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Novel thiazolidine-2,4-dione mannich bases: Synthesis, characterization and antimicrobial activity

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ABSTRACT

A series of novel (5E)-5-arylidene-3-substituted-1,3-thiazolidine-2,4-diones were prepared by treating 1,3-thiazolidine-2,4-dione with substituted aromatic aldehydes in the presence of sodium acetate followed by Mannich reaction with primary/secondary amines. Structures of the newly synthesized compounds were assigned on the basis of elemental analyses, IR, 1H NMR and mass spectral studies. The newly synthesized compounds were tested for their in vitro antibacterial and antifungal activity against a variety of microorganism

Key words 1,3-thiazolidine-2,4-dione, Mannich reaction, antibacterial, antifungal

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INTRODUCTION

4-Thiazolidinone derivatives are an important group of heterocyclic compounds possessing a variety of biological effects [1], including antitumor [2-4], anti-inflammatory [5], antimicrobial [6], antiviral [7], anticonvulsant [8], antifungal [9], antibacterial [10] activities and so on. Among them, 5-benzylidene-4-thiazolidinone derivatives have been reported to show marked antitumor activities with different biotargets and mechanism, such as phosphatase of a regenerating liver (PRL-3) [11], Sphingosine Kinase (SK) [12], JNKstimulating phosphatase-1 (JSP-1) [13] and non membrane protein tyrosine phosphatase (SHP-2) [14]. Moreover, 5-benzylidene-4-thiazolidinone derivatives exhibited potent antitumor activities against non-small cell lung cancer cell line H460, paclitaxel-resistant$H460_{taxR}$, human colon cancer cell line HT-29 and human breastcancer cell line MDA-MB-231[15].These observations led to the conception that 5-benzylidene derivatives of 3-substituted thiazolidine-2,4-diones would possess potential anti-microbial properties along with potent antitumor activities. Several methods were reported in the literature for the preparation of thiazolidinone derivatives [16].

MATERIALS AND METHODS

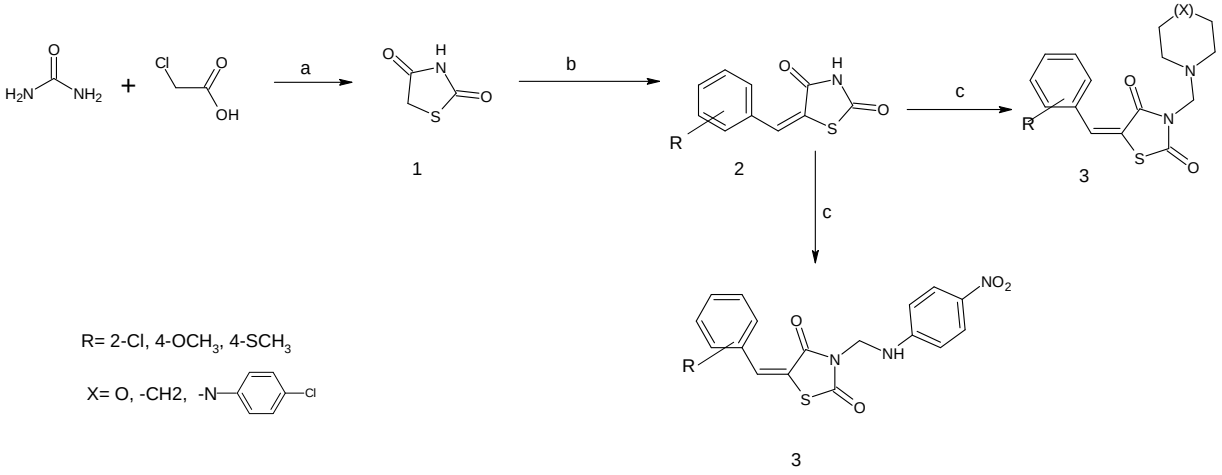
Melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded by dispersing the compounds in KBr pellets on a Shimadzu FT-IR 157 spectrophotometer. 1H NMR spectra were recorded on a 400 MHz Bruker Avance spectrometer and all the chemical shift values were reported as δ. The DART-MS was recorded on a JEOL-ACCUTOF JMS-T100LC mass spectrometer having a DART source.

Materials

All the reagents and solvents are from spectrochem and Aldrich and they were used as received without further purification.

