaction mixture and stirred for 10 min, then filtered and washed with water and dried in vacuum and the corresponding product was further recrystallized from ethanol. The synthesized compounds were characterized by IR, ^{1}H NMR and mass spectroscopy.



Scheme-I: Synthetic scheme

Physico chemical data of synthesized compounds

Methyl-4-phenyl-3,4-dihydropyrimidin-2-(1*H*)-one: m.p. 202-204 ºC; ^{1}H-NMR: δ (400 MHz) 9.22 (1H, bs), 7.78 (1H, bs), 7.41-7.22 (5H, m), 5.17 (1H, s), 4.03 (2H, q, *J* = 6.5 Hz), 2.28 (3H, s), 1.12 (3H, t, *J* = 6.5 Hz). ^{13}C NMR: δ (100 MHz): 166.2, 153.0, 149.2, 145.7, 129.3, 128.1, 127.1, 100.1, 60.1, 54.8, 18.6, 14.9. Anal. calcd. for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.41; H, 6.28; N, 10.71.

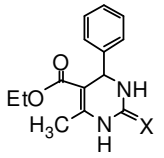
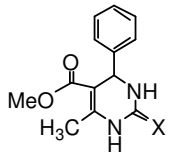
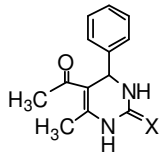
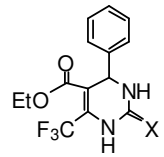
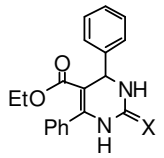
5-Acetyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2-(1*H*)-one: m.p. 234-236 ºC; IR (KBr, ν_{max}, cm^{-1}): 3257, 1699, 1673; ^{1}H NMR: δ 9.16 (1H, s, NH), 7.78 (1H, s, NH), 7.22-7.36 (5H, m, ArCH), 5.25 (1H, d, *J* = 2.4 Hz, CH), 2.24 (3H, s, CH_3CO), 2.07 (3H, s, CH_3); ^{13}C NMR: δ 194.4, 158.5, 152.1, 147.8, 136.9, 127.7, 113.9, 109.6, 55.1, 53.3, 30.18, 18.8; MS (70 eV, EI): m/z (%): 230 (M, 57), 229 (100); HRMS for $C_{13}H_{14}N_2O_2$: 230.1102; found. 230.1055.

Ethyl-6-methyl-4-(4-methylphenyl)-2-oxo-1,2,3,4-tetrahydro-5-pyrimidine carboxylate (1): m.p. 220-222 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.18 (3 H, t, *J* = 7.2 Hz, OCH_2CH_3), 2.32-2.34 (6H, m, $ArCH_3$), 4.08 (2H, q, *J* = 7.2 Hz, CH_2), 5.38 (1H, s, CH), 5.50 (1H, bs, NH), 7.11-7.22 (4H, m, ArH), 7.55 (1H, bs, NH) ppm. MS (EI): m/z = 274 [M$^+$]. Anal. (%): calcd for $C_{15}H_{18}N_2O_3$ (274.35): C 65.67, H 6.61, N 10.21; found. C 65.56, H 6.74, N 10.02.

5-Ethoxycarbonyl-6-methyl-4-(4-methylphenyl)-3,4-dihydroyrimidin-2-(1*H*)-thione (2): m.p. 192-194 ºC; IR (KBr, ν_{max}, cm^{-1}): 3255, 1659, 1562; ^{1}H NMR: δ = 10.27 (1H, s, NH), 9.58(1H, s, NH), 7.16-7.07 (4H, m, C_6H_4), 5.12 (1H, s, CH), 4.00 (2H, q, *J* = 7.0Hz, CH_2CH_3), 2.27 (3H, s, C_6H_5-CH_3), 2.25 (3H, s, CH_3), 1.10 (3H, t, *J* = 7.0Hz, CH_2CH_3); ^{13}C NMR : δ = 174.2, 165.2, 144.9, 140.6, 136.9,

129.1, 126.3, 100.9, 59.6, 53.8, 20.7, 17.2, 14.1; MS (70 eV, EI): m/z (%): 290 (M, 100), 261 (M-C_2H_5, 77); Anal. (%): calcd. for $C_{15}H_{18}O_2N_2S$: C, 62.02; H, 6.25; N, 9.65. Found: C, 62.00; H, 6.47; N, 9.62.

