# SYNTHESIS AND BIOLOGICAL EVALUATION OF NOVEL 3,4-DIHYDROPYRIMIDIN-2-(1 *H*)-ONES

**M.Vijey Aanandhi *[a], R.Kamal Raj[a], G.Devdass[a],R.Sujatha[b], P.Shanmugasundaram[a]**

[a] Vels College Of Pharmacy,Chennai-600117,Tamilnadu,India.
[b] Govt arts and science college for women, Bargur-635104,Tamilnadu,India.
E-mail: mvaanandhi@yahoo.co.in

**ABSTRACT**

*Eight new novel 3,4-dihydropyrimidin-2-(1H)-ones have been synthesized and the structures of the compound have been conformed by $^1$H NMR,IR spectra, mass and elemental analysis. The compound show antimicrobial activity against E.coli and Staphylococcus aureus and antifungal activity against Candida albicans by Disc diffusion method*

***Keywords:*** *Novel 3,4-Dihydropyrimidin-2-(1H)-ones ,Antibacterial Activity and Antifungal Activity*

## INTRODUCTION

Dihydropyrimidin-2-(1 *H*)-ones and their derivatives play an vital role in natural and synthetic organic chemistry mainly due to their wide range of biological activities[1-2] notably as calcium channel blockers[3-4]. More recently ,ethyl-4-(3-hydroxyphenyl)-6-methyl-2-thioxo,1,2,3,4,tetrahydro pyrimidine-5-carboxylate, also known as monastrol , was identified as a novel low molecular weight cell-permeable molecule for the development of potentially new anticancer drugs[5]. And the activity of monastrol is based on the specific and reversible inhibition of the motility of mitotic kinesin eg5, a motor protein required for bipolar spindle formation during mitosis.[6-10] . Most Of these compound have significant biological and antimicrobial activity[11-14]

Thus, in the present study , Various novel biological active 3,4,-dihydropyrimidin-2-(1 *H*)-ones were synthesized by condensation of some novel 1,3 dicarbonyl compounds with thiourea and various aromatic aldehyde in acetonitrile under reflux condition using catalytic $Cecl_3 7H_2o$ **(Scheme 1)** and the various substituents are shown in **Table I** and Their structures were established by elemental and spectral studies The antimicrobial properties of all the compounds synthesized were investigated by using the Disc diffusion method.

## EXPERIMENTAL

**General:** Melting points were determined using an open-ended capillary method and are uncorrected. The reaction was monitored by TLC. FT-IR was recorded on a Jasco FT-IR spectrophotometer , $^1$H NMR spectra were recorded at 300 MHZ on a Bruker FT-NMR spectrophotometer and mass spectra on a Varian atlas CH-7 mass spectrometer at 70 ev. The elemental analysis was obtained on a VARIO-EL instrument and all compds(a-h) showed satisfactory elemental analysis.

### 3-oxo-N-((R)-1-Phenylethyl)butanamide(1)

A solution of (R)-Phenyl ethyl amine(1.21g), t- Butylacetoacetate(1.58g) was heated in the presence of O-Xylene(5ml) for 1 hr . Then reaction mixture was poured over crushed ice and

separated product was filtered and recrystallized from ethanol. Their characterization data are given in Table II. IR:(KBr): 3252, 370, 3029, 2966, 2924, 1723,1656,1623,1589,1340,1305,1273,1212,1179cm$^{-1}$.
$^1$HNMR(200 MHz,DMSO-$d_6$): δ 1.46-1.57(d, 3H), 2.25(s, 3H), 3.36(s, 2H), 5.0-5.16(q, 1H), 7.1-7.5(m, 6H).MASS: *m/e* (Abundance): 206(100%), 170(15%).

**4(3-hydroxy phenyl)-6-methyl-N-[1-phenyl ethyl]-2-thioxo-1,2,3,4-tetrahydro pyrimidine-5-carboxamide.(compd a**)0.61 gm of 3-Hydroxy Benzaldehyde , 0.38gm of thiourea ,1.025 gm of 1,3dicarbonylcompound 1 ,were dissolved in 5ml of acetonitrile and refluxed in the presence of $Cecl_3.7H_2O$ (0.931gm) as a catalyst for 6 hr. Then reaction mixture was poured over crushed ice and separated product was filtered and recrystallized from ethanol. Their characterization data are given Table II. This typical experimental procedure was followed to prepare other analogs of this series(compound a-h). IR (KBr):3257, 3237, 2974, 2926, 1689, 1619, 1619, 1563, 1490,1194,1152.cm$^{-1}$.
$^1$HNMR(200MHz,DMSO-$d_6$):δ1.2-1.4(m,3H),2.1(s,3H),4.9-5.1(m,1H),5.2-5.4(d,1H),6.6-6.8(m,4H),7.4-7.5(d,5H),8.6-8.9(d,1H),9.0(s,2H),9.3,9.4(m,1H).
MASS:*m/e*(Abundance):368(10%),336(10%),262(15%),188(14%)105(95%).

