HL **ISSN: 2231 – 3087(print) / 2230 – 9632(Online)**
http://heteroletters.org **Vol. 4: (1), 2014, 65-71**

SYNTHESIS AND ANTIMICROBIAL SCREENING OF 2-[(5,6-DIMETHOXY-2,3-DIHYDRO-1*H*-INDEN-1-YLIDENE)HYDRAZINYLIDINE]-1,3-THIAZOLIDIN-4-ONE AND ITS 5-ARYLIDINE DERIVATIVES

Chandra Kant Belwal*[1] Chetna M. Rajyaguru[2] and Kaushik A. Joshi[3]

1. Department of Chemistry, J.J.T. University, Rajasthan, India
2. Department of Micro-biology, M.V.M. Science & Home Science College, Rajkot, India
3. Department of Chemistry, D.K.V. Arts & Science College, Jamnagar, India
Email: belwalck@yahoo.co.in

Abstract
2-[(5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-ylidene)hydrazinylidene]-1,3-thiazolidin-4-one **[4]** was prepared from 5,6-dimethoxy-2,3-dihydro-1H-inden-1-one and it was used as a key intermediate for the synthesis of a series of novel 5-Arylidene-1,3-thiazolidin-4-one derivatives [**5a-e]** in good yields. Identification and characterization of the compounds were achieved by IR, NMR and MS spectroscopic techniques. The antimicrobial activities of all the synthesized compounds were evaluated against two gram positive bacteria (*Staphylococcus aureus, Bacillus subtilis*), two gram negative bacteria (*Pseudomonas aeruginosa, Escherichia coli*) and two fungus (*Candida albicans, Aspergillus niger*) and found that, 5-Arylidene-1,3-thiazolidin-4-one derivatives [**5a-e]** are less to moderately active against selected bacterial stains. And antifungal activity screening of the compounds reveals that among all the tested compounds, the compounds with chloro substitution are promisingly active against *Candida albicans* and *Aspergillus niger.*

Key words
Thiazolidinone, 5-Arylidene-1,3-thiazolidin-4-one, 5,6-dimethoxy-2,3-dihydro-1H-inden-1-one, antimicrobial activity.

Introduction

Thiazolidinone derivatives have been studied extensively because of their diverse chemical reactivity and wide range of biological activity, the pharmaceutical importance of thiazolidinone derivatives lies in the fact that thiazolidinone derivatives shows a variety of biological activities like antimicrobial, [i-v] anticancer, [vi-vii] anticonvulsant, [viii-ix] antiviral [x] and anti-HIV activity [xi] etc.

On the other hand indenone moiety is also a core structure in various biologically active molecules. 5,6-dimethoxy-2,3-dihydro-1H-inden-1-one is a key raw material for antialzheimer drug Donepezil hydrochloride [xii]. Looking to the interesting properties of thiazolidinone and indenone moiety, it was considered worthwhile to synthesize a series of 5-Arylidene-1,3-

thiazolidin-4-one derivatives of 5,6-dimethoxy-2,3-dihydro-1H-inden-1-one for obtaining biologically potent agents.

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 and mass spectra were recorded on waters Q Tof Mass Spectrometer.

Experimental procedure

Procedure for the synthesis of 5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-ylidene hydrazine [2]

A mixture of 5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-one **[1]** (20g, 0.104 mol) and hydrazine hydrate (40 ml) in 200 ml of commercial ethanol is heated to reflux for 4 hours. After the completion of reaction, the solvent is evaporated on rotary evaporator under reduced pressure. The residue obtained is recrystalized from ethanol, filtered and dried at 50-55°C till constant weight to furnish a pale yellow solid. Yield 16.8g (78%); ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.07- 6.98 (2H, Ar-H), 3.79 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 2.91 (t, 2H, CH_2 of indene ring), 2.81 (t, 2H, CH_2 of indene ring); MS: *m/z* = 207.11 [M+•].

