Available online at www.derpharmachemica.com

Scholars Research Library

Der Pharma Chemica, 2014, 6(5):14-18
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X
CODEN (USA): PCHHAX

Synthesis, spectroscopic characterization and antimicrobial activity of 5-arylidene-2-substituted-1,3-thiazol-4-one

Prajwal L. Lobo[1*], Boja Poojary[2], D. Jagadeesh prasad[2] and Nalilu Suchetha Kumari[4]

[1]Department of Chemistry, Maharani's Science College for Women, Bangalore-560001, Karnataka, India
[2]Department of Chemistry, Mangalore University, Mangalagangothri-574199, Karnataka, India.
[c]Department of Biochemistry, K.S. Hegde Medical Academy, Deralakatte-574162, Karnataka, India

---

ABSTRACT

*Various substituted 5-arylidene-2-substituted-1,3-thiazol-4-one derivatives **3a-h** were synthesized in good yield by the reaction of methyl thiocyanatoacetate **1** with various secondary amines to afford 2-substituted 1,3-thiazol-4(5H)-one which on further reaction with various aryl aldehydes afforded the title compounds **3a-h**. All structures of the newly synthesized compounds were elucidated by elemental analyses, spectral data and a few by single crystal XRD study and screened for their antimicrobial activity.*

Key words: methylthiocyanatoacetate, thiazole, secondary amine, chair conformation

---

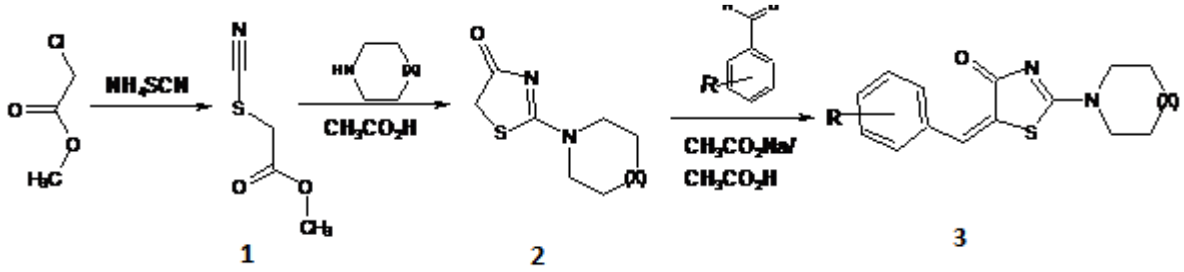
INTRODUCTION

The development of simple synthetic routes for widely used organic compounds from readily available reagents is one of the major challenges in organic synthesis. Heterocycles form the basis of a variety of pharmaceutical compounds [1]. Certain small heterocyclic molecules act as highly functionalized scaffolds and are known pharmacophores of a number of biologically active and medicinally useful molecules [2,3]. Thiazolidine template is one such privileged structure fragments in modern medicinal chemistry considering its broad pharmacological spectrum and affinity for various biotargets of these class heterocyclic compounds [4]. Therefore, the synthesis of combinatorial libraries of these compounds was elaborated [5-8]. The thiazolidinone derivatives are well known in medicinal and biological chemistry due to their diverse pharmacological displays as anti-inflammatory, antimicrobial [9, 10], antitumor [11], anticonvulsant [12], analgesic [13], anticancer properties. The biological and synthetic significance, places this group (thiazolidinone) in an important position in medicinal chemistry research. As a part of our continuing interest in biologically active thiazolidinone derivatives and on the basis of the assumption that a benzylidene moiety at the 5-position of the 4-thiazolidinone is necessary for the antimicrobial activity, we are reporting a simple root for the synthesis of novel thiazolidinones starting from ethyl chloro acetate and secondary amines.In this contribution, results of synthesis, spectroscopic studies and antimicrobial activity of thiazolidinone derivatives are presented.

