Available online at www.derpharmachemica.com

Scholars Research Library

Der Pharma Chemica, 2012, 4(5):1873-1878
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X
CODEN (USA): PCHHAX

Pharmacological examination and synthesis of some schiff bases and thiazolidinone derivatives of 5-amino-1*H*-imidazole-4-carboxamide

Chandra Kant Belwal [1*] and Kaushik A. Joshi [2]

[1]Department of Chemistry, JJT University, Rajasthan, India
[2]M.V.M. Science & Home Science College, Rajkot, India

ABSTRACT

Schiff bases and thiazolidinone derivatives of 5-amino-1H-imidazole -4-carboxamide have been prepared and tested for pharmacological activities. Schiff base derivatives have been obtained by reacting 5-amino-1H-imidazole -4-carboxamide with suitable aromatic aldehyde which were further converted to thiazolidinone derivatives by reaction of Schiff bases with mercaptoacetic acid. The structure of synthesized compounds have been established on the basis of their spectral (IR, ^{1}H NMR and mass) data. The purity of the synthesized compounds was confirmed by TLC. Good level of pharmacological activity has been displayed by both categories of compounds against tested pathogenic microorganism. Thiazolidinone derivatives ***(2a-f)*** *showed higher activity than schiff base derivatives* ***(1a-f)****.*

Key Words: 5-amino-1*H*-imidazole-4-carboxamide, Thiazolidinone, Pharmacological activity, Schiff base, Heterocyclic compounds

---

INTRODUCTION

The wide range of biological activities exhibited by thiozolidinones [1,2] and imidazole [3] derivatives, the aim of this study is to prepare thiazolidinones containing imidazole ring in the molecule and to explore the pharmacological activity of this combination product.

Imidazole is a heterocyclic compound of five-membered diunsaturated ring structure composed of three carbon atoms and two nitrogen atoms at nonadjacent positions. The chemistry of imidazole compounds have been of much interest due to the presence of such heterocycles in a large variety of biologically important molecules. For example, some amino imidazole derivatives have shown interesting antifungal and antitumor properties [4]. Two clinically useful azole families, the imidazoles and the triazoles, have good antimicrobial activity. The most commonly prescribed drugs are fluconazole, itraconazole, ketoconazole, miconazole and econazole.

5-amino-1*H*-imidazole-4-carboxamide is the key raw material for the preparation of well known anticancer drug Temozolomide [5,6] and Dacarbazine [7]. Imidazole derivatives have antibacterial, antifungal, antiprotozoal, anthelmintic and other pharmacological activities [8-15]. Several distinct phenylimidazoles are therapeutically useful antifungal agents against either superficial or systemic infections. Imidazole has two nitrogen atoms. The one is slightly acidic, while the other is basic. Imidazole derivatives are widely used as intermediates in synthesis of pharmaceuticals.

At the same time 4-thiazolidinones are the most common and important groups among the small ring heterocyclic compounds. Thiazolidinones are derivatives of thiazolidine belonging to important group of heterocyclic compounds. There are many references reported in the literature highlighting their chemistry and use. 4-Thiazolidinones exhibited various biological activities such as analgesic, antibacterial, antifungal, anti-oxidant, anti-inflammatory, anticonvulsant, anticancer, anti-HIV, anti-tubercular and anthelmintic activities [16-25].

MATERIALS AND METHODS

All solvents and chemicals used were of commercial or LR grade, and were used without further purification. Purity of the compounds was checked by TLC. Melting points were measured on Buchi melting point apparatus and are uncorrected. The IR spectra were recorded on Perkin-Elmer spectrometer, using KBr pellets. ^{1}H-NMR spectra were scanned on Bruker-NMR spectrometer at 500 MHz, using TMS as an internal standard and DMSO d6 as solvent.

