ISSN: 2249 –4820

Chemistry & Biology Interface, 2011, 1, 1, 128-134

Chemistry & Biology Interface

An official Journal of ISCB, Journal homepage; www.cbijournal.com

Research Article

Synthesis and Antimicrobial Evaluation of New 1,4-Benzothiazinyl Thioacetates

Jyotirling R. Mali,[a] Nanasaheb B. Dharbale,[b] Manisha R. Bhosle [a] and Ramrao A. Mane[a*]

[a]*Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad-431004, India.*
[b]*Department of Pharmaceutical Chemistry, Shri. Bhagwan College of Pharmacy, Aurangabad-431 004, India.*
Received 27 July 2011; Accepted 16 August 2011

Keywords: Benzo[1,4]thiazin-3(4H)-one, 1,4-Benzothiazinyl Thioacetates, Antibacterial, Antifungal Activity.

Abstract: New ethyl 2-[(Z)-(2-arylidenyl-2H-benzo[b][1,4]thiazin-3-ylthio]acetates were synthesized using benzo[1,4]thiazin-3(4H)-one as a starting material in successive three steps. The structures to the new products and the intermediates have been assigned on the basis of IR, ^{1}H NMR, ^{13}C NMR and MS analyses. In vitro antimicrobial activity of the newly synthesized compounds has been evaluated for bacterial strains viz. *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeruginosa* and Fungi, *Candida albicans* and *Aspergillus niger* and results are presented.

Introduction

1,4-Thiazines are an important class of nitrogen and sulfur containing heterocycles and are widely used as key building blocks for pharmaceutical agents [1]. 1,4-Benzothiazines have highly important fused heterocyclic scaffold responsible for the diverse range of biological activities like, *anti*-inflammatory [2], immunostimulating [3], *anti*-cancer [4], *anti*-fungal [5], *anti*-rheumatic [6], K_{ATP}-Channel Openers [7], *anti*-hypertensive [8], *anti*-HIV [9], and anti-bacterial [10]. Benzo[1,4]thiazin-3(4*H*)-ones are also used as herbicides [11]. The clinical agents used in the treatment of hypertensive [12], calcium antagonist [13], fungal infections [14], cataract ion [15], diabetics [16] etc. diseases are having 1,4-benzothiazine ring system as core structural unit. It is also reported that the thiazines are also used as pigments and dyestuffs [17].

Keeping in view the multifarious applications of 1,4-benzothiazines and in continuation of our earlier interest in synthesizing new bioactive 1,4-benzothiazines [18], here we report synthesis of new ethyl 2-[(Z)-2-arylidenyl-2*H*-benzo[*b*][1,4]thiazin-3-ylthio] acetates (**5a-g**) and their antimicrobial *in vitro* evaluation against *Gram*-positive and *Gram*-negative bacteria and fungi. Some of the screened molecules have displayed moderate antimicrobial activity.

*[*]Corresponding author E-mail:manera@indiatimes.com
Fax: +91 240 2400291, phone No. +91 240 2403313

ISSN: 2249 –4820

Chemistry & Biology Interface, 2011, 1, 1, 128-134

Results and Discussion

Chemistry

The synthesis of the titled compounds is outlined in **Scheme 1.** Benzo[1,4]thiazin-3(4*H*)-one (**1**), freshly prepared by following literature procedure [2a] was condensed with various aromatic aldehydes (**2a-g**) in the presence of sodium methoxide in dimethylformamide (DMF) at reflux and obtained (Z)-2-arylidenyl-2*H*-benzo[b][1,4]thiazin-3(4*H*)-ones (**3a-g**) with moderated to high yields.

The configurations of the compounds (**3**) were established with their ^{1}H NMR spectra and the spectral data have been found to be in good agreement with the reported [19]. It was confirmed that 2-arylidenyl-2*H*-benzo[b][1,4]thiazin-3(4*H*)-ones (**3a-g**) have Z isomeric forms as their ^{1}H NMR spectra have shown chemical shifts for their vinylic protons δ in the region 7.74-7.82 ppm. This was in good agreement with the chemical shifts for the Z isomers for the series of compounds reported in the literature [19].