MATERIALS AND METHODS

The melting points were determined by an open capillary method and are uncorrected. The IR spectra (in KBr pellets) were recorded on a Shimadzu FT-IR 157 spectrophotometer. The ^{1}H-NMR spectra were recorded ($CDCl_3$) on a BRUKER AVANCE II - 400 (400 MHz) spectrometer using TMS as an internal standard. The DART-MS was

recorded on a JEOL-ACCUTOF JMS-T100LC mass spectrometer having a DART source. Dry helium was used with 4LPM flow rate for ionization at 350^{0}C. Elemental analysis (CHNS) was performed on the CHNS Elementar Vario EL III. The progress of the reaction was monitored by thin layer chromatography (TLC) on silica gel plates. All the spectral data of newly synthesized compounds are consistent with proposed structure and microanalysis within ±0.3 of the calculated values. The synthetic strategies adopted to obtain the target compounds are depicted in **Scheme 1**.



X=O, CH_2, N-CH_3

R= 4-OCH_3, 2,4-Cl_2, 3,4-$(OCH_3)_2$, 3,4,5-$(OCH_3)_3$

Scheme 1: Synthesis of 5-arylidene-2-substituted-1,3-thiazol-4-ones

General procedure for the synthesis of thiocyanatoacetate (1)

An equimolar mixture of sodium thiocyanate and methylchloroacetate in acetonitrile was stirred and heated to approximately 30^{0}C and held at this temperature for 20hours. The precipitated NaCl is filtered and acetonitrile was removed by rotary evaporation (the concentrate contained approximately 10%of acetonitrile). The crude product was washed with water. The separated organic layer was dried over anhydrous Na_2SO_4. After Na_2SO_4 was filtered off, the product methyl thiocyanatoacetate was used as such for the second step without further purification.

General procedure for the synthesis of 2-substituted-1,3-thiazol-4(5*H*)-one (2a-c)

A mixture of thiocyanatoacetate (0.01mol), secondary amine (0.01mol) and acetic acid in ethanol was refluxed for 30 hours. The course of the reaction was monitored by T LC. After cooling the reaction mixture the precipitate formed was filtered, washed and recrystallised from terahydrofuran.

General procedure for the synthesis of 5-benzylidene-2-substituted-1,3-thiazol-4(5*H*)-one (3a-h)

To a mixture of 2-substituted-1,3-thiazol-4(5H)-one(0.01mole), appropriate aromatic aldehyde (0.01mole),anhydrous sodium acetate(0.8g) and glacial acetic acid (10ml) was heated under reflux for 1.5 hours. The reaction mixture was cooled to room temperature and poured to ice water. The separated solid was filtered, washed with water, recrystallised from tetrahydrofuran.

2-(Morpholin-4-yl)-5-(3,4,5-trimethoxybenzylidene)-1,3-thiazol-4(5H)-one (3b)

IR (KBr, ν_{max} cm^{-1}): 3059 (Ar-H), 2946 (C-H), 1684 (C=O), 1567 (C=C); ^{1}H NMR (400MHz, $CDCl_3$, δ ppm): 3.65 (t, 2H, *J* = 4.9 Hz, CH_2 of morpholine), 3.69 (s, 6H, OCH_3), 3.79 (s, 3H, OCH_3), 3.80-3.85 (m, 4H, $(CH_2)_2$N of morpholine), 4.09 (t, 2H, *J* = 4.9 Hz, CH_2 of morpholine), 7.00 (s, 2H, Ar-H), 8.06 (s, 1H, =CH); DART MS (m/z): 364.01 (M^+); Anal. for $C_{17}H_{20}N_2O_5S$: C 56.03, H 5.53, N7.69; Found: C 56.07, H 5.55, N 7.72.

2-(Piperidin-1-yl)-5-(3,4,5-trimethoxybenzylidene)-1,3-thiazol-4(5H)-one (3e)

IR (KBr, ν_{max} cm^{-1}): 3054 (Ar-H), 2948 (C-H), 1682 (C=O), 1569 (C=C); ^{1}H NMR (400MHz, $CDCl_3$, δ ppm): 1.78 (s, 6H, CH_2 of pipyridine), 3.56 (m, 2H, CH_2 of pipyridine), 3.66 (s, 6H, OCH_3), 3.81 (s, 3H, OCH_3), 4.04-4.06 (m, 2H, CH_2 of pipyridine), 7.01 (s, 2H, Ar-H), 7.98 (s, 1H, =CH); DART MS (m/z) : 362.1 (M^+); Anal. for $C_{18}H_{22}N_2O_4S$: C 59.65, H 6.12, N 7.73; Found: C 59.68, H 6.15, N 7.77.

