Indian Journal of Chemistry
Vol. 47B, May 2008, pp. 787-791

Note

Synthesis and nematicidal activity of 2-(1*H*-benzo[*d*]imidazol-2-ylmethyl)-4-aryl-1-thia-4-azaspiro[4.5]decan-3-one

A Srinivas, A Nagaraj & Ch Sanjeeva Reddy*

Department of Chemistry, Kakatiya University, Warangal 506 009, India

E-mail: chsrkuc@yahoo.co.in

Received 30 April 2007; accepted (revised) 19 February 2008

A series of *N*-cyclohexylidene-*N*-phenylamines **3** are prepared by the condensation of cyclohexanone **1** with aryl amine **2**, subsequent treatment of **3** with thiomalic acid give the corresponding 2-(3-oxo-4-aryl-1-thia-4-azaspiro[4.5]dec-2-yl)acetic acid **4**, which on reaction with *o*-phenylenediamine give 2-(1*H*-benzo[*d*]imidazol-2-ylmethyl)-4-aryl-1-thia-4-azaspiro[4.5]decan-3-one **5**. Characterization of all the compounds has been done by IR, ^{1}H NMR, MS and elemental analyses. The antibacterial, antifungal and nematicidal activities of the compounds have also been evaluated.

Keywords: Spirothiazolidinone, benzimidazole, antibacterial activity, antifungal activity, nematicidal activity

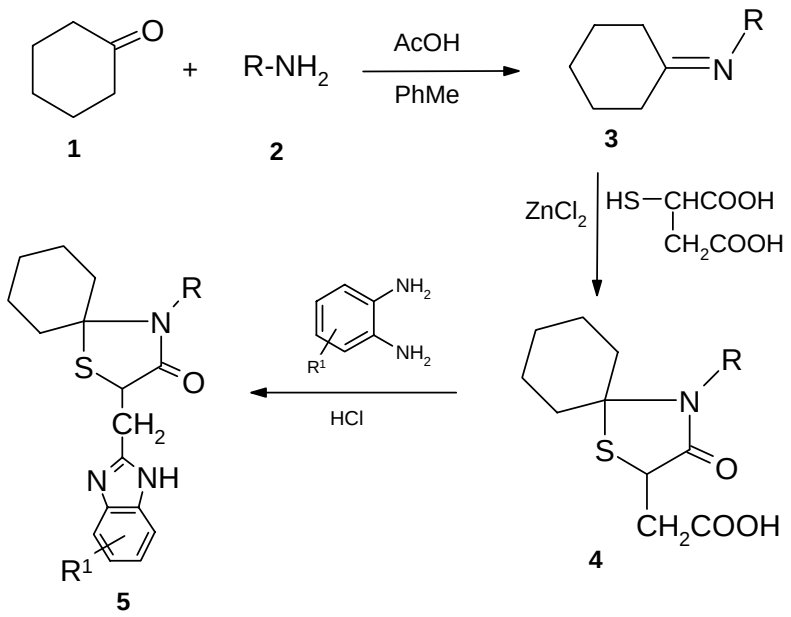
The thiazole nucleus appears frequently in the structure of various natural products and biologically active compounds, notably thiamine (vitamin-B), penicillin, antibiotics such as micrococcin[1a], troglitazone[1b] and many metabolic products of fungi and primitive marine animals, including 2-(aminoalkyl)thiazole-4-carboxylic acids[1c]. Numerous thiazolidinone derivatives have shown significant pharmacological and biological activities[2] like sedative[3], anti-inflammatory[4], antibacterial[5], antifungal[6], antitubercular[7], analgesic and hypothermic[8], local[9] and spinal[10] anesthetic, CNS stimmulant[11], hypnotic[3], anti-HIV[12], nematicidal[13]. Moreover, benzimidazole derivatives are an important class of bioactive molecules[14], which exhibit significant activity against several viruses including HIV[15], herpes (HSV-I)[16], RNA[17], influenza[18] and human cytomegalovirus (HCMV)[19]. Inspired the biological profile of thiazolidinone and benzimidazole derivatives and their increasing importance in pharmaceutical and biological field, and in continuation of our work on biologically active heterocycles[20,21], it was considered worthwhile to synthesize certain new chemical entities incorporating two active pharmacophores, namely thiazolidinone and benzimidazole in a single molecular framework and to get them evaluated for their antibacterial, antifungal and nematicidal activity.