General method for the synthesis of Schiff base derivatives

5-amino-1*H*-imidazole-4-carboxamide hydrochloride (0.06mol) was suspended in 50 ml of methanol, pH of the suspension adjusted to 8 with the help of methanolic solution of sodium hydroxide, stirred for 15 min. and separated sodium chloride was removed by filtration. To the filtrate 0.06mol of suitable aldehyde added and reaction mixture was refluxed for four hours, cooled to room temperature, solid collected by filtration and purified by crystallization from suitable solvents **(scheme-1)**. Physical data of compounds **(1*a-f*)** are presented in **table -1**.

5-(benzylideneamino)-1*H*-imidazole-4-carboxamide (1*a*)

Light purple colored crystals; yield 62 %; mp 263 °C (decomposition); IR (KBr / cm^{-1}) absorption bands at 3197 (NH), 3028 (CH), 1622 (C=N); ^{1}H NMR (500MHz, DMSO-d6) 7.50 (d, 3H, Ar-H), 7.98 (d, 2H, Ar-H), 7.72 (s, 1H, -N=CH), 9.16 (s, 1H, CH of Imidazole ring); Mass (TOF MS ES+) 215.06 (M+), 237.08 (M+Na)

5-(4-chlorobenzylideneamino)-1*H*-imidazole-4-carboxamide (1*b*)

Off white colored crystals; yield 60 %; mp 274 °C (decomposition); IR (KBr / cm^{-1}) absorption bands at 3178 (NH), 3008 (CH), 1620 (C=N); ^{1}H NMR (500MHz, DMSO-d6) 7.54 (d, 2H, Ar-H), 7.92 (d, 2H, Ar-H), 7.77 (s, 1H, -N=CH), 9.10 (s, 1H, CH of Imidazole ring); Mass (TOF MS ES+) 249.40(M+), 271.06 (M+Na)

5-(4-methoxybenzylideneamino)-1*H*-imidazole-4-carboxamide (1*c*)

Ivory colored crystals; yield 55 %; mp 269 °C (decomposition); IR (KBr / cm^{-1}) absorption bands at 3213 (NH), 3055 (CH), 1623 (C=N); ^{1}H NMR (500MHz, DMSO-d6) 3.83 (s, 3H, -OCH_3), 7.06 (d, 2H, Ar-H), 7.92 (d, 2H, Ar-H), 7.69 (s, 1H,C=N), 9.08 (s, 1H, CH of Imidazole ring); Mass (TOF MS ES+) 245.15 (M+), 267.09 (M+Na)

5-(2-hydroxybenzylideneamino)-1*H*-imidazole-4-carboxamide (1*d*)

Off white colored crystals; yield 65 %; mp 270 °C (decomposition); IR (KBr / cm^{-1}) absorption bands at 3166 (NH), 3020 (CH), 1628 (C=N); ^{1}H NMR (500MHz, DMSO-d6) 6.82 – 7.44 (m, 4H, Ar-H), 7.82 (s, 1H, -N=CH), 8.99 (s, 1H, CH of Imidazole ring); Mass (TOF MS ES+) 231.20 (M+), 253.08 (M+Na)

5-(4-tolylideneamino)-1*H*-imidazole-4-carboxamide (1*e*)

Off white colored crystals; yield 59 %; mp 265 °C (decomposition); IR (KBr / cm^{-1}) absorption bands at 3186 (NH), 3021 (CH), 1620 (C=N); ^{1}H NMR (500MHz, DMSO-d6) 3.39 (s, 3H, -CH_3), 7.11 (d, 2H, Ar-H), 7.64 (d, 2H, Ar-H), 7.88 (s, 1H,C=N), 8.98 (s, 1H, CH of Imidazole ring); Mass (TOF MS ES+) 229.19 (M+), 251.19 (M+Na)

5-((pyridin-4-yl)methyleneamino)-1*H*-imidazole-4-carboxamide (1*f*)