5-(2,4-Dichlorobenzylidene)-2-(4-methylpiperazin-1-yl)-1,3-thiazol-4(5H)-one (3f)

IR (KBr, ν_{max} cm^{-1}): 3058.4 (Ar-H), 2942 (C-H), 1685 (C=O), 1613 (C=N), 1562 (C=C), 772 (C-Cl); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.27 (s, 3H, CH_3), 2.44-2.47 (m, 4H, CH_2 of piperazine), 3.26 (t, 2H, *J* = 5.2 Hz, CH_2 of piperazine), 3.82 (t, 2H, *J* = 5.2 Hz, CH_2 of piperazine), 7.31-7.35 (dd, 1H, Ar-H, *J* = 8.4 Hz and 2.4 Hz), 7.50 (d, 1H, Ar-H, *J* = 2.4 Hz,), 7.52 (d, 1H, Ar-H, *J* = 8.4 Hz), 8.0 (s, 1H, =CH); DART MS (m/z) : 356.07 (M^+); Anal. for $C_{15}H_{15}Cl_2N_3OS$: C 50.57, H 4.24, N 11.79; Found: C 50.60, H 4.26, N 11.82.

5-(3,4-Dimethoxybenzylidene)-2-(4-methylpiperazin-1-yl)-1,3-thiazol-4(5H)-one (3g)

IR (KBr, ν_{max} cm^{-1}): 3062 (Ar-H), 2939 (C-H), 1687 (C=O), 1564 (C=C); ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 2.27 (s, 3H, CH_3), 2.44-2.48 (m, 4H, CH_2 of piperazine), 3.26 (t, 2H, CH_2 of piperazine, J = 5.2 Hz), 3.82 (t, 2H, CH_2 of piperazine, J = 5.2 Hz,), 3.94 (s, 6H, OCH_3), 6.93 (d, 1H, J = 8.5 Hz, Ar-H), 7.05 (d, 1H, J = 2.0 Hz, Ar-H), 7.15 (dd, 1H, J = 8.5 Hz, J = 2.0 Hz, Ar-H), 7.98 (s, 1H, =CH) ; DART MS (m/z) : 347.01 (M^+); Anal. for $C_{17}H_{21}N_3O_3S$: C 58.77, H 6.09, N 12.09; Found: C 58.79, H 6.12, N 12.12.

2-(4-Methylpiperazin-1-yl)-5-(3,4,5-trimethoxybenzylidene)-1,3-thiazol-4(5H)-one (3h)

IR (KBr, ν_{max} cm^{-1}): 3054 (Ar-H), 2947 (C-H), 1687 (C=O), 1566 (C=C); ^1H NMR (400MHz, $CDCl_3$, δ ppm): 2.27 (s, 3H, CH_3), 2.45- 2.48 (s, 4H, CH_2 of piperazine), 3.27 (t, 2H, J = 5.2 Hz, CH_2 of piperazine), 3.66 (s, 6H, OCH_3), 3.81 (s, 3H, OCH_3), 3.83 (t, 2H, J = 5.2 Hz, CH_2 of piperazine), 7.03 (s, 2H, Ar-H), 7.99 (s, 1H, =CH); DART MS (m/z) : 377.1 (M^+); Anal. for $C_{18}H_{23}N_3O_4S$: C 57.28, H 6.14, N 11.13; Found: C 57.31, H 6.17, N 11.17.