Experimental methods

In the present study a novel series (5E)-5-arylidene-3-substituted-1,3-thiazolidine-2,4-diones(**3a-l**) are synthesized. Our synthetic strategy for thiazolidinone derivatives is illustrated in **Scheme 1**. The synthesis starts with refluxing thiourea and chloroacetic acid in water media in the presence conc. sulphuric acid for about 10-12 hours, followed by cooling to afford thiazolidin-2,4-dione (**1**) which on further reaction with substituted aryl aldehydes in the presence of anhydrous sodium acetate in acetic acid media afforded 5-arylidene derivatives of thiazolidin-2,4-dione (**2**). These steps were carried out according to the procedures reported in the literature[17]. The resulting compound on Mannich reaction with formaldehyde and primary/secondary amines in the presence of trace of triethyl amine in absolute alcohol media yielded the title compounds (**3**) with 60-85% yield. Formation of the compounds was confirmed by spectral and analytical data.



Scheme1*. Reagents and Conditions: a) Conc. H2SO4, water, 100 ^{0}C, 12h, yield: 90% b)Subt. Aldehyde, anhy. CH_3COONa, AcOH, 110 ^{0}C, yield:84-86% c)HCHO, Sec. amine/p-NO_2 aniline, Triethylamine, abs. alcohol, r.t., yield: 62-87%*

General Procedure for the Preparation of (5E)-5-arylidene-3-substituted-1,3-thiazolidine-2,4-diones***(3a-l)***

A mixture of 5-arylidene derivatives of thiazolidin-2,4-dione **(2)** (1mmol), formaldehyde (1 mmol), and primary/secondary amines(1mmol) in the presence of trace of triethyl amine in absolute alcohol media was stirred at room temperature for 2-3h and the completion of the reaction was ascertained by TLC. The reaction mixture was allowed to settle down. The reaction mixture was then gradually poured into crushed ice with stirring. The product separated was filtered, washed, dried and was recrystallized using ethanol.

*(5E)-5-(2-chlorobenzylidene)-3-(morpholin-4-ylmethyl)-1,3-thiazolidine-2,4-dione (**3a**)*.

yield: 78%; m.p. 137-150 °C; IR: (KBr: γ/cm^{-1}): 2958 (C–H), 1667 (C= O); ^{1}H NMR(δ ppm, $CDCl_3$, 400 MHz): 2.51(t, 4H, *J* = 6.0 Hz, $N(CH_2)_2$), 3.54 (t, 4H, *J* = 6.0 Hz, $(CH_2)_2O$), 4.56 (s, 2H, CH_2), 7.10-7.30 (m, 4H, ArH), 7.87 (s, 1H, =CH); DART–MS (m/z): 338.8 (M^+). Anal. calcd. for $C_{15}H_{15}ClN_2O_3S$: C 53.17, H 4.46, N 8.27; Found: C 53.19, H 4.49, N 8.30.

*(5E)-5-(2-chlorobenzylidene)-3-(piperidin-1-ylmethyl)-1,3-thiazolidine-2,4-dione (**3b**)*.

yield: 68%; m.p. 105 °C; IR: (KBr: γ/cm^{-1}): 2954 (C–H), 1669 (C=N); ^{1}H NMR(δ ppm, $CDCl_3$, 400 MHz): 2.59(t, 4H, J = 6.3 Hz, $N(CH_2)_2$), 3.48 (m, 4H, $(CH_2)_2$), 4.48 (m, 2H, CH_2-piperidine), 4.59 (s, 2H, CH_2), 7.08-7.29 (m, 4H, ArH), 7.87 (s, 1H, =CH); DART–MS (m/z): 336.8 (M^+). Anal. calcd. for $C_{16}H_{17}ClN_2O_2S$: C 57.05, H 5.09, N 8.32; Found: C 57.09, H 5.13, N 8.34.

*(5E)-5-(2-chlorobenzylidene)-3-{[4-(4-chlorophenyl)piperazin-1-yl]methyl}-1,3-thiazolidine-2,4-dione (**3c**)*.

yield: 78%; m.p. 137-150 °C; IR: (KBr: γ/cm^{-1}): 2959 (C–H), 1664 (C= O); ^{1}H NMR(δ ppm, $CDCl_3$, 400 MHz): 2.51(t, 4H, J = 6.0 Hz, $N(CH_2)_2$), 3.54 (t, 4H, J = 6.0 Hz, $(CH_2)_2N$), 4.56 (s, 2H, CH_2), 7.10-7.28 (m, 4H, ArH), 7.87

(s, 1H, =CH), 6.82(d,2H, J=7.8Hz, ArH), 7.08(d,2H, J=7.8Hz, ArH) ; DART–MS (m/z): 448.01 (M^+). Anal. calcd. for $C_{21}H_{19}Cl_2N_3O_2S$: C 59.06, H 4.51, N 6.26; Found: C 59.09, H 4.55, N 6.30.

