



Scholars Research Library

Der Pharma Chemica, 2012, 4 (1):106-115
(<http://derpharmachemica.com/archive.html>)



ISSN 0975-413X
CODEN (USA): PCHHAX

***In-vitro* anti-HIV activity of new thiazol-2-ylidene substituted benzamide analogues**

Aamer Saeed^{a,*} Najim A. Al-Masoudi^{b,*} and Christopher Pannecouque^c

^aDepartment of Chemistry, Quaid-I-Azam University 45320, Islamabad, Pakistan.

^bDepartment of Chemistry, College of Science, University of Basrah, Basrah, Iraq

^cRega Institute for Medical Research, Katholieke Universiteit Leuven, B-3000 Leuven, Belgium

ABSTRACT

A new series of *N*-(5-acetyl-4-methyl-3-(substituted phenyl)-thiazol-2-ylidene)-4-methyl (substituted) benzamides **2a-o** was synthesized by heterocyclization of the corresponding 1-substituted benzoyl-3-arylthioureas **1a-o** with 3-chloropentane-2,4-dione under microwave irradiation in the absence of any solvent or catalyst. All synthesized compounds have been evaluated for their antiviral activity against the replication of HIV-1 and HIV-2 activity in MT-4. However, compounds **2j** and **2n** showed activity against HIV-2 with EC_{50} of $2.44 \mu\text{g ml}^{-1}$ and $1.89 \mu\text{g ml}^{-1}$ (CC_{50} of $60.68 \mu\text{g ml}^{-1}$ and $49.38 \mu\text{g ml}^{-1}$), respectively, resulting in a selectivity index of 25 and 26. The results suggest that these compounds can be considered as a new lead in the development of antiviral agents.

Keywords: Anti-HIV activity, benzamides, imino-1,3-thiazolines, 1,3-disubstituted thioureas, NNRTIs.

INTRODUCTION

N-(5-Acetyl-4-methyl-3-(substituted phenyl)-thiazol-2(3*H*)-ylidene)-4-methyl substituted benzamide derivatives bearing 2-imino-1,3-thiazoline or thiazol-2-imine nucleus possess important pharmacological activities, such as antifungal [1,2], anti-allergic [3], anti-hypertensive [4], anti-inflammatory [5], antibacterial [6], analgesic, antirheumatic, antipyretic and anti-HIV [7] activities. Some fused thiazolines possessed medicinal applications in the treatment of allergies, hypertension, inflammation, schizophrenia, bacterial and HIV infections [8], meanwhile 2-thiazolylimino-5-arylidene-4-thiazolidinones showed noticeable antimicrobial activity against bacteria, yeasts and mould [9]. 3-Substituted 2-(cyanoimino)thiazolidines have been used in agriculture due to their neonicotinoid insecticidal activity [10]. Moreover, some 3-substituted thiazolidines exhibited radioprotective properties against γ -radiations [11]. Quantitative structural-activity relationship (QSAR) study for fungicidal activities of 2-imino-1,3-thiazoline derivatives against rice blast fungus *Pyricularia oryzae* [12] has revealed their

potent use as fungicides. KHG22394, a 2-imino-1,3-thiazoline derivative, significantly inhibited melanin production in a dose-dependant manner thus act as a skin whitening agent [13], whereas pifithrin- α , an imino thiazoline, is a reversible inhibitor of p53-mediated apoptosis and p53-dependent gene transcription [14]. Amidine derivatives, synthesized by condensation of 2-cyanopyridine with various 3,4-diaryl-2-imino-4-thiazolines, exhibited good antiinflammatory activity and analgesic activity [15]. 3-Alkyl-3*H*-thiazoline derivative PS 028, GP IIb/IIIa receptor antagonist, is a lead compound for orally active potent platelet aggregation inhibitor [16]. On the other hand, acridinyl-thiazoline derivatives have been found to exhibit moderate CDK1 inhibitor activity [17]. Several derivatives of 2-acylimino-1,3-thiazolines showed bleaching herbicidal activity against up-land weeds and proved selectivity against crops [18], while 2-acylimino-3-alkyl-3*H*-thiazoline derivatives have been considered as novel β -turn mimics [19]. Recently, 2-alkylimino-1,3-thiazolines have exhibited promising T-Type calcium channel inhibitory activity [20], whereas Patil *et al.* [21] reported that 5-benzylidene-3-(3-fluoro-4-yl-morpholin-4-ylphenylimino)-thiazolidin-4-one derivatives showed remarkable antimicrobial activity.

Shi *et al.* [22] have reported recently the condensation of *N*-aryl thioureas with 3-bromo-acetylacetone in neutral solvent acetone, as well as the antiproliferative activity of the products. Such reaction led to the formation of not only 5-acetyl-4-methyl-2-(substituted anilino)thiazoles but 2-imino-3-(substituted phenyl)-4-methyl-5-acetyl-2,3-dihydrothiazoles, as well.

The above mentioned biological and significance synthetic pathways and in continuation of our ongoing studies on *N*-(4-phenyl-3-aryolthiazol-2(3*H*)-ylidene)-substituted-benzamides [23], thiazoline [24] and thiazol-2-ylidene derivatives [25], we report here the synthesis of some new thiazol-2-ylidene benzamide derivatives with evaluation of their anti-HIV activity.

MATERIALS AND METHODS

Melting points were recorded using a digital Gallenkamp (SANYO) model MPD BM 3.5 apparatus and are uncorrected. ^1H NMR spectra were determined as CDCl_3 solutions at 300 MHz using a Bruker AM-300 spectrophotometer. FT IR spectra were recorded using an FTS 3000 MX spectrophotometer. Mass Spectra (EI, 70eV) were measure on GC-MS instrument. The reactions were carried out in microwave oven (MW 900 W, frequency 2450 MHz, Power level 1, Dawlance, Pakistan). All compounds were purified by thick layer chromatography using silica gel from Merck.

General procedure for the synthesis of (E)-N-(5-acetyl-4-methyl-3-(substituted phenyl)-thiazol-2(3H)-ylidene)-4-methyl substituted benzamides (2a-o).

A completely homogenized mixture of 1-(substituted aroyl)-3-(substituted phenyl)thioureas (**1a-o**) (1.0 mmol) with 3-chloropentane-2,4-dione (1.0 mmol), was irradiated for 10-30 seconds in an alumina bath inside a microwave oven. The progress of reaction was followed by TLC examination using hexane ethyl acetate (4:1). On completion, the residue was purified either by recrystallization from EtOH or MeOH or by preparative thin layer chromatography to furnish the desired product.

