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Synthesis and antimicrobial activity of novel 1,3,4-thiadiazine derivatives

Vijay V. Dabholkar*, Prem Naik, Abhishek Karekar and Navnath Shinde

Organic Research Laboratory, Department of Chemistry, KC College, Churchgate, Mumbai

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ABSTRACT

Compound (1) was treated with phenacyl bromide to yield compound (3), which was brominated to yield compound (4) and Further condensed with piperazine ester to obtained compound (6). Compound (6) was treated with hydrazine hydrate to obtained compound (7), which on further treatment with aromatic aldehydes which yielded corresponding Schiff base compound (8). Compound (8) in acidic medium undergoes cyclization to yield respective novels thiadiazine derivatives(9). The structures of the newly synthesized compounds were confirmed by IR, 1H NMR and mass spectroscopic analysis.

Keywords: Triazole, Oxadiazole, Thiadiazine and Antimicrobial.

INTRODUCTION

Various substituted 1,2,4-triazolo[3,4-b]-1,3,4-thiadiazines and Schiff's bases are associated with diverse pharmacological activities, such as analgesic, anthelmintic, antitubercular, plant growth regulating, antiviral, antifungal and anticancer properties [1-8]. 3-Substituted-4-amino-5-mercapto-1,2,4-triazole is the key intermediate in the formation of these heterocyclic compounds. Based on the principle of activity addition, we made a compound having substitutions at different positions of 3-substituted-4-amino-5-mercapto-1,2,4-triazole derivatives.

In view of the biological importance of these heterocycles a new series of 7-{4-[5-(4-Methoxy-phenyl)-4,5-dihydro-[1,3,4]oxadiazol-2-yl]-piperazin-1-yl}-3-methyl-6-phenyl-5H-[1,2,4]triazolo[3,4-b][1,3,4]Thiadiazine(9) were synthesized and evaluated for their in vitro antimicrobial activity against gram-positive as well as gram-negative microorganisms.

MATERIALS AND METHODS

Melting points of all synthesized compounds were determined in open capillary tubes on an electro thermal apparatus and are uncorrected. The progress of reaction was monitored by thin layer chromatography on silica gel coated aluminum plates (Merck) as adsorbent and UV light as visualizing agent. ^{1}H NMR spectra were recorded on Varian 500 MHz NMR spectrophotometer using $CDCl_3$/DMSO-d_6 as solvent and TMS as an internal standard (chemical shifts in δ ppm). C, H, N estimation was recorded on Carlo Erba 1108 (CHN) Elemental Analyzer.

General Procedure:

Synthesis of 3-Methyl-6-phenyl-5H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (3).

The Mixture of 3-substituted-4-amino-5-mercapto-1,2,4-triazoles (0.01 mol) (**1**) , 2-bromo-1-phenyl-ethanone (0.01 mol) **(2)** , K_2CO_3 (0.01 mol) and Ethanol (20 ml) was refluxed for 3 hrs. The progress of the reaction was monitored on TLC. Upon Completion, the reaction mixture was quenched into crushed ice. Brown colored solid was obtained on filtration which was then crystallized using alcohol, to yield compound (**3**).

Synthesis of 7-Bromo-3-methyl-6-phenyl-5H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (4).

Bromine (0.01 mol) was added drop wise to the mixture of compound (3) (0.01 mol) & GAA in the presence of Iodine as a catalyst. The mixture was vigorously stirred for 2hr at room temperature. The progress of reaction was monitored on TLC. Upon Completion, the reaction mixture was poured onto crushed ice. Solid thus obtained was then filtered and recrystallized using alcohol, to yield compound (**4).**

Synthesis of 4-(3-substituted-6-phenyl-5H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine-7-yl-piprazine-1-carboxylic acid ethyl ester (6)

A mixture of compound **(4)** (0.01 mol), Piprazine ester (0.01 mol), K_2CO_3 (0.02 mol), CuI and Acetonitrile (20 ml) was stirred for 2 hrs at room temperature. The progress of reaction was monitored on TLC. Upon Completion, the reaction mixture was poured onto crushed ice. Solid thus obtained was washed with water and recrystallized from alcohol to yield compound (**6**).