Off white colored crystals; yield 62 %; mp 255 °C (decomposition); IR (KBr / cm^{-1}) absorption bands at 3193 (NH), 3018 (CH), 1621 (C=N); ^{1}H NMR (500MHz, DMSO-d6) 8.02 (d, 2H, Ar-H), 8.82 (d, 2H, Ar-H), 7.56 (s, 1H,C=N), 8.99 (s, 1H, CH of Imidazole ring); Mass (TOF MS ES+) 216.02 (M+), 238.18 (M+Na)

Scheme-1 Synthesis of schiff bases of 5-amino-1H-imidazole-4-carboxamide
(i): Methanol, Reflux

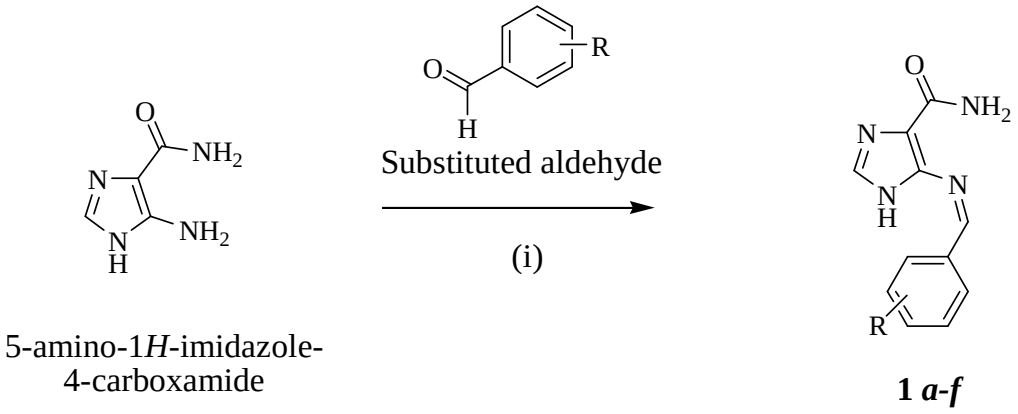


Table-1 Physical data of schiff bases

Compound	Aromatic aldehyde	Mol. Formula	Mol. Weight	Melting Point (°C)	Yield (%)
1*a*	Benzaldehyde	$C_{11}H_{10}N_4O$	214.22	263	62
1*b*	p-Chlorobenzaldehyde	$C_{11}H_9ClN_4O$	248.66	274	60
1*c*	Anisaldehyde	$C_{12}H_{12}N_4O_2$	244.24	269	55
1*d*	Salicyldehyde	$C_{11}H_{10}N_4O_2$	230.22	270	65
1*e*	p-Tolualdehyde	$C_{12}H_{12}N_4O$	228.24	265	59
1*f*	Pyridine-4-aldehyde	$C_{10}H_9N_5O$	215.21	255	62

General method for the synthesis of thiazolidinone derivatives
Schiff base derivative (0.01mol), mercaptoacetic acid (0.02 mol) and a catalytic amount of anhydrous zinc chloride was added to 20 ml of anhydrous dioxane, reaction mixture was refluxed for eight hours, reaction progress was monitored by TLC using a mixture of 10% methanol and 90% dichloromethane as mobile phase. After completion of reaction solvent recovered under reduced pressure, residue dissolved in dichloromethane, dichloromethane layer washed with 10% sodium bicarbonate solution to remove unreacted mercaptoacetic acid, dried over anhydrous sodium sulphate and recovered under reduced pressure. Residue obtained was recrystalized from ethanol **(scheme-2)**. Physical data of thiazolidinone compounds **(2*a-f*)** are presented in **table -2**.

