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Investigation of 1, 3, 4-Oxadiazole Scaffold as Potentially Active Compounds

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ABSTRACT: In the present work, various Schiff's bases of isoniazid bearing 1, 3, 4-oxadiazole nucleus were synthesized. These compounds were purified, characterized and evaluated *in vitro* for antibacterial, antifungal and antiviral activities. Compound **5** showed better biological profile.

KEYWORDS: 2, 5-Disubstituted-1,3,4-Oxadiazole; Schiff's base; antibacterial; antifungal; antiviral activity

Introduction

Oxadiazoles have occupied a unique place in the field of medicinal chemistry due to its wide range of activities. The oxdiazole derivatives have been reported to have various biological activities including anti-microbial[1], anti-cancer[2], anti-inflammatory[3], anti-infective[4] and anti HIV[5] etc. Particularly, 2,5-disubstituted-1,3,4-oxadiazoles have grabbed the most attention during last three decades as potential biomolecules. Also, other structural modifications like conversion into Mannich bases, Schiff's bases have yielded better results in terms of pharmacological activities than the unsubstituted heterocyclic ring. It is seen from the current literature that pyridine congeners are associated with different biological properties. The molecules comprising of pyridine and 1,3,4- oxadiazole scaffold have been attracting wide spread attention due to their varied pharmacological properties such as anti bacterial[6], anti-angiogenetics[7], tyrosinase inhibitor[8], antimitotic agents[9], cardiovascular[10], anti-HIV[11]. Schiff's bases of pyridine have also been found bioactive[12,13].

Inspired from these facts, we attempted to synthesize new heterocyclic systems containing 1, 3, 4-oxadiazoles linked with 4-pyridyl and conversion into Schiff's bases. The incorporation of heterocyclic moieties in carbohydrates has been gaining impetus[14-16]. So we also wished to prepare some 5-(4-pyridyl)-1, 3, 4-oxadiazole derivatives containing carbohydrate. Our interest in the synthesis of such compounds was to shed some light on their biological study as antibacterial, antifungal and antiviral agents.

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Results and Discussion

Isoniazid was treated with carbon disulfide in alcoholic potassium hydroxide at reflux temperature to afford corresponding oxadiazole **1**. The structure of **1** was confirmed by IR in which strong bands for -C–O–C, -C=S, and -C=N stretching were observed at 1130–1137, 1235–1245 and 1610–1647 cm^{-1}, respectively. Reaction of **1** with ethyl chloroacetate yielded corresponding ester **2** which was confirmed by -C=O stretching at 1690–1700 cm^{-1}. Compound **3** was obtained by treatment of **2** with hydrazine hydrate in ethanol. Its IR showed -C=O and -NH stretching bands at 1655–1670 and 3110–3223 cm^{-1}, respectively. The targeted compounds, N'-substituted-2-[(5-pyridin-4-yl-1,3,4-oxadiazol-2-yl)thio]aceto hydrazide **(4-13)** were synthesized employing reaction with five different aldehydes and sugars in presence of either base or acid (Scheme 1). The physical data of compounds **4-13** are presented in **Table 1**.

Table 2 shows that the compounds **4**, **5, 8, 9, 13** exhibited good antibacterial activities against *S. aureus* while compounds **6, 8, 9, 10** were effective against *E. coli*. Compound **5** possessing chloro group showed promising activity against *S. aureus* but did not exhibit any activity against *E. coli.* Compound **9** was also active against both the organisms while others were either active against one of the microorganism or inactive.