***N*-(3-([1,1'-Biphenyl]-2-yl)-5-acetyl-4-methylthiazol-2-ylidene)benzamide (**2a**)**

Yield: 65%; mp 156-157 °C. IR (KBr, ν : cm^{-1}): 2932, 1698, 1640 (C=O), 1632, 1555 (Ar-C=C), 1448 (C=N), 1511, 1316, 1292 (C-S), 1165 (C-N), 1152, 971, 718, 685. ^1H NMR (CDCl_3): δ 7.68 (dd, 2H, $J = 1.8, 7.8$ Hz, Ar-H); 7.64 (dd, 2H, $J = 1.8, 7.8$ Hz, Ar-H); 7.40-7.33 (s, 8H, Ar-H); 7.14 (t, $J = 1.8, 2\text{H}$, Ar-H); 2.74 (s, 3H, CH_3); 2.47 (s, 3H, CH_3CO). ^{13}C NMR (CDCl_3): δ

171.9 (CH₃C=O); 165.0 (NC=O); 159.5 (C²_{thiazol=N}); 150.7 (C⁴_{thiazol}); 149.80, 143.2, 141.3, 137.0, 133.2, 129.8, 128.9, 126.3, 124.4, 126.2, 123.3, 124.8, 124.6 (C_{arom}); 104.3 (C⁵_{thiazol}); 30.3 (CH₃CO), 14.7 (CH₃). EIMS: *m/z* 412. Anal. Calcd. for C₂₅H₂₀N₂O₂S (412.50): C, 72.79; H, 4.89; N, 6.79. Found: C, 72.83; H, 4.91; 6.76%.

N-(5-Acetyl-3-(3-fluorophenyl)-4-methylthiazol-2-ylidene)-4-nitrobenzamide (**2b**)

Yield: 75%; mp 212-213 °C. IR (KBr, v: cm⁻¹): 2940, 1690, 1645 (C=O), 1630, 1560 (Ar-C=C), 1538 (asym NO₂), 1448 (C=N), 1343 (sym NO₂), 1316, 1292 (C-S), 1165 (C-N), 1152, 971. ¹H NMR (CDCl₃): δ 7.58 (d, 2H, *J* = 1.8, 7.8 Hz, H^{3,5}_{arom-NO₂}); 7.44 (d, 2H, *J* = 1.8, 7.8 Hz, H^{2,6}_{arom-NO₂}); 7.39-7.31 (m, 4H, Ar-H); 2.72 (s, 3H, CH₃); 2.45 (s, 3H, CH₃CO). ¹³C NMR (CDCl₃): δ 173.6 (CH₃C=O); 164.6 (NC=O); 160.0 (C²_{thiazol=N}); 157.7, 155.0 (d, *J*_{C3'arom,F} = 251 Hz, C^{3'}_{arom}); 152.5 (C⁴_{thiazol} + C⁴_{arom-NO₂}); 140.8, 140.2 (d, *J*_{C1'arom,F} = 7.5 Hz, C^{1'}_{arom}); 133.9, 132.0, 131.2 (C_{arom}); 130.5, 29.5 (d, *J*_{C5'arom,F} = 12.8 Hz, C^{5'}_{arom}); 125.1, 124.6 (d, *J*_{C2'arom,F} = 20.0 Hz, C^{2'}_{arom}); 116.7 (d, *J*_{C6'arom,F} = 3.8 Hz, C^{6'}_{arom}); 106.2, 104.3 (d, *J*_{C4'arom,F} = 19.5 Hz, C^{4'}_{arom}); 105.0 (C⁵_{thiazol}); 30.2 (CH₃CO); 14.5 (CH₃). EIMS 398/400. Anal. Calcd. for C₁₉H₁₄FN₃O₄S (399.40): C, 57.14; H, 3.53; N, 10.52. Found: C, 75.24; H, 3.57; 10.61%.

N-(5-Acetyl-3-(3-chloro-4-fluorophenyl)-4-methylthiazol-2-ylidene)-4-nitrobenzamide (**2c**)

Yield: 78%; mp 204-206 °C. IR (KBr, v: cm⁻¹): 2973, 1697, 1651 (C=O), 1632, 1556 (Ar-C=C), 1542 (asym NO₂), 1451 (C=N), 1350 (sym NO₂), 1511, 1316, 1290 (C-S), 1165 (C-N), 1152, 971, 718, 685. ¹H NMR (CDCl₃): δ 8.37 (d, 2H, *J* = 1.8, 7.8, H^{3,5}_{arom-NO₂}); 8.19 (d, 2H, *J* = 1.8, 7.8 Hz, H^{2,6}_{arom-NO₂}); 7.42 (d, 1H, *J*_{C6'arom,F} = 5.5 Hz, C^{6'}_{arom}); 7.21 (d, 1H, *J*_{C5'arom,F} = 8.3 Hz, C^{5'}_{arom}); 6.35 (d, 1H, *J*_{C2'arom,F} = 5.0 Hz, C^{2'}_{arom}); 2.72 (s, 3H, CH₃); 2.39 (s, 3H, CH₃CO). ¹³C NMR (CDCl₃): δ 175.2 (CH₃C=O); 165.8 (NC=O); 159.9 (C²_{thiazol=N}); 154.5 (C⁴_{thiazol} + C⁴_{arom-NO₂}); 149.5, 152.2 (d, *J*_{C4'arom,F} = 250 Hz, C^{4'}_{arom}); 136.5 (C_{arom}); 134.7, 134.2 (d, *J*_{C1'arom,F} = 7.2 Hz, C^{1'}_{arom}); 130.3, 128.3 (C_{arom}); 123.4, 123.9 (d, *J*_{C6'arom,F} = 12.0 Hz, C^{6'}_{arom}); 121.3, 120.1 (d, *J*_{C3'arom,F} = 20.5 Hz, C^{3'}_{arom}); 119.0, 119.8 (d, *J*_{C2'arom,F} = 13.5 Hz, C^{2'}_{arom}); 113.3, 112.2 (d, *J*_{C5'arom,F} = 20.3 Hz, C^{5'}_{arom}); 104.5 (C⁵_{thiazol}); 30.3 (CH₃CO); 14.6 (CH₃). EIMS 432/434. Anal. Calcd. for C₁₉H₁₃ClF₂N₃O₄S (433.84): C, 52.60; H, 3.02; N, 9.69. Found: C, 52.67; H, 3.08; 9.45%.