Procedure for the synthesis of 2-chloro-*N*'-[5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-ylidene]acetohydrazide [3]

A mixture of 5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-ylidene hydrazine **[2]** (0.073 mol) and chloroacetyl chloride (0.080 mol) is refluxed in ethyl acetate (160 ml) in the presence of potassium carbonate (0.109 mol) for 6 hours. After the completion of reaction, water (160 ml) is added to the reaction mixture at room temperature, stirred and the solid filtered, washed with water and recrystalized from ethanol. Wet material dried at 50-55°C till constant weight to furnish a pale yellow solid. Yield 15.5g (75%); ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.05- 6.96 (2H, Ar-H), 4.29 (s, 2H, CH_2Cl), 3.81 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 2.90 (t, 2H, CH_2 of indene ring), 2.80 (t, 2H, CH_2 of indene ring); MS: *m/z* = 283.08 [M+•].

Procedure for the synthesis of 2-[(5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-ylidene)hydrazinylidene]-1,3-thiazolidin-4-one [4]

A mixture of 2-chloro-*N*'-[5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-ylidene]acetohydrazide **[3]** (0.053 mol) and NH_4SCN (0.080 mol) is refluxed in absolute ethanol (150 ml) for 6 hours. After the completion of reaction, the solvent is evaporated on rotary evaporator under reduced pressure. The residue obtained is recrystalized from ethanol, filtered and dried at 50-55°C till constant weight to furnish a brownish yellow solid. Yield 12.5g (77%); mp 179 °C; IR (KBr / cm^{-1}) absorption band at 1702 (C=O), 1212 (C-S); ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.83 (bs, 1H, NH of thiazolidinone ring), 7.07- 6.99 (2H, Ar-H), 4.00 (s, 2H, CH_2 of thiazolidinone ring), 3.80 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 2.94 (t, 2H, CH_2 of indene ring), 2.84 (t, 2H, CH_2 of indene ring); ^{13}C NMR (DMSO-d_6): δ 170.1 (C=O), 152.8-103.5 (Ar-C and C=N), 56.0 (OCH_3), 55.9 (OCH_3), 33.1 (CH_2 of thiazolidinone ring), 29.5 (CH_2 of indene ring), 28.3 (CH_2 of indene ring); MS: *m/z* = 306.09 [M+•]; Anal. Calcd. for $C_{14}H_{15}N_3O_3S$: C(55.07%) H(4.95%) N(13.76%). Found: C(55.11%) H(5.00%) N(13.70%).

General procedure for the synthesis of 5-Arylidene-1,3-thiazolidin-4-one derivatives [5a-e]

A mixture of 2-[(5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-ylidene)hydrazinylidene]-1,3-thiazolidin-4-one **[4]** (0.020 mol), suitable aromatic aldehydes (0.020 mol) and anhydrous

sodium acetate (0.010 mol) is refluxed in glacial acetic acid (50 ml) for 4 to 6 hours depending upon the completion of reaction. After the completion of reaction, the solvent is evaporated on rotary evaporator under reduced pressure. The residue obtained is suspended in water and filtered which is further recrystalized from ethanol, filtered and dried at 50-55°C till constant weight to furnish a light brown coloured solid. Aryl substituent of compounds, their melting points and yield of synthesis is tabulated in table-1.

Spectral data of 5-Arylidene-1,3-thiazolidin-4-one derivatives [5a-e]

5-benzylidene-2- [(5,6-dimethoxy-2,3-dihydro-1H-inden-1-ylidene) hydrazinylidene]-1,3-thiazolidin-4-one ***[5a]****:* Yield 61%; mp 226 °C; IR (KBr / cm^{-1}) absorption band at 1700 (C=O), 1205 (C-S); ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.96 (bs, 1H, NH of thiazolidinone ring), 7.44 (s, 1H, C=CH), 7.31- 6.96 (7H, Ar-H), 3.79 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 2.92 (t, 2H, CH_2 of indene ring), 2.82 (t, 2H, CH_2 of indene ring); ^{13}C NMR (DMSO-d_6): δ 169.4 (C=O), 164.1 (C=N), 163.0 (C=N), 152.2-112.2 (Ar-C), 56.1 (OCH_3), 55.9 (OCH_3), 32.2 (CH_2 of indene ring), 28.0 (CH_2 of indene ring); MS: *m/z* = 394.12 [M+•]; Anal. Calcd. for $C_{21}H_{19}N_3O_3S$: C (64.10%) H (4.87%) N (10.68%). Found: C (64.18%) H (4.81%) N (10.61%).