Synthesis of 4 -(3-substituted-6-phenyl-5H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine-7-yl-piprazine-1-carboxylic hydrizide (7).

A mixture of previously synthesized compound **(6)** (0.01 mol), hydrazine hydrate (2 gm, 0.02 mol) and ethanol (20 ml) was refluxed for 2 hrs. Progress of reaction was monitored by TLC. Upon completion, the reaction was cooled, poured on crushed ice. Solid thus obtained on filteration was washed with water and recrystallized from alcohol to yield compound (**7**).

Synthesis of 4 -(3-substituted-6-phenyl-5H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine-7-yl-piprazine-1-carboxylic acid (4-methoxy-benzylidene)-hydrazide (8).

A mixture of compound **(7)** (0.01 mol), substituted aromatic aldehyde (0.01 mol), KOH (0.01 mol) and ethanol (20 ml) was refluxed for 2 hrs. Progress of reaction was monitored by TLC. Upon completion, the reaction was cooled, poured on crushed ice. Solid thus obtained on filteration was washed with water and recrystallized from alcohol to yield compound (8**)**.

Synthesis of 7-{5-(4-substituted-phenyl)-4,5-+dihydro-[1,3,4]oxadiazol-2yl]-piprazin-1-yl}-3-substituted-6-phenyl-5H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (9).

A mixture of previously synthesized compound **(8)** (0.01 mol), ethanol (20ml) and GAA was refluxed for 2 hrs. Progress of reaction was monitored by TLC. Upon completion, the reaction was cooled, poured on crushed ice. Solid thus obtained on filteration was washed with water and recrystallized from alcohol to yield compound (9**)**.

Antimicrobial activities

All the newly synthesized compounds were evaluated for their antibacterial activity against gram-negative bacteria, E coli and P aeruginosa and gram-positive, S aurreus, and C diphtheria using disc diffusion method [9-10] .The zone of inhibition was measured in mm and the activity was compared with standard drug. The antimicrobial data was given in Table **2**.

Spectral Data of **7-{5-(4-methoxy-phenyl)-4,5-dihydro-[1,3,4]oxadiazol-2yl]-piprazin-1-yl}-3-methyl-6-phenyl-5H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (9a).**

Yield: 81 %; m.p. =112-114°C: IR (cm^{-1}): 1545 (C=N), 3345 (NH)**,** ; ^{1}H NMR(DMSO-d_6,δ/ ppm):2.40(t, 4H,N-CH_2), 2.56(t, 4H,N-CH_2), 2.89 (s,3H, CH_3), 3.65 (s,3H, OCH_3),4.18 (s,1H, CH), 5.05(s,1H,NH),7.23-7.86 (m, 9H, Ar- H), 8.55 (s, 1H, NH). ; ^{13}C NMR (DMSO-d_6, δ/ ppm): 18.45 (CH_3), 40.12-45.56(CH_2), 51.42 (CH), 60.28 (OCH_3), 122.46-131.53 (Ar-C),168.51 (C=N), 174.79 (C=N) 177.89 (C=N).; Anal. Calcd for $C_{24}H_{26}N_8O_2S$: C,58.76;H,5.34;N,22.84%.Found: C,58.74;H,5.32;N,22.82%.

Spectral Data of **7-{5-(4-Hydroxy-phenyl)-4,5-dihydro-[1,3,4]oxadiazol-2yl]-piprazin-1-yl}-3-methyl-6-phenyl-5H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (9b).**
Yield: 83 %; m.p. =108-110°C: IR (cm^{-1}): 1539 (C=N), 3323 (NH), 3478 (-OH).; ^{1}H NMR (DMSO-d_6, δ/ ppm): 2.40(t, 4H,N-CH_2), 2.56(t, 4H,N-CH_2), 2.91 (s, 3H, CH_3), 4.39 (s, 1H, CH), 5.13(s,1H,NH), 5.89 (s,1H, OH) 7.41-8.10 (m, 9H, Ar- H), 8.43 (s, 1H, NH).; ^{13}C NMR (DMSO-d_6, δ/ ppm): 18.39 (CH_3), 39.63-44.96(CH_2), 51.65 (CH), 121.58-133.25 (Ar-C), 167.23 (C=N), 176.53 (C=N) 178.45 (C=N).; Anal.Calcd for $C_{23}H_{24}N_8O_2S$: C,57.97;H,5.08;N,23.51%.Found: C,57.93;H,5.04;N,23.48%.