TABLE-1
COMPARISION OF THE REACTION RATES OF BENZALDEHYDE AND UREA OR THIOUREA WITH DIVERGENT ACETOACETATES

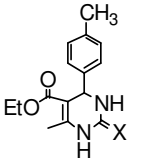
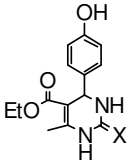
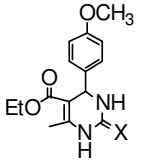
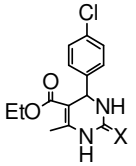
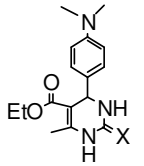
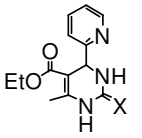
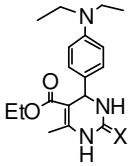
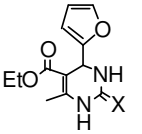
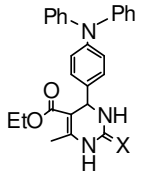
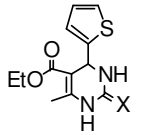
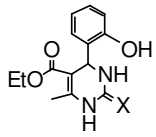
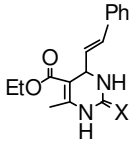
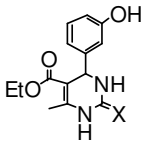
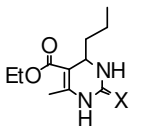
Entry	Product		Time (h)	Yield (%)
I		X = O	1	98
II		X = S	1	99
III		X = O	1	97
IV		X = S	1	98
V		X = O	1	92
VI		X = S	1	95
VII		X = O	3.0	45
VIII		X = S	3.0	62
IX		X = O	2.5	64
x		X = S	2.5	76

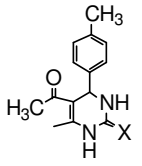
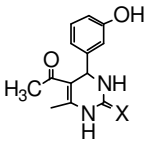
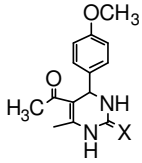
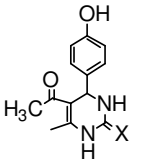
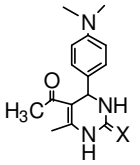
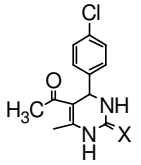
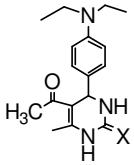
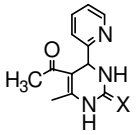
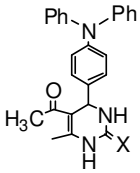
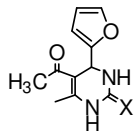
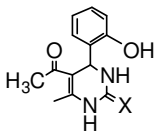
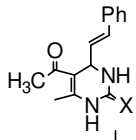
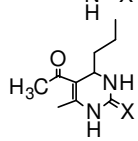
5-Ethoxycarbonyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydroyrimidin-2-(1*H*)-one (3): m.p. 202-204 ºC; ^{1}H NMR: δ = 9.14 (1H s, NH), 7.66 (1H, s, NH), 7.15-6.84 (4H, m, C_6H_4), 5.07 (1H, s, CH), 3.96 (2H, q, *J* = 6.8Hz, CH_2), 3.70(s, 3H, CH_3), 2.23 (3H, s, CH_3), 1.09 (3H, t, *J* = 6.8Hz, CH_2CH_3).

5-Ethoxycarbonyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydroyrimidin-2-(1*H*)-thione (4): m.p. 150-152 ºC; IR (KBr, ν_{max}, cm^{-1}): 3250, 1651, 1598, 1561; ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO): δ = 10.29 (1H, s, NH), 9.59 (1H, s, NH), 7.14-6.87 (4H, m, C_6H_4), 5.10 (1H, s, CH), 3.99 (2H, q, *J* = 7.20Hz, CH_2CH_3), 3.71 (3H, s, OCH_3), 2.27 (3H, s, CH_3), 1.09 (3H, t, *J* = 7.0Hz, CH_2CH_3); ^{13}C NMR: δ = 174.0,

165.2, 158.8, 1.7, 135.8, 127.7, 113.9, 101.1, 59.6, 55.1, 53.5, 17.2, 14.1; MS (70 eV, EI): m/z (%): 306 (M, 82), 277 (M, 80), 32 (100); Anal. (%): calcd for $C_{15}H_{18}O_3N_2S$: C, 58.78; H, 5.93; N, 9.15. Found: C, 58.83; H, 5.77; N, 9.03.