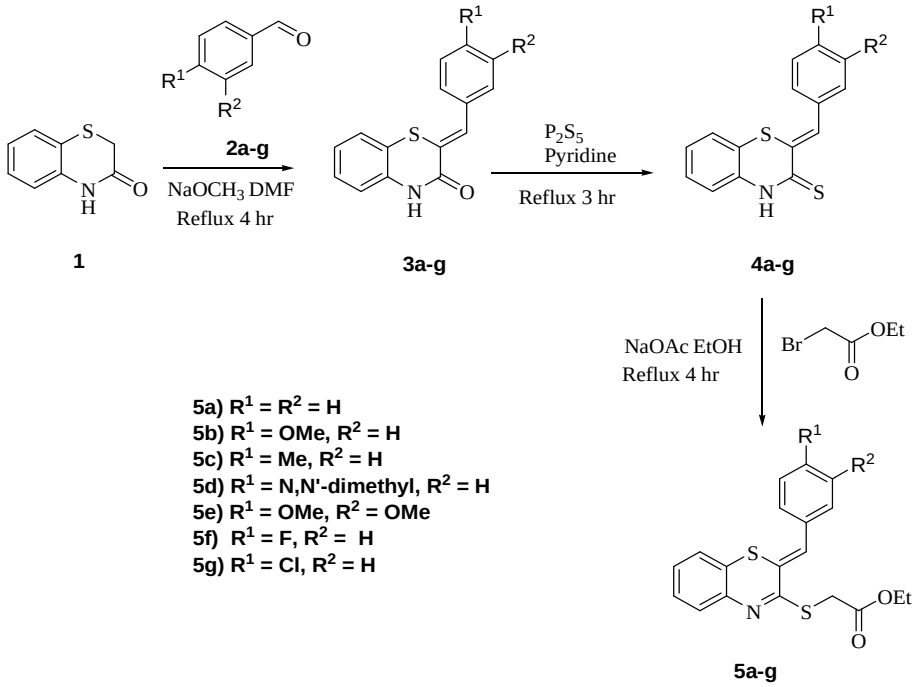
The thionation of (Z)-2-arylidenyl-2*H*-benzo[b][1,4]thiazin-3(4*H*)-ones (**3a-g**) has been carried using phosphorus pentasulfide in refluxed pyridine and obtained the respective (Z)-2-arylidenyl-2*H*-benzo[b][1,4]thiazine-3(4*H*)-thiones (**4a-g**) with good yields. Some of the compounds (**4**) have been found to be reported in the literature [20]. In the reported route compound (**1**) was first thionated and then successively the thionated product was condensed with aryl aldehydes in benzene using pyridine by following Knoevenagel condensation and obtained (Z)-2-arylidenyl-2*H*-benzo[b][1,4]thiazine-3(4H)-thiones (**4**) [21]. Here in the above developed route we obtained single isomer of (**4**) with Z configuration by avoiding volatile benzene and THF. Also the developed route is having advantage over the reported route as here the isolation of the products and intermediates is relatively non-tedious.

(Z)-2-Arylidenyl-2*H*-benzo[b][1,4]thiazine-3(4H)-thiones (**4**) on S-alkylation, carried using ethylbromoacetate in the presence of sodium acetate in ethanol gave new ethyl 2-[(Z)-2- arylidenyl-2H-benzo[b][1,4]thiazin-3-ylthio] acetates (**5a-g**) with moderate to better yields. The structures to the compounds, (**5a-g**) were assigned on the basis of their IR, ^{1}H NMR, ^{13}C NMR and MS analyses.

The IR spectra of the compounds (**5a-g**) have shown the characteristic bands at 3100-3250 cm^{-1} (C-H, aromatic stretching), 2781-2930 cm^{-1} (C-H stretching), 1736-1750 cm^{-1} (ester carbonyl group) and 769-778 cm^{-1} (C-S-C stretching). ^{1}H NMR spectra of the 1, 4-benzothiazinyl thioacetates displayed noticeable peaks for the S-C$\underline{H}_2$ protons at δ(ppm) 3.99-4.03. The signals of the vinylic protons have been found between in the region 7.35-7.46 ppm. The peaks of methylene carbons (S-$\underline{C}H_2$) of the compounds (**5a-g**) have been observed in ^{13}C NMR at 33.1-33.5 ppm. The expected molecular ion peaks of the compounds (**5a-g**) have also been recorded in their mass spectra.