**6-methyl-4(3-nitrophenyl)-6-methyl-N-[1-phenylethyl]-2-thioxo-1,2,3,4-tetrahydro pyrimidine-5-carboxamide.(compd b).** IR (KBr):3278, 2925, 2854, 1679, 1618, 1522, 1345, 127, 1109, 856cm$^{-1}$.$^1$HNMR(200MHz,DMSO-$d_6$):δ1.3(m,3H),2.0-2.4(m,3H),4.9-5.1(m,1H),5.4-5.5(d,1H),6.7-7.9(m,9H),8.8-9.2(d,2H),9.7(s,1H).
MASS:*m/e*(Abundance):398(13%),365(100%),319(35%)

**4(3,4-dimethoxyphenyl)-6-methyl-N-[1-phenylethyl]-2-thioxo-1,2,3,4-tetrahydro pyrimidine-5-carboxamide(compd c).** IR(KBr):3291,3181,3090,2968,2930,1681, 1617,1561,1514,1447,1262,12007,1138,1022cm$^{-1}$.$^1$HNMR(200MHz,DMSO-$d_6$): δ1.3(m,3H), 2.1-2.4(m,3H), 3.7-3.8(t,3H), 4.95(s,1H), 5.4-5.6(d,1H), 6.85(d,3H),6.9-7.0(m,1H),7.2-7.4(m,5H),7.8-8.0(d,1H). MASS:*m/e*(Abundance):412(85%),380(100%),349(13%).
4(4-methoxyphenyl)-6-methyl-N-[1-phenylethyl]-2-thioxo-1,2,3,4-tetrahydro pyrimidine-5-carboxamide.(compd d).IR (KBr):3327, 2924, 2855, 1660, 1606, 1556, 1510,1244,1174cm$^{-1}$.$^1$HNMR(200MHz,DMSO-$d_6$):δ1.2-1.5(m,3H),2.5(s,3H),3.7-3.9(m,3H),5.0-5.2(t,1H),5.3-5.5(d,1H),6.7-6.8(m,3H),7.0-7.6(m,9H),7.75(s,1H),8.8-9.2(q,2H),9.4(s,1H).MASS:*m/e*(Abundance)382(M+2,2%),350(100%).

**4(3,4,5-trimethoxy phenyl)-6-methyl-N-[1-phenyl ethyl]-2-thioxo-1,2,3,4-tetrahydro pyrimidine-5-carboxamide.(compd e**).IR (KBr):3201, 2934, 2835, 1628, 1593, 1504, 1480,1326,1197,1124,1001cm$^{-1}$.$^1$HNMR(200MHz,DMSO-$d_6$):δ1.12-1.22(t,3H) 2.15(s,3H),3.6-3.9(t,9H),4.9-5.12(t,1H),5.3-5.4(d,1H),6.5-6.6(s,2H),7.17.3(m,5H),7.6-7.8(m,1H),8.7-8.9(d,1H),9.5(s,1H).MASS;*m/e*(Abundance):442(87%), 410(25%),384(5%).

**Ethyl-6-methyl-4-[3-phenoxyphenyl]-2-thioxo-1,2,3,4-tetrahydro pyrimidine-5-carboxylate(compd f).**IR(KBr) :3175, 2979, 1705, 1668, 1574,1474, 1374, 1324,1272,1228,1168.cm$^{-1}$.$^1$HNMR(200MHz,DMSO-$d_6$):δ1.02-1.20(t,3H),2.35(s,3H), 3.9-4.2(q,2H),5.3-5.4(d,1H),6.8-7.4(m,9H), 8.8(s,1H), 9.5(s,1H). MASS: *m/e* (Abundance):369(100%),370(25%),371(2%).

**Ethyl4(3-hydroxyphenyl)6-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate.(compd g).**IR(KBr):3127, 2979, 1665, 1570, 1456, 1371, 1271, 1197, 1136, 1096.cm$^{-1}$.$^{1}$HNMR (200MHz,DMSO-$d_6$): δ 0.7-0.9(t, 3H), 1.2-1.3(m, 1H), 2.5(s, 1H), 3.7-3.8(q, 2H), 5.2-5.3(d, 1H), 6.6-7.6(m, 9H), 9.5(s, 1H). MASS: *m/e* (Abundance): 355(M+1,15%),356(2%),323(100%),324(25%).