TABLE-2
CITRIC ACID MEDIATED MINILIBRARY SYNTHESIS OF DIVERGENT BIGINELLI COMPOUNDS

Entry	Product		Time (h)	Yield (%)	Entry	Product		Time (h)	Yield (%)
1		X = O	1	68	**15**		X = O	2	76
2		X= S	2	73	**16**		X= S	1.5	88
3		X = O	1	79	**17**		X = O	1	68
4		X= S	3	84	**18**		X= S	4	72
5		X = O	1	75	**19**		X = O	5	56
6		X= S	5	72	**20**		X= S	5	63
7		X = O	1	75	**21**		X = O	1	94
8		X= S	4	71	**22**		X= S	2	92
9		X = O	1	71	**23**		X = O	2	58
10		X= S	5	92	**24**		X= S	3.5	62
11		X = O	3	63	**25**		X = O	1.5	75
12		X= S	3	52	**26**		X= S	4	79
13		X = O	1	56	**27**		X = O	2	58
14		X= S	3.5	48	**28**		X= S	2	61

Entry	Product		Time (h)	Yield (%)	Entry	Product		Time (h)	Yield (%)
31		X = O	1.0	73	**43**		X = O	3.0	61
32		X= S	2.5	86	**44**		X= S	2.0	76
33		X = O	1.0	99	**45**		X = O	2.0	71
34		X= S	1.0	84	**46**		X= S	4.0	88
35		X = O	1.0	75	**47**		X = O	1.0	60
36		X= S	5.0	79	**48**		X= S	3.0	78
37		X = O	1.0	71	**49**		X = O	5.0	74
38		X= S	4.0	76	**50**		X= S	5.0	62
39		X = O	1.0	84	**51**		X = O	2.0	84
40		X= S	5.0	90	**52**		X= S	1.0	91
41		X = O	2.0	96	**53**		X = O	1.5	93
42		X= S	4.0	98	**54**		X= S	2.0	97
					55		X = O	2.0	62
					56		X= S	2.0	78

Reaction conditions: 1:1.5: 1.3: 0.5 (aldehyde, urea or thiourea, 1,3 diketone and citric acid) at 80 ^{0}C.
[a]Yields refer to isolated pure products.

1-(6-Methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydro-5-pyrimidinyl)-1-ethanone (6): m.p. 200-202 ºC; IR (KBr, ν_{max}, cm^{-1}): 3266, 1697, 1565, 1460; ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO): δ 10.01 (1H, bs, N-H), 9.42 (1H, bs, N-H), 7.21-7.39 (5H, m), 5.36 (1H, d, *J* = 5.36), 2.38 (3H, s), 2.09 (3H, s); MS (ESI): m/z = M^{+1} = 246.

Ethyl-2-oxo-4-phenyl-6-(trifluoromethyl)-1,2,3,4-tetrahydro-5-pyrimidine carboxylate (7): m.p. 203-205 ºC; ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO): δ = 9.44 (1H, bs, N-H), 9.29 (1H, bs, N-H), 7.208-7.29 (5H, m), 5.21 (1H, d, *J* = 3.125), 3.60 (3H, s), 2.34 (3H, s); MS (ESI): m/z= M^{+1} = 315.

Ethyl-2-oxo-4, 6-diphenyl-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (9): m.p. 208-210 ºC, IR (KBr, ν_{max}, cm^{-1}): 3232, 3015, 2953, 1692, 1647; ^1H NMR (300 MHz, $CDCl_3$ + DMSO): δ 9.81 (1H, bs, N-H), 9.62 (1H, bs, N-H), 7.28-7.6 (10H, m), 5.21 (1H, d, *J* = 3.125), 3.731 (2H, q, *J* = 7.813), 0.801 (3H, t, *J* = 7.031); MS (ESI): m/z = M^{+1} = 323.

5-Ethoxycarbonyl-4-(3-hydroxyphenyl)-6-methyl-3,4-dihydropyrimidin-2-(1*H*)-one (13): m.p. 163-165 ºC; ^1H NMR: δ (400 MHz) 9.37 (1H, bs), 9.16 (1H, s), 7.69 (1H, s), 7.12-6.61 (4H, m), 5.07 (1H, s), 3.99 (q, 2H, *J* = 7 Hz), 2.24 (3H, s), 1.12 (3H, t, J = 7 Hz); ^{13}C NMR: δ (100 MHz) 166.2, 158.2, 153.1, 148.9, 147.1, 130.2, 117.7, 115.0, 113.9, 100.2, 60.1, 54.7, 18.6, 15.0. Anal. calcd. for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.84; H, 5.81; N, 10.10.