ISSN: 2249 –4820

Chemistry & Biology Interface, 2011, 1, 1, 128-134



Scheme 1: Synthesis of new 1, 4-benzothiazinyl thioacetates

Antimicrobial Evaluation

All the newly synthesized 1, 4-benzothiazinyl thioacetates (**5a-g**) were screened for their antibacterial and antifungal activities. The microorganism selected for the antibacterial study were *Staphylococcus aureus* ATCC 6538, *Bacillus subtilis* NCIM 2250 (Gram positive) and *Escherichia coli* ATCC 8739, *Pseudomonas aeruginosa* ATCC 9027 (Gram negative). Ampicillin was used as a reference standard. Antifungal screening has been carried using Candida *albicans* B017 and *Aspergillus niger*. Ketoconazole was used as reference standard in the antifungal study. Both microbial studies were assessed by minimum inhibitory concentration (MIC) using serial dilution methods [21]. For this the compounds whose MIC has to be determined was dissolved in DMF and its various concentrations were prepared in the medium. Then standard drop of the culture, prepared for the assay was added to each of the dilutions (solutions) and it was then incubated for 24 h at 37 °C for bacteria and in case of fungi at 28 °C for 48 h. The MIC determination was performed in triplicate for each organism and experiments were repeated wherever necessary.

All the newly synthesized compounds were screened for their antibacterial and antifungal activities. Among the screened compounds **5a, 5b, 5c and 5d** have exhibited potent inhibitory activity against *B. subtilis*. Likewise compound **5a** have shown better activity against *E. coil* and *P. aeruginosa*. The MIC values of the synthesized compounds were found to be moderate as compared to the standard. The antifungal screening results showed that the compounds **5c**, **5d**, **5e** and **5g** have displayed noticeable inhibitory activity aganist *C. albicans*. The compounds **5a** and **5f** have also displayed good antifungal activity against *A. niger*.

The data (Table 1 and 2) indicate that, the presence of ester functionality and nature of substituentes might be governing antimicrobial activities of the synthesized compounds (**5a-g**). It has been found that the compounds with functional groups R^1

ISSN: 2249 –4820

Chemistry & Biology Interface, 2011, 1, 1, 128-134

= R^2 = H, R^1 = Me, R^1 = OMe, and R^1 = *N*-dimethyl exhibit potent antibacterial activity against *Bacillus subtilis.* The most of the synthesized compounds have shown moderate bacterial activity against *Staphylococcus aureus.* The compounds having substituents like R^1 = R^2 = H, and R^1 = OMe have displayed better activity against *Escherichia coil*. The products bearing functionalities like R^1 = Me, R^1 = *N*-dimethyl R^1 = R^2 = OMe and R^1 = Cl have positional interference regarding their antifungal activity against *Candida albicans*. The compounds bearing R^1 = R^2 = H and R^1 = F as substituents were found to exhibit potent antifungal activity against *Aspergillus niger*

Table 1
Antibacterial data for newly synthesized 1,4-benzothiazinyl thioacetates (**5a-g**)

Compound No.	Antibacterial activity data in MIC (µg/mL)			
	B. Subtilis	*S. aureus*	*P. aeruginosa*	*E. coli*
5a	31.25	62.5	62.5	62.5
5b	31.25	125	62.5	62.5
5c	31.25	125	125	125
5d	31.25	125	62.5	125
5e	62.5	125	125	125
5f	62.5	125	62.5	125
5g	62.5	125	62.5	125
Ampicillin (Std)	6.25	3.125	3.125	< 3.125
DMF (Control)	-	-	-	-

Table 2
Antifungal data for newly synthesized 1,4-benzothiazinyl thioacetates (**5a-g**)

Compound No.	Antifungal activity data in MIC (µg/mL)	
	C. albicans	*A. niger*
5a	125	62.5
5b	125	125
5c	62.5	125
5d	62.5	125
5e	62.5	125
5f	125	62.5
5g	62.5	125
Ketoconazole (Std)	3.125	1.562
DMF (Control)	-	-

ISSN: 2249 –4820

Chemistry & Biology Interface, 2011, 1, 1, 128-134

Experimental

All the chemicals and the solvents used for the work were procured from Spectrochem and S. D. Fine-chem. (India). All the melting points were determined by open capillary method and are uncorrected. IR spectra were recorded on JASCO FT-IR 4100, using KBr discs. ^{1}H and ^{13}C NMR spectra were recorded with Bruker Avance 400 spectrometer operating at 400 MHz and 100 MHz using DMSO-d_6 as solvent and tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded on Single-Quadrupole Mass Detector 3100, Waters. The observed molecular ions are having 1 amu higher m/z in the spectra than the expected as the scans were run with ESI^{+}-MS mode.