The *N*-cyclohexylidene-*N*-arylamines **3a-e** were prepared[22] by the reaction of cyclohexanone **1** with aryl amine **2** in presence of acetic acid. The compounds **3** were reacted with thiaomalic acid in presence of anhyd. $ZnCl_2$ gave 2-(3-oxo-4-aryl-1-thia-4-azaspiro[4.5]dec-2-yl)acetic acids **4a-e**. The compounds **4** on further condensation with *o*-phenylenediamine yielded 2-(1*H*-benzo[*d*]imidazol-2-ylmethyl)-4-aryl-1-thia-4-aza-spiro [4.5]decan-3-one **5a-j** (**Scheme I**). The structures of synthesized compounds (**Table I**) were confirmed by IR, ^{1}H NMR, MS and elemental analyses. Further, the compounds were tested for antibacterial, antifungal and nematicidal activity.

Antimicrobial activity

The compounds **4a-e** and **5a-j** were screened for their antibacterial and antifungal activity using cup-plate method[23] by measuring the inhibition zones in mm against a variety of bacterial strains such as *Staphylococcus aureus*, *Bacillus pumilis*, *Escherichia coli* and *Proteus vulgaris*, fungi such as *Aspergillus niger* and *Aspergillus flavus*. The antimicrobial activity was compared with the known antibiotic ciprofloxacin and nystatin and the results are given in **Table II**.

The compounds **5b**, **5d**, **5h** and **5i** were highly active and showed a very good zone of inhibition of all the four organisms employed. Compound **5h** showed 23 mm, 19 mm, 22 mm and 22 mm zone of inhibition for *S. aureus*, *B. pumilis*, *E. coli* and *P. valgaris* respectively. Compound **5b** showed 22 mm zone of inhibition for *S. aureus.* Compound **5d** showed 22 mm zone of inhibition for *P. vulgaris* and compound **5i** showed 23 mm zone of inhibition for *E. coli*. Compounds **5b** and **5h** were also highly active against *A. niger* and *A. flavus* and zone of inhibition is 19 mm, 21 mm respectively for *A. flavus*. Other compounds showed moderate to good antimicrobial activity.



Scheme I

Nematicidal activity

The compounds **4a-e** and **5a-j** were screened for nematicidal activity by aq. *in vitro* screening technique[24] at various concentrations on *Ditylenchus myceliophagus* and *Caenorhabditis elegans,* both species were raised on mushrooms on wheat media. The results have been expressed in terms of LD_{50} *i.e.*. median lethal dose at which 50% nematodes became immobile (dead). The screened data reveal that compounds **5d** and **5i** showed promising nematicidal activity on both species *D. myceliophagus* and *C. elegans,* with LD_{50} value of 220 ppm and 260 ppm respectively. The carbamoyl oxime nematicide oxamyl (Vydate L Du Pont® ; 24% Oxamyl in methanol) was used for comparative treatment (**Table II**).

Experimental Section

Melting points were determined using Fisher-Johns apparatus and are uncorrected. Homogeneity of the compounds was checked using silica gel G coated TLC plates and iodine vapour as a visualizing agent. IR spectra were recorded on a FT-IR 5000 Perkin-Elmer spectrophotometer, using KBr pellets. ^{1}H NMR was recorded on a Varian Gemini 200 MHz spectrometer using DMSO-d_6 or $CDCl_3$ as solvent, TMS was used as an internal standard. Mass spectra were recorded on a VG-micromass 7070H mass spectrometer. Elemental analyses were performed on a Perkin-Elmer 240 CHN elemental analyzer.

Synthesis of *N*-cyclohexylidene-*N*-phenylamine 3a. A mixture of cyclohexanone **1** (0.01 mole), aniline **2** (0.01 mole) and acetic acid (0.5 mL) was refluxed in toluene for 3 hr using a Dean-Stark apparatus and the water formed was removed azeotropically. The progress of the reaction was checked by TLC using toluene:ethyl acetate (4:1) as an eluent. After completion of the reaction, solvent was removed by distillation to give solid, which was filtered, and recrystallized from ethyl alcohol. m.p. 125-26°C, yield 86% (Found: C, 82.81; H, 8.47; N, 7.93. $C_{12}H_{15}N$ requires C, 83.19; H, 8.73; N, 8.08%); IR (KBr): 3065, 1625 cm^{-1}; ^{1}H NMR: δ 1.59-1.62 (m, 2H), 2.28-2.34 (m, 4H), 2.40-2.50 (m, 4H), 7.00-7.30 (m, 5H); MS: *m*/*z* 173 (M^+). Similarly, other compounds **3b-e** were prepared and physical data are given in **Table I**.