N-(5-Acetyl-3-(4-fluorophenyl)-4-methylthiazol-2-ylidene)-4-fluorobenzamide (**2d**)

Yield: 73%; mp 117-119 °C. IR (KBr, v: cm⁻¹): 2945, 1698, 1640 (C=O), 1632, 1555 (Ar-C=C), 1448 (C=N), 1511, 1316, 1292 (C-S), 1165 (C-N), 1152, 971, 718, 685. ¹H NMR (CDCl₃): δ 7.94 (m, 2H, H^{2,6}_{arom-F}); 7.64 (m, 2H, H^{3,5}_{arom-F}); 7.34 (m, 2H, H^{2,6}_{arom-F}); 7.25 (m, 2H, H^{3,5}_{arom-F}); 2.72 (s, 3H, CH₃); 2.47 (s, 3H, CH₃CO). ¹³C NMR (CDCl₃): δ 172.8 (CH₃C=O); 167.2 (NC=O); 165.0, 163.0 (d, *J*_{C4'arom,F} = 252 Hz, C^{4'}_{arom}); 161.4 (C²_{thiazol=N}); 159.5, 157.3 (d, *J*_{C4'arom,F} = 251 Hz, C^{4'}_{arom}); 150.7 (C⁴_{thiazol}); 137.0, 136.7 (d, *J*_{C1'arom,F} = 3.5 Hz, C^{1'}_{arom}); 129.8, 128.9 (d, *J*_{C3'arom,F} = 20.1 Hz, C^{3'}_{arom}); 123.3, 124.8 (d, *J*_{2'arom,F} = 12.8 Hz, C^{2'}_{arom}); 118.5, 117.04 (d, *J*_{3'arom,F} = 23.2 Hz, C^{3'}_{arom}); 116.1, 115.0 (d, *J*_{C3'arom,F} = 12.5 Hz, C^{3'}_{arom}); 104.2 (C⁵_{thiazol}); 30.1 (CH₃CO); 14.6 (CH₃). EIMS 371/373. Anal. Calcd. for C₁₉H₁₄F₂N₂O₂S (372.39): C, 61.28; H, 3.79; N, 7.52. Found: C, 61.86; H, 3.64; 7.47%.

N-(5-Acetyl-3-(2-bromophenyl)-4-methylthiazol-2-ylidene)-3,4-dichlorobenzamide (**2e**)

Yield: 81%; mp 160-161 °C. IR (KBr, v: cm⁻¹): 2937, 1708, 1640 (C=O), 1632, 1555 (Ar-C=C), 1448 (C=N), 1511, 1316, 1292 (C-S), 1165 (C-N), 1152, 971, 718, 685. ¹H NMR (CDCl₃): δ 7.66 (dd, 1H, *J* = 3.7, 1.6 Hz, C²_{aromCl₂}); 7.34-7.02 (m, 6H, C_{arom}); 2.72 (s, 3H, CH₃); 2.45 (s, 3H, CH₃CO). ¹³C NMR (CDCl₃): δ 172.9 (CH₃C=O); 168.2 (NC=O); 161.2 (C=N); 150.7 (C⁴_{thiazol}); 149.8 (C¹_{arom-Br}); 141.3 (C⁴_{aromCl₂}); 137.0 (C¹_{aromCl₂}); 133.2 (C³_{aromCl₂} + C³_{aromCl}); 129.8 (C²_{aromCl₂} + C⁶_{aromCl₂}); 128.9 (C⁵_{aromCl}); 126.3 (C⁴_{aromCl}); 118.5 (C⁶_{aromCl}); 117.0 (C²_{aromCl}); 104.5 (C⁵_{thiazol});

30.3 (CH_3CO); 14.7 (CH_3). EIMS 484. Anal. Calcd. for $C_{19}H_{13}BrCl_2N_2O_2S$ (484.19): C, 47.13; H, 2.71; N, 5.79. Found: C 47.18; H, 2.61; N, 5.81%.

N-(5-Acetyl-3-(2-bromophenyl)-4-methylthiazol-2-ylidene)-3,5-dichlorobenzamide (**2f**)

Yield: 65%; mp 150-151 °C. IR (KBr, v: cm^{-1}): 2920, 1688, 1640 (C=O), 1632, 1555 (Ar-C=C), 1448 (C=N), 1511, 1316, 1292 (C-S), 1165 (C-N), 1152, 971, 718, 685. 1H NMR ($CDCl_3$): δ 7.66 (t, 1H, $J = 2.8$ Hz, $C^4_{aromCl_2}$); 7.34 (d, 2H, $J = 2.7$ Hz, $C^{2,6}_{aromCl_2}$); 7.25-7.02 (m, 4H, $C_{arom-Br}$); 2.73 (s, 3H, CH_3); 2.46 (s, 3H, $COCH_3$). ^{13}C NMR ($CDCl_3$): δ 172.8 ($CH_3C=O$), 168.1 (NC=O); 161.3, (C=N); 150.9 ($C^4_{thiazol}$); 149.8 ($C^1_{arom-Br}$); 141.3 ($C^1_{aromCl_2}$); 137.0 ($C^{3,5}_{aromCl_2}$); 133.2 ($C^4_{aromCl_2} + C^3_{aromBr}$); 129.8 ($C^2_{aromCl_2}$); 128.9 ($C^6_{aromCl_2} + C^5_{aromBr}$); 126.3 (C^4_{aromBr}); 118.5 (C^6_{aromBr}); 117.0 (C^2_{aromBr}); 104.3 ($C^5_{thiazol}$); 30.2 (CH_3CO); 14.5 (CH_3). EIMS 484. Anal. Calcd. for $C_{19}H_{13}BrCl_2N_2O_2S$ (484.19): C, 47.13; H, 2.71; N, 5.79. Found: C, 47.20; H, 2.65; N, 5.89%.

N-(5-Acetyl-3-(2-fluorophenyl)-4-methylthiazol-2-ylidene)-3,4,5-trimethoxybenzamide (**2g**)

Yield: 68%; mp 172-173 °C. IR (KBr, v: cm^{-1}): 2925, 1670, 1640 (C=O), 1632, 1555 (Ar-C=C), 1448 (C=N), 1511, 1316, 1292 (C-S), 1165 (C-N), 1152, 971, 718, 685. 1H NMR ($CDCl_3$): δ 7.79-(d, 2H, $J = 2.7$ Hz, $C^{2,6}_{arom-OMe_3}$); 7.23-7.02 (m, 4H, C_{arom-F}); 3.52 (s, 3H, OMe); 3.33 (s, 6H, OMe); 2.72 (s, 3H, CH_3); 2.43 (s, 3H, CH_3CO). ^{13}C NMR ($CDCl_3$): δ 173.5 ($CH_3C=O$); 168.2 (NC=O); 161.2 (C=N); 152.7, 150.1 (d, $J_{C2',F} = 252$ Hz, $C^4_{thiazol} + C^{2'}_{arom-F}$); 149.8 ($C^{3,5}_{arom-OMe_3}$); 143.4 ($C^4_{arom-OMe_3}$); 134.2, 133.7 (d, $J_{C1',F} = 26.3$ Hz, $C^{1'}_{arom-F}$); 128.9 ($C^{1''}_{arom-OMe_3}$); 126.3 ($C^{5'}_{arom-F}$); 126.2, 125.8 (d, $J_{C6',F} = 12.4$ Hz, $C^{6'}_{arom-F}$); 123.3, 122.8 (d, $J_{C6',F} = 12.3$ Hz, $C^{4'}_{arom-F}$); 117.0, 116.1 (d, $J_{C3',F} = 26.0$ Hz, $C^{3'}_{arom-F}$); 116.1 ($C^{2,6}_{arom-OMe_3}$); 109.2 ($C^1_{arom-OMe_3}$); 104.4 ($C^5_{thiazol}$); 59.8 (OMe); 55.2 (2xOMe); 30.5 (CH_3CO); 14.7 (CH_3). EIMS 443/445. Anal. Calcd. for $C_{22}H_{21}FN_2O_5S$ (444.48): C, 59.45; H, 4.76; N, 6.30. Found: C, 59.69; H, 4.77; N, 6.35%.