Table 1 Physical data of titled compounds

Compound	R	Mol. form. (Mol. Wt.)	m.p.(°C) (Yield %)	IR cm^{-1}
1	-	$C_7H_5N_3OS$ (179.20)	271-272 (83)	3051(-CH of pyridyl), 3033 (NH), 1552 (C=N), 1369 (C=S),1022 (C-O-C).
2	-	$C_{11}H_{11}N_3O_3S$ (265.28)	b.p.:130-131 (87.25)	3419 (NH), 2984 (*Ar* C-H), 1731 (C=0 *str*).
3	-	$C_9H_9N_5O_2S$ (251.26)	172-173 (71.56)	3269, (NH *str*), 3045 (*Ar* C-H), 1672 (C=O), 1539 (NH).
4	Phenyl	$C_{16}H_{13}N_5O_2S$ (339.37)	64-65 (81.60)	3055, 2943 (*Ar* C-H), 1687 (C=O),1622 (N=C *str*), 1533 (NH).
5	2-Chlorophenyl	$C_{16}H_{12}N_5O_2SCl$ (373.81)	134-136 (68)	3064, 2954 (*Ar* C-H), 1668 (C=O), 1612 (N=C), 1434 (NH).
6	4-Methoxyphenyl	$C_{17}H_{15}N_5O_3S$ (369.39)	154-155 (82.76)	2925, (*Ar* C-H), 1656 (C=O), 1508 (N=C), 1461 (NH).
7	4-Chlorophenyl	$C_{16}H_{12}N_5O_2SCl$ (373.81)	204-205 (82.44)	3049, 2943 (*Ar* C-H), 1625 (C=O), 1593 (N=C *str*), 1487 (NH).
8	3-Nitrophenyl	$C_{16}H_{12}N_6O_4S$ (384.36)	79-80 (87)	3184, 3074 (*Ar* C-H), 1610 (C=O), 1597 (NH), 1350 (N=O *str*).
9	*D-glucose* -[1,2,3,4,5-pentahydroxypenta-1-yl]	$C_{15}H_{19}N_5O_7S$ (413.40)	160-162 (70.20)	3334 (OH), 3053 (C-H), 1678 (CO), 1604 (NH) 1549 (N=C *str*).
10	*D-Galactose*-[1,2,3,4,5-pentahy droxypenta-1-yl]	$C_{15}H_{19}N_5O_7S$ (413.40)	151-153 (58.51)	3186 (OH), 3032 (*Ar* C-H), 1662 (CO), 1527 (N=C *str*).
11	*D-Arabinose*-[1,2,3,4-tetrahydroxybuta-1-yl]	$C_{14}H_{17}N_5O_6$ (383.37)	125-127 (68.80)	3246 (OH), 2935 (*Ar* C-H), 1602 (N=C *str*),1672 (C=O), 1552 (NH).
12	*D-Ribose*-[1,2,3,4-tetrahydroxybuta-1-yl]	$C_{14}H_{17}N_5O_6S$ (383.37)	161-163 (71.08)	3325 (OH), 2933 (*Ar* C-H), 1666 (C=O), 1603 (N=C *str*).
13	*D-Xylose*-[1,2,3,4-tetrahydroxybuta-1-yl]	$C_{14}H_{17}N_5O_6S$ (383.37)	177-178 (67.70)	3304 (OH), 2933 (*Ar* C-H), 1670 (C=O),1604 (N=C), 1529 (NH).

Table 2 *In vitro* antibacterial activity of compounds **4-13**

Compound	Zone of inhibition (mm)			
	S. aureus		*E. coli*	
	100#	**200**	**100**	**200**
4	15	22	-	10
5	16	23	-	9
6	-	14	12	16
7	-	-	-	-
8	14	20	12	17
9	15	22	14	20
10	-	-	12	18
11	-	12	-	10
12	-	10	-	-
13	17	24	-	-
Ampicillin	17	-	14	-
DMSO	-	-	-	-

Concentration is expressed in µg /mL.

The antifungal activity of targeted compounds is mentioned in **Table 3** which shows that compounds **4, 5, 10, 11, 12** were effective against *C. albicans* and compounds **7, 8, 9, 12** were active against *A. niger*. Sugar containing molecules did not show any significant antifungal activity which can be attributed to its low penetration power into the cell wall due to hydrophilic nature.

Anti HIV activity of targeted molecules is shown in **Table 4.** Compound **9** showed better activity against HIV 2 strain with SI value of 3 whereas other compounds were inactive. In this case also, the sugar containing molecules did not show any significant activity.

The results of antiviral activities against some other viruses like para-influenza-3 virus, reovirus-1, sindbis virus, coxsackie B4 virus, punta toro virus in African green monkey kidney (Vero) human embryonic lung fibroblast (HEL) and is reported in **Table 5** and **Table 6.** It was found that compounds **4, 5, 6** exhibited good antiviral activity.

