ISSN: 0974 - 7516 Volume 11 Issue 7

Organic CHEMISTRY

An Indian Journal

Full Paper

OCAIJ, 11(7), 2015 [261-266]

# Synthesis of potential antibacterial and antifungal agents: n-(5-(2-chlorobenzylidene)-4-oxo-2-arylthiazolidin-3-yl)-2-(6-methoxy-naphthalen-2-yl) propanamide

**A.P.Zala[1*], V.D.Dave[1], N.K.Undavia[2]**

**[1]Chemistry Department, Sir P.P.Institute of Science, Bhavnagar University, Bhavnagar – 364 002, (INDIA)**

**[2]Department of Chemistry, Bhavnagar University, Bhavnagar – 364 002, (INDIA)**

**E-mail: ashishzala@gmail.com**

## ABSTRACT

Synthesis of few N-(5-(2-Cholrobenzylidene)-4-oxo-2-arylthiazolidine-3-yl)-2-(6-methoxynephthalen-2-yl) propanamide was planned on account of the potential nature of Naproxen as analgesic and anti-inflammatory agents. N-(5-(2-Cholrobenzylidene)-4-oxo-2-arylthiazolidine-3-yl)-2-(6-methoxy-nephthalen-2-yl)propanamide are prepared by condensation of 2-(6-methoxynephthalen-2-yl)-N-(4-oxo-2-arylthiazolidin-3-yl)propanamide with 2-chlorobenzaldehyde in presence of strong base sodium ethoxide. The structures of these compounds have been established on the basis elemental analysis and spectral data. All the synthesized compounds were tested for their anti-bacterial and anti-fungal activities. Some of the synthesized compounds have shown excellent anti-bacterial and anti-fungal activities. 

## KEYWORDS

Synthesis;
Naproxen;
Thiazolidines;
Arylidines;
Antibacterial;
Antifungal.

## INTRODUCTION

*Naproxen* is a non-steroidal anti-inflammatory drug (NSAID)[1] commonly used for the reduction of moderate to severe pain[2], fever, inflammation[3] and stiffness caused by conditions such as osteoarthritis, rheumatoid arthritis, psoriatic arthritis, gout, ankylosing spondylitis, menstrual cramps, tendinitis, bursitis, and the treatment of primary dysmenorrhea[4]. It works by inhibiting both the *COX-1* and *COX-2*[5][6][7] enzymes.

Moreover, 5 – Arylidines has shown anticancer[8], anti-HIV[9], antibacterial[10], anti-tubercular[11] and antifungal[12]-[16] activities. These interesting biological activities have attracted our attention to the chemistry of nitrogen and sulphur containing heterocycles. Hence it was thought of interest that 5-Arylidines, if coupled to Naproxen moiety; the resulting compounds may possess significant biological potency.

Keeping in view of these varied pharmacological activities, we have planned to synthesise new N-(5-(2-Cholrobenzylidene)-4-oxo-2-arylthiazolidine-3-yl)-2-(6-methoxynephthalen-2-yl) propanamide by condensation of 2-(6-methoxynephthalen-2-yl)-N-(4-oxo-2-arylthiazolidin-3-yl) propanamide with 2-chlorobenzaldehyde in presence of strong base so-

dium ethoxide. The constitution of all the products has been characterized by using elemental analyses, IR, $^1$H NMR and mass spectral study. All the compounds were screened for their *in vitro* antibacterial and antifungal activities.

## EXPERIMENTAL

The identity of 6-Methoxy-α-methyl-2-naphthalene acetic acid (Naproxen) sample was established by taking the I.R. of the sample and I.R. was compared with that given in pharmacopeia. The IR spectra were recorded on Bio – Rad FTS – 40 spectrophotometer as KBr pellets at CSMCRI, Bhavnagar, between 4000 – 400 cm $^{-1}$. The PMR spectra were recorded on model DPX – 200 Brucker FT – NMR instrument at CSMCRI, Bhavnagar and using appropriate deuterated solvent (Acetone – D6, DMSO – D6, $CDCl_3$ etc.). FAB mass spectra were recoreded on JOEL SX 102/DA 600 spectrophotometer. All the compounds gave satisfactory elemental analyses. All the Melting points were determined in open capillaries and are uncorrected. All the synthesized compounds were tested for their anti-bacterial and anti-fungal activities. Some of the synthesized compounds have shown excellent anti-bacterial and anti-fungal activities.