N-(5-Acetyl-3-(3-fluorophenyl)-4-methylthiazol-2-ylidene)-3,4,5-trimethoxybenzamide (**2h**)

Yield: 76%; mp 173-174 °C. IR (KBr, v: cm^{-1}): 2929, 1685, 1640 (C=O), 1632, 1555 (Ar-C=C), 1448 (C=N), 1511, 1316, 1292 (C-S), 1165 (C-N), 1152, 971, 718, 685. 1H NMR ($CDCl_3$): δ 7.87 (d, 2H, $J = 2.8$ Hz, $C^{2,6}_{arom-OMe_3}$); 7.02 (dt, 1H, $J_{4,5',arom,F} = J_{5',6',arom,F} = 7.9$ Hz, $J_{2',5',arom,F} = 5.5$ Hz, , 3.55 (s, 3H, OMe); 3.35 (s, 6H, OMe); 2.73 (s, 3H, CH_3); 2.47 (s, 3H, CH_3CO). ^{13}C NMR ($CDCl_3$): δ 172.4 ($CH_3C=O$); 169.9 (NC=O); 162.8, 162.3 (d, $J_{C3',arom,F} = 251$ Hz, $C^{3'}_{arom-F}$); 160.2 ($C^2_{thiazol=N}$); 154.3 ($C^4_{thiazol}$); 153.2 (2xC, 3,5-OMe-C-Ar); 144.3 (4-OMe-C-Ar); 138.4, 138.6 (d, $J_{C1',arom,F} = 9.8$ Hz, C^1_{arom}); 132.7, 132.2 (d, $J_{C5',arom,F} = 8.3$ Hz, $C^{5'}_{arom}$); 130.7 (C_{arom}); 123.9, 123.4 (d, $J_{C2',arom,F} = 18.8$ Hz, $C^{2'}_{arom-F}$); 116.7 (d, $J_{C6',arom,F} = 0.8$ Hz, $C^{6'}_{arom-F}$); 109.2 (d, $J_{C4',arom,F} = 20.1$ Hz, $C^{4'}_{arom-F}$); 105.7 ($C^5_{thiazol} + C_{arom}$); ($C^5_{thiazol}$); 104.0 ($C^5_{thiazol}$); 59.8 (OMe); 55.7 (2xOMe); 30.3 (CH_3CO); 14.6 (CH_3). EIMS 443/ 445. Anal. Calcd. for $C_{22}H_{21}FN_2O_5S$ (444.48): C, 59.45; H, 4.76; N, 6.30. Found: C, 59.49; H, 4.79; N, 6.43%.

N-(5-Acetyl-3-(4-fluorophenyl)-4-methylthiazol-2-ylidene)-3,4,5-trimethoxybenzamide (**2i**)

Yield: 75%; mp 236-237 °C. IR (KBr, v: cm^{-1}): 2938, 1709, 1640 (C=O), 1632, 1555 (Ar-C=C), 1448 (C=N), 1511, 1316, 1292 (C-S), 1165 (C-N), 1152, 971, 718, 685. 1H NMR ($CDCl_3$): δ 7.66 (d, 2H, $J = 2.7$ Hz, $C^{2,6}_{arom-OMe_3}$); 7.34-7.02 (m, 4H, C_{arom-F}); 3.53 (s, 3H, OMe); 3.34 (s, 6H, OMe); 2.71 (s, 3H, CH_3); 2.45 (s, 3H, CH_3CO). ^{13}C NMR ($CDCl_3$): δ 172.8 ($CH_3C=O$), 168.2 (NC=O); 165.2, 163.0 (d, $J_{C4',F} = 250$ Hz, $C^{4'}_{arom-F}$); 161.5 (C=N), 153.5 ($C^4_{thiazol}$); 150.7 ($C^{3'',5''}_{arom-OMe_3}$); 143.4 ($C^4_{arom-OMe_3}$); 141.3, 140.0 (d, $J_{C1',F} = 12.6$ Hz, C^1_{arom-F}); 133.2, 131.7 (d, $J_{C5',F} = 12.3$ Hz, $C^{5'}_{arom-F}$); 129.8 ($C^{1''}_{arom-OMe_3}$); 118.5, 117.04 (d, $J_{C6',F} = 3.8$ Hz, $C^{4'}_{arom-F}$); 116.1 (d, $J_{C2',6',F} = 25.1$ Hz, $C^{2',4'}_{arom-F}$); 107.2 ($C^{2,6'}_{arom-OMe_3}$); 104.6 ($C^5_{thiazol}$); 60.0 (OMe); 55.3 (2xOMe); 30.3 (CH_3CO); 14.8 (CH_3). EIMS 443/ 445. Anal. Calcd. for $C_{22}H_{21}FN_2O_5S$ (444.48): C, 59.45; H, 4.76; N, 6.30. Found: C, 59.49; H, 4.69; N, 6.43%.

N-(5-Acetyl-3-(3-chlorophenyl)-4-methylthiazol-2-ylidene)-3,4,5-trimethoxybenzamide (**2j**)

Yield: 69%; mp 93-94 °C. IR (KBr, ν : cm^{-1}): 2921, 1710, 1640 (C=O), 1632, 1555 (Ar-C=C), 1448 (C=N), 1511, 1316, 1292 (C-S), 1165 (C-N), 1152, 971, 718, 685. ^1H NMR (CDCl_3): δ 8.06 (d, 2H, $J = 2.6$ Hz, $\text{C}^{2,6}$ _{arom-OMe3}); 7.37-6.96 (m, 4H, $\text{C}_{\text{arom-Cl}}$); 3.54 (s, 3H, OMe); 3.31 (s, 6H, OMe); 2.73 (s, 3H, CH_3); 2.45 (s, 3H, CH_3CO). ^{13}C NMR (CDCl_3): δ 173.4 ($\text{CH}_3\text{C=O}$); 169.9 (NC=O); 162.7 (C=N); 153.9 (C^4 _{thiazol}); 151.6 ($\text{C}^{3,5}$ _{arom-OMe3}); 143.9 (C^4 _{arom-OMe3}); 138.4 ($\text{C}^{1''}$ _{arom-Cl}); 133.9 ($\text{C}^{3''}$ _{arom-Cl}); 133.0 ($\text{C}^{5''}$ _{arom-Cl}); 130.0 ($\text{C}^{1''}$ _{arom-OMe3}); 105.1 ($\text{C}^{2,6''}$ _{arom-OMe3} + C^5 _{thiazol}); 59.8 (OMe); 55.0 (2xOMe); 30.3 (CH_3CO); 14.6 (CH_3). EIMS 460. Anal. Calcd. for $\text{C}_{22}\text{H}_{21}\text{ClN}_2\text{O}_5\text{S}$ (460.93): C, 57.33; H, 4.59; N, 6.08. Found: C, 57.23; H, 4.62; N, 6.10%.