*(5E)-5-(2-chlorobenzylidene)-3-{[(4-nitrophenyl)amino]methyl}-1,3-thiazolidine-2,4-dione(**3d**).* yield: 78%; m.p. 198-200 °C; IR: (KBr: γ/cm^{-1}) : 2914 (C–H), 3355(NH),1590(-NO_2asy),1307(-NO_2sy) 1664 (C= O); ^{1}H NMR(δ ppm, $CDCl_3$, 400 MHz): 4.50(t, 1H, J = 6.0 Hz, NH),5.17(d, 2H, J=6.0Hz, CH_2), 6.85 (d, 2H, J = 9.0 Hz, ArH), 8.07 (d, 2H,J=9.0Hz, ArH), 7.10-7.28 (m, 4H, ArH), 7.43 (s, 1H, =CH), ; DART–MS (m/z): 389.8 (M^+). Anal. calcd. for $C_{17}H_{12}ClN_3O_4S$: C 52.38, H 3.10, N 10.78; Found: C 52.42, H 3.14, N10.81.

*(5E)-5-(4-methoxybenzylidene)-3-(morpholin-4-ylmethyl)-1,3-thiazolidine-2,4-dione(**3e**)*.
yield: 87%; m.p. 138-140 °C; IR: (KBr: γ/cm^{-1}) : 2954 (C–H), 1668 (C=0), 1589(C=C); ^{1}H NMR ($CDCl_3$): δ 2.51(t, 4H, J = 6.0 Hz, $N(CH_2)_2$), 3.54 (t, 4H, J = 6.0 Hz, $(CH_2)_2O$),3.84(s, 3H, OCH_3), 4.56 (s, 2H, CH_2), 7.12(d, 2H,J=9.0Hz, ArH), 7.61(d, 2H, J=9.0Hz, ArH) 7.89 (s, 1H, =CH); DART–MS (m/z): 334.4 (M^+). Anal. calcd. for $C_{16}H_{18}N_2O_4S$: C 57.47, H 5.43, N 8.38; Found: C 57.49, H 5.46, N 8.42.

*(5E)-5-(4-methoxybenzylidene)-3-(piperidin-1-ylmethyl)-1,3-thiazolidine-2,4-dione (**3f**)*.
yield: 72%; m.p. 108 °C; IR (KBr) γ/cm^{-1}: 2957 (C–H), 1666 (C=O); ^{1}H NMR(δ ppm, $CDCl_3$, 400 MHz): 2.58(t, 4H, J = 6.6 Hz, $N(CH_2)_2$), 3.49 (m, 4H, $(CH_2)_2$), 3.84(s, 3H, OCH_3), 4.50 (m,2H,CH_2-piperidine) 4.58 (s, 2H, CH_2), 7.12 (d, 2H,J=8.9Hz, ArH), 7.62(d, 2H, J=8.9Hz, ArH), 7.85 (s, 1H, =CH); DART–MS (m/z): 332.4 (M^+). Anal. calcd. for $C_{17}H_{20}N_2O_3S$: C 61.42, H 6.06, N 8.43; Found: C 61.46, H 6.08, N 8.46.

(5E)-5-(4-methoxybenzylidene)-3-{[4-(4-chlorophenyl)piperazin-1-yl]methyl}-1,3-thiazolidine-2,4-dione ***(3g)***.
yield: 60%; m.p. 142-144 °C; IR: (KBr: γ/cm^{-1}) : 2959 (C–H), 1668 (C=O),762(C-Cl); ^{1}H NMR(δ ppm, $CDCl_3$, 400 MHz): 2.52(t, 4H, J = 6.0 Hz, $N(CH_2)_2$), 3.54 (t, 4H, J = 6.0 Hz, $(CH_2)_2N$), 3.84(s, 3H, OCH_3), 4.56 (s, 2H, CH_2), 7.14 (d, 2H,J=8.8Hz, ArH), 7.67(d, 2H, J=8.8Hz,Ar), 7.88 (s, 1H, =CH), 6.91(d,2H, J=7.6Hz, ArH), 7.28(d,2H, J=7.6Hz, ArH) ; DART–MS (m/z): 443.9 (M^+). Anal. calcd. for $C_{22}H_{22}ClN_3O_3S$: C 62.36, H 5.23, N 6.32; Found: C 62.42, H 5.27, N 6.30.