Synthesis of 2-(3-oxo-4-phenyl-1-thia-4-aza-spiro[4.5]dec-2-yl)acetic acid 4a. A mixture of **3a** (0.01 mole), thiomalic acid (0.015 mole) and 1g anhyd. $ZnCl_2$ was heated gradually to 160°C using an oil-bath and maintained for 2 hr at the same temperature. The progress of the reaction was checked by TLC using benzene:ether (3:1) as an eluent. After completion of the reaction it was poured into crushed ice and stirred vigorously, the solid separated was filtered, dried and purified by recrystallization, m.p. 140-41°C, yield 79% (Found: C, 62.66; H, 6.30; N, 4.51. $C_{16}H_{19}NO_3S$ requires C, 62.93; H, 6.27; N, 4.59%); IR (KBr): 3130, 3065, 1735, 1690, 1572, 752 cm^{-1}; ^{1}H NMR: δ 1.50-2.50

Table I — Characterization data of compounds **3a-e**, **4a-e** and **5a-j**

Compd	R	R^1	Mol. formula	Yield (%)	m.p. °C	Calcd (Found) % C	H	N
3a	C_6H_5	--	$C_{12}H_{15}N$	86	125-26	83.19 (82.81	8.73 8.47	8.08 7.93)
3b	4-ClC_6H_4	--	$C_{12}H_{14}ClN$	79	180-82	69.39 (69.27	6.79 6.68	6.74 6.51)
3c	4-$NO_2C_6H_4$	--	$C_{12}H_{14}N_2O_2$	86	139-41	66.04 (65.73	6.47 6.29	12.84 12.61)
3d	3-OHC_6H_4	--	$C_{12}H_{15}NO$	90	121-22	76.16 (75.96	7.99 7.87	7.40 7.19)
3e	4-$CH_3C_6H_4$	--	$C_{13}H_{17}N$	92	142-44	83.37 (83.21	9.15 8.98	7.48 7.24)
4a	C_6H_5	--	$C_{16}H_{19}NO_3S$	79	140-41	62.93 (62.66	6.27 6.30	4.59 4.51)
4b	4-ClC_6H_4	--	$C_{16}H_{18}ClNO_3S$	82	169-71	56.55 (56.27	5.34 5.06	4.12 4.01)
4c	4-$NO_2C_6H_4$	--	$C_{16}H_{18}N_2O_5S$	83	190-92	54.85 (54.64	5.18 5.03	7.99 7.85)
4d	3-OHC_6H_4	--	$C_{16}H_{19}NO_4S$	87	181-83	59.80 (59.62	5.96 5.67	4.36 4.27)
4e	4-$CH_3C_6H_4$	--	$C_{17}H_{21}NO_3S$	90	143-44	63.92 (63.77	6.63 6.70	4.39 4.27)
5a	C_6H_5	H	$C_{22}H_{23}N_3OS$	76	192-94	70.00 (69.62	6.14 6.07	11.13 11.03)
5b	4-ClC_6H_4	H	$C_{22}H_{22}ClN_3OS$	81	248-50	64.14 (64.02	5.38 5.40	10.20 10.11)
5c	4-$NO_2C_6H_4$	H	$C_{22}H_{22}N_4O_3S$	83	252-54	62.54 (62.43	5.25 5.09	13.26 13.21)
5d	3-OHC_6H_4	H	$C_{22}H_{23}N_3O_2S$	91	265-66	67.15 (67.10	5.89 5.77	10.68 10.63)
5e	4-$CH_3C_6H_4$	H	$C_{23}H_{25}N_3OS$	93	211-12	70.56 (69.87	6.44 6.22	10.73 10.52)
5f	C_6H_5	3-Cl	$C_{22}H_{22}ClN_3OS$	88	227-29	64.14 (64.01	5.38 5.07	10.20 10.52)
5g	4-ClC_6H_4	3-Cl	$C_{22}H_{21}Cl_2N_3OS$	86	232-34	59.19 (58.97	4.74 4.43	9.41 9.33)
5h	4-$NO_2C_6H_4$	3-Cl	$C_{22}H_{21}ClN_4O_3S$	87	247-48	57.83 (57.65	4.63 4.32	12.26 12.21)
5i	3-OHC_6H_4	3-Cl	$C_{22}H_{22}ClN_3O_2S$	90	222-23	61.75 (61.32	5.18 5.20	9.82 9.67)
5j	4-$CH_3C_6H_4$	3-Cl	$C_{23}H_{24}ClN_3OS$	89	231-33	64.85 (64.72	5.68 5.52	9.86 9.69)

(m, 10H), 2.67 (d, 2H), 3.60 (t, 1H), 6.70-7.10 (m, 5H), 10.60 (s, 1H); MS: *m*/*z* 305 (M^+). Similarly, other compounds **4b-e** were prepared and physical data are given in **Table I**.