Synthesis of (Z)-2-(4-methoxybenzylidene)-2H-benzo[b][1,4]thiazin-3(4H)-one (3b)

Benzo[1,4]thiazin-3(4H)-one **1** (0.02 mol), 4-methoxy benzaldehyde **2b** (0.02 mol) and sodium methoxide (0.026 mol) were dissolved in dimethylformamide (15 mL) and the solution was refluxed. The progress of the reaction was monitored by TLC using hexane–ethyl acetate (7:3). After 4 h of reflux, the reaction mixture was poured on crushed ice and the solid formed was filtered and then washed with water. The crude was crystallized from ethanol–DMF.

Yellow solid: Yield: 75 %, mp: 207-209 °C. IR (KBr cm^{-1}): 3650, 3110, 3010, 2928, 2864, 1690, 1500 and 1330. ^{1}H NMR (400 MHz, DMSO-d_6): δppm 3.81 (s, 3H), 7.03 (dd, 2H, J = 8 Hz), 7.05-7.08 (m, 2H), 7.17 (dd, 1H, J = 6.8 Hz), 7.32 (dd, 1H, J = 8 Hz), 7.67 (dd, 2H, J = 8 Hz), 7.74 (s, 1H, vinylic-H) and 10.93 (s, 1H, NH). ESI^{+}-MS (m/z): 284 (M^{+}).

Synthesis of (Z)-2-(4-methoxybenzylidene)-2H-benzo[b][1,4]thiazine-3(4H)-thione (4b)

A mixture of (Z)-2-(4-ethoxybenzylidene)-2H-benzo[b][1,4]thiazin-3(4H)-one 3b (0.01 mol), and phosphorus pentasulfide (0.005 mol) was dissolved in pyridine (10 mL) and the reaction solution was refluxed. The progress of the reaction was monitored by TLC using hexane–ethyl acetate (7:3). After 3 h of reflux, the reaction mixture was poured on crushed ice. Solid appeared was filtered and then washed with water (3 times). The crude was then crystallized from ethanol.

Yellow solid: Yield: 80 %, mp: 193-195 °C. Yield: 75 %, mp: IR (KBr cm^{-1}): 3645, 3109, 3006, 2928, 2864, 1330 and 1117. ^{1}H NMR (400 MHz, DMSO-d_6): δppm 3.87 (s, 3H), 7.06 (d, 2H, J = 8 Hz), 7.14-7.30 (m, 4H), 7.67 (d, 2H, J = 8 Hz), 8.45 (s, 1H, vinylic-H) and 10.91 (s, 1H, NH). ESI^{+} MS (m/z):300 (M^{+}).

Synthesis of ethyl 2-[(Z)-2-(4-methoxybenzylidene)-2H-benzo[b][1,4]thiazin-3-ylthio]acetate (5b):

A mixture of (Z)-2-(4-methoxybenzylidene)-2H-benzo[b][1,4]thiazine-3(4H)-thione 4b (0.005 mol), sodium acetate (0.01 mol), and ethylbromoacetate (0.0055 mol) was dissolved in ethanol (10 mL) and the reaction solution was refluxed. The progress of the reaction was monitored by TLC using hexane–ethyl acetate (7:3). After 4 h of reflux, the reaction mixture was poured on crushed ice and solid formed was filtered then washed with water. The crude solid obtained was crystallized from ethanol.

Yellow solid, Yield: 80%, mp: 119-121 °C. IR (KBr cm^{-1}): 3199, 3058, 2985,

ISSN: 2249 –4820
Chemistry & Biology Interface, 2011, 1, 1, 128-134

2985, 1740 and 774. ^{1}H NMR (400 MHz, DMSO-d_6): δppm 1.23 (t, 3H, *J* = 7.2 Hz), 3.82 (s, 3H), 4.01 (s, 2H), 4.17 (q, 2H, *J* = 7.2 Hz), 7.08 (d, 2H, *J* = 8 Hz), 7.15-7.31 (m, 4H), 7.44 (s, 1H, vinylic-H) and 7.61 (d, 2H, *J* = 8 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): 14.7, 33.5, 55.8, 61.4, 114.5, 118.7, 120.8, 125.5, 127.0, 127.7, 127.8, 128.1, 128.6, 132, 138.9, 158.7, 160.1 and 169.2. ESI$^+$ MS (m/z): 386 (M^+).