### Preparation of 2-(6-methoxynaphthalen-2-yl) – N-(4-oxo-2-arylthiazolidin-3-yl) propanamide (IV)

To a solution of N'-benzylidene-2-(6-methoxynaphthalen-2-yl)propanehydrazide (3.31 gm ; 0.01 M) in 1 : 4 dioxane (25 ml) was added thioglycolic acid (0.925 gm ; 0.01 M). The mixture was refluxed at 110 - 115 $^0$C for 8 hours. The reaction mixture was allowed to cool at room temperature and triturated with 10 % sodium bicarconate solution to remove unreacted mercaptoacetic acid. The solid product was thus separated, filtered and washed with water. Recrystallised from ethanol (95 %). Yield : 65.44 % ; M.P.: 152 $^0$C ; M.F. : $C_{23}H_{21}N_2O_3S$ ; M.W.: 405.26; Required : N, 6.91 % ; S, 7.90%; Found : N, 6.87% ; S, 7.95%.

### Preparation of N-(5-(2-Chlorobenzylidene)-4-oxo-2-(arylthiazolidine-3-yl)-2-(6-methoxynaphthalen-2-yl) propanamide (V)

Sodium metal (0.23 gm ; 0.01 mole) was added in absolute alcohol (15 ml ; 95 %) with external cooling. After 30 minutes 2-(6-methoxynaphthalen-2-yl) – N-(4-oxo-2-arylthiazolidin-3-yl) propanamide (4.05 gm ; 0.01 mole) was added and contents were refluxed for 5 minutes. Solution of 2-Chloro Benzaldehyde (1.40 gm ; 0.01 mole) in absolute alcohol (10 ml ; 95 %) was added to it and refluxed for six hours. Reaction mixture was allowed to cool at room temperature and poured into acidified ice water. The product which separated was filtered, washed several times with cold water, dried and recrystallised from ethanol (95%). Yield : 67 % ; M.P. :190 $^0$C; M.F. : $C_{30}H_{24}N_2O_3SCl$ ; M.W. : 528; Required : N, 5.30% ; S, 6.06% ; Found : N, 5.25% ; S, 6.18%.

Other compounds of TABLE – 1 were prepared by the above mentioned procedure and reaction conditions.