General procedure for the synthesis of 5. To the solution of **4** (0.01 mole) in methanol (5 mL) was added *o*-phenylenediamine (0.02 mole) and catalytic amount of HCl (3-4 drops), and the reaction mixture was refluxed for 45 min. The reaction mixture was then cooled and poured into dilute NH_4OH (10 mL) and allowed to stand for 1 hr. The product separated was filtered, dried and purified by recrystallization

Table II — Antimicrobial and nematicidal activity of **4a-e** and **5a-j**

Compd	Antibacterial activity (zone of inhibition in mm at 50 μg/mL)				Antifungal activity		Nematicidal activity LD_{50} values (ppm)	
	S. aureus	*B. pumilis*	*E. coli*	*P. vulgaris*	*A. niger*	*A. flavus*	*D. myceliophagus*	*C. elegans*
4a	--	07	--	11	05	09	940	960
4b	16	13	12	17	07	11	850	870
4c	11	10	07	14	09	13	440	360
4d	14	--	13	16	11	07	610	650
4e	19	11	14	--	10	13	1070	1010
5a	07	--	09	11	03	11	910	900
5b	22	16	20	20	13	19	1020	1070
5c	15	11	14	09	06	07	710	650
5d	19	15	21	22	11	18	220	660
5e	--	11	09	08	10	09	1030	1010
5f	18	09	11	17	07	14	910	900
5g	16	10	15	19	08	15	820	840
5h	23	19	22	22	14	21	660	540
5i	20	16	23	19	12	18	440	260
5j	17	11	13	10	06	14	1020	1040
Ciprofloxacin	24	18	24	24	—	—	—	—
Nystatin	—	—	—	—	15	22	—	—
Oxamyl	—	—	—	—	—	—	150	180

from ethanol. (**Table I**). The spectral data of the newly synthesized compounds **5a-j** are given below.

2-(1*H*-Benzo[*d*]imidazol-2-ylmethyl)-4-phenyl-1-thia-4-azaspiro[4.5]decan-3-one 5a: IR (KBr): 3414, 3065, 1780, 1622, 1534, 1417, 858, 688 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.50-2.12 (m, 10H, -CH_2-), 2.90 (d, 2H, -CH_2), 3.97 (t, 1H, >CH), 6.60-7.00 (m, 5H, Ar-H), 7.10-8.00 (m, 4H, Ar-H), 9.32 (s, 1H, -NH); MS: *m*/*z* 377 (M^+).

2-(1*H*-Benzo[*d*]imidazol-2-ylmethyl)-4-(4-chlorophenyl)-1-thia-4-azaspiro[4.5]decan -3-one 5b: IR (KBr): 3410, 3065, 1775, 1612, 1534, 1417, 858, 687, 660 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.50-2.12 (m, 10H, -CH_2-), 2.90 (d, 2H, -CH_2), 3.99 (t, 1H, >CH), 6.90 (d, 2H, *J* = 8.70 Hz, Ar-H), 7.08 (d, 2H, *J* = 8.70 Hz, Ar-H), 7.10-8.00 (m, 4H, Ar-H), 9.32 (s, 1H, -NH); MS: *m*/*z* 412 (M^+).

2-(1*H*-Benzo[*d*]imidazol-2-ylmethyl)-4-(4-nitrophenyl)-1-thia-4-azaspiro[4.5]decan-3-one 5c: IR (KBr): 3414, 3065, 1782, 1620, 1530, 1420, 858, 688 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.50-2.12 (m, 10H, -CH_2-), 2.92 (d, 2H, -CH_2), 3.99 (t, 1H, >CH), 7.00 (d, 2H, *J*=9.03 Hz, Ar-H), 7.20 (m, 2H, Ar-H), 8.00 (m, 2H, Ar-H), 8.20 (d, 2H, *J* = 9.03 Hz, Ar-H), 9.32 (s, 1H, -NH); MS: *m*/*z* 422 (M^+).