Spectral Data of **7-{5-(4-methoxy,3-hydroxy-phenyl)-4,5-dihydro-[1,3,4]oxadiazol-2yl]-piprazin-1-yl}-3-methyl-6-phenyl-5H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (9c).**
Yield: 79 %; m.p. =105-107°C: IR (cm^{-1}): 1573 (C=N), 3356 (NH), 3489 (-OH).; ^{1}H NMR(DMSO-d_6,δ/ ppm): 2.41(t, 4H,N-CH_2), 2.66(t, 4H,N-CH_2), 2.84 (s, 3H, CH_3), 3.10 (s,3H, OCH_3),4.49 (s,1H, CH), 5.14(s,1H,NH), 5.86 (s,1H, OH), 7.13-7.95 (m, 8H, Ar- H), 8.49 (s, 1H, NH).; ^{13}C NMR (DMSO-d_6,δ/ ppm): 18.56 (CH_3), 41.23-47.53(CH_2), 52.22 (CH), 61.32 (OCH_3) 127.35-137.23 (Ar-C),170.14 (C=N), 172.58 (C=N) 177.25 (C=N).; Anal.Calcd for $C_{24}H_{26}N_8O_3S$: C,56.90;H,5.17;N,22.12%.Found: C,56.87;H,5.14,N,22.09%.

Spectral Data of **7-{5-(4-chlorophenyl)-4,5-dihydro-[1,3,4]oxadiazol-2yl]-piprazin-1-yl}-3-methyl-6-phenyl-5H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (9d).**
Yield: 84%; m.p.=107-109°C: IR (cm^{-1}): 1524 (C=N**),** 3324 (NH)**.**; ^{1}H NMR(DMSO-d_6,δ/ ppm): 2.41(t, 4H,N-CH_2), 2.66(t, 4H,N-CH_2), 2.76 (s,3H, CH_3), 4.29 (s,1H, CH), 5.12(s,1H,NH), 7.23-8.24 (m, 9H, Ar- H), 8.65 (s, 1H, NH). ^{13}C NMR (DMSO-d_6,δ/ ppm): 22.81 (CH_3), 40.58-48.74(CH_2), 55.20 (CH), 125.50-135.60 (Ar-C),177.85 (C=N), 179.63 (C=N) 181.25.; Anal.Calcd for $C_{23}H_{23}ClN_8OS$: C,55.81;H,4.68;N,22.64%.Found: C,55.76;H,4.64,N,22.61%.

Spectral Data of **7-{5-phenyl-4,5-dihydro-[1,3,4]oxadiazol-2yl]-piprazin-1-yl}-3-methyl-6-phenyl-5H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (9e).**
Yield: 76%; m.p.=101-103°C: IR (cm^{-1}): 1556 (C=N**),** 3341 (NH)**,;** ^{1}H NMR (DMSO-d_6,δ/ ppm): 2.41(t, 4H,N-CH_2), 2.66(t, 4H,N-CH_2), 2.83 (s,3H, CH_3), 4.19 (s,1H, CH), 4.95(s,1H,NH), 7.02-8.12 (m, 10H, Ar- H), 8.84 (s, 1H, NH). ^{13}C NMR (DM; SO-d_6,δ/ ppm): 21.70 (CH_3), 41.57-46.49(CH_2), 51.37 (CH), 54.28(CH), 125.49-137.01(Ar-C),161.90 (C=N), 164.33 (C=N) 166.58 (C=N); Anal.Calcd for $C_{23}H_{24}N_8OS$: C,59.98; H,5.25;N,24.33%.Found: C,59.94;H,5.21;N,24.30%.