5-(4-hydroxybenzylidene) -2-(5,6-dimethoxy-2,3-dihydro- 1H-inden-1-ylidene) hydrazinylidene]-1,3-thiazolidin-4-one ***[5b]****:* Yield 58%; mp 247 °C; IR (KBr / cm^{-1}) absorption band at 1702 (C=O), 1210 (C-S); ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.00 (bs, 1H, NH of thiazolidinone ring), 7.41 (s, 1H, C=CH), 7.29- 6.93 (6H, Ar-H), 3.79 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 2.93 (t, 2H, CH_2 of indene ring), 2.83 (t, 2H, CH_2 of indene ring); MS: *m/z* = 410.11 [M+•]; Anal. Calcd. for $C_{21}H_{19}N_3O_4S$: C (61.60%) H (4.68%) N (10.26%). Found: C (61.65%) H (4.70%) N (10.31%).

5-(4-methoxybenzylidene) -2-(5,6-dimethoxy-2,3-dihydro-1H-inden-1-ylidene) hydrazinylidene]-1,3-thiazolidin-4-one ***[5c]*** *:* Yield 54%; mp 251 °C; IR (KBr / cm^{-1}) absorption band at 1707 (C=O), 1212 (C-S); ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.98 (bs, 1H, NH of thiazolidinone ring), 7.42 (s, 1H, C=CH), 7.30- 6.95 (6H, Ar-H), 3.80 (s, 6H, OCH_3), 3.77 (s, 3H, OCH_3), 2.93 (t, 2H, CH_2 of indene ring), 2.83 (t, 2H, CH_2 of indene ring); MS: *m/z* = 424.13 [M+•]; Anal. Calcd. for $C_{22}H_{21}N_3O_4S$: C (62.40%) H (5.00%) N (9.92%). Found: C (62.47%) H (4.96%) N (9.99%).

5-(4-chlorobenzylidene)-2-(5,6-dimethoxy-2,3-dihydro-1H-inden-1-ylidene)hydrazinylidene]-1,3-thiazolidin-4-one ***[5d]*** *:* Yield 52%; mp 238 °C; IR (KBr / cm^{-1}) absorption band at 1700 (C=O), 1204 (C-S); ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.99 (bs, 1H, NH of thiazolidinone ring), 7.42 (s, 1H, C=CH), 7.30- 6.96 (6H, Ar-H), 3.80 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 2.90 (t, 2H, CH_2 of indene ring), 2.80 (t, 2H, CH_2 of indene ring); MS: *m/z* = 428.08 [M+•]; Anal. Calcd. for $C_{21}H_{18}ClN_3O_3S$: C (58.94%) H (4.24%) N (9.82%). Found: C (58.90%) H (4.19%) N (9.80%).

5-(2-chlorobenzylidene)-2-(5,6-dimethoxy-2,3-dihydro-1H-inden-1-ylidene)hydrazinylidene]-1,3-thiazolidin-4-one ***[5e]*** *:* Yield 61%; mp 232 °C; IR (KBr / cm^{-1}) absorption band at 1701 (C=O), 1210 (C-S); ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.96 (bs, 1H, NH of thiazolidinone ring), 7.76 (s, 1H, C=CH), 7.31- 6.96 (6H, Ar-H), 3.79 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 2.92 (t, 2H, CH_2 of indene ring), 2.82 (t, 2H, CH_2 of indene ring); MS: *m/z* = 428.08 [M+•]; Anal. Calcd. for $C_{21}H_{18}ClN_3O_3S$: C (58.94%) H (4.24%) N (9.82%). Found: C (58.89%) H (4.19%) N (9.78%).