## SPECTRAL STUDY

### IR spectra

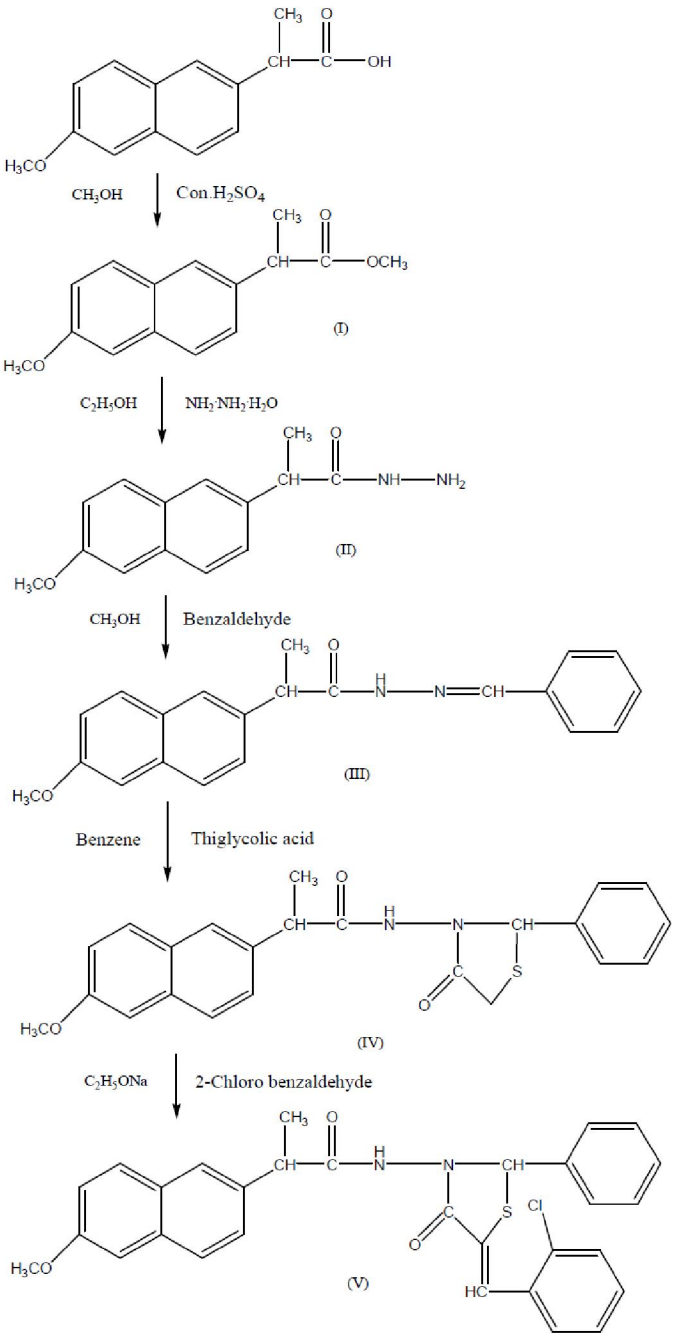
The IR spectra of N-{5-(2-chlorobenzylidene)-2-(4-methoxyphenyl)-4-oxothiazolidin-3-yl}-2-(6-methoxynaphthalen-2-yl)propanamide showed following characteristic bands :

3052 cm$^{-1}$ (C-H Str., aromatic ring), 2905 cm$^{-1}$ (C-H str., aliphatic), 2838 cm$^{-1}$ (C-H str., Ar-$OCH_3$), 1662 cm$^{-1}$ (C=O str., thiazolidinone ring), 1562 cm$^{-1}$ (N-H ben., Secondary amide), 1503 cm$^{-1}$ (C=C str., aromatic ring), 1368 cm$^{-1}$ (C-H ben., methyl groups), 1264 cm$^{-1}$ (C-O-C str., aromatic ether), 815 cm$^{-1}$ (C-H ben., 1:4- substituted benzene), 755 cm$^{-1}$ (C-H ben., 1:4- substituted benzene), 725 cm$^{-1}$ (C-Cl str., monochloro), 654 cm$^{-1}$ (C-S-C str., thiazolidinone ring)

### PMR spectra

The $^1$H NMR spectra of N-{5-(2-chlorobenzylidene)-2-(4-methoxyphenyl)-4-oxothiazolidin-3-yl}-2-(6-methoxynaphthalen-2-yl) propanamide showed following signals.

7.983 δ (1H, -NH), 6.751 – 7.771 δ (aromatic




**Scheme**

protons), 6.019 δ (1H, –CH< thiazolidinonering), 3.899 δ (H –CH-,-$CH_3$-), 3.729 δ (1H, -$CH_3$,),1.581 δ (H, –$CH_3$).

## RESULTS AND DISCUSSION

All the synthesized compounds were tested for their anti-bacterial and anti-fungal activities. We have used *Broth dilution method* to evaluate the antibacterial and anti fungal activities. The results of the TABLE – 2 and TABLE – 3 indicates that Naproxen derivatives are potential anti-bacterial and anti fungal agents. The close look at TABLE – 2 and TABLE – 3 indicates that the introduction of chloro, methoxy and hydroxy group in the aromatic ring increases the anti-bacterial and anti fungal activity and some are even better anti bacterial and anti fungal agents.