N-(5-Acetyl-3-(3-chloro-2-fluorophenyl)-4-methylthiazol-2-ylidene)-3,4,5-trimethoxybenzamide (**2k**)

Yield: 76%; mp 255-256 °C. IR (KBr, ν : cm^{-1}): 2926, 1701, 1640 (C=O), 1632, 1555 (Ar-C=C), 1448 (C=N), 1511, 1316, 1292 (C-S), 1165 (C-N), 1152, 971, 718, 685. ^1H NMR (CDCl_3): δ 7.81 (ddd, $J = 2.1, 7.7$ Hz, $J_{5',\text{F}} = 1.8$ Hz, C^5 _{arom-F,Cl}); 7.76-7.15 (m, 4H, $\text{C}^{3'',5''}$ _{arom-OMe3} + $\text{C}^{4',6'}$ _{arom-F,Cl}); 2.72 (s, 3H, CH_3); 3.56 (s, 3H, OMe); 3.36 (s, 6H, OMe); 2.45 (s, 3H, CH_3CO). ^{13}C NMR (CDCl_3): δ 174.0 ($\text{CH}_3\text{C=O}$); 170.2 (NC=O); 162.6 (C=N); 154.1 (C^4 _{thiazol}); 151.6 ($\text{C}^{3'',5''}$ _{arom-OMe3}); 150.6, 147.9 (d, $J_{\text{C}2',\text{F}} = 245$ Hz, $\text{C}_{\text{arom-F,Cl}}$); 136.3, 135.0 (d, $J_{\text{C}1',\text{F}} = 25.8$ Hz, C^1 _{arom-F}); 129.9 ($\text{C}^{1''}$ _{arom-OMe3}); 126.2, 125.7 (d, $J_{\text{C}5',\text{F}} = 1.2$ Hz, C^5 _{arom-F,Cl}); 123.9, 122.8 (d, $J_{\text{C}6',\text{F}} = 12.7$ Hz, C^6 _{arom-F,Cl}); 116.6, 115.5 (d, $J_{\text{C}4',\text{F}} = 12.5$ Hz, C^4 _{arom-F,Cl}); 107.5 ($\text{C}^{2,6''}$ _{arom-OMe3}); 104.8 (C^5 _{thiazol}); 59.8 (OMe); 55.6 (2xOMe); 30.2 (CH_3CO); 14.7 (CH_3). EIMS 477/479. Anal. Calcd. for $\text{C}_{22}\text{H}_{20}\text{ClFN}_2\text{O}_5\text{S}$ (478.92): C, 55.17; H, 4.21; N, 5.85. Found: C, 55.24; H, 4.19; N, 5.81%.

N-(5-Acetyl-3-(3-methoxyphenyl)-4-methylthiazol-2-ylidene)-3,4,5-trimethoxybenzamide (**2l**)

Yield: 81%; mp 210-211 °C. IR (KBr, ν : cm^{-1}): 2928, 1698, 1640 (C=O), 1632, 1555 (Ar-C=C), 1448 (C=N), 1511, 1316, 1292 (C-S), 1165 (C-N), 1152, 971, 718, 685. ^1H NMR (CDCl_3): δ 7.39-7.35 ((m, 3H, $\text{C}^{3'',5''}$ _{arom-OMe3} + C^4 _{arom-OMe}); 7.28-6.47 (m, 3H, $\text{C}^{2'',4'',6''}$ _{arom-OMe}); 3.66 (s, 6H, 2xOCH₃), 3.59 (s, 6H, 2xOCH₃), 2.75 (CH_3); 2.47 (s, 3H, CH_3CO). ^{13}C NMR (CDCl_3): δ 173.0 ($\text{CH}_3\text{C=O}$), 168.1 (NC=O); 162.9 (C^3 _{arom-OMe}); 161.8 (C=N); 154.9 (C^4 _{thiazol}); 152.0 ($\text{C}^{3'',5''}$ _{arom-OMe3}); 143.5 (C^4 _{arom-OMe3}); 142.3 ($\text{C}^{1''}$ _{arom-OMe}); 132.1 (C^5 _{arom-OMe3}); 130.2 ($\text{C}^{1''}$ _{arom-OMe3}); 116.2 (C^6 _{arom-OMe}); 111.2 (C^4 _{arom-OMe}); 106.1 ($\text{C}^{2'',6''}$ _{arom-OMe3}); 104.5 (C^5 _{thiazol}); 101.2 ($\text{C}^{2''}$ _{arom-OMe}); 60.9 (OMe), 56.0 (OMe); 55.8 (2xOMe); 30.4 (CH_3CO); 14.7 (CH_3). EIMS 456. Anal. Calcd. for $\text{C}_{23}\text{H}_{24}\text{N}_2\text{O}_6\text{S}$ (456.51): C, 60.51; H, 5.30; N, 6.14. Found: C, 60.07; H, 5.19; N, 6.36%.

N-(5-Acetyl-3-(tert-butyl)-4-methylthiazol-2-ylidene)-2-chloro-4-nitrobenzamide (**2m**)

Yield: 67%; mp 141.142 °C. IR (KBr, ν : cm^{-1}): 3010, 1676, 1640 (C=O), 1632, 1555 (Ar-C=C), 1542 (asym NO₂), 1453 (C=N), 1343 (sym NO₂), 1316, 1292 (C-S), 1165 (C-N), 1152, 971, 718, 685. ^1H NMR (CDCl_3): δ 7.89-7.71 (m, 2H, $\text{C}^{3,5}$ _{arom}); 6.43 (dd, 1H, $J = 7.8, 0.9$ Hz, C^6 _{arom}); 2.65 (s, 3H, CH_3); 2.37 (s, 3H, CH_3CO); 1.17 (s, 9H, *tert*-Bu). ^{13}C NMR (CDCl_3): δ 172.4 ($\text{CH}_3\text{C=O}$), 170.1 (NC=O), 162.6 (C=N); 153.9 (C^4 _{thiazol}); 149.2 (C^1 _{arom}); 140.1 (C^4 _{arom}); 129.1 (C^2 _{arom}); 125.2 (C^3 _{arom}); 123.4 (C^5 _{arom}); 116.7 (C^6 _{arom}); 104.9 (C^5 _{thiazol}); 41.2 (C-CH₃); 30.0 (CH_3CO); 27.5 (3xCH₃); 15.0 (CH_3). EIMS 395. Anal. Calcd. for $\text{C}_{17}\text{H}_{18}\text{ClN}_3\text{O}_4\text{S}$ (395.86): C, 51.58; H, 4.58; N, 10.61. Found: C, 51.62; H, 4.61; N, 10.45%.