**Methyl 6(3-hydroxy phenyl)6-phenyl-2-thioxo-1,2,3,4-tetrahydro pyrimidine-5-carboxylate.(compd h)** IR(KBr): 3298, 2935, 1729, 1684, 1565, 1462, 1423, 1362,1331,1282,1182,1109cm$^{-1}$ $^{1}$HNMR: δ 2.9(s,2H), 3.6(s,3H), 3.75(s,3H), 5.1(d,1H), 6.6-6.9(m,3H),7.-7.1(t,1H), 8.9(s,1H), 9.3(s,1H), 10.15(s,1H). MASS;*m/e* (Abundance):337(M+1,100), 305(60%).

**Antimicrobial activities**

All the compound (a-h) were screened(doses 25,50,100μg/ml) for their antibacterial activities against the gram-ve bacteria *E.coli* and gram+ve bacteria *staphylococcus aureus* Using standard antibiotic drug ciprofloxacin.HCL(50μg/ml)) as a control. The biological activities of these compound have been evaluated by using Disc diffusion method. Dimethyl formamide was used as a solvent. Activities were determined by using the cultivated Disc and the inhibition zones were measured in mm and results obtained are shown in **Table III** . All compound showed moderate bactericidal activities against both bacteria .These compounds were also tested for their fungicidal activities against *Candida albicans* using ketoconazole(50μg/ml)) as a control and Dimethyl formamide as a solvent by above method. All the compound showed excellent fungicidal activities , the results are shown in **Table III.**

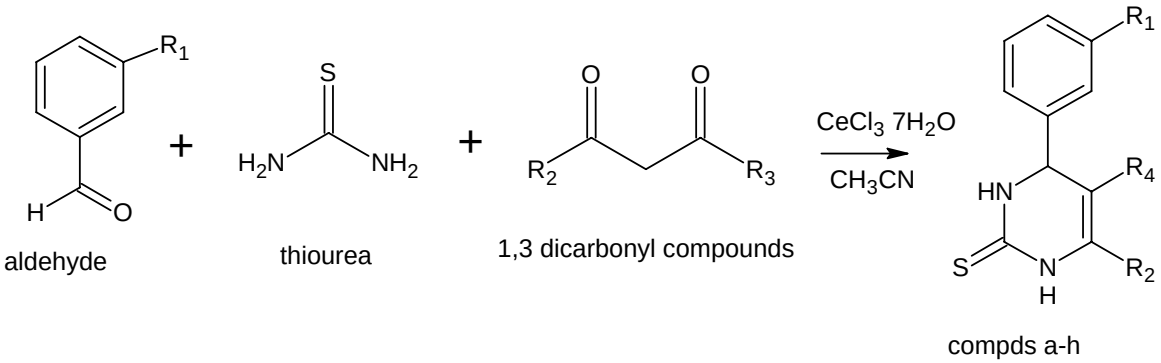
## RESULTS AND DISCUSSION

The compound **compd h** in the concentration of 100 μg/ml was found to possess good antibacterial activity against *Staphylococcus aureus*. Compound **compd g** in the concentration of 100μg/ml was found to possess good antibacterial activity against *E.coli.* When compared with the synthesized compound and standard *Ciprofloxacin.* The compound **compd b** was found to possess good activity against *Candida albicans* in the concentration of 100 μg/ml .the other compounds are found to moderate to high activity.

## REFERENCES


1. C.O. Kappe, *Acc. Chem. Res.*, **33**, 879–888 (2000).
2. C.O. Kappe, *Eur. J. Med. Chem.* ,**35**, 1043–1052 (2000).
3. C.O. Kappe, *Molecules* ,**3**,1–30 (1998).
4. B. Jauk, T. Pernat and C.O. Kappe, *Molecules*,**5**, 227–239 (2000).
5. T.U. Mayer, T.M. Kapoor, S.J. Haggarty, R.W. King, S.I. Schreiber and T.J. Mitchison, *Science* , **268**, 971–974 (1999)
6. J.C. Cochran, J.E. Gatial, T.M. Kapoor and S.P. Gilbert, *J. Biol. Chem.*, **280**, 12658–12667 (2005).
7. R. Sakowicz, J.T. Finer, C. Beraud, A. Crompton, E. Lewis, A. Fritsch, Y. Lee, J. Mak, R. Moody, R. Turincio, J.C. Chabala, P. Gonzales, S. Roth, S. Weitman and K.W. Wood, *Cancer Res.*, **64**, 3276–3280 (2004).
8. S. Brier, D. Lemaire, S. DeBonis, E. Forest and F. Kozielski, *Biochemistry*, **43**,13072–13082 (2004).
9. R. Heald, *Cell* , **102**, 399–402 (2000).
10. T. Peters, H. Lindenmaier, W.E. Haefeli and J. Weiss, *Arch. Pharmacogyl.*, **372**, 291–299 (2006)
11. S.S. Bokaeva, *Tr. Kaz. Nauch.-lssled. Inst.-Onkol. Radiol.*,**3**, 305–309(1967) [Chem. Abstr. *68* **1968** ]