Ethyl-4-(3-hydroxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro-5-pyrimidine carboxylate (14): m.p. 122-124 ºC; IR (KBr, ν_{max}, cm^{-1}): 3308, 3183, 1667, 1573, 1284, 1192; ^1H NMR (300 MHz, $CDCl_3$ + DMSO): δ = 9.44 (1H, bs, N-H), 9.29 (1H, bs, N-H), 7.208-7.29 (5H, m), 5.21 (1H, d, *J* = 3.125), 2.34 (s, 3H), 3.60 (s, 3H); MS (ESI): m/z = M^{+1} = 293.

Ethyl-l4-(4-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidine carboxylate (15): m.p. 222-224 ºC; IR (KBr, ν_{max}, cm^{-1}): 3182, 1686, 1647, 1579, 1312, 1200; ^1H NMR (300 MHz, $CDCl_3$ + DMSO): δ = 9.44 (1H, bs, N-H); 9.29 (1H, bs, N-H), 7.208-7.29 (5H, m), 5.21 (1H, d, *J* = 3.125), 3.60 (3H, s), 2.34 (3H, s); MS (ESI): m/z = M^{+1} = 277.

4-(4-Chlorophenyl)-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (17): m.p. 212-214 ºC, IR (KBr, ν_{max}, cm^{-1}): 3255, 1657, 1560; ^1H NMR : δ = 9.24 (1H, s, NH), 7.78 (1H, s, NH), 7.40 -7.21 (m, 4H, C_6H_4), 5.12 (1H, s, CH), 3.97 (2H, q, *J* = 6.9 Hz, CH_2CH_3), 2.24 (3H, s, CH_3), 1.08 (3H, t, *J* = 6.9Hz, CH_2CH_3). ^{13}C NMR: δ = 174.3, 165.0, 145.3, 142.4, 132.3, 128.6, 128.4, 100.4, 59.7, 53.5, 17.2, 14.0; MS (70 eV, EI): m/z (%): 310 (M, 99), 281 (M-C_2H_5, 82), 199 (100); Anal. (%): calcd for $C_{14}H_{15}N_2O_2$: C, 54.08; H, 4.87; N, 9.02. Found: C, 54.23; H, 4.71; N, 8.99.

Ethyl-6-methyl-2-oxo-4-(2-pyridyl)-1,2,3,4-tetrahydro-5-pyrimidine carboxylate (19): m.p. 195-197 ºC; ^1H NMR (300 MHz, $CDCl_3$ + DMSO): δ = 9.44 (1H, bs, NH), 9.29 (1H, bs, NH), 7.208-7.29 (5H, m), 5.21 (1H, d, *J* = 3.125), 3.60 (3H, s), 2.34 (3H, s); MS (ESI): m/z = M^{+1} = 262.

5-Ethoxycarbonyl-4-(2-furfuryl)-6-methyl-3,4-dihyropyrimidin-2(1*H*)-one (21): m.p. 209-211 ºC; IR (KBr, ν_{max}, cm^{-1}): 3320, 3225, 3100, 1695 , 1640; ^1H NMR: δ = 9.24 (1H, s, NH), 7.75 (1H, s, NH), 7.54 (1H, s, ArCH), 6.34 (1H, s, ArCH), 6.08 (1H, s, ArCH), 5.19 (1H, s, CH), 4.01 (2H, q, *J* = 6.9Hz, CH_2CH_3), 2.22 (3H, s, CH_3), 1.12 (3H, t, *J* = 6.9Hz, CH_2CH_3); ^{13}C NMR: δ = 165.0, 155.9, 152.4, 149.2, 142.1, 110.3, 105.2, 96.8, 59.2, 47.7, 17.7, 14.1; MS (70 eV, EI): m/z (%): 250 (M, 80), 221 (99), 177 (100); Anal. (%): calcd. for $C_{12}H_{14}N_2O_4$: C, 57.57; H, 5.64; N, 11.20. Found: C, 57.63; H, 5.59; N, 11.28.

Ethyl-4-(2-furyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro-5-pyrimidine carboxylate (22): m.p. 196-198 ºC; IR (KBr, ν_{max}, cm^{-1}): 3270, 3120, 1715, 1680, 1600, 1591, 1485; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52 (1H, brs, NH), 7.35 (1H, s, furyl-H), 6.96 (1H, brs, NH), 6.30 (1H, s, furyl-H), 6.17 (d, *J* = 2.4 Hz, 1H), 5.50 (1 H, s, furyl-H), 4.16 (2 H, m, OCH_2), 2.38 (3 H, s, CH_3), 1.22 (t, *J* = 7.2 Hz, 3 H, OCH_2CH_3), MS (ESI): m/z = M^{+1} = 267.