Full Paper

**TABLE 1**

| Com. No | -----Ar----- | M.F. | M.P.$^0$C | % Yield | M.W. |
|---|---|---|---|---|---|
| AR1 | $C_6H_5$- | $C_{30}H_{25}N_2O_3S$ | 208 | 63 | 493.55 |
| AR2 | 2-(Cl)-$C_6H_4$- | $C_{30}H_{24}ClN_2O_3S$ | 190 | 67 | 528.00 |
| AR3 | 3-(Cl)-$C_6H_4$- | $C_{30}H_{24}ClN_2O_3S$ | 142 | 62 | 528.00 |
| AR4 | 4-(Cl)-$C_6H_4$- | $C_{30}H_{24}ClN_2O_3S$ | 168 | 61 | 528.00 |
| AR5 | 4-($OCH_3$)-$C_6H_4$- | $C_{31}H_{27}N_2O_4S$ | 136 | 68 | 523.58 |
| AR6 | 2-($NO_2$)-$C_6H_4$- | $C_{30}H_{24}N_3O_5S$ | 159 | 70 | 538.55 |
| AR7 | 3-($NO_2$)-$C_6H_4$- | $C_{30}H_{24}N_3O_5S$ | 145 | 66 | 538.55 |
| AR8 | 4-($NO_2$)-$C_6H_4$- | $C_{30}H_{24}N_3O_5S$ | 187 | 68 | 538.55 |
| AR9 | 2-(OH)-$C_6H_4$- | $C_{30}H_{25}N_2O_4S$ | 118 | 64 | 509.55 |
| AR10 | 3-(OH)-$C_6H_4$- | $C_{30}H_{25}N_2O_4S$ | 97 | 58 | 509.55 |
| AR11 | 4-(OH)-$C_6H_4$- | $C_{30}H_{25}N_2O_4S$ | 135 | 60 | 509.55 |
| AR12 | $C_4H_3O$- (Furfural) | $C_{28}H_{23}N_2O_4S$ | 153 | 59 | 483.51 |
| AR13 | $C_6H_5$-O-$C_6H_4$- | $C_{36}H_{29}N_2O_4S$ | 110 | 71 | 585.65 |
| AR14 | $C_6H_5$-CH=CH- | $C_{32}H_{27}N_2O_3S$ | 179 | 69 | 519.59 |
| AR15 | 3-($OCH_3$)-4-(OH)-$C_6H_3$- | $C_{31}H_{27}N_2O_5S$ | 223 | 63 | 539.58 |

**TABLE 2 : Antibacterial activity table minimal bactericidal concentration**

| CODE NO. | E.COLI MTCC 443 MG/ML | P. AERUGINOSA MTCC 1688 MG/ML | S. AUREUS MTCC 96 MG/ML | S. PYOGENUS MTCC 442 MG/ML |
|---|---|---|---|---|
| AR - 1 | 500 | 250 | 500 | 250 |
| AR - 2 | 50 | 250 | 50 | 100 |
| AR - 3 | 500 | 250 | 100 | 500 |
| AR - 4 | 100 | 500 | 1000 | 250 |
| AR - 5 | 500 | 1000 | 500 | 200 |
| AR - 6 | 250 | 100 | 500 | 500 |
| AR - 7 | 500 | 500 | 250 | 250 |
| AR - 8 | 100 | 200 | 500 | 500 |
| AR - 9 | 25 | 50 | 500 | 500 |
| AR - 10 | 500 | 1000 | 250 | 500 |
| AR - 11 | 100 | 500 | 250 | 1000 |
| AR - 12 | 500 | 500 | 200 | 25 |
| AR - 13 | 100 | 100 | 500 | 500 |
| AR - 14 | 200 | 500 | 200 | 250 |
| AR - 15 | 250 | 250 | 250 | 100 |
| AMPICILLIN | 100 | 100 | 250 | 100 |
| CHLORAMPHENICOL | 50 | 50 | 50 | 50 |