Ethyl 2-[(Z)-2-benzylidene-2H-benzo[b][1,4]thiazin-3-ylthio]acetate (**5a**): Yellow solid, Yield: 85%, mp: 97-99 °C. IR (KBr cm^{-1}): 3201, 3058, 2985, 1736 and 769. ^{1}H NMR (400 MHz, DMSO-d_6): δppm 1.23 (t, 3H, *J* = 7.2 Hz), 4.03 (s, 2H), 4.17 (q, 2H, *J* = 7.2 Hz), 7.17-7.33 (m, 4H), 7.42 (t, 1H, *J* = 7.2 Hz), 7.49 (s, 1H, vinylic-H), 7.52 (d, 2H, *J* = 7.2 Hz) and 7.62 (d, 2H, *J* = 7.6 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): 14.7, 33.4, 61.5, 120.6, 120.8, 125.7, 127.8, 127.9, 128.3, 128.7, 129.1, 129.4, 130.1, 134.4, 138.8, 158.3 and 169.2. ESI$^+$ MS (m/z): 356 (M^+).

Ethyl 2-[(Z)-2-(4-methylbenzylidene)-2H-benzo[b][1,4]thiazin-3-ylthio]acetate (**5c**): Yellow solid, Yield: 79%, mp: 79-81 °C. IR (KBr cm^{-1}): 3200, 3058, 2986, 1745 and 770. ^{1}H NMR (400 MHz, DMSO-d_6): δppm 1.23 (t, 3H, *J* = 7.2 Hz), 2.36 (s, 3H), 4.02 (s, 2H), 4.17 (q, 2H, *J* = 7.2 Hz), 7.16-7.32 (m, 6H), 7.47 (s, 1H, vinylic-H) and 7.53 (d, 2H, *J* = 7.2 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): 14.7, 21.5, 33.3, 61.5, 120.3, 120.7, 125.6, 127.7, 127.9, 128.2, 128.6, 129.6, 130.1, 131.7, 138.9, 139.3, 158.4 and 169.2. ESI$^+$ MS (m/z): 370 (M^+).

Ethyl 2-[(Z)-2-(4-(dimethylamino)benzylidene)-2H-benzo[b][1,4]thiazin-3-ylthio]acetate (**5d**): Reddish Brown solid, Yield: 77%, mp: 105-107 °C. IR(KBr cm^{-1}): 3262, 3058, 2982, 1736and 778. ^{1}H NMR (400 MHz, DMSO-d_6): δppm 1.23 (t, 3H, *J* = 7.2 Hz), 3.01 (s, 6H), 3.99 (s, 2H), 4.16 (q, 2H, *J* = 7.2 Hz), 6.81 (d, 2H, *J* = 8 Hz), 7.20-7.27 (m, 4H), 7.35 (s, 1H, vinylic-H) and 7.50 (d, 2H, *J* = 8 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): 14.1, 33.1, 39, 60.9, 111.6, 111.5, 120.6, 121.4, 125.1, 127, 127.1, 127.4, 128.9, 131.4, 131.8, 138.6, 150.3, 158.7 and 168.2. ESI$^+$ MS (m/z) :399 (M^+).

Ethyl 2-[(Z)-2-(3,4-dimethoxybenzylidene)-2H-benzo[b][1,4]thiazin-3-ylthio]acetate (**5e**): Yellow solid, Yield: 75%, mp: 161-163 °C. IR (KBr cm^{-1}): 3231, 3058, 2982, 1750 and 769. ^{1}H NMR (400 MHz, DMSO-d_6): δppm 1.23 (t, 3H, *J* = 7.2 Hz), 3.81 (s, 6H), 4.02 (s, 2H), 4.17 (q, 2H, *J* = 7.2 Hz), 7.09-7.30 (m, 7H), 7.44 (s, 1H, vinylic-H) and 7.75 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): 14.2, 33.2, 55.5, 60, 111.4, 113.4, 118.3, 122.8, 123.2, 125.2, 126.7, 127.6, 128.4, 138.4, 148.4, 149.4, 158.7, 159 and 168.7. ESI$^+$ MS (m/z): 416 (M^+).