RESULTS AND DISCUSSION

The synthetic route for the target compounds is outlined in scheme **1.** Target Compounds **(3a-h)** were prepared by the above method by taking sodium thiocyanate and ethyl chloroacetate as the starting material. The final product was obtained in two steps. In the first step the thiocyanatoacetate formed is treated with secondary amines in alcohol media in the presence of a few drops of glacial acetic acid, to bring about the cyclisation, to form the 2-substituted thiazolone. In the second step equimolar quantities of thiazolone formed in the first step and suitable aromatic aldehyde were refluxed in glacial acetic acid in the presence of anhydrous sodium acetate to obtain the desired compound **(3a-h)** in good yield. The chemical structures of the synthesized compounds were established by spectroscopic (FT-IR, ^{1}HNMR, mass), elemental analysis and X-ray crystallographic data. The spectral data are reported in the experimental section. The elemental analysis, yield, molecular weight and melting point data of the newly synthesized compounds are given in **Table 1.**

Table 1. Characterization data of compounds 3a-h.

Comp	X	R	Mol. formula	Mol. wt	m.p (^oC)	Yield (%)	Analysis Found (Calculated) % C	H	N
3a	O	2,4-Cl_2	$C_{14}H_{12}Cl_2N_2O_2S$	344.22	140-142	90	48.99(48.97)	3.52 (3.55)	8.16 (8.19)
3b	O	3,4,5-$(OCH_3)_3$	$C_{17}H_{20}N_2O_5S$	364.41	178-180	67	56.03 (56.06)	5.53 (5.55)	7.69 (7.65)
3c	CH_2	4-OCH_3	$C_{16}H_{18}N_2O_2S$	302.39	192-194	89	63.55 (63.58)	6.00 (6.03)	9.26 (9.28)
3d	CH_2	2,4-Cl_2	$C_{15}H_{14}Cl_2N_2OS$	342.3	198-200	86	52.79 (52.83)	4.14 (4.17)	8.21(8.24)
3e	CH_2	3,4,5-$(OCH_3)_3$	$C_{18}H_{22}N_2O_4S$	362.44	172-174	64	59.65 (59.68)	6.12(6.15)	7.73(7.77)
3f	N-CH_3	2,4-Cl_2	$C_{15}H_{15}Cl_2N_3OS$	357.27	174-176	80	50.57 (50.60)	4.24(4.27)	11.79(11.81)
3g	N-CH_3	3,4-$(OCH_3)_2$	$C_{17}H_{21}N_3O_3S$	347.43	196-198	69	58.77 (58.81)	6.09(6.11)	12.09 (12.13)
3h	N-CH_3	3,4,5-$(OCH_3)_3$	$C_{18}H_{23}N_3O_4S$	377.45	190-192	61	57.28 (57.31)	6.14(6.11)	11.13 (11.16)

IR spectrum of 2-(morpholin-4-yl)-1,3-thiazol-4(5*H*)-one **2a** showed a characteristic C=O absorption peak at 1667.07 cm^{-1}. Absorption bands at 2958.7 cm^{-1} and 2846.7 cm^{-1} were due to C-H stretching vibrations. A band at 1280.1 cm^{-1} was due to C-O stretching. The 400 MHz ^1H NMR spectra of **2a** showed two characteristic triplets at δ 3.53 and δ 3.99 integrating for methylee protons of morpholine with coupling constant J = 5.2 Hz. A characteristic multiplet integrating for four protons of morpholine was observed at δ 3.75 - 3.81. The methylene proton of thiazolone ring appeared as a singlet at δ 3.97. Further, the DART mass spectrum of **2a** confirmed the formation of the compound with m/z 186 in conformity with its molecular formula $C_7H_{10}N_2O_2S$.