5-(4-oxo-2-phenylthiazolidin-3-yl)-1*H*-imidazole-4-carboxamide (2*a*)
Off white colored crystals; yield 39 %; mp 124 °C (decomposition); IR (KBr / cm^{-1}) absorption bands at 3256 (NH), 3012 (CH), 1690 (C=O of thiazolidinone ring); ^{1}H NMR (500MHz, DMSO-d6) 3.52 – 3.62 (dd, 2H, CH_2 of thiazolidinone ring), 5.78 (s 1H, N-CH-S), 7.37 – 7.38 (m, 5H, Ar-H), 9.00 (s, 1H, -N=CH); Mass (TOF MS ES+) 289.06 (M+), 311.07 (M+Na)

5-(2-(4-chlorophenyl)-4-oxothiazolidin-3-yl)-1*H*-imidazole-4-carboxamide (2*b*)
Off white colored crystals; yield 37 %; mp 132 °C (decomposition); IR (KBr / cm^{-1}) absorption bands at 3217 (NH), 3039 (CH), 1688 (C=O of thiazolidinone ring); ^{1}H NMR (500MHz, DMSO-d6) 3.48 – 3.58 (dd, 2H, CH_2 of thiazolidinone ring), 5.80 (s 1H, N-CH-S), 7.10 – 7.15 (m, 5H, Ar-H), 9.01 (s, 1H, -N=CH); Mass (TOF MS ES+) 223.28 (M+), 345.03 (M+Na)

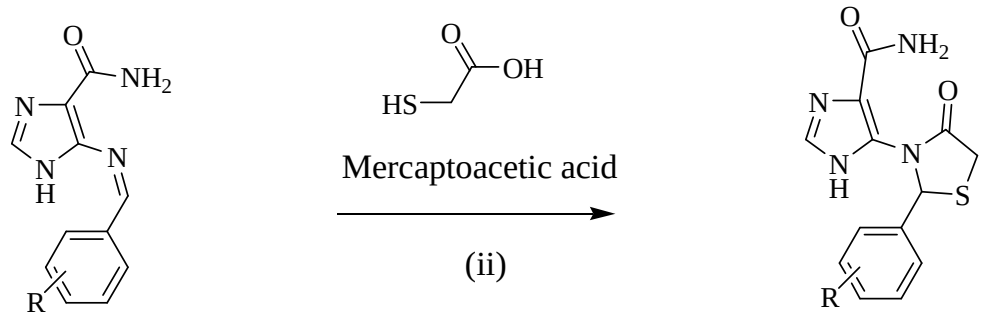
5-(2-(4-methoxyphenyl)-4-oxothiazolidin-3-yl)-1*H*-imidazole-4-carboxamide (2*c*)
Off white colored crystals; yield 37 %; mp 110 °C (decomposition); IR (KBr / cm^{-1}) absorption bands at 3159 (NH), 3024 (CH), 1682 (C=O of thiazolidinone ring); ^{1}H NMR (500MHz, DMSO-d6) 3.48 – 3.57 (dd, 2H, CH_2 of thiazolidinone ring), 3.74 (s, 3H, $-OCH_3$), 5.75 (s 1H, N-CH-S), 6.91 (d, 2H, Ar-H), 7.31 (d, 2H, Ar-H), 8.96 (s, 1H, -N=CH); Mass (TOF MS ES+) 319.15(M+), 341.08 (M+Na)

5-(2-(2-hydroxyphenyl)-4-oxothiazolidin-3-yl)-1*H*-imidazole-4-carboxamide (2*d*)
Off white colored crystals; yield 40 %; mp 119 °C (decomposition); IR (KBr / cm^{-1}) absorption bands at 3190 (NH), 3041 (CH), 1687 (C=O of thiazolidinone ring); ^{1}H NMR (500MHz, DMSO-d6) 3.38 – 3.48 (dd, 2H, CH_2 of thiazolidinone ring), 5.79 (s 1H, N-CH-S), 6.60 - 6.91 (m, 4H, Ar-H), 8.86 (s, 1H, -N=CH); Mass (TOF MS ES+) 305.30 (M+), 327.06 (M+Na)