**TABLE 3 : Antifungal activity table minimum fungicidal concentration**

| CODE NO. | C.ALBICIANS MTCC 227 MG/ML | A.NIGER MTCC 282 MG/ML | A.CLAVATUS MTCC 1323 MG/ML |
|---|---|---|---|
| AR - 1 | >1000 | 250 | 250 |
| AR - 2 | 200 | 1000 | 250 |
| AR - 3 | 1000 | 500 | 500 |
| AR - 4 | 500 | 100 | 500 |
| AR - 5 | 500 | 1000 | 1000 |
| AR - 6 | >1000 | >1000 | >1000 |
| AR - 7 | >1000 | 500 | 250 |
| AR - 8 | >1000 | >1000 | >1000 |
| AR - 9 | 250 | 1000 | 1000 |
| AR - 10 | 250 | 250 | 500 |
| AR - 11 | >1000 | >1000 | >1000 |
| AR - 12 | 250 | 500 | 500 |
| AR - 13 | >1000 | 1000 | 500 |
| AR - 14 | 500 | 1000 | 200 |
| AR - 15 | 100 | 500 | 500 |
| NYSTATIN | 100 | 100 | 100 |
| GRESEOFULVIN | 500 | 100 | 100 |


## ACKNOWLEDGEMENT

Authors are thankful to Dr. Reddy's Laboratory for providing free sample of pure *Naproxen*. We are thankful to Microcare laboratory, Surat for anti-bacterial and anti fungal screening of our compounds and CSMCRI, Bhavnagar for spectral analysis. We are also thankful to Gujarat Cancer research Institute and authorities of Bhavnagar University, Bhavnagar, for providing research facilities. One of the authors (APZ) is thankful to Government of Gujarat for providing financial assistance.


## REFERENCES


**[1]** M.Mouelhi et al.; Drug Metab.Dispos; **15(6)**, 767-72.

**[2]** Journal of the americal osteopathic association, **113(8)**, 620-627.

**[3]** S.Rossy; Australian medicines hand book, ISBN – 978-0-9805790-9-3

**[4]** A.French; "Dysmenorrhea", Am.Farm Physician, **71(2)**, 285-91.

**[5]** Duggan et al.; J.Biol.Chem, **285(45)**, 34950–9.

**[6]** H.B.Cheremina et al.; Int.J.Clin.Pharmacol Ther., **46(4)**, 180-6.

**[7]** Van Hecken et al.; Int.J.Clin.Pharmacol Ther., **40(10)**, 1109–20.

**[8]** J.J.Bhatt; Ph.D.Thesis, Bhavnagar University, Bhavnagar, **(1993)**.

**[9]** Jadeja, B.Raghuvirsinh; Ph.D.Thesis, Bhavnagar University, Bhavnagar **(1997)**.

**[10]** U.S.Pandya, R.R.Astik, K.A.Thakar; J.Inst.Chem., **53**, 65.

Full Paper

**[11]** T.A.Rao, R.R.Astik, K.A.Thakar; J.Inst.Chem., **53**, 174.
**[12]** M.R.Manrao et.al.; Indian J.Heterocycl.Chem., **5(1)**, 85–86; Chem.Abstr.; **124**, 175921g.
**[13]** Kutty, N.Gopalan; A.R.Bhatt; J.Inst.Chem., **67(1)**, 22–23; Chem.Abstr., **125**, 10681m.
**[14]** Nailesh Joshi, Pankaj Patel, Hansa Parekh; Indian J.Chem., **35(B)**, 867–870; Chem.Abstr.; **125**, 195487u.
**[15]** M.B.Hogale, A.C.Uthale, B.P.Nikam; Indian J.Chem., **30B**, 717–720.
**[16]** V.N.Patolia, P.K.Patel, A.J.Baxi; J.Ind.Chem.Soc., **71(11)**, 683 – 685; Chem.Abstr.; **123**, 256582d.