The IR spectrum of 5-(2,4-dichlorobenzylidene)-2-(morpholin-4-yl)-1,3-thiazol-4(5*H*)-one **3a** displayed absorption bands at 2931 cm^{-1} and 2856.5 cm^{-1} for C-H, 1680 cm^{-1} for C=O, 1566 cm^{-1} for C=C and 746 cm^{-1} C-Cl. The 400 MHz ^1H NMR spectrum of **3a** displayed two characteristic triplets at δ 3.61 and δ 4.09 with coupling constant J = 4.7 Hz, each triplet attributed to the methylene unit of the morpholine ring. A multiplet at δ 3.80-3.85 was attributed to the remaining two methylene units of the morpholine ring. The three protons of 2,4-dichlorophenyl moiety resonated as a doublet of doublet at δ 7.30 -7.32 with coupling constant J = 8.4 Hz and J = 2.1 Hz and as a doublet overlapped with another doublet at δ 7.48-7.51. The signal due to methylene protons of thiazolidinone ring is absent. A characteristic singlet at δ 8.07 was observed for benzylidene proton. Further the DART mass spectrum of **3a** showed protonated molecular ion peak at m/z 343.02, in conformity with its molecular formula $C_{14}H_{12}N_2Cl_2O_2S$ along with its isotopic peaks.

In the IR spectrum of 5-(2,4-dichlorobenzylidene)-2-(piperidin-1-yl)-1,3-thiazol-4(5*H*)-one **3d** showed a strong absorption band at 3059 cm^{-1} for Ar-H , 2939 cm^{-1} and 2858 cm^{-1} for C-H, 1681 cm^{-1} for C=O, 1552 cm^{-1} for C=C and 769 cm^{-1} for C-Cl. The 400 MHz ^1H NMR spectrum **3d** displayed a broad singlet at δ 1.76 for the three methylene units of pipyridine ring thus integrating for six protons. Two multiplets for N-CH_2 protons of piperidine

were observed at δ 3.56-3.58 and δ 4.02-4.05 each integrating for two protons. One of the aromatic protons resonated as a doublet of doublet at δ 7.29-7.32 with coupling constant J = 8.4 Hz and J = 2.4 Hz. One more aromatic proton between two Cl atoms resonated as a doublet at δ 7.48 with coupling constant J = 2.4 Hz. The third aromatic proton was observed at δ 7.52 as a doublet with coupling constant J = 8.4 Hz. A singlet observed at δ 8.039 was due to benzylidene proton. Further, DART mass spectrum of **3d** showed the M+1 molecular ion peak at m/z 341.05 in conformity with its molecular formula $C_{15}H_{14}N_2Cl_2OS$.

Crystal Structure Analysis

The structure of (5*E*)-5-(4-Methoxybenzylidene)-2-(piperidin-1-yl)-1,3-thiazol-4(5H)-one (**3c**) and (5*E*)-5-(2,4-Dichlorobenzylidene)-2-(piperidin-1-yl)-1,3-thiazol-4(5*H*)-one (**3d**), is confirmed by single crystal X-ray study [14,15,16].

Pharmacological activity

Antibacterial activity

All the newly synthesized compounds were screened for their antibacterial activity against four bacterial strains, viz., *Staphylococcus aureus* (ATTC-25923), *Escherichia coli* (ATTC-25922), *Psuedomonus aeruginosa* (ATTC-27853) *and Klebsiella pneumoniae* (recultured) species by disc diffusion method [17]. The discs measuring 6.25 mm in diameter were punched from Whatman no.1 filter paper. Batches of 100 discs were dispensed to each screw capped bottles and sterilized by dry heat at 140 ^oC for an hour. The test compounds were prepared with different concentrations using DMF. 1mL containing 100 times the amount of chemical in each disc was added to each bottle, which contains 100 discs. The discs of each concentration were placed in triplicate in nutrient agar medium seeded with fresh bacteria separately. The incubation was carried out at 37 ^oC for 24 h. Ampicillin was used as a standard drug. Amphicillin has 16-22 mm inhibition length. The minimum inhibitory concentrations (MIC) of each compound were determined.

The antibacterial study revealed that the compound **3a, 3b, 3d** and **3f** containing dichloro or trimethoxy substituted phenyl group showed excellent activity towards all the four bacterial strains. The compounds **3c, 3e, 3h** showed moderate activity towards all the four bacterial strains. The significant activity of these compounds may attributed to the presence of pharmacologically active groups 2, 4-Cl_2 attached to the phenyl ring or trimethoxy groups. Compounds substituted with mono methoxy and dimethoxy groups showed dramatic decline in the activity. The results are summarized in **Table 2**.