2-(1*H*-Benzo[*d*]imidazol-2-ylmethyl)-4-(3-hydroxyphenyl)-1-thia-4-azaspiro[4.5]decan-3-one 5d: IR (KBr): 3410-3380, 3060, 1780, 1624, 1531, 1420, 858, 688 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.50-2.12 (m, 10H, -CH_2-), 2.92 (d, 2H, -CH_2), 3.99 (t, 1H, >CH), 6.00-6.80 (m, 4H, Ar-H), 7.20 (m, 2H, Ar-H), 8.00 (m, 2H, Ar-H), 8.42 (s, 1H, -NH), 8.50 (s, 1H, -OH); MS: *m*/*z* 393 (M^+).

2-(1*H*-Benzo[*d*]imidazol-2-ylmethyl)-4-(4-methylphenyl)-1-thia-4-azaspiro[4.5]decan-3-one 5e: IR (KBr): 3410, 3060, 2980, 1780, 1610, 1534, 1422, 858, 688, 660 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.50-2.12 (m, 10H, -CH_2-), 2.20 (s, 3H, -CH_3), 2.92 (d, 2H, -CH_2), 3.99 (t, 1H, >CH), 6.70 (d, 2H, *J* = 8.31 Hz, Ar-H), 7.10 (d, 2H, *J* = 8.31 Hz, Ar-H), 7.20 (m, 2H, Ar-H), 8.00 (m, 2H, Ar-H), 9.32 (s, 1H, -NH); MS: *m*/*z* 391 (M^+).

2-[(6-Chloro-1*H*-benzo[*d*]imidazol-2-yl)methyl]-4-phenyl-1-thia-4-azaspiro[4.5]decan-3-one 5f: IR (KBr): 3410, 3065, 1780, 1622, 1534, 1417, 858, 688, 660 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.50-2.12 (m, 10H, -CH_2-), 2.92 (d, 2H, -CH_2), 3.99 (t, 1H, >CH), 6.60-7.00 (m, 5H, Ar-H), 7.10-7.80 (m, 3H, Ar-H), 9.32 (s, 1H, -NH); MS: *m*/*z* 412 (M^+).

2-[(6-Chloro-1*H*-benzo[*d*]imidazol-2-yl)methyl]-4-(4-chlorophenyl)-1-thia-4-azaspiro [4.5]decan-3-one 5g: IR (KBr): 3410, 3065, 1775, 1620, 1532, 858, 688, 662 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.50-2.12 (m, 10H, -CH_2-), 2.92 (d, 2H, -CH_2), 3.99 (t, 1H, >CH),

6.90 (d, 2H, J = 8.70 Hz, Ar-H), 7.10 (d, 2H, J = 8.70 Hz, Ar-H), 7.15-7.80 (m, 3H, Ar-H), 9.32 (s, 1H, -NH); MS: m/z 447 (M^+).

2-[(6-Chloro-1*H*-benzo[*d*]imidazol-2-yl)methyl]-4-(4-nitrophenyl)-1-thia-4-azaspiro [4.5]decan-3-one 5h: IR (KBr): 3410, 3060, 1775, 1620, 1535, 1425, 858, 688, 666 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.50-2.12 (m, 10H, $-CH_2-$), 2.92 (d, 2H, $-CH_2$), 3.99 (t, 1H, >CH), 7.00 (d, 2H, J = 9.03 Hz, Ar-H), 7.15-7.80 (m, 3H, Ar-H), 8.15 (d, 2H, J = 9.03 Hz, Ar-H), 9.32 (s, 1H, -NH); MS: m/z 457 (M^+).

2-[(6-Chloro-1*H*-benzo[*d*]imidazol-2-yl)methyl]-4-(3-hydroxyphenyl)-1-thia-4-azaspi ro[4.5]decan-3-one 5i: IR (KBr): 3410-3380, 3065, 1780, 1624, 1531, 1420, 858, 688, 660 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.50-2.12 (m, 10H, $-CH_2-$), 2.92 (d, 2H, $-CH_2$), 3.99 (t, 1H, >CH), 6.00-6.80 (m, 4H, Ar-H), 7.10-7.80 (m, 3H, Ar-H), 8.42 (s, 1H, -NH), 8.48 (s, 1H, -OH); MS: m/z 428 (M^+).