N-(5-Acetyl-3-(tert-butyl)-4-methylthiazol-2-ylidene)-3-chloro-4-fluorobenzamide (**2n**)

Yield: 83%; mp 144-145 °C. IR (KBr, ν : cm^{-1}): 2935, 1670, 1630 (C=O), 1632, 1555 (Ar-C=C), 1542 (asym NO₂), 1453 (C=N), 1343 (sym NO₂), 1316, 1292 (C-S), 1165 (C-N), 1152, 971, 718, 685. ^1H NMR (CDCl_3): δ 7.51-7.20 (m, 2H, $\text{C}^{5,6}$ _{arom}); 6.16 (m, 1H, C^2 _{arom}); 2.62 (s, 3H, CH_3); 2.39 (s, 3H, CH_3CO); 1.19 (s, 9H, *tert*-Bu). ^{13}C NMR (CDCl_3): δ 173.8 ($\text{CH}_3\text{C=O}$), 169.5 (NC=O), 162.7 (C=N); 153.5 (C^4 _{thiazol}); 149.0, 147.6 (d, $J_{\text{C}4,\text{F}} = 252$ Hz, C^4 _{arom}); 139.8, 139.1 (d,

$J_{C1,F} = 1.3$ Hz, C^4_{arom} ; 123.7, 122.0 ($J_{C2,F} = 26.2$ Hz, C^3_{arom}); 121.2, 120.1 (d, $J_{C6,F} = 12.6$ Hz, C^6_{arom}); 116.2, 114.3 ($J_{C5,F} = 25.8$ Hz, C^5_{arom}); 104.6 (C^5_{thiazol}); 30.3 (CH_3CO) 26.9 ($3 \times CH_3$); 14.6 (CH_3). EIMS 367/369. Anal. Calcd. for $C_{17}H_{18}ClFN_2O_2S$ (368.85): C, 55.36; H,

N-(5-Acetyl-4-methyl-3-styrylthiazol-2-ylidene)-2,3-dichloroenzamide (**2o**)

Yield: 83%; mp 93-94 °C. IR (KBr, ν : cm^{-1}): 1671, 1635 (C=O), 1632, 1555 (Ar-C=C), 1542 (asym NO_2), 1453 (C=N), 1343 (sym NO_2), 1316, 1292 (C-S), 1165 (C-N), 1152, 971, 718, 685. 1H NMR ($CDCl_3$): δ 7.64 (d, 1H, $J = 16.0$ Hz, $CHa=CHb$); 7.30-7.02 (m, 7H, C_{arom}); 6.95 (d, $J = 16.0$ Hz, $CHa=CHb$); 6.42 (m, 1H, $C^6_{\text{arom-Cl2}}$); 2.64 (s, 3H, CH_3); 2.41 (s, 3H, CH_3CO). ^{13}C NMR ($CDCl_3$): δ 173.9 ($CH_3C=O$); 164.0 (C=N); 160.1 (NC=O); 153.1 (C^4_{thiazol}); 149.0 ($HCa=CHb$); 142.8 ($C^1_{\text{arom-Cl2}}$); 135.4, 133.0, 131.6, 130.2, 128.3, 128.1, 126.2, 124.5, 120.3 ($C_{\text{arom}} + CHa=CHb$); 104.4 (C^5_{thiazol}); 30.3 (CH_3CO), 14.5 (CH_3). EIMS 431. Anal. Calcd. for $C_{21}H_{16}Cl_2N_2O_2S$ (431.33): C, 58.48; H, 3.74; N, 6.49. Found: C, 58.57; H, 3.66; N, 6.46%.

Table 1. *In vitro* anti-HIV-1 and HIV-2 activity of some new thiazol-2-ylidene benzamides

Comp.	Virus strain	EC ₅₀ ($\mu g\ ml^{-1}$)	CC ₅₀ ($\mu g\ ml^{-1}$)	SI
2a	III _B	>70.68	70.68	<1
	ROD	>70.68	70.68	<1
2b	III _B	>69.45	69.45	<1
	ROD	>69.45	69.45	<1
2c	III _B	>65.00	65.00	<1
	ROD	>65.00	65.00	<1
2d	III _B	>65.63	65.63	<1
	ROD	>65.63	65.63	<1
2e	III _B	>125.00	>125.00	X1
	ROD	>125.00	>125.00	X1
2f	III _B	>53.30	53.30	<1
	ROD	>53.30	53.30	<1
2g	III _B	> 5.08	5.08	<1
	ROD	> 5.08	5.08	<1
2h	III _B	>103.08	103.08	<1
	ROD	>103.08	103.08	<1
2i	III _B	>75.38	75.38	<1
	ROD	>75.38	75.38	<1
2j	III _B	>60.68	60.68	<1
	ROD	2.44	60.68	25
2k	III _B	>111.00	≥ 111.00	<orX1
	ROD	>111.00	≥ 111.00	<orX1
2l	III _B	>125.00	>125.00	X1
	ROD	>125.00	>125.00	X1
2m	III _B	>125.00	>125.00	X1
	ROD	20.55	>125.00	>6
2n	III _B	>49.38	49.38	<1
	ROD	1.89	49.38	26
2o	III _B	>125.00	>125.00	<1
	ROD	>125.00	>125.00	<1
DDN/AZT	III _B	= 0.00147	> 25	> 17003
	ROD	= 0.000341	> 25	> 73258

^a Anti-HIV-1 activity measured with strain III_B; ^b anti-HIV-2 activity measured with strain ROD;

^c compound concentration required to achieve 50 % protection of MT-4 cells from the HIV-1 and 2-induced cytopathogenic effect; ^d compound concentration that reduces the viability of mock-infected MT-4 cells by 50 %; ^e SI: selectivity index (CC_{50}/EC_{50}).

***In vitro* anti-HIV assay**

Compounds **4**, **5c,d** and **5f-l** were tested for their *in vitro* anti-HIV-1 (strain IIIB) and HIV-2 (strain ROD) activity in human T-lymphocyte (MT-4) cells. based on MTT assay [29]. The results are summarized in Table 1, in which the data for azidothymidine (DDN/AZT) [30] were included for comparison purposes. Compound induced cytotoxicity was also measured in MT-4 cells parallel with the antiviral activity.

Compounds **2j** and **2n** were found to be the only compounds from the series inhibiting HIV-2 replication in a cell culture, which showed an EC₅₀ of 2.44 µg ml⁻¹ and 1.89 µg ml⁻¹ with CC₅₀ of 60.68 µg ml⁻¹ and 49.38 µg ml⁻¹, respectively, resulting in a selectivity index of 25 and 26.