Table-1
Aryl substituent of compounds, their melting points and yield of synthesis

Comp.	Aryl substituent	Mol. formula	Mol. weight	M.P. (°C)	Yield (%)
4	--	$C_{14}H_{15}N_3O_3S$	305.35	179	77
5a	C_6H_5	$C_{21}H_{19}N_3O_3S$	393.45	226	61
5b	4-OH-C_6H_5	$C_{21}H_{19}N_3O_4S$	409.45	247	58
5c	4-OCH_3-C_6H_5	$C_{22}H_{21}N_3O_4S$	423.48	251	54
5d	4-Cl-C_6H_5	$C_{21}H_{18}ClN_3O_3S$	427.90	238	52
5e	2-Cl-C_6H_5	$C_{21}H_{18}ClN_3O_3S$	427.90	232	61

Antibacterial Activities

2-[(5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-ylidene)hydrazinylidene]-1,3-thiazolidin-4-one **[4]** and 5-Arylidene-1,3-thiazolidin-4-one derivatives **[5a-e]** have been screened in vitro for their antibacterial activity at 2mg/ml concentration using DMF as solvent. All the compounds were studied for their antibacterial activity at 37°C against freshly cultured stains of gram positive (*S. aureus* & *B. Subtilis)* and gram negative (*P. aeruginosa & E. coli)* bacteria by using nutrient agar media in filter paper disc diffusion technique [xiii] and zone of inhibition was measured after 24 hour. Ampicillin and Streptomycin were used as standard antibacterial agent for comparison.

Antifungal Activities

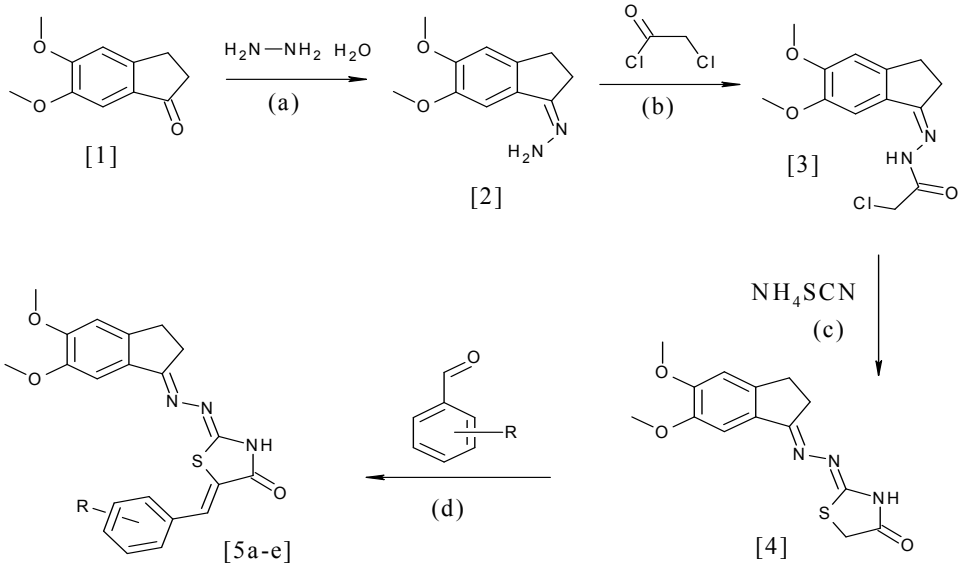
The antifungal activity of 2-[(5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-ylidene)hydrazinylidene]-1,3-thiazolidin-4-one **[4]** and 5-Arylidene-1,3-thiazolidin-4-one derivatives **[5a-e]** was studied at 2mg/ml concentration using DMF as solvent. All the compounds were studied for their antifungal activity at 25°C against freshly cultured stains of *C. albicans* and *A. niger* by using Sabouraudís agar media in filter paper disc diffusion technique [xiii] and zone of inhibition was measured after 24 hour. Miconazole was used as standard antifungal agent.