Ethyl 2-[(Z)-2-(4-fluorobenzylidene)-2H-benzo[b][1,4]thiazin-3-ylthio]acetate (**5f**): Light greenish solid, Yield: 78%, mp: 101-102 °C. IR (KBr ν_{max}/cm^{-1}): 3241, 3058, 2997, 1745, 1112 and 776. ^{1}H NMR (400 MHz, DMSO-d_6): δppm 1.23 (t, 3H, *J* = 7.2 Hz), 4.03 (s, 2H), 4.17(q, 2H, *J* = 7.2 Hz), 7.17-7.37 (m, 6H), 7.49 (s, 1H, vinylic-H) and 7.70 (d, 2H, *J* = 8 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): 14.7, 33.1, 61.5, 116, 116.2, 121.1, 125.7, 127.7, 127.8, 127.9, 128.3, 132.4, 132.5, 138.8, 158.7, 161.1, 163.6 and 169.1. ESI$^+$ MS (m/z): 374 (M^+).

Ethyl 2-[(Z)-2-(4-chlorobenzylidene)-2H-benzo[b][1,4]thiazin-3-ylthio]acetate (**5g**): Yellow Solid, Yield: 79%, mp: 95-97 °C. IR (KBr ν_{max}/cm^{-1}): 3200, 3058, 2985, 1750, 774 and 724. ^{1}H NMR (400 MHz, DMSO-d_6): δppm 1.23 (t, 3H, *J* = 7.2 Hz), 3.01 (s, 6H), 3.99 (s, 2H), 4.16 (q, 2H, *J* = 7.2 Hz), 6.81 (d, 2H, *J* = 8 Hz), 7.20-7.27 (m, 4H), 7.35 (s, 1H, vinylic-H) and

ISSN: 2249 –4820

Chemistry & Biology Interface, 2011, 1, 1, 128-134

7.50 (d, 2H, J = 8 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): 14.2, 33.3, 61, 119.8, 121.5, 125.2, 126.7, 127.4, 127.5, 127.9, 128.5, 131.3, 132.8, 133, 138.2, 157.5 and 168.6. ESI$^+$ MS (m/z): 390 (M^+) and 392 (M+2).

Conclusion

Here we have synthesized some new 1,4-benzothiazinyl thioacetates and reported their antimicrobial activity against pathogenic organisms. All the compounds have shown moderate inhibition against the strains. The importance of this work lies in the possibility that the new compounds might be more efficacious drugs against bacteria and fungi and could be helpful in designing more potent antibacterial and antifungal agents for therapeutic use.

Acknowledgement

The authors are thankful to Professor D. B. Ingle for his invaluable discussions and guidance.

References

[1] T. Eicher, S. Hauptmann, *The Chemistry of Heterocycles*, 2nd edn, Wiley VCH, Weinheim, **2003**; (b) R. A. Aitken, K. M. Aitken, Chapter 8.09 *in Comprehensive Heterocyclic Chemistry* 3rd Edition, Elsevier, **2008**, 8, 607; (c) R. R.Gupta, K. G. Ojha, *In Phenothiazines and 1,4-Benzothiazines*: *Chemical and Biochemical Aspects*; R. R. Gupta, ed., Elsevier: Amsterdam, **1988**, 163.

[2] (a) J. Krapcho, C. F. Turk, *J. Med. Chem.*, **1973**, 16, 776-779; (b) R. C. Millonig, M. B. Goldlust, W. E. Rubin, B. Maguire, E. Schulze, R. J. Wojnar, A**.** R Turkheimer, W. F. Schreiber, R. J. Brittain., *J. Med. Chem*., **1973**, 16, 780-782; (c) J. G. Lombardino, E. H. Wiseman, *Med. Res. Rev.*, **1982**, 2, 127-152.

[3] L. D. Corona, G. Signorelli, A. Pinzetta, G. Coppi., *Eur. J. Med. Chem.*, **1992**, 27, 419-423.