5-Ethoxycarbonyl-6-methyl-4-(2-thienyl)-3,4-dihyropyrimidin-2-(1*H*)-one (23): m.p. 215-217 ºC; (KBr, ν_{max}, cm^{-1}): 3165, 1680, 1633; ^{1}H NMR: δ = 9.31 (1H, s, NH), 7.88 (1H, s, NH), 7.34 (1H, d, *J* = 5.3 Hz, ArCH), 6.93-6.88 (2H, m, ArCH), 5.39 (1H, s, CH), 4.05 (2H, q, *J* = 7.1 Hz, CH_2CH_3), 2.20 (3H, s, CH_3), 1.15 (3H, t, *J* =7.1 Hz, CH_2CH_3); ^{13}C NMR: δ = 165.0, 152.2, 148.8, 126.6, 124.6, 123.5, 99.8, 59.3, 49.4, 17.7, 14.1; IR MS (70 ev, EI): m/z (%): 266 (M, 84), 237 (100), 193 (91); Anal. (%): calcd for $C_{12}H_{14}O_3N_2S$: C, 54.0; H, 5.30; N, 10.52. Found: C, 54.27; H, 5.19; N, 10.33.

5-Ethoxycarbonyl-6-methyl-4-(2-thienyl)-3,4-dihyropyrimidin-2-(1*H*)-thione (24): m.p. 214-216 ºC; IR (KBr, ν_{max}, cm^{-1}): 3245, 1650, 1555; ^{1}H NMR: δ = 10.46 (1H, s, NH), 9.76 (1H, s, NH), 7.39 (1H, d, *J* = 4.1 Hz, ArCH), 6.95-6.89 (2H, m, ArCH), 5.41 (1H, s, CH), 4.07 (2H, q, *J* = 6.7 Hz, CH_2CH_3), 2.26 (3H, s, CH_3), 1.15 (3H, t, *J* = 6.7 Hz, CH_2CH_3); ^{13}C NMR: δ = 174.7, 164.8, 147.0,145.3, 126.8, 125.3, 124.2,101.3, 59.8, 49.4, 17.1, 14.1; MS (70 ev, EI): m/z (%): 282 (M, 99), 253 (50), 109 (100); Anal. (%): calcd for $C_{12}H_{14}N_2O_2S_2$: C, 51.02; H, 5.00; N, 9.93. Found: C, 51.2; H, 4.91; N, 9.71.

5-Ethoxycarbonyl-6-methyl-4-styryl-3,4-dihydropyrimidin-2(1*H*)-one (25): m.p. 232-234 ºC; ^{1}H NMR: δ (400 MHz) 9.13 (1H, bs), 7.51 (1H, bs), 7.48-7.23 (5H, m), 6.36 (1H, d, *J* = 15.8 Hz), 6.20 (1H, dd, *J* = 16 Hz, *J* = 6 Hz), 4.72 (1H, d, *J* = 6 Hz), 4.11 (2H, m), 2.20 (3H, s), 1.15 (3H, t, *J* = 7 Hz); ^{13}C NMR: δ (100 MHz) 164.8, 152.3, 148.1, 136.2, 130.1, 128.8, 128.0, 127.5, 126.0, 97.8, 59.1, 51.7, 17.7, 14.4.

Ethyl-6-methyl-4-propyl-2-thioxo-1,2,3,4-tetrahydro-5-pyrimidine carboxylate (28): m.p. 188-190 ºC; ^{1}H NMR (400MHz, $CDCl_3$): δ = 7.56 (1H, bs, NH), 7.05 (1H, bs, NH), 4.37 (1H, t, J = 3.2 Hz, CH), 4.20 (2H, m, CH_2), 2.31 (3H, s, CH_3), 1.62 (3H, t, *J* = 10.5 Hz, $(CH_2)_2CH_3$), 1.34 (4H, m, CH_2), 0.92 (3H, t, *J* = 7.2 Hz, OCH_2CH_3); MS (EI): m/z = 242 [M^+]. $C_{11}H_{18}N_2O_2S$ (242.38): calcd. C 54.51, H 7.49, N 11.56; found C 54.13, H 7.37, N 11.47.

1-[4-(4-Methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro-5-pyrimidinyl]-1-ethanone (34): m.p. 152-154 °C; IR (KBr, ν_{max}, cm^{-1}): 3240, 3120, 2964, 1725, 1715, 1685, 1650, 1510, 1455, 1330, 1270, 770; ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO): δ = 9.44 (1H, bs, N-H), 9.29 (1H, bs, NH), 7.208-7.29 (5H, m), 5.21 (1H, d, *J* = 3.125), 3.60 (3H, s), 2.34 (3H, s), MS (ESI): m/z = M^{+1} = 307.