Table 2. Antibacterial activity of compounds 3a-h

Compound	MIC (in µgmL^{-1}) and zone of inhibition (mm) in parentheses			
	S.aureus **(ATTC-25923)**	***E.Coli*** **(ATTC-25922)**	***P.aeruginosa*** **(ATTC-27853)**	***K.pneumonia*** **(recultured)**
3a	6.25 (16-20)	6.25 (16-20)	6.25 (16-20)	6.25 (16-20)
3b	6.25 (16-20)	6.25 (16-20)	6.25 (16-20)	6.25 (16-20)
3c	12.5 (11-15)	12.5 (11-15)	12.5 (11-15)	12.5 (11-15)
3d	6.25 (16-20)	6.25 (16-20)	6.25 (16-20)	6.25 (16-20)
3e	12.5 (11-15)	12.5 (11-15)	12.5 (11-15)	12.5 (11-15)
3f	6.25 (16-20)	6.25 (16-20)	6.25 (16-20)	6.25 (16-20)
3g	25 (< 10)	25 (< 10)	25 (< 10)	25 (< 10)
3h	12.5 (11-15)	12.5 (11-15)	12.5 (11-15)	12.5 (11-15)
Standard (Ampicillin)	1.56 (22-30)	6.25 (30-40)	6.25 (25-33)	6.25 (23-27)

**The MIC values were evaluated at a concentration range 1.56 – 25 µg mL^{-1}.*

Antifungal activity

The compounds screened for antibacterial activity were also tested for their antifungal activity against *Penicillium marneffei* (recultred), *Trichophyton mentagrophytes* (recultured), *Aspergilus flavus* (NICM No.524) and *Aspergilus fumigates* (NCIM No.902) by serial plate dilution method [18]. Sabourands agar media was prepared by dissolving peptone (1g), D-glucose (4g) and agar (2g) in distilled water (100ml) and adjusting pH to 5.7. Normal saline was used to make a suspension of spore of fungal strain for lawning. A loopful of particular fungal strain was transferred to 3 mL saline to get a suspension of corresponding species. Twenty ml of agar media was poured in to each petri dishes. Excess of suspension was decanted and the plates were dried by placing in an incubator at 37 ^oC for 1h. Using an agar punch wells were made in to each well labeled. A control was also prepared in triplicate and maintained at 37 ^oC for 3-4 days. Activity of each compound was compared with itraconozole as standard. Itraconozole has a MIC value of 0.03-16 micro g mL^{-1}. The minimum inhibitory concentrations of each compound were determined.

The study revealed that the compound **3a, 3d** and **3f**showed very good activity against all the four fungal strains. The structure of these compounds contains biologically active 2, 4-Cl_2 attached to the phenyl ring .The compound **3c, 3e, 3g** showed moderate activity against all the four fungal strains.The results are presented in **Table 3**.

Table 3. Antifungal activity of the compounds 3a-h

Compounds	MIC (in µgmL^{-1}) and zone of inhibition (mm) in parentheses			
	P. marneffei (recultured)	*T. mentagrophy* (recultured)	*A. flavus* (NCIM No.524)	*A. fumigates* (NCIM No.902)
3a	6.25 (16-20)	6.25 (16-20)	6.25 (16-20)	6.25 (16-20)
3b	25 (< 10)	25 (< 10)	25 (< 10)	12.5 (11-15)
3c	12.5 (11-15)	12.5 (11-15)	12.5 (11-15)	6.25 (16-20)
3d	6.25 (16-20)	6.25 (16-20)	6.25 (16-20)	6.25 (16-20)
3e	12.5 (11-15)	6.25 (16-20)	6.25 (16-20)	12.5 (11-15)
3f	6.25 (16-20)	6.25 (16-20)	12.5 (11-15)	6.25 (16-20)
3g	12.5 (11-15)	12.5 (11-15)	12.5 (11-15)	12.5 (11-15)
3h	25 (< 10)	25 (< 10)	25 (< 10)	25 (< 10)
Itraconozole	6.25 (25-33)	6.25 (23-27)	1.56 (22-30)	6.25 (30-40)