5-(4-oxo-2-p-tolylthiazolidin-3-yl)-1*H*-imidazole-4-carboxamide (2*e*)
Off white colored crystals; yield 39 %; mp 112 °C (decomposition); IR (KBr / cm^{-1}) absorption bands at 3147 (NH), 3032 (CH), 1689 (C=O of thiazolidinone ring); ^{1}H NMR (500MHz, DMSO-d6) 2.39 (s, 3H, $-CH_3$), 3.48 – 3.57 (dd, 2H, CH_2 of thiazolidinone ring), 5.87 (s 1H, N-CH-S), 6.99 (s, 4H, Ar-H), 8.96 (s, 1H, -N=CH); Mass (TOF MS ES+) 303.08 (M+), 325.08 (M+Na)

5-(4-oxo-2-(pyridin-4-yl)thiazolidin-3-yl)-1*H*-imidazole-4-carboxamide (2*f*)
Off white colored crystals; yield 37 %; mp 118 °C (decomposition); IR (KBr / cm^{-1}) absorption bands at 3199 (NH), 3019 (CH), 1690 (C=O of thiazolidinone ring); ^{1}H NMR (500MHz, DMSO-d6) 3.38 – 3.48 (dd, 2H, CH_2 of thiazolidinone ring), 5.71 (s 1H, N-CH-S), 7.41 (d, 2H, Ar-H), 8.61 (d, 2H, Ar-H), 8.90 (s, 1H, -N=CH); Mass (TOF MS ES+) 290.03 (M+), 312.06 (M+Na)

Scheme-2 Synthesis of thiazolidinone derivatives of 5-amino-1H-imidazole-4-carboxamide
(ii): 1,4-Dioxane, Anh. Zinc chloride, Reflux



1 *a-f* **2 *a-f***

Table-2 Physical data of thiazolidinone derivatives

Compound	Aromatic aldehyde	Mol. Formula	Mol. Weight	Melting Point (°C)	Yield (%)
2*a*	Benzaldehyde	$C_{13}H_{12}N_4O_2S$	288.32	124	39
2*b*	p-Chlorobenzaldehyde	$C_{13}H_{11}ClN_4O_2S$	322.77	132	37
2*c*	Anisaldehyde	$C_{14}H_{14}N_4O_3S$	318.35	110	37
2*d*	Salicyldehyde	$C_{13}H_{12}N_4O_3S$	304.32	119	40
2*e*	p-Tolualdehyde	$C_{14}H_{14}N_4O_2S$	302.35	112	39
2*f*	Pyridine-4-aldehyde	$C_{12}H_{11}N_5O_2S$	289.31	118	37

RESULTS AND DISCUSSION

Antimicrobial activity
The antimicrobial activity of both categories of compounds was determined by the disc diffusion method [26]. The *in vitro* antimicrobial activity was carried out in two gram positive bacteria, two gram negative bacteria and two fungi against 24 h culture. The gram positive bacteria used were *Staphylococcus aureus* and *Bacillus subtilis*, gram negative bacteria used were *Escherichia coli* and *Klebsiella pneumonia*, while the fungi used were *Aspergillus niger* and *Candida albicans*. The compounds were tested at a concentration of 100µg/ml in Dimethylformamide. The zone of inhibition was compared after 24 h of incubation at 37° against Ciprofloxacin (100µg/ml) as standards for comparison of antibacterial activity **(table-3)** and 72 h at 25° against Ciclopirox olamine (100µg/ml) as standards for comparison of antifungal activity **(table-4)**. In general, all synthesized compounds exhibited good inhibitory activity

against tested pathogenic microorganism. Thiazolidinone derivatives (**2*a-f*)** showed higher activity than schiff base derivatives **(1*a-f*)**.