5-Methoxycarbonyl-4-(4-dimethylaminophenyl)-6-methyl-3,4-dihydropyrimidin-2-(1*H*)-one (35): m.p. 213-215 °C; IR (KBr, ν_{max}, cm^{-1}): 3250, 3120, 2928, 2835, 1700, 1651, 1613, 1583, 1230; ^{1}H NMR δ : 8.98 (1H, bs, N-H), 7.31 (3H, bs,

N-H), 7.18 (2H, d, *J* = 9.1 Hz), 6.63 (2H, d, *J* = 9.1 Hz), 5.18 (1H, s), 3.62 (3H, s), 2.91 (6H, s), 2.30 (3H, s). EIMS: m/z (%) 289 (M^+, 33), 274 (66), 260 (37), 216 (65), 183 (25), 169 (36), 121 (80), 120 (100), 69 (43), 43 (68). Anal. calcd for $C_{15}H_{19}N_3O_3$: C, 62.27; H, 6.61; N, 14.52. Found: C, 62.01; H, 6.54; N, 14.06.

5-Methoxycarbonyl-4-(4-dimethylaminophenyl)-6-methyl-3,4-dihydropyrimidine-2-(1*H*)-thione (36): m.p. 152-154 °C. IR (KBr, ν_{max}, cm^{-1}): 3280, 3185, 2928, 1710, 1651, 1613, 1583; ^{1}H NMR δ : 9.98 (1-H, bs, NH), 9.31 (3-H, bs, NH), 7.16 (2H, d, *J* = 9.1Hz), 6.62 (2H, d, *J* = 9.1 Hz), 5.13 (1H, s), 3.60 (3H, s), 2.92 (6H, s), 2.30 (3H, s); ^{13}C NMR δ: 74.1, 166.2, 150.3, 144.9, 131.2, 127.4, 112.6, 101.3, 53.7, 51.3, 17.4. EIMS: m/z (%) 305 (M^+, 21), 246 (25), 231 (8), 185 (22), 171 (18), 141(37), 120 (32), 78 (100), 43 (87). Anal. calcd for $C_{15}H_{19}N_3O_2S$: C, 58.99; H, 6.27; N, 13.76. Found: C, 58.78; H, 6.18; N, 13.68.

1-[4-[4-(Diethylamino)phenyl]-6-methyl-2-thioxo-1,2,3,4-tetrahydro-5-pyrimidinyl]-1-ethanone (38): m.p. 202-204 ºC; ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO): δ = 9.44 (1H, bs, NH); 9.29 (1H, bs, NH), 7.208-7.29 (5H, m), 5.21 (1H, d, *J* = 3.125), 3.60 (3H, s), 2.34 (3H, s); MS (ESI): m/z = M^{+1} = 348.

1-[4-[4-(Diphenylamino)phenyl]-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinyl]-1-ethanone (39): m.p. 172-174 ºC; ^{1}H NMR (300 MHz, $CDCl^3$ + DMSO): δ = 9.44 (1H, bs, N-H), 9.29 (1H, bs, N-H), 7.208-7.29 (5H, m), 5.21 (1H, d, *J* = 3.125), 3.60 (3H, s), 2.34 (3H, s); MS (ESI): m/z = M^{+1} = 414.

5-(Methoxycarbonyl)-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (47): m.p. 207-208 ºC; IR (KBr, ν_{max}, cm^{-1}): 3231, 1700, 1641; ^{1}H NMR: δ = 9.23 (1H, s, NH), 7.77 (1H, s, NH), 7.35-7.25 (5H, m, ArCH), 5.15 (1H, d, CH), 3.53 (3H, s, OCH_3), 2.20 (3H, s, CH_3).

1-[4-(4-Chlorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro-5-pyrimidinyl]-1 -ethanone (48): m.p. 160-162 ºC; IR (KBr, ν_{max}, cm^{-1}): 3260, 2900, 1700, 1650, 780; ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO): δ = 9.44 (1H, bs, N-H), 9.29 (1H, bs, N-H), 7.208-7.29 (5H, m), 5.21 (1H, d, *J* = 3.125), 3.60 (3H, s), 2.34 (3H, s); MS (ESI): m/z = M^{+1} = 265.