[4] R. R. Gupta, P. K. Dev, M. L. Sharma, C. M. Rajorla, A. Gupta, M. Nyatl., *Anti-Cancer Drugs.*, **1993**, 4, 589-592.

[5] R. Fringuelli, F. Schiaffella, F. Bistoni, L. Pitzurra, A. Vecchiarelli., *Bioorg. Med.Chem.*, **1998**, 6, 103-108.

[6] H. Matsuoka, N. Ohi, M. Mihara, H. Suzuki, K. Miyamoto, N. Maruyama, K. Tsuji, N. Kato, T. Akimoto, Y. Takeda, K. Yano, T. Kuroki, *J. Med.Chem.*, **1997**, 40, 105-111.

[7] V. Cecchetti, V. Calderone, O. Tabarrini, S. Sabatini, E. Filipponi, L. Testai, R. Spogli, E. Martinotti, A. Fravolini, *J. Med. Chem.*, **2003**, *46*, 3670-3679.

[8] (a) R. N. Prasad, *J. Med. Chem.*, **1969**, *12*, 290-294; (b) V. Cecchetti, A. Fravolini, F. Schiaffella, M. DeRegis, G. Orzalesi, I. Volpato, *Farmaco Ed. Sci.*, **1983**, 38, 35-44.

[9] G. Grandolini, L. Perioli, V. Ambrogi, *Eur. J. Med. Chem.*, **1999**, 34, 701-709.

[10] (a) V. L. Guarda, M. De, M. Parrissin, F. Thomasson, E. A. Ximenes, S. L. Galdino, I. R. Pitta, C. Luu-Duc, *IL Farmaco*, **2001**, 56, 689; (b) V. L. Guarda, M. De, M. Parrissin, F. Thomasson, E. A. Ximenes, S. L. Galdino, I. R. Pitta, C. Luu-Duc, J. Barbe, *Eur. J. Med. Chem.*, **2003**, 38, 789.

[11] T. Wuemachu, H. Oshio, *K R Patent* 820000849, **1982**.

[12] T. Morino, T. Yamamoto, *J. Chem. Eng. Jpn.*, **1997**, 30, 1005-1012.

[13] F. Corelli, F. Manetti, A. Tafi, G. Campiani, V. Nacci, M. Botta, *J.Med.Chem.*, **1997**, 40, 125-131.

[14] A. Macchiarulo, G. Costantatino, D. Fringuelli, A. Vecchiarelli, F. Chiaffella, R. Fringuelli, *Bioorg. Med. Chem.*, **2002**, 10, 3415-3423.

[15] Y. Kawashima, A. Ota, H. Mibu, *W O Patent* 9405647, **1994**.

[16] T. Matsui, Y. Nakamura, H. Ishikawa, A. Matsuura, F. Kobayashi, *Jpn. J. Pharmacol.*, **1994**, 64, 115-124.

[17] R. Tanaka, K. Teramura, S. Yokoyama, *Jpn. Pat. 5833*, **1966**; *Chem. Abstr*.**1966**, 65, 9062.

[18] (a) R. V. Dengle, R. D. Ingle, S. P. Bondge, R. A. Mane, *Ind. J. Chem. Sec. B.*,**1999**, 38, 390-393; (b) S. B. Munde, S. P. Bondge, V. E. Bhingolikar, R. A. Mane, *Green Chem.*, **2003**, 5, 278-279. (c) S. N. Karale, U. R. Pratap, S. R. Mahalle, R. A. Mane, *J of Sulfur chem.***2011**, 32, 303-309.

[19] (a) J. W. Worley, K. W. Ratts, K. L. Cammack, *J. Org. Chem.*, **1975**, 40, 1731-1734; (b) A. M. A. Souza, V. L. M. Guarda, L. F. C. Leite, J. M. Barbosa Filho, M. C. A. Lima, S. L. Galdino, I. R. Pitta, *Quim. Nova.*, **2006**, 29, 1106-1109.

[20] S.Kamila, B. Koh, H. Zhang, E. R. Biehl., *Arkivo*c, **2006**, 2, 1-14.

[21] Mackie, Mc. Cartney, in: J. G. Collee, J. P. Duguid, A. G. Fraser, B. P Marmion, (Eds.), *Practical Medicinal Microbiology*, 13th ed. **1989**, 87.