*(5E)-5-(4-methoxybenzylidene)-3-{[(4-nitrophenyl)amino]methyl}-1,3-thiazolidine-2,4-dione (**3h**)*.
yield: 82%; m.p. 200-201 °C; IR: (KBr: γ/cm^{-1}) : 2916 (C–H), 3355 (NH),1590 (-NO_2asy),1307 (-NO_2sy) 1664 (C=O); ^{1}H NMR(δ ppm, $CDCl_3$, 400 MHz): 3.84(s, 3H, OCH_3), 4.50(t, 1H, J = 6.8 Hz, NH), 5.14 (d, 2H, J=6.8Hz,CH_2), 6.90 (d, 2H, J = 9.2 Hz, ArH), 8.04 (d, 2H,J=9.2Hz, ArH), 7.39 (d, 2H, J=8.4Hz, ArH), 7.55(d, 2H, J=8.4Hz, ArH), 7.91 (s, 1H, =CH),; DART–MS (m/z): 385.4 (M^+). Anal. calcd. for $C_{18}H_{15}N_3O_5S$: C 56.10, H 3.92, N 10.90; Found: C 56.14, H 3.95, N 10.88.

*(5E)-5-[4-(methylsulfanyl)benzylidene]-3-(morpholin-4-ylmethyl)-1,3-thiazolidine-2,4-dione(**3i**)*. yield: 87%; m.p. 142-144 °C; IR: (KBr: γ/cm^{-1}) : 2958 (C–H), 1667.5 (C=O), 1578(C=C); ^{1}H NMR ($CDCl_3$): δ 2.51(t, 4H, J = 6.0 Hz, $N(CH_2)_2$), 3.54 (t, 4H, J = 6.0 Hz, $(CH_2)_2O$),2.49(s, 3H, SCH_3), 4.55 (s, 2H, CH_2), 7.39(d, 2H,J=8.4Hz, ArH), 7.54(d, 2H,J=8.4Hz, ArH) 7.87(s, 1H, =CH); DART–MS (m/z): 350.4 (M^+). Anal. calcd. for $C_{16}H_{18}N_2O_3S_2$: C 54.83, H 5.18, N 7.99; Found: C 54.80, H 5.21, N 7.95.

*(5E)-5-[4-(methylsulfanyl)benzylidene]-3-(piperidin-1-ylmethyl)-1,3-thiazolidine-2,4-dione(**3j**)*. yield: 78%; m.p. 142-144 °C; IR: (KBr: γ/cm^{-1}) : 2958 (C–H), 1667(C=O); ^{1}H NMR(δ ppm, $CDCl_3$, 400 MHz): 2.52(t, 4H, J = 6.6 Hz, $N(CH_2)_2$), 3.53 (m, 4H, $(CH_2)_2$), 2.49(s, 3H, SCH_3), 4.50(m,2H,CH_2-piperidine) 4.58 (s, 2H, CH_2), 7.38 (d, 2H,J=8.5Hz, ArH), 7.56(d, 2H, J=8.5Hz, ArH), 7.84 (s, 1H, =CH); DART–MS (m/z): 348.5 (M^+). Anal. calcd. for $C_{17}H_{20}N_2O_2S_2$: C 58.59, H 5.78, N 8.04; Found: C 58.55, H 5.81, N 8.06**.**
(5E)-5-[4-(methylsulfanyl)benzylidene]-3-{[4-(4-chlorophenyl)piperazin-1-yl]methyl}-1,3-thiazolidine-2,4-dione ***(3k)***
yield: 62%; m.p. 157-158 °C; IR: (KBr: γ/cm^{-1}) : 2959 (C–H), 1668 (C=O), 762(C-Cl); ^{1}H NMR(δ ppm, $CDCl_3$, 400 MHz): δ 2.52(t, 4H, J = 6.0 Hz, $N(CH_2)_2$), 3.54 (t, 4H, J = 6.0 Hz, $(CH_2)_2N$), 2.49(s, 3H, SCH_3), 4.56 (s, 2H, CH_2), 7.38(d, 2H,J=8.8Hz, ArH), 7.56(d, 2H, J=8.8Hz,ArH), 7.88 (s, 1H, =CH), 6.96(d,2H, J=7.8Hz, ArH), 7.16(d,2H, J=7.8Hz, ArH) ; DART–MS (m/z): 460.0 (M^+). Anal. calcd. for $C_{22}H_{22}ClN_2O_2S_2$: C 60.18, H 5.05, N 6.10; Found: C 60.22, H 5.07, N 6.07.