Results and discussion

Chemical synthesis

Chemical synthesis started with the synthesis of 5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-ylidene hydrazine **[2]** from 5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-one using hydrazine hydrate in the media of refluxing ethanol which is further converted to 2-chloro-*N*'-[5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-ylidene]acetohydrazide **[3]** by the reaction of chloroacetyl chloride in presence of potassium carbonate in the media of refluxing ethyl acetate, 2-chloro-*N*'-[5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-ylidene]acetohydrazide **[3]** when refluxed with ammonium thiocyanate in the media of absolute ethanol furnished cyclized compound 2-[(5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-ylidene)hydrazinylidene]-1,3-thiazolidin-4-one **[4]**. Formation of 1,3-thiazolidin-4-one confirmed by spectroscopic techniques, IR absorption band observed at 1702 cm^{-1} for (C=O) and 1212 cm^{-1} for (C-S) confirming the thiazolidinone ring formation, ^1H NMR in DMSO-d6, show the appearance of peaks around 4.00 ppm for CH_2 of thiazolidinone, ^{13}C NMR in DMSO-d6, show the appearance of peak at 170.1 ppm for carbonyl carbon and peak at 28.3 ppm for thiazolidinone CH_2 , DEPT spectra shows three CH_2 carbons at 33.1 ppm (CH_2 thiazolidinone), 29.5 ppm (CH_2 indenone) and 28.3 ppm (CH_2 indenone). Appearance of m/z peaks [M+·] also confirm the formation of 1,3-thiazolidin-4-one.

5-arylidine derivatives of 2-[(5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-ylidene)hydrazinylidene]-1,3-thiazolidin-4-one **[4]** were prepared by refluxing 2-[(5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-ylidene)hydrazinylidene]-1,3-thiazolidin-4-one **[4]** with suitable aromatic aldehydes and anhydrous sodium acetate in glacial acetic acid and solids were purified by recrystalized from ethanol. Formation of 5-arylidine derivatives confirmed by spectroscopic techniques, ^{1}H NMR in DMSO-d6, show the disappearance of CH_2 proton peak of thiazolidinone at 4.00 ppm and appearance of C=CH proton peak around 7.4 ppm, ^{13}C NMR in DMSO-d6, and DEPT spectra show the disappearance of peaks of thiazolidinone CH_2 carbon. Appearance of m/z peaks [M+·] also confirm the formation of 5-Arylidene-1,3-thiazolidin-4-one derivatives **[5a-e]**.



Reaction scheme-1: Synthesis of 2-[(5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-ylidene)hydrazinylidene]-1,3-thiazolidin-4-one and its 5-arylidine derivatives
(a). Ethanol, reflux, 4Hr. (b). Ethyl acetate, Potassium carbonate, reflux, 6Hr.
(c). Absolute ethanol, reflux, 6Hr. (d). Glacial acetic acid, Anh. NaOAc, reflux, 6Hr.

Antimicrobial activity

All synthesized compounds have been screened in vitro for their antibacterial activity at 37°C against gram positive (*S. aureus & B. Subtilis)* and gram negative (*P. aeruginosa & E. coli)* bacteria at 2mg/ml concentration using DMF as solvent and for their antifungal activity at 25°C against stains of *C. albicans* and *A. niger* by using filter paper disc diffusion technique.

Antimicrobial activity screening of the synthesized compounds revealed that, 5-Arylidene-1,3-thiazolidin-4-one derivatives **[5a-e]** are less to moderately active against selected bacterial stains. And antifungal activity screening of the compounds reveals that among all the tested compounds, the compounds with chloro substitution are promisingly active against *Candida albicans* and *Aspergillus niger.* Observations of antibacterial and antimicrobial screening are tabulated in table-2.