12. Zidermane, G. Duburs, A. Zilbere, R. Verpele, J. Uldrikis and K. Kumsars, *Latv. PSR Zinat. Akad. Vestis.*, 77–83 (1971 )[Chem. Abstr. *75* **1971**].
13. K. Kumsars, A. Velena, G. Duburs, J. Uldrikis and A. Zidermane, *Biokhimiya* **36,** 1201–1209 (1971).
14. T. Kato, *Japn. Kokai Tokkyo Koho JP Chem. Abstr*. **102,** 22-26 (1985).




aldehyde thiourea 1,3 dicarbonyl compounds compds a-h

**Scheme-1**

**Table-1**

| Compds | $R_1$ | $R_2$ | $R_3$ | $R_4$ |
|---|---|---|---|---|
| a | 3-(OH) | $CH_3$ | NH-CH($CH_3$)-$C_6H_5$ | CO-(NH)-CH($CH_3$)-$C_6H_5$ |
| b | 3-($NO_2$) | $CH_3$ | NH-CH($CH_3$)-$C_6H_5$ | CO-(NH)-CH($CH_3$)-$C_6H_5$ |
| c | 3,4-($OCH_3$)$_2$ | $CH_3$ | NH-CH($CH_3$)-$C_6H_5$ | CO-(NH)-CH($CH_3$)-$C_6H_5$ |
| d | 3- ($OCH_3$) | $CH_3$ | NH-CH($CH_3$)-$C_6H_5$ | CO-(NH)-CH($CH_3$)-$C_6H_5$ |
| e | 3,4,5-($OCH_3$)$_3$ | $CH_3$ | NH-CH($CH_3$)-$C_6H_5$ | CO-(NH)-CH($CH_3$)-$C_6H_5$ |
| f | 3-(O-$C_6H_5$) | $CH_3$ | $OC_2H_5$ | CO-($OC_2H_5$) |
| g | 3-(OH) | $C_6H_5$ | $OC_2H_5$ | CO-($OC_2H_5$) |
| h | 3-(OH) | $COOCH_3$ | $OCH_3$ | $CH_2$($COOCH_3$) |

**Table-2:Characterization data for compds a-h**

| compds | m.p $^0$c | Yield(%) | Mol.formula | Mol.wt | Appearence |
|---|---|---|---|---|---|
| a | 180-82 | 92 | $C_{20}H_{21}N_3O_2S$ | 368 | White |
| b | 134-36 | 93 | $C_{20}H_{20}N_4O_3S$ | 397 | Yellow |
| c | 134-36 | 92 | $C_{22}H_{25}N_3O_3S$ | 412 | White |
| d | 128- 30 | 94 | $C_{21}H_{23}N_3O_2S$ | 381 | White |
| e | 148-51 | 90 | $C_{23}H_{27}N_3O4S$ | 441 | White |
| f | 196-98 | 92 | $C_{20}H_{20}N_2O_3S$ | 368 | White |
| g | 185-87 | 90 | $C_{19}H_{18}N_2O_3S$ | 354 | White |
| h | 192-94 | 92 | $C_{15}H_{16}N_2O_5S$ | 336 | White |

**Table-3: Antimicrobial activity of the compds a-h**

| Organism | Conc of compds | Antimicrobial activity(zone of inhibition in mm) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Compd a | Compd b | Compd c | Compd d | Compd e | Compd f | Compd g | Compd h |
| ***E.coli*** | 25µg | 15 | 14 | 12 | 15 | 14 | 16 | 17 | 14 |
| | 50µg | 19 | 18 | 17 | 18 | 19 | 18 | 20 | 16 |
| | 100µg | 22 | 21 | 24 | 22 | 20 | 22 | 25 | 19 |
| | Standard | 30 | 30 | 30 | 30 | 29 | 30 | 30 | 30 |
| ***S.aureus*** | 25µg | 16 | 15 | 15 | 16 | 14 | 13 | 15 | 16 |
| | 50µg | 20 | 18 | 19 | 17 | 18 | 17 | 18 | 21 |
| | 100µg | 23 | 21 | 22 | 21 | 20 | 20 | 23 | 25 |
| | Standard | 31 | 30 | 29 | 29 | 29 | 28 | 29 | 29 |
| ***C.albicans*** | 25µg | 17 | 19 | 17 | 18 | 14 | 13 | 15 | 16 |
| | 50µg | 20 | 22 | 19 | 22 | 17 | 16 | 17 | 19 |
| | 100µg | 28 | 27 | 23 | 24 | 19 | 20 | 21 | 20 |
| | Standard | 30 | 30 | 30 | 31 | 30 | 29 | 30 | 29 |

(Received:12 August 2008 Accepted: 23 August 2008 RJC-225)