Table 3 *In vitro* antifungal activity of compounds **4-13**

Compound	Zone of inhibition (mm)			
	C. albicans		*A. niger*	
	100#	200	100	200
4	13	20	-	-
5	12	18	-	-
6	11	16	-	11
7	-	-	11	16
8	10	15	10	15
9	-	-	10	14
10	12	17	-	10
11	12	19	-	-
12	-	-	10	14
13	12	17	-	-
Fluconazole	13	-	11	-
DMSO	-	-	-	-

Concentration is expressed in µg /mL.

Table 4 Anti HIV activity of compounds **4-1**

Compd.	HIV 1 (µg/ml)		SI	HIV 2(µg/ml)		SI
	IC50	CC50		IC50	CC50	
4	>50	=50	<1	> 57	=57	<1
5	>65	=65	<1	>60	=60	<1
6	>125	>125	X1	>125	>125	X1
9	>125	>125	X1	>38	>125	>3
10	>125	>125	X1	>125	>125	X1
11	>125	>125	X1	>125	>125	X1
12	>125	>125	X1	>125	>125	X1
13	>125	>125	X1	>125	>125	X1
Nevirapine (µM)	0.25	>200	>800	-	-	-
DDI (µM)	5.37	>529	>98	2.71	>529	>195

Table 5 Cytotoxicity and antiviral activity of compounds **(4-13)** in Vero cell cultures:

Compd.	Minimum cytotoxic concentration[a] (µg/mL)	EC_{50}[b] (µg/mL)				
		Para-influenza-3 virus	Reovirus-1	Sindbis virus	Coxsackie B4 virus	Punta Toro virus
4	20	>20	>20	>20	>20	>20
5	100	>20	>20	>20	>20	>20
6	100	>20	>20	>20	>20	>20
9	>100	>100	>100	>100	>100	>100
10	>100	>100	>100	>100	>100	>100
11	>100	>100	>100	>100	>100	>100
12	>100	>100	>100	>100	>100	>100
13	>100	>100	>100	>100	>100	>100
Ribavirin (µM)	>250	146	250	>250	>250	146

[a]Concentration required to cause a microscopically detectable alteration of normal cell morphology.

[b]Concentration required to reduce virus-induced cytopathogenicity by 50 %.

Table 6 Cytotoxicity and antiviral activity of compounds **(4-13)** in HEL cell cultures:

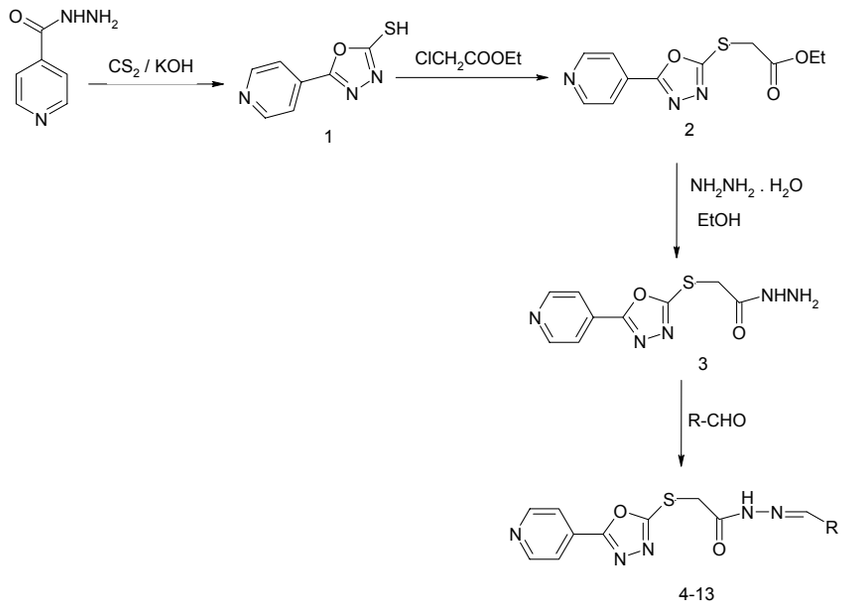
Compd.	Minimum cytotoxic concentration[a] (µg/mL)	EC_{50}[b] (µg/ml)			
		Herpes simplex virus-1	Herpes simplex virus-2	Vaccinia Virus	Vesicular stomatitis virus
4	>100	50	100	45	> 100
5	100	>20	>20	>20	>20
6	>100	>100	>100	>100	>100
9	>100	>100	>100	>100	>100
10	>100	>100	>100	>100	>100
11	>100	>100	>100	>100	>100
12	>100	>100	>100	>100	>100
13	>100	>100	>100	>100	>100
Brivudin (µM)	>250	0.04	50	2	250
Cidofovir (µM)	>250	1	1	2	>250
Ganciclovir (µM)	>100	0.02	0.07	>100	>100

[a]Concentration required to cause a microscopically detectable alteration of normal cell morphology.