2-[(6-Chloro-1*H*-benzo[*d*]imidazol-2-yl)methyl-4-(4-methylphenyl)-1-thia-4-azaspiro [4.5]decan-3-one 5j: IR (KBr): 3414, 3065, 2985, 1780, 1615, 1534, 1428, 858, 680, 660 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.50-2.12 (m, 10H, $-CH_2-$), 2.22 (s, 3H, $-CH_3$), 2.92 (d, 2H, $-CH_2$), 3.99 (t, 1H, >CH), 6.72 (d, 2H, J = 8.31 Hz, Ar-H), 7.10 (d, 2H, J = 8.31 Hz, Ar-H), 7.10-7.80 (m, 3H, Ar-H), 9.32 (s, 1H, -NH); MS: m/z 426 (M^+).

Acknowledgement

The authors are thankful to the Director, Indian Institute of Chemical Technology, Hyderabad, for ^1H NMR and mass spectral analysis, and to the Head, Department of Microbiology, Kakatiya University, Warangal for providing facilities for biological screening.

References

1 (a) James M N G & Watson K J, *J Chem Soc*, **1966**, 1361; (b) Ghazzi M N, Perez J E, Antonucci T K, Driscoll J H, Huang S M & Faja B W, *Diabetes*, 46, **1997**, 433; (c) Scmidt U, Utz R, Lieberknecht A, Griesser H, Potzolli B, Bahr J, Wagner K & Fischer P, *Synthesis*, **1987**, 233.
2 (a) Singh A K & Birendra Kumar, *Asian J Chem*, 9(2), **1997**, 234; (b) Dave C V & Shukla M C, *Indian J Chem*, 39B, **2000**, 210.
3 Doran W J & Shoule H A, *J Org Chem*, 3, **1939**, 193.
4 Menozzi G & Filippelli W, *Farmaco*, 49(2), **1994**, 115.
5 Barot V M, *Asian J Chem*, 8(4), **1996**, 802.
6 Khan M H, & Nizamuddin, *J Food Agric Chem*, 43, **1995**, 2719.
7 (a) Gangiee A & Adaer G, *J Med Chem*, 42, **1999**, 2447; (b) Buu-Hoi N P, Xuong N D & Binon F, *J Chem Soc*, 70, **1948**, 3436.
8 Ahluwalia V K & Gupta C, *Heterocycles*, 32(5), **1991**, 907.
9 Trautman H D & Longe L M, *J Am Chem Soc*, 70 **1948**, 3436.
10 Surray A R, *J Am Chem Soc*, 71, **1949**, 3354.
11 French G, *Chem Abstr*, 65, **1966**, 4439.
12 Shah B R, Desai N C & Trivedi P B, *Indian J Heterocycl Chem*, 2(4), **1993**, 249.
13 Manrao M R, Monika J & Kaul V K, *Pl Dis Res*, 12, **1997**, 70.
14 Valdez J, Cedillo R, Hernandez-Campos A, Yepez L, Hernandez-Luis F, Navarrete-Vazquez G, Tapia A, Cortes R, Hernandezc M & Castilloa R, *Bioorg Med Chem Lett*, 12, **2002**, 2221.
15 Roth M, Morningstar M L, Boyer P L, Hughes S H Jr, Buckheit R W & Michejda C J, *J Med Chem*, 40, **1997**, 4199.
16 Migawa M T, Girardet J L, Walker J A, Koszalka G W, Chamberlain S D, Drach J C & Townsend L B, *J Med Chem*, 41, **1998**, 1242.
17 Tamm I & Sehgal P B, *Adv Virus Res*, 22, **1978**, 187.
18 Tamm I, *Science*, 126, **1957**, 1235.
19 Porcari A R, Devivar R V, Kucera L S, Drach J C & Townsend L B, *J Med Chem*, 41, **1998**, 1252.
20 Sanjeeva Reddy Ch, Nagaraj A & Jalapathi P, *Indian J Chem*, 46B, **2007**, 660
21 Smitha G & Sanjeeva Reddy Ch, *Synth Commun*, 36, **2006**, 1795.
22 Venkateswarlu P & Nageswara Rao V, *J Chem Res*, **2004**, 288.
23 Barry A I, *The Antimicrobial Susceptibility Test, Principles and Practices*, 4th Edn (ELBS), **1976**, P 80-93.
24 McBeth C W & Bergeson G B, *Phytopathology*, 43, **1953**, 264.