*(5E)-5-[4-(methylsulfanyl)benzylidene]-3-{[(4-nitrophenyl)amino]methyl}-1,3-thiazolidine-2,4-dione (**3l**)*.
yield: 86%; m.p. 202-204 °C; IR: (KBr: γ/cm^{-1}) : 2916 (C–H), 3355(NH),1590(-NO_2asy),1307(-NO_2sy) 1664 (C=O); ^{1}H NMR(δ ppm, $CDCl_3$, 400 MHz): δ 2.49(s, 3H, SCH_3), 4.50(t, 1H, J = 6.8 Hz, NH),5.14(d, 2H, J=6.8Hz,CH_2), 6.93 (d, 2H, J = 9.2 Hz, ArH), 8.03 (d, 2H,J=9.2Hz, ArH), 7.40(d, 2H, J=8.4Hz, ArH), 7.55(d, 2H, J=8.4Hz, ArH), 7.91 (s, 1H, =CH) ; DART–MS (m/z): 401.5 (M^+). Anal. calcd. for $C_{18}H_{15}N_3O_4S_2$: C 53.85, H 3.77, N 10.47; Found: C 53.82, H 3.75, N 10.51

RESULTS AND DISCUSSION

^{1}H NMR spectrum of compound **3e** showed a singlet at 7.89 ppm for one proton which is characteristic value of benzylidene proton. The aromatic protons resonated at 7.12ppm and 7.61ppm as two doublets with coupling constant 9.0 Hz. The –CH_2 protons resonated at 4.46ppm. The-OCH_3 protons resonated at 3.84ppm and the morpholine protons resonated as two triplets at 2.51ppm and 3.54ppm. The absence of absorption bands corresponding to –NH group in IR spectrum confirmed the formation of Mannich base (**3e**). The DART-mass spectrum of compound **3e** showed the molecular ion peak at m/z = 334.13, in conformity with its molecular formula $C_{16}H_{18}N_2O_4S$.

Antimicrobial activity

The antimicrobial activity was determined using disc diffusion method by measuring zone of inhibition in mm [18]. All the compounds, **3a-l** were screened *in-vitro* at a concentration of 10 µg/disc for their antibacterial activity against two Gram-positive strains (Staphylococcus aureus and Bacillus subtilis) and two Gram-negative strains (Escherichia coli and Pseudomonas aeruginosa). Antifungal evaluation was also carried out against Candida albicans and Aspergillus niger at a concentration of 10 µg/disc. Standard antibacterial drug ciprofloxacin (10µg/disc) and antifungal drug fluconazole (10µg/disc) were also tested under similar conditions against these organisms. Each experiment was done in triplicate and the average reading was taken. The antibacterial activity was classified as highly active (≥26 mm), moderately active (11-25 mm) and least active (<11 mm). The results of antibacterial and antifungal activities are expressed in terms of zone of inhibition and presented in **Table 1**.

Table 1 Antimicrobial activity of the tested compounds 3a-l

Compd	Zone of inhition in mm					
	Antibacterial activity				Antifungal activity	
	S. aureus	*B. subtilis*	*E. coli*	*P. aeruginosa*	*C. albicans*	*A. niger*
3a	18	18	20	21	16	18
3b	22	22	20	22	18	11
3c	20	20	19	20	20	18
3d	28	26	28	24	27	25
3e	22	20	20	22	18	16
3f	18	16	20	18	19	18
3g	20	18	22	20	20	16
3h	28	28	26	24	26	24
3i	10	12	08	08	10	11
3j	12	10	10	10	14	16
3k	10	12	08	10	14	11
3l	22	20	22	18	20	18
Ciprofloxacin	26	26	28	25	-	-
Flucanazol	-	-	-	-	26	25

The newly synthesized compounds were tested to evaluate their antibacterial and antifungal activity. All these compounds were found to exhibit moderate antibacterial and antifungal activity against different species of bacteria and fungi. From the activity data (**Table 1**) it was observed that among all the compounds tested, compound **3d** and **3h** showed good activity against all the tested bacteria and fungi. Among the other compounds **3b, 3c, 3e** and **3g** showed moderate activity against bacterial and fungal strains. The compounds **3a, 3b** and **3c** showed least activity against all the pathogens.