[b]Concentration required to reduce virus-induced cytopathogenicity by 50 %.

Experimental

All the chemicals were obtained from commercial suppliers and used without further purification. All the melting points were determined on 'Veego' VMP-D apparatus and are uncorrected. The IR spectra were recorded in the range of 4000—400 cm^{-1} using KBr discs on an FT-IR 8400 Shimadzu spectrometer.^{1}H NMR spectra were recorded on Varian Mercury (300 MHz) spectrometer in $CDCl_3$ or DMSO- d_6 as solvent using trimethylsilane (TMS) as an internal reference standard and values are expressed in δ ppm. Mass spectra and elemental analyses were recorded at IIT, Mumbai. Elemental analyses were performed for C, H, N and were found within ±0.4% of theoretical values.



Scheme 1 Synthesis of the titled compounds.

Compd.	R
4	Phenyl
5	2-Chlorophenyl
6	4-Methoxyphenyl
7	4-Chlorophenyl
8	3-Nitrophenyl
9	*D-glucose* -[1,2,3,4,5-pentahydroxypenta-1-yl]
10	*D-Galactose*-[1,2,3,4,5-pentahydroxypenta-1-yl]
11	*D-Arabinose*-[1,2,3,4-tetrahydroxybuta-1-yl]
12	*D-Ribose*-[1,2,3,4-tetrahydroxybuta-1-yl]
13	*D-Xylose*-[1,2,3,4-tetrahydroxybuta-1-yl]

Synthesis

Synthesis of 5-(pyridin-4-yl)-1,3,4-oxadiazole-2(3H)-thione (1)[17, 18]

In the solution of potassium hydroxide (6.13 g, 0.010 mole) in water (36 mL) was added a mixture of isoniazide (15 g, 0.010 mole), carbon disulphide (8.75 g, 0.010 mole) and absolute ethanol (100 mL). The mixture was refluxed till complete evolution of H_2S gas took place which was monitored by blackening of moist lead acetate paper. It required 9-10 h. The solvent was removed under vacuum and the residue was poured into ice-cold water. It was filtered to remove suspended impurities and acidified with 10% hydrochloric acid and the solid thus precipitated was filtered, washed twice with cold water and recrystallised with 50% ethanol to give **1** as yellow crystals. ^{1}HNMR (DMSO—d_6): δ 8.80 (d, 2H, pyridyl), 7.80 (d, 2H, pyridyl), 7.60 (s, 1H, NH). Anal. Calcd. for $C_7H_5N_3OS$: C, 46.87; H, 27.90; N, 23.43. Found: C, 46.80; H, 27.86; N, 23.40.

Synthesis of ethyl [(5-pyridin-4-yl-1,3,4-oxadiazol-2-yl)thio]acetate (2)[19,20]

To a solution of **1** (8.9 g, 0.050 mole) in absolute ethanol (40 mL), were added ethyl bromoacetate (8.35 g, 0.050 mole) and anhydrous potassium carbonate (3 g). The reaction mixture was refluxed for 14-16 h. The mixture was filtered off and the excess of solvent was removed under reduced pressure to give red colour liquid (**2**).

Synthesis of 2-[(5-pyridin-4-yl-1,3,4-oxadiazol-2-yl)thio]acetohydrazide (3) [21,22]

To a solution of **2** (2.83 g, 0.01 mole) in ethanol (15 mL), hydrazine hydrate (1 g, 0.02 mole) was added and the reaction mixture was refluxed for 6-7 h. The excess of solvent was removed and then diluted with ice cold water to yield white precipitate which was collected by filtration, washed with ice cold water, dried and recrystallised from ethanol.