Spectral Data of**7-{5-(4-methoxy-phenyl)-4,5-dihydro-[1,3,4]oxadiazol-2yl]-piprazin-1-yl}-3-ethyl-6-phenyl-5H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (9f).**
Yield: 82 %; m.p. =114-116°C: IR (cm^{-1}): 1547 (C=N), 3369 (NH),; ^{1}H NMR(DMSO-d_6,δ/ ppm): 2.31(t, 4H,N-CH_2), 2.46(t, 4H,N-CH_2), 2.59 (s,3H, CH_3), 2.82 (s,2H, CH_2), 3.28 (s,3H, OCH_3),4.34 (s,1H, CH), 5.11(s,1H,NH),7.23-7.86 (m, 9H, Ar- H), 8.55 (s, 1H, NH).; ^{13}C NMR (DMSO-d_6,δ/ ppm): 18.21 (CH_2), 22.21 (CH_3), 38.48-42.562(CH_2), 50.47 (CH), 59.47 (OCH_3), 120.18-134.78 (Ar-C),167.34 (C=N), 173.48 (C=N) 176.58 (C=N).; Anal.Calcd for $C_{25}H_{28}N_8O_2S_2$: C,59.51;H,5.59;N,22.21%.Found: C,59.47;H,5.56;N,22.17%.

Spectral Data of Spectral Data of **7-{5-(4-Hydroxy-phenyl)-4,5-dihydro-[1,3,4]oxadiazol-2yl]-piprazin-1-yl}-3-ethyl-6-phenyl-5H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (9g).**
Yield: 85 %; m.p. =117-119°C: IR (cm^{-1}): 1547 (C=N), 3356 (NH)**.;** ^{1}H NMR (DMSO-d_6, δ/ ppm): 2.41(t, 4H,N-CH_2), 2.59(t, 4H,N-CH_2), 2.74 (s, 3H, CH_3), 2.98 (s,2H, CH_2), 4.17 (s, 1H, CH), 5.01(s,1H,NH), 5.65 (s,1H, OH) 7.18-7.84 (m, 9H, Ar- H), 8.41 (s, 1H, NH).; ^{13}C NMR (DMSO-d_6, δ/ ppm): 12.93 (CH_2), 18.39 (CH_3), 40.77-46.24(CH_2), 53.58 (CH), 120.35-135.68 (Ar-C), 166.23 (C=N), 174.21 (C=N), 177.12 (C=N).; Anal.Calcd for $C_{24}H_{26}N_8O_2S$: C,58.76;H,5.34;N,22.84%.Found: C,58.73;H,5.31;N,22.80%.

Spectral Data of **7-{5-(4-methoxy,3-hydroxy-phenyl)-4,5-dihydro-[1,3,4]oxadiazol-2yl]-piprazin-1-yl}-3-ethyl-6-phenyl-5H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (9h).**
Yield: 84 %; m.p. =122-124°C: IR (cm^{-1}): 1554 (C=N), 3347 (NH)**, ;** ^{1}H NMR(DMSO-d_6,δ/ ppm): 2.31(t, 4H,N-CH_2), 2.48(t, 4H,N-CH_2), 2.64 (s, 3H, CH_3), 2.88 (s,2H, CH_2), 3.15 (s,3H, OCH_3),4.41 (s,1H, CH), 5.01(s,1H,NH), 5.98 (s,1H, OH), 7.52-8.14 (m, 8H, Ar- H), 8.75(s, 1H, NH).; ^{13}C NMR (DMSO-d_6,δ/ ppm): 12.56 (CH_2), 18.47 (CH_3), 40.13-46.59(CH_2), 51.12 (CH), 60.12 (OCH_3), 126.48-134.47 (Ar-C),169.14 (C=N), 173.29 (C=N) 178.57 (C=N).; Anal.Calcd for $C_{25}H_{28}N_8O_3S$: C,57.68;H,5.42;N,21.52%.Found: C,57.65;H,5.39,N,21.48%