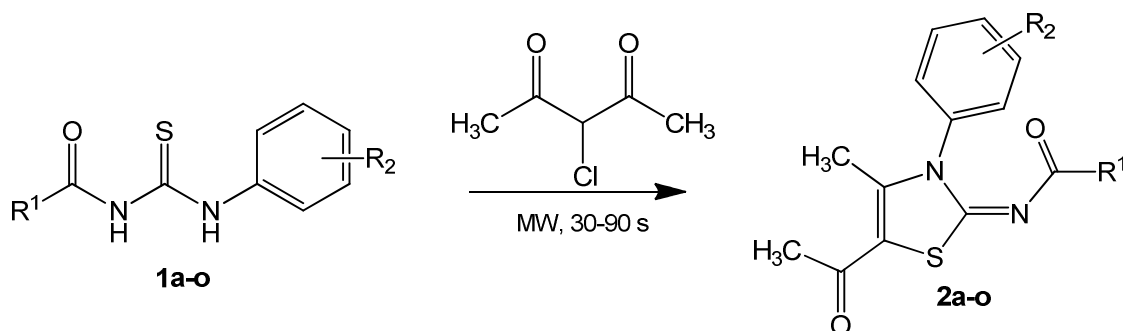
Based on the chemical structure of compounds **2j** and **2n**, these molecules can be proposed to act as NNRTIs. However, the activity spectrum that is limited to HIV-2 is completely in contrast with what was observed with NNRTIs. On the other hand, **2m** showed some activity against HIV-2 with IC₅₀ 20.55 µg ml⁻¹ and a CC₅₀ >125 µg ml⁻¹, but with a low selectivity (SI >6).

The synthesis of new analogues of thiazol-2-ylidene substituted benzamide may lead to the discovery of more potent and selective analogues that will allow the elucidation of their molecular mode-of-action.

RESULTS AND DISCUSSION

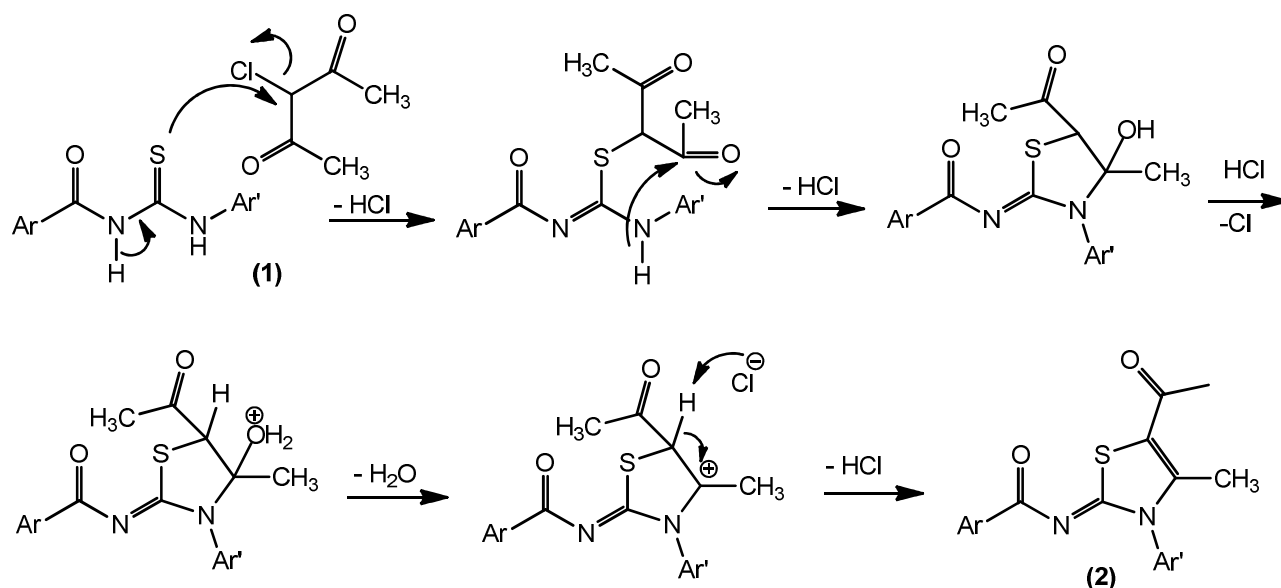
Synthesis

The cyclocondensation of 1-aryl-3-arylthioureas with carbonyl compounds bearing an α -H is usually achieved in the presence of base in dry solvents like acetone, dichloromethane or acetonitrile in an inert atmosphere [26-28]. However, in the conventional heating, such condensation required longer reaction time (3-5 h reflux). Microwave irradiation can incredibly shorten the reaction time with increasing in product yields and purities. Thus, cyclization of thioureas **1a-o** with 3-chloropentane-2,4-dione under microwave irradiation (MWI) for 10-30 seconds led to the formation of the corresponding *N*-(5-acetyl-4-methyl-3-(substituted phenyl)-thiazol-2-ylidene)-4-methyl substituted benzamides **2a-o** in good to excellent yields (65-83%). The precursor were prepared according to the procedure reported earlier involving the reaction of a aryl isocyanate with a suitable substituted aniline [27]. The structures **2a-o** were confirmed by the IR, ¹H-, ¹³C NMR and mass spectra. The IR spectra showed absorptions at 1440-1480 cm⁻¹ and 1630-1660 cm⁻¹ were characterized for the C=N and acetyl stretchings, respectively. In addition, the disappearance of the free and associated thiourea NH stretching absorption at the region 3351-3200 cm⁻¹ as well as the thiocarbonyl (C=S) group at the region 1630-1660 cm⁻¹, is an indicative for the cyclization of thiourea molecules **1a-o** to the corresponding products **2a-o**. These newly synthesized compounds showed a similar NMR spectral pattern, especially for the CH₃ and CH₃CO groups at C-4 and C-5 of the thiazoline ring at the region δ 2.62-2.74 and 2.37-2.47 ppm, respectively. In the ¹³C-NMR spectra of **2a-o**, the resonances at the region δ 175.2-171.9 ppm were assigned to the carbon atom of the carbonyl group (CH₃C=O) at C-5 of the thiazole ring, while the two high-field signals at the region δ 170.1-164.6 ppm and δ 162.7-159.5 ppm were attributed to NC=O and C=N, respectively. C-4 and C-5 of the thiazole ring displayed signals at the region δ 154.9-150.7 ppm and δ 105.1-104.0 ppm, respectively. CH₃ and CH₃ of the acetyl group at C-4 and C-5 were resonated at the region δ 15.0-14.5 ppm and δ 30.5-30.0 ppm, respectively. The carbons of aromatic ring and other substituents were assigned.



	R ¹	R ²		R ¹	R ²
1a,2a	ph	4-ph	1i,2i	3,4,5-tri-OCH ₃ -Ph	4-F
1b,2b	4-NO ₂ -Ph	3-F	1j,2j	3,4,5-tri-OCH ₃ -Ph	3-Cl
1c,2c	4-NO ₂ -Ph	3-Cl, 4-F	1k,2k	3,4,5-tri-OCH ₃ -Ph	2-F, 3-Cl
1d,2d	4-F-Ph	4-F	1l,2l	3,4,5-tri-OCH ₃ -Ph	3-OMe
1e,2e	2-Br-Ph	3,4-di-Cl	1m,2m	<i>t</i> -butyl	4-NO ₂ , 2-Cl
1f,2f	2-Br-Ph	3,5-di-Cl	1n,2n	<i>t</i> -butyl	4-F, 3-Cl
1g,2g	3,4,5-tri-OCH ₃ -Ph	2-F	1o,2o	PhCH=CH-	2,3-di-Cl
1h,2h	3,4,5-tri-OCH ₃ -Ph	3-F			

Scheme-1. Synthesis of (*E*)-*N*-(5-acetyl-4-methyl-3-(substituted phenyl)-thiazol-2(3*H*)-ylidene)-4-methyl substituted benzamides



Scheme 2

The mechanism of heterocyclization possibly involves the attack of N-1 proton of (1) with low pK_a via nucleophilic sulphur to the halobearing carbon of the 3-chloro-pentane-2,4-dione to give isothiurea intermediate, together with the attack of N-3 to the carbonyl group resulting in the intramolecular cyclization. Proton transfer and dehydration was followed by E1 elimination to yield (2) (Scheme 2).