5-Acetyl-6-methyl-4(2-pyridinyl)-3,4-dihydropyrimidin-2-(1*H*)-one (49): m.p.: 224-226 °C; IR (KBr, ν_{max}, cm^{-1}): 3290, 1712, 1679, 1587; ^{1}H NMR: δ 9.13 (1H s), 8.47 (1H, m), 7.71 (2H, m), 7.23 (2H, m), 5.31 (1H, d, *J* = 3.3 Hz,), 2.21 (3H, s), 2.17 (3H, s); ^{13}C NMR: δ 194.7, 162.7, 152.8, 149.5, 148.3, 137.2, 122.9, 121.0, 109.4, 56.0, 30.7, 19.2. Anal. calcd for $C_{12}H_{13}N_3O_2$: C, 62.33; H, 5.67; N, 18.17. Found: C, 62.01; H, 5.59; N, 17.99.

5-Acetyl-4-(2-furfuryl)-6-methyl-3,4-dihydropyrimidin-2-(1*H*)-one (51): m.p. 210-212 °C; IR (KBr ν_{max}, cm^{-1}): 3278, 1716, 1681, 1591; ^{1}H NMR δ = 9.21 (1H, s), 7.82 (1H, s), 7.53 (1H, s), 6.33 (1H, s), 6.10 (1H, d, *J* = 2.7 Hz), 5.30 (1H, d, *J* = 2.7 Hz), 2.22 (3H, s), 2.14 (3H, s); ^{13}C NMR: δ 194.1, 156.2, 152.8, 149.1, 142.6, 110.6, 107.5, 105.9, 48.1, 30.3, 19.2; Anal. calcd for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.81; H, 5.38; N, 12.59.

5-Acetyl-4-butyl-6-methyl-1,2,3,4-tetrahydro-2-pyrimidinone (55): m.p. 202-204 °C; ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO): δ = 9.44 (1H, bs, N-H), 9.29 (1H, bs, N-H), 7.208-7.29 (5H, m), 5.21 (1H, d, *J* = 3.125), 3.60 (3H, s), 2.34 (3H, s); MS (ESI): m/z= (M^{+1}) 196.

***In vitro* cytotoxicity evaluation:** Compounds **4**, **9, 10, 11, 32, 35, 42** and **54** were subjected for anticancer activity on HeLa and HT29 cell lines. Toxicity of test compound in cells was determined by MTT assay[9] based on mitochondrial reduction of yellow MTT tetrazolium dye to a highly colored blue formazan product. Cells in 96- well plates were incubated with compounds tested for 48 h at 37 ºC in RPMI with 10 % FBS medium. Then the above media was replaced with 90 µL of fresh serum free RPMI and 10 µL of MTT reagent (5 mg/mL) and plates were incubated at 37 ºC for 4 h, there after the above media was replaced with 200 µL of DMSO and incubated at 37 ºC for 15 min. The absorbance at 570 nm was measured on a spectrophotometer (spectra max, molecular devices). The values for each point were calculated from triplicate wells. All experiments were carried out in triplicate. The toxicity of compounds with different concentrations tested was calculated from plot: cell viability (% from control) *versus* concentration of compounds tested in medium.

Antiinflammatory activity: The synthesized compounds **4, 9, 10, 11, 32, 35, 42** and **54** were evaluated for antiinflammatory activity by carrageenan induced paw oedema method[10] using indomethacin as standard drug. Albino rats of either sex, weighing between 200-250 g were used in the experiment. They were divided into ten groups of six animals each. All groups were fasted for overnight and allowed water *ad libitum*. The test compounds were administered to the animals orally and after 1 h of the treatment, 0.1 mL of 1 % carrageenan suspension was injected subcutaneously into the subplantar tissue of the right hind foot and 0.1 mL of saline was injected into the sub plantar tissue of the left hind foot. The thickness of the both paws of each rat, lower and upper surface was measured using Zeitlin's constant load lever consisting of a graduated micrometer combined with a constant loaded lever system to magnify the small changes in paw thickness during the course of the experiment. The paw thickness was determined at 1, 2, 3, 4 and 5 h after induction of inflammation.

RESULTS AND DISCUSSION

Anticancer activity: Among the compounds subjected for anticancer activity, compound (ethyl-4-[4-(diphenylamino)phenyl]-6-methyl-2-thioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate) (**10**) has shown more percentage of inhibition on both the cell lines. It has shown 98.88 % of inhibition on HeLa cell line and 99.51 % on HT29 cell lines. Compounds (1-[6-methyl-4-(4-methylphenyl)-2-thioxo-1,2,3,4-tetrahydro-5-pyrimidinyl]-1-ethanone) (**32**) and (1-[4-(2-hydroxyphenyl)-6-methyl- 2-thioxo-1,2,3,4 -tetrahydro-5- pyrimidinyl]-1-ethanone) (**42**) have shown 87.62 and 78.60 on HeLa cell line and 87.97-71.39 % of inhibition on HT29 cell lines, respectively (Table-3).