Table 1.Characterization of the synthesized compounds

Compound	R	R'	Molecular formula*	Melting point (°C)	Yield (%)
9a	$-CH_3$	4-OCH_3	$C_{24}H_{26}N_8O_2S$	112-114	81 85/834 72/9
9b	$-CH_3$	4-OH	$C_{23}H_{24}N_8O_2S$	108-110	83 84/794 68/8
9c	$-CH_3$	4-OH, 3-OCH_3	$C_{24}H_{26}N_8O_3S$	105-107	79
9d	$-CH_3$	4-Cl	$C_{23}H_{23}ClN_8OS$	107-109	84 80/3 62/8
9e	$-CH_3$	4-H	$C_{23}H_{24}N_8OS$	101-103	76 82/3 65/8
9f	$-C_2H_5$	4-OCH_3	$C_{25}H_{28}N_8O_2S_2$	114-116	82
9g	$-C_2H_5$	4-OH	$C_{24}H_{26}N_8O_2S$	117-119	85
9h	$-C_2H_5$	4-OH, 3-OCH_3	$C_{25}H_{28}N_8O_3S$	122-124	84
9i	$-C_2H_5$	4-Cl	$C_{24}H_{25}ClN_8OS$	126-129	81
9j	$-C_2H_5$	4-H	$C_{24}H_{26}N_8OS$	120-123	78
**All the compounds gave satisfactory elemental analysis*					