CONCLUSION

In conclusion, the above data suggest that the substitution of aromatic ring carrying by thiazol-2-ylidene benzamide backbone, by some potential groups would enhance the anti-HIV-2 activity. Such groups are 3,4,5-trimethoxy or halogen atom (fluorine or chlorine).

Acknowledgements

The author gratefully acknowledges the research grant from Quaid-I-Azam University Islamabad.

REFERENCES

- [1] A. N. Krasovskii, E. I. Bogatyrev, I. I. Soroka, P. M. Kochergin, N. P. Grin, *Khim. Farm. Zhurnal*, **1977**, ii, 51.
- [2] J. S. Song, T. Moon, K. D. Nam, J. K. Lee, H. G. Hahn, E. J. Choic, C. NoYoon, *Bioorg. Med. Chem. Lett.* **2009**, 18, 2133.
- [3] I. Hutchinson, S. A. Jennings, B. R. Vishnuvajjala, A. D. Westwell, M. F. G. Stevens, *J. Med. Chem.*, **2002**, 45, 744.
- [4] D. Hargrave, F. K. Hess, J. T. Oliver, *J. Med. Chem.*, **1983**, 26, 1158.
- [5] B. A. Steinbaugh, B. L. Batley, C. A. Painchaud, S. T. Rapundalo, B. M. Michniewicz, S. C. J. Olson, S. C. J. *J. Med. Chem.*, **1992**, 35, 2562.
- [6] K. Sharma, S. N. Sawhney, A. Gupta, G. B. Singh, S. Bani, S. *Indian J. Chem.*, **1998**, 37B, 376.
- [7] K. Tsuji, H. Ishikawa, *Bioorg. Med. Chem. Lett.*, **1994**, 4, 1601.
- [8] B. N. Naidu, M. E. Sorenson, Y. Zhang, O. K. Kim, J. D. Matiskella, J. A. Wichtowski, T. P. Connolly, W. Li, K. S. Lam, J. J. Bronson, M. J. Pucci, J. M. Clark, Y. Ueda, Y. *Bioorg. Med. Chem. Lett.*, **2004**, 14, 5573.
- [9] P. Vicini, A. Geronikaki, K. Anastasia, M. Incertia, F. Zania, F. *Bioorg. Med. Chem.*, **2006**, 14, 3859.
- [10] a) A. Zhang, H. Kayser, P. Maienfisch, J. E. Casida, *J. Neurochem.*, **2000**, 75, 1294.
b) Maienfisch, P.; Haettenschwiler, J.; Rindlisbacher, A.; Decock, A.; Wellmann, H.; Kayser, H. *Chimia*, **2003**, 57, 710.
- [11] S. J. Hosseinimehr, A. Shafiee, H. Mozdarani, S. Akhlagpour, M. Froughizadeh, *J. Radiat. Res.*, **2002**, 43, 293.
- [12] S. Bae, H.-G. Hahn and, K. D. Nam, *J. Comb. Chem.*, **2005**, 7, 826.
- [13] D.-S. Kim, Y.-M. Jeong, I.-K. Park, H.-G. Hahn, H.-K. Lee, *Biol. Pharm. Bull.*, **2007**, 30, 180.
- [14] N. Pietrancosta, A. Moumen, R. Dono, P. Lingor, V. Planchamp, F. Lamballe, M. Bahr, Jean-L Kraus and F. Maina, *J. Med. Chem.* **2006**, 49, 3645.
- [15] S. M. Sondhi, J. Singh, A. Kumar, H. Jamal, P. P. Gupta, *Eur. J. Med. Chem.*, **2008**, 43, 2824.
- [16] A. Manaka, M. Sato, M. Aoki, M. Tanaka, T. Ikeda, Y. Toda, Y. Yamanane, S. Nakaike, *Bioorg. Med. Chem. Lett.*, **2001**, 11, 1031.
- [17] S. M. Sondhi, N. Singh, A. M. Lahoti, K. Bajaj, A. Kumar, O. Lozach, L. Meijer, *Bioorg. Med. Chem.*, **2005**, 13, 4291.
- [18] Y. Sanemitsu, S. Kawamura, J. Satoh, T. Katayama, S. Hashimoto, *J. Pestic. Sci.*, **2006**, 31, 305.
- [19] A. Manaka, T. Ishii, K. Takahashi, M. Sato, *Tetrahedron Lett.*, **2005**, 46, 419.
- [20] M. Han, K. D. Nam, D. Shin, N. Jeong, H.-G. Hahn, *J. Comb. Chem.* **2010**, 12, 518.
- [21] S. G. Patil, R. R. Bagul, M. S. Swami, N. Kotharkar K. Darade, *Chinese Chem. Lett.*, **2011**,

22, 883.

[22] H. Shi, S. Zhang, Y. Lin, W. Hu, C. Cai, *J. Heterocycl. Chem.* **2011**, 48, 1061.

[23] A. Saeed, N. A. Al-Masoudi, A. A. Ahmed, C. Pannecouque, *Z. Naturforsch.* **2011**, 66b, 512.

[24] A.Saeed, S. Zaman, M. Bolte, *Synth. Comm.* **2008**, 38, 2185.

[25] A.Saeed, M. Bolte, *J. Crystalliz. Process Techn.* **2011**, 1, 41.

[26] A. Saeed, M. Parvez, *Cent. Eur. J. Chem.* **2005**, 3, 780.

[27] A. Saeed and M. Parvez, *J. Heterocycl. Chem.* **2006**, 43, 1027.

[28] R.-S. Zeng, J.-P. Zou, S.-J. Zhi, J. Chen, Q. Shen, *Org. Lett.* **2003**, 5, 1657.

[29] R. Pauwels, J. Balzarini, M. Baba, R. Snoeck, D. Schols, P. Herdewijn, J. Desmyter, E. De Clercq, *J. Virol. Methods* **1988**, 20, 309.

[30] H. Mitsuya, K. J. Weinhold, P. A. Furman, M. H. St. Clair, S. N. Lehrman, R. C. Gallo, D. Bolognesi, D. W. Barry, S. Broder, *Proc. Natl. Acad. Sci. USA* **1985**, 82, 7096.