TABLE-3
CYTOTOXIC ACTIVITY OF THE SYNTHESIZED COMPOUNDS

Compound	% of inhibition	
	HT29 cell line	HeLa cell line
4	32.02	37.35
9	35.32	38.09
10	49.21	55.48
11	71.39	78.60
32	99.51	98.88
35	24.76	14.66
42	34.24	39.76
54	87.97	89.62

Antiinflammatory studies: Among the eight compounds, compounds (ethyl 4-[4-(diphenylamino)phenyl]-6-methyl-2-thioxo-1,2,3,4-tetrahydro-5-pyrimidine carboxylate) (**10**) and (1-[4-(2-hydroxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro-5-pyrimidinyl]-1-ethanone) (**42**) have shown significant reduction in paw oedema when compared to the other compounds. The antiinflammatory activity of the compounds by carrageenan induced paw oedema was tabulated (Table-4).

TABLE-4
ANTIINFLAMMATORY ACTIVITY OF DIHYDROPYRAMIDINONE DERIVATIVES

Group	1 h	2 h	3 h	4 h	5 h
Control 1 % water (1 mL/kg)	0.32 ± 0.01	0.58 ± 0.04	0.64 ± 0.02	0.72 ± 0.01	0.84 ± 0.02
Compound **4** (20 mg/kg)	0.30 ± 0.02 (7.28 %)	0.46 ± 0.01 (20.26 %)	0.57 ± 0.03 (38.42 %)	0.26 ± 0.04 (58.24 %)	0.22 ± 0.02 (72.64 %)
Compound **9** (20mg/kg)	0.29 ± 0.03 (8.26 %)	0.48 ± 0.02 (20.86 %)	0.57 ± 0.03 (38.42 %)	0.21 ± 0.01Z (66.46 %)	0.22 ± 0.04** (72.64 %)
Compound **10** (20 mg/kg)	0.26 ± 0.02 (8.42 %)	0.52 ± 0.04 (34.10 %)	0.56 ± 0.02 (40.48 %)	0.28 ± 0.03 (65.29 %)	0.16 ± 0.02* (79.42 %)
Compound **11** (20 mg/kg)	0.31 ± 0.01 (06.52 %)	0.50 ± 0.03 (28.46 %)	0.52 ± 0.04 (34.28 %)	0.26 ± 0.02 (58.14 %)	0.19 ± 0.01** (75.28 %)
Compound **32** (20 mg/kg)	0.28 ± 0.02 (10.24 %)	0.52 ± 0.03 (28.46 %)	0.34 ± 0.02 (57.60 %)	0.28 ± 0.01 (64.64 %)	0.21 ± 0.02** (73.84 %)
Compound **35** (20 mg/kg)	0.28 ± 0.03 (10.86 %)	0.53 ± 0.04 (29.64 %)	0.35 ± 0.02 (50.52 %)	0.29 ± 0.02 (63.86 %)	0.18 ± 0.03** (76.52 %)
Compound **42** (20 mg/kg)	0.28 ± 0.01 (10.64 %)	0.50 ± 0.03 (32.10 %)	0.42 ± 0.04 (41.48%)	0.27 ± 0.03 (64.29 %)	0.17 ± 0.01* (78.22 %)
Compound **54** (20 mg/kg)	0.30 ± 0.02 (7.62 %)	0.50 ± 0.01 (22.92 %)	0.44 ± 0.02 (32.68 %)	0.28 ± 0.04 (62.82 %)	0.20 ± 0.03** (74.04 %)
Standard-indomethacin (10 mg/kg)	0.24 ± 0.01 (15.55 %)	0.52 ± 0.02 (36.92 %)	0.32 ± 0.01** (62.40 %)	0.24 ± 0.03*** (76.66 %)	0.15 ± 0.02*** (82 %)

All values are mean ± SEM values using 6 animals in each group. Significant differences with respect to control group was evaluated by ANOVA, Dunnets 't' test . *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

Conclusion

Anticancer activity: Compounds **10**, **32** and **42** with N,N-diphenyl,3-hydroxy and methyl groups attached to the phenyl ring in dihydropyrimidinones have shown very good percentage of inhibition on both HeLa and HT29 cell lines.

Antiinflammatory activity: Among the eight compounds subjected for anti-inflammatory activity, compounds **10** and **42** with diphenyl and 3-hydroxy groups attached to the phenyl ring in dihydropyrimidinones have shown significant reduction in paw oedema when compared to the other compounds.

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