General Scheme

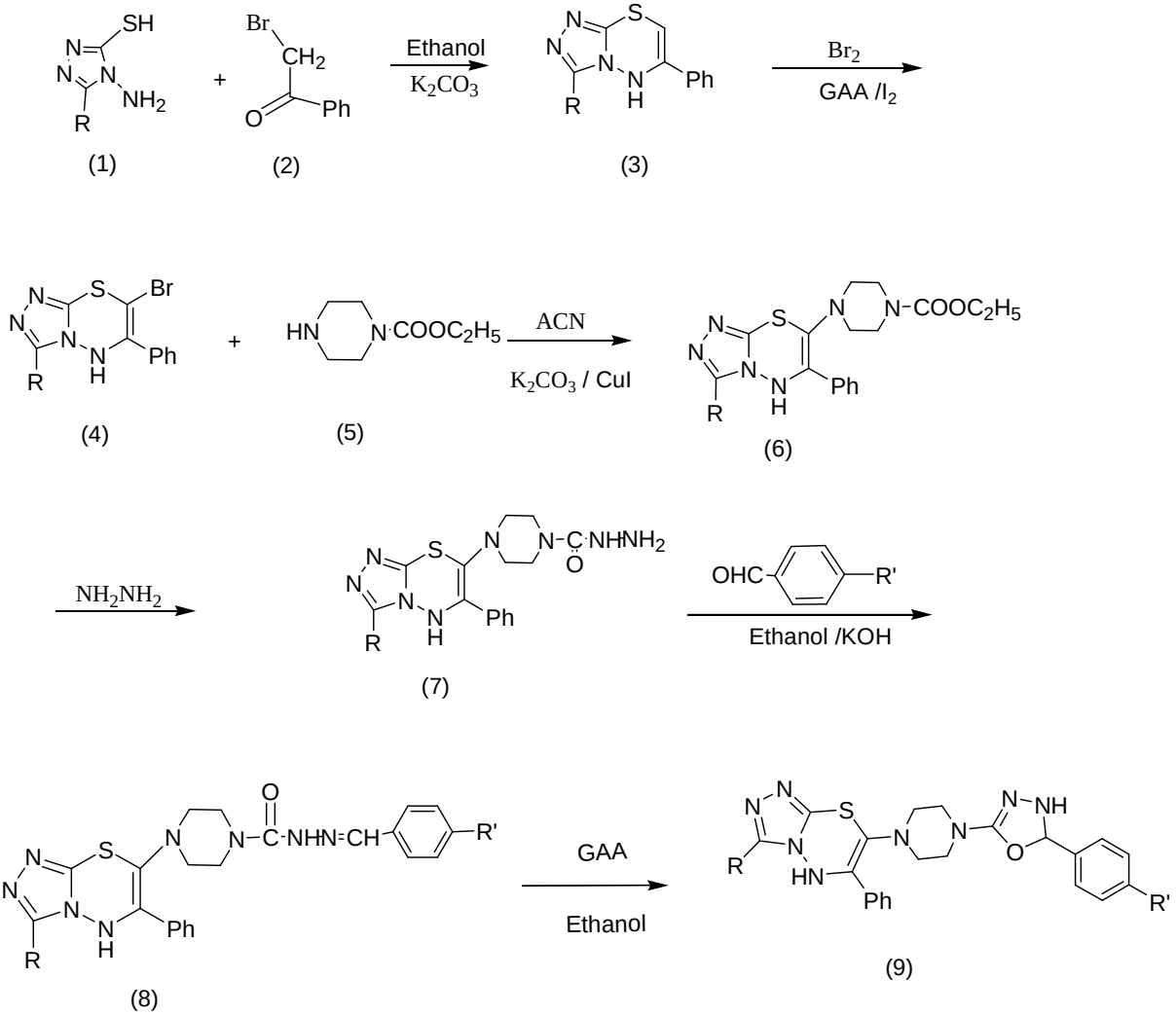

Table 2. Antimicrobial activities of some newly synthesized compounds

Compound	Inhibition Zone (mm)			
	Gram-negative		Gram-positive	
	E.coli	*P.Putide*	*B.Subtilis*	*S.lactis*
9a	11	9	17	17
9b	9	9	15	15
9c	13	11	18	16
9d	8	6	13	12
9e	6	1	11	9
Ampicilin®	24	19	20	23

E.coli. = Escherichia coli; P.Putide = Pseudomonas Putide; B. Subtilis = Bacillus Subtilis; S. lactis = Sterptococcus lactis.
The sensitivity of microorganisms to the tested compounds is identified in the following manner;*
Highly Sensitive = Inhibition zone: 15-20 mm
Moderately Sensitive = Inhibition zone: 10-15 mm
Slightly Sensitive = Inhibition zone: 5-10 mm
Not Sensitive = Inhibition zone: 0 mm
** Each result represents the average of triplicate readings.*

RESULTS AND DISCUSSION

Compound (3) was formed by treating 3-substituted-4-amino-5-mercapto-1,2,4-triazoles (1) with phenacyl bromide, which was brominated to yield compound (4) and then condensed with piperazine to obtain 4-(3-substituted-6-phenyl-5H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine-7-yl-piprazine-1-carboxylic acid ethyl ester (6), which on further treatment with hydrazine hydrate yielded compound (7) and then was converted to Schiff base compound (8) on treatment with aromatic aldehyde. Compound (8) in presence of acidic condition undergoes cyclization and gives respective novels thiadiazine derivatives. The formation of the all compounds was confirmed using different spectroscopic techniques.

REFERENCES

[1] Chadha, V. K.; Ranwa, N. S.; Dadheech, P. K. *J. Phytol. Res.* **1998**, 11, 201-202.
[2] Sakata, M.; Shirakawa, Y.; Kamata, N.; Hiroshino, Y.S.; Jie, O. Y. *J. Heterocycl. Chem*. **2000**, 37, 269-271.
[3] Nadkarni, B. A.; Kamat, V. R.; Khadse, B. G. *Arzneim. Forsch*. **2001**, 51, 569-573.
[4] Holla, B. S.; Akberali, P. M.; Shivananda, M. K. *Farmaco* **2001**, 56, 919-927.
[5] Hui, X. P.; Zhang, Y.; Xu, P. F.; Wang, Q.; Zhang, Q.; Zhang, Z. Y. *Chin. J. Org. Chem*. **2005**, 25, 700-704.
[6] Holla, B. S.; Rao, B. S.; Sarojini, B. K.; Akberali, P. M.; Kumari, N. S. *Eur. J. Med. Chem*. **2006**, 41, 657-663.
[7] Holla, B. S.; Rao, B.S.; Shridhara, K.; Akberali, P. M. *Farmaco* **2000**, 55, 338-344.
[8] Marina, K.; Anastssia, M.; Panagiotis, M.; Nicole, P.; Spyroula, P. G.;Christophe, P.; Myriam, W.;Erik, D. C. *Farmaco* **2002**, 57, 253-257.
[9] Cruickshank R, Duguid J P, Marmion B P, Medicinal Microbiology, 12th edn, Vol 11,**1975**.
[10] Arthington-Skaggs B A, Motley M, Morrision C J, *J Clin Microbiology*,38,2254(**2000**).