CONCLUSION

In conclusion, we have synthesized a series of novel thiazolidine-2,4-dione Mannich bases and have screened for antibacterial and antifungal activities. The results from our biological activity studies showed that compound **3d** and

3h having a secondary–NH group attached to a phenyl ring with the nitro group at the para position showed very good activity against all tested bacteria and fungi as good as the standard itself.

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REFERENCES

[1] T. Tomasic , L. P. Masic, *Curr. Med. Chem.*, **2009,** 16,1596.
[2] R. Lesyk, B. Zimenkovsky, D. Atamanyuk, F. Jensen, K. Kiec-Kononowicz, A. Gzell, *Bioorg. Med. Chem.*, **2006,**14,5230.
[3] D. Havrylyuk, B. Zimenkovsky, O. Vasylenko, L. Zaprutko, A. Gzella, R. Lesyk, *Eur. J. Med. Chem.*, **2009**, 44, 1396.
[4] D.Kaminskyy, B.Zimenkovsky, R. Lesyk, *Eur. J.Med.Chem.*, **2009**, 44, 3627.
[5] R. Ottana, R. Maccari, M.L. Barreca, G. Bruno, A. Rotondo, A. Rossi, G. Chiricosta, R. Di Paola, L. Sautebin, S. Cuzzocrea, M.G. Vigorita, *Bioorg. Med. Chem*., **2005**, 13, 4243.
[6] P. Vicini, A. Geronikaki, K. Anastasia, M. Incerti, F. Zani, *Bioorg. Med. Chem.*, **2006**, 14, 3859.
[7] A.A. Elbarbary, A.I. Khodair, E.B. Pedersen, C. Nielsen, *Monatsh. Chem.*, **1994,** 125, 593.
[8] E. Rydzik, A. Szadowska, A. Kaminska, *Acta Pol. Pharm.*, **1984**, 41, 459-464.
[9] H.L. Liu, Z.C. Li, T. Anthonsen, *Molecules* , **2000**, 5, 1055.
[10] B. Samir, K. Wesam, A.F. Ahmed, *Eur. J. Med. Chem.*, **2007**, 42, 948.
[11] J.H. Ahn, S.J. Kim, W.S. Park, S.Y. Cho, J.D. Ha, S.S. Kim, S.K. Kang, D.G. Jeong, S.K. Jung, S.H.Lee, H.M. Kim, S.K. Park, K.H. Lee, C.W. Lee, S.E. Ryu, J.K.Choi, *Bioorg.Med. Chem. Lett*., **2006**, 16 , 2996.
[12] K.J. French, R.S. Schrecengost, B.D. Lee, Y. Zhuang, S.N. Smith, J.L. Eberly, J.K. Yun, C.D. Smith, *Cancer Res*., **2003**, 63, 5962.
[13] N.S. Cutshall, C. O'Day, M. Prezhdo, *Bioorg. Med. Chem. Lett.*, **2005**, 15, 3374.
[14] A. Geronikaki, P. Eleftheriou, P. Vicini, I. Alam, A. Dixit, A.K. Saxena , *J. Med.Chem.*, **2008,** 51 ,5221.
[15] H.Y. Zhou, S.H. Wu, S.M. Zhai, A.F. Liu, Y. Sun, R.S. Li, Y. Zhang, S. Ekins, P.W. Swaan, B.L. Fang, B. Zhang, B. Yan, *J. Med. Chem.*, **2008**, 51 , 1242.
[16] (a) J.F. Dubreuil , J.P. Bazureau, *Tetrahedron*, **2003**, 59, 121.
(b) A. Verma , S.K. Saraf, *Eur. J. Med. Chem.*, **2008,** 43, 897.
(c) T. Srivastava, W. Haq , S.B. Katti, *Tetrahedron*, **2002** , 58 , 7619.
[17] L. V. Sonawane, S. B. Bari, *International Journal of Biological Chemistry*, **2011**, 5, 68.
[18] A. N. Bauer, W. N. M. Kirby, J. C. Sherries, M. Truck, *Am. J. Clin. Pathol.*, **1996**, 45, 493.