Table-2
Antibacterial and antifungal activities of the compounds 4 and 5a-e

Comp.	Gram positive bacteria		Gram negative bacteria		Fungi	
	S. aureus	*B. subtilis*	*P. aeruginosa*	*E. coli*	*C. albicans*	*A. niger*
4	07	06	07	07	06	06
5a	10	12	11	11	05	06
5b	11	10	08	10	08	07
5c	10	06	09	10	06	07
5d	11	08	08	10	14	15
5e	09	12	10	10	15	15
Ampicillin	25	22	23	25	--	--
Streptomycin	25	24	25	25	--	--
Miconazole	--	--	--	--	20	19

Conclusion

2-[(5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-ylidene)hydrazinylidene]-1,3-thiazolidin-4-one, it's 5-Arylidene-1,3-thiazolidin-4-one derivatives were synthesized in good yields. Identification and characterization of the compounds were achieved by IR, NMR and MS spectroscopic techniques. The antimicrobial activities of all the synthesized compounds were evaluated against two gram positive bacteria (*Staphylococcus aureus, Bacillus subtilis*), two gram negative bacteria (*Pseudomonas aeruginosa, Escherichia coli*) and two fungus (*Candida albicans, Aspergillus niger*) and found that, 5-Arylidene-1,3-thiazolidin-4-one derivatives **[5a-e]** are less to moderately active against selected bacterial stains. And antifungal activity screening of the compounds reveals that among all the tested compounds, the compounds with chloro substitution are promisingly active against *Candida albicans* and *Aspergillus niger*.

Acknowledgement

Authors are thankful to the department of chemistry, J J T University, Rajasthan, India and department of chemistry, D K V Arte & Science College, Jamnagar, India for providing laboratory facilities and analytical support. Authors are also thankful to the Department of Micro-biology, M V M Science & Home Science College, Rajkot, India for evaluating antimicrobial activities of the synthesized compounds.

References

i. A. A. Chavan, N. R. Pai, ARKIVOC, (xvi), 148 (2007)
ii. R. P. Pawar, N. M. Andurkar, B. R. Patil, Y. B. Vibhute, Hindustan Antibiot. Bull., 40, 51 (1998)
iii. N. B. Patel, F. M. Shaikh, Saudi Pharmaceutical Journal, 18 (3), 129 (2010)
iv. C. Belwal, K. A. Joshi, Heteroletters, 3 (3), 349 (2013)
v. P. S. Kenderekar, R. F. Siddiqui, P. S. Patil, S. R. Bhusare, R. P. Pawar, Indian journal of pharmaceutical science, may-june, 313 (2003)

vi. D. Havrylyuk, L. Mosula, B. Zimenkovsky, O. Vasylenko, A. Gzella, R. Lesyk, Eur J Med. Chem., 45 (11), 5012 (2010)
vii. D. Kaminskyy, D. Khyluk, O. Vasylenko, L. Zaprutko, R. Lesyk, Sci. Pharm., 79 (4), 763 (2011)
viii. N. Siddiqui, M. F. Arshad, S. A. Khan, W. Ahsan, *J Enzyme Inhib. Med. Chem.,* 25 (4), 485, (2010)
ix. N. Ulusoy, N. Ergenç, A. C. Ekinci, H. Ozer, *Monatshefte für Chemie*., 127 (11), 1197, (1996)
x. N. Terzioglu, N. Karal, A. Gursoy, C. Pannecouque, P. Leysen, J. Paeshuyse, J. Neyts, E. De Clercq, *ARKIVOC,* (i), 109, (2006)
xi. V. Ravichandran, B. R. Prashantha Kumar, S. Sankar, R. K. Agrawal, *Eur. J Med. Chem.,* 44 (3), 1180, (2009)
xii. R. Janki Rama Rao, A. K. S. Bhujanga Rao, Y. L. N. Murthy, *Synthetic Communications*, 37 (17), 2847 (2007)
xiii. J. G. Vincent, H. W. Vincent, *Proc. Soc. Exptl. Biol. Med*., 55, 162 (1944)

Received on October 15, 2013.