Table-3 Antimicrobial activity of schiff bases

Compound	Zone of inhibition (mm)					
	Gram positive bacteria		Gram negative bacteria		Fungi	
	S. aureus	*B. subtilis*	*E. coli*,	*K. pneumonia*	*A. niger*	*C. albicans*
1*a*	6.0	6.0	6.5	6.0	6.0	6.0
1*b*	6.0	6.5	6.0	6.0	6.0	6.0
1*c*	5.5	5.5	6.0	5.5	5.5	6.0
1*d*	6.0	6.0	6.5	5.5	6.0	5.5
1*e*	5.5	6.0	6.0	5.5	5.5	6.0
1*f*	6.0	6.0	6.5	6.0	6.0	6.0
*	10.0	10.0	9.5	9.5	NA	NA
**	NA	NA	NA	NA	10.0	10.0

*****Ciprofloxacin (Standard)*
*******Ciclopirox olamine (Standard)*

Table-4 Antimicrobial activity of thiazolidinone derivatives

Compound	Zone of inhibition (mm)					
	Gram positive bacteria		Gram negative bacteria		Fungi	
	S. aureus	*B. subtilis*	*E. coli*,	*K. pneumonia*	*A. niger*	*C. albicans*
2*a*	7.0	7.5	7.0	7.5	8.0	8.5
2*b*	7.0	8.0	6.5	7.5	7.5	7.5
2*c*	7.5	7.5	7.5	7.5	8.5	8.5
2*d*	8.0	7.5	7.0	7.0	8.0	8.5
2*e*	7.5	7.5	7.5	7.5	7.5	7.5
2*f*	7.0	7.0	7.5	7.0	8.5	8.5
*	10.0	10.0	9.5	9.5	NA	NA
**	NA	NA	NA	NA	10.0	10.0

*****Ciprofloxacin (Standard)*
*******Ciclopirox olamine (Standard)*

Chemical synthesis

The chemical synthesis started with the conversion of commercially available 5-amino-1*H*-imidazole-4-carboxamide hydrochloride in to 5-amino-1*H*-imidazole-4-carboxamide free base which was then converted to Schiff base by the reaction of 5-amino-1*H*-imidazole-4-carboxamide with suitable aromatic aldehyde, six aromatic aldehydes were used namely benzaldehyde, p-chlorobenzaldehyde, anisaldehyde, salicylaldehyde, p-tolualdehyde, and pyridine-4-aldehyde to synthesize Schiff bases **(1*a-f*)**. Schiff bases upon reaction with mercaptoacetic acid gave thiazolidinone derivative of 5-amino-1*H*-imidazole-4-carboxamide (**2*a-f*)**. Purity of the synthesized compounds was confirmed by TLC and structures were confirmed by mass, infrared and nuclear magnetic spectroscopic techniques.

The structures of schiff bases **(1*a-f*)** and thiazolidinone derivatives **(2*a-f*)** were supported by elemental analyses and IR spectra, conversion of schiff bases to thiazolidinone derivatives confirmed by IR as disappearance of 1620 - 1630 $cm^{-1}$for -N=CH- band of schiff base with appearance of 1680 - 1690 cm^{-1} for >C=O of thiazolidinone. The ^{1}H-NMR singlet signals of cyclilized thiazolidinones were observed at δ 3.38–3.58, corresponding to -CH_2- in the thiazolidinone ring and other peak also support the formation of compound.

CONCLUSION

The present study reports the successful synthesis of Schiff bases **(1*a-f*)** and thiazolidinone derivatives (**2*a-f*)** of 5-amino-1*H*-imidazole -4-carboxamide with several structural variations. Pharmacological examination of synthesized compounds exhibited good inhibitory activity against tested pathogenic microorganism. Thiazolidinone derivatives (**2*a-f*)** showed higher activity than schiff base derivatives **(1*a-f*)**.

Acknowledgement

The authors are thankful to the Department of Chemistry, JJT University, Rajasthan, India and M.V.M. Science & Home Science College, Rajkot, India for providing laboratory facilities and analytical support.