**The MIC values were evaluated at a concentration range 1.56 – 25µg mL^{-1}.*

CONCLUSION

This study reports the successful synthesis of the title compounds. The crystal structure of the compound (**3c** and **3d)** revealed that the piperidine ring adopts a chair conformation. An intramolecular C—H_ _ _S hydrogen bond stabilizes the molecular structure and generates an S(6) ring motif. In the crystal, molecules are linked into a tape along the c axis by intermolecular C—H_ _ _O hydrogen bonds. The antimicrobial activity study showed that 5-benzylidene-2- substituted thiazolones containing 2,4-dichlorophenyl ring and trimethoxy phenyl ring showed very good antibacterial activity and compounds having 2,4-dichlorophynyl ring showed very good antifungal activity against all the tested microbial species.

Acknowledgments
The authors are thankful to UGC for the financial assistance and to the Head, SAIF, CDRI, Lucknow, the Chairman, Indian institute of science, Bangalore and the Head, USIC, Mangalore University for providing mass, ^{1}H NMR and IR spectral data.

REFERENCES

[1] T. Eicher, S. Hauptmann, The Chemistry of Heterocycles, 2nd edition, Wiley-VCH, Weinheim, **2003.**
[2] R.B. Silverman, Organic Chemistry of Drug Design and Drug Action, Academic Press, San Diego, **1992**.
[3] L.A. Thompson, J. A. Ellman, *Chem Rev*, **1996**, 96, 555-600.
[4] R.B. Lesyk , B.S. Zimenkovsky, *Curr Org Chem*, **2004**, 8, 1547–1577.
[5] C.P. Holmes, J. P. Chinn, G. C. Look, E. M. Gordon ,M. A. Gallop *J Org Chem*, **1995**, 60, 7328-7333.
[6] M. Pulici, F. Quartieri, *Tetrahedron Lett*, **2005**, 46, 2387-2391.
[7] D. Maclean, F. Holden, A. M. Davis, R. A. Scheuerman, S. Yanofsky, C. P. Holmes, W. L. Fitch,K. Tsutsui, R. W. Baratt , M. A. Gallop, *J Comb Chem*, **2004**, 6, 196-204.
[8] J. Fraga-Dubreuil, J. P. Bazureau, *Tetrahedron*, 2003, 59, 6121-6130.
[9] C. Dwivedi, T. K. Gupta, S. S. Parmar, *J Med Chem***, 1973,** 16, 178.
[10] A. Grafe, M. Liebig , G. Dransch, *Chem Abstr*, **1973**, 79, 143522.
[11] S.P. Singh, S. K. Anyyong , S. S. Parmar, *J Pharm Sci*, **1974**, 63, 960-967.
[12] M.I. Hussain, S.K. Agarwal, *Indian J Pharm*, **1975**, 37, 89.
[13] H. L. Liu, Z. C. Li, T. Anthonsen. *Molecules*, **2000**, 5, 1055-1061.
[14] H.K. Fun, M. Hemamalini, P. L. Lobo, D. J. Prasad, Boja Poojary, *Acta Crystallogr*. **2011**, E67, o2884.
[15] H.K. Fun, C. S. Yeap, P. L. Lobo, D. J. Prasad, Boja Poojary, *Acta Crystallogr*. **2011,** E67, o1915.
[16] CCDC 841125 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/ data_request/cif.
[17] A. L. Barry, Procedure for testing antimicrobial agents in agar media; V. L. Corian (Ed), Antibiotics in Laboratory Medicine, Williams and Wilkins, Baltimore, MD, **1991**, p.1.
[18] R. S. Verma, Z. K. Khan, A. P. Singh et al .(Eds.), Antifungal Agents: Past, Present and Future Prospects, National Academy of Chemistry and Biology, Lucknow, India, **1986** p.55.