REFERENCES

[1] A. Verma and K.S. Saraf, European *Journal of Medicinal Chemistry*, Volume 43, Issue 5, **2008**, 897–905
[2] T.P. Singh, P. K. Sharma, P. K. Kaur, S. C. Mondal and A. Gupta, *Der Pharma Chemica*, **2011**, 3(1), 194-206
[3] K. Shalini, P. K. Sharma and N. Kumar, *Der Chemica Sinica*, **2010**, 1 (3), 36-47
[4] U. Sandbhor, P. Kulkarni, S. Padhye, G. Kundu, G. Mackenzie and R. Pritchard. *Bioorg Med Chem Lett*., **2004,** 14(11), 2877-82.
[5] M.F. Stevens, J.A. Hickman, R. Stone, N.W. Gibson, G.U. Baig, E. Lunt and C.G. Newton. *J Med Chem*., **1984**, 27(2), 196-201.
[6] Shen-Chun Kuo, Synthesis of temozolomide and analogs, *US patent 6844434* (**2005**)
[7] Y.F. Shealy, A.K. Charles and J.A. Montgomery. *JOC*., 1962 Vol.27, 2150-2154
[8] A.F. Pozharskii. Heterocycles in Life and Society. *John Wiley & Sons*, **1997**.
[9] C. Congiu, M. T. Cocco and V. Onnis. *Bioorganic & Medicinal Chemistry Letters*., **2008**,18, 989–993.
[10] Y.I. Lin, P.J. Peterson, Y. Yang, W.J. Weiss, D.M. Shales and T.S. Mansour, *Bioorg. Med. Chem*., **2008**, 16, 1890–1902.
[11] S. Bhushankumar. J. Sathe, A. J. Vijay and S. D. Deshmukh. *Der Pharma Chemica*, **2011**, 3(2), 305-309
[12] M. S. Han and D. H. Kim, *Bioorganic & Medicinal Chemistry Letters*, **2001**, 11, 1425-1427.
[13] G. Roman, J.G. Riley, J. Z. Vlahakis, R.T. Kinobe, J.F. Brien, K. Nakatsu and W.A. Szarek. *Bioorg. Med. Chem*., **2007**, 15, 3225–3234.
[14] Bosserman, D. Colussi, D.R. McMasters, J.P. Vacca, H.G. Selnick, *Bioorg. Med. Chem. Lett*., **2004**, 14, 2141–2145.
[15] J. Fraga-Dubrevil and J. P. Bazureau, *Tetrahedron*, **59** (2003) 6121
[16] A.V. Dobaria, J.R. Patel, J.V. Padalia. *Ind. J. Heterocyclic Chem*., **2001**, 11, 115-118.
[17] M. Amir and F. Azam. *Ind. J. Heterocyclic Chem*., **2004**, 14, 119-121.
[18] D. Kumar, F.B. Bux, V. Parmar and A. Singh. *Der Pharma Chemica*, **2012**, 4 (1), 538-543
[19] S.T. Dhanashire, R.P. Singh and M.P. Toraskar, *Der Pharma Chemica*, **2010**, 2(4), 17-20
[20] R. Mishra, I. Tomar, S. Singhal and K. K. Jha, *Der Pharma Chemica*, **2012**, 4 (1), 489-496
[21] N.J. Gaikwad, M. Yunus, H.A. Husain and D.B. Meshram. *Indian Journal of Heterocyclic Chem*. **2002**, 12, 165-168.
[22] S. P. Vartale, D. B. Kadam , and N. K. Halikar. *Der Pharma Chemica*, **2011**, 3 (6), 213-223
[23] A. Rao, J. Balzarini, A. Cafbone, A. Chimirri, E.D. Clercq, A.M. Monforte, P. Monforte, C. Pannecouque and M. Zappala. *Antiviral Res*. **2004**, 63, 79-83.
[24] A. Saeed, N. Abbas and U. Florke. *J. Braz Chem. Soc.*, **2007**, 18 (3), 559-565.
[25] S.M. Kudari, K.H. Lagili and S.E. Badiger. *Ind. J. Heterocyclic Chem*., **1996**, 6, 153-159.
[26] R. Cruickshank, J.P. Duguid, B.P. Marmion and R.H. Swain . *Medicinal Microbiology*, 12th ed. Churchil Livingstone, London, **1975**, 196-202