Synthesis of N'-substituted-2-[(5-pyridin-4-yl-1,3,4-oxadiazol-2-yl)thio]acetohydrazide (4-13):

1) **Using aromatic aldehyde (4- 8)** [23,24]

To a suspension of **3** (2.51 g, 0.01 mole) in 15 mL ethanol, were added appropriate aromatic aldehyde (0.015 mole), glacial acetic acid (5 mL) and the reaction mixture was refluxed for 2-3h. Then it was cooled and poured over crushed ice. The precipitated solid thus obtained was filtered, washed with ice-cold water and recrystallised from absolute ethanol.

2) **Using aldose sugar (9 – 13)** [25]

A solution of the sugar (0.01 mole) in 3 mL water was added in the solution of **3** (2.51 g, 0.01 mole) in 20 mL ethanol along with glacial acetic acid (5 mL). This mixture was refluxed for 4–5 h. The excess of ethanol was evaporated under vacuum and the residue was triturated with diethyl ether. The product thus obtained was filtered off, washed with ether, and recrystallised from ethanol. Analytical data of compounds **4-13** is as follows:

N'-[phenylmethylidene]-2-{[5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl]sulfanyl}acetohydrazide (4)

^{1}HNMR ($CDCl_3$): δ 11.30 (s, 1H, NH), 8.80 (d, 2H, pyridyl), 8.42 (s, 1H, N=CH), 7.80 (d, 2H, pyridyl), 7.50-7.00 (m, 5H, Ar-H), 4.10 (s, 2H, SCH_2). Anal.Calcd. for $C_{16}H_{13}N_5O_2S$: C, 56.57; H, 3.83; N, 20.62. Found: C, 56.50; H, 3.80; N, 20.58.

N'-[(2-chlorophenyl)methylidene]-2-{[5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl]sulfanyl} acetohydrazide (**5**):

375 (M+1, 16%), 374 (M, 64%), 235 (M-139, 58%) 220 (M -154, 100%), 146 (M-228, 81%). Anal. Calcd for $C_{16}H_{12}N_5O_2SCl$: C, 51.47; H, 3.21; N, 18.76. Found: C,51.40; H, 3.18; N, 18.70.

N'-[(4-methoxyphenyl)methylidene]-2-{[5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl]sulfanyl} acetohydrazide (**6**) :

^{1}HNMR ($CDCl_3$): δ 11.20 (s, 1H, NH), 8.90 (d, 2H, pyridyl), 8.40 (s, 1H, N=CH), 7.50–7.30 (m, 4H, phenyl ring), 3.70 (s, 3H, p-OCH_3), 4.20 (s, SCH_2).

N'-[(4-chlorophenyl)methylidene]-2-{[5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl]sulfanyl} acetohydrazide (**7**) :

^{1}HNMR (DMSO-d_6) : δ 11.30 (s, 1H,NH), 8.80 (d, 2H, pyridyl), 8.30 (s, 1H, N=CH), 7.70 (d, 2H, pyridyl), 7.50-6.90 (m, 4H, Ar-H), 3.80 (s, 2H, SCH_2).

N'-[(3-nitrophenyl)methylidene]-2-{[5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl]sulfanyl} acetohydrazide (**8**) :

Anal. Calcd. for $C_{16}H_{12}N_6O_4S$: C, 50.00; H, 3.15; N, 21.86. Found: C, 50.51; H, 3.11; N, 21.73.

Aldehydo-D-glucose N'-[2,3,4,5,6-pentahydroxyhexylidene]-2-{[5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl]sulfanyl}acetohydrazide (**9**) :

^{1}HNMR (DMSO-d_6) : δ 11.10 (s, NH), 8.70 (d, 2H, pyridyl), 8.20 (s, 1H, N=CH), 7.70 (d, 2H, pyridyl), 7.40 (d, H-1), 4.70–4.40 (br, s, 5-OH), 4.10 (s, SCH_2), 3.89–3.44 (m, H-2, H-3, H-4, H-5, H-6).

Aldehydo-D-galactose N'-[2,3,4,5,6-pentahydroxyhexylidene]-2-{[5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl]sulfanyl}acetohydrazide (**10**):

413 (M+, 39%), 235 (M-178, 42%), 220 (M-193, 74%),193 (M-220, 100%), 146 (M-267, 55%). Anal. Calcd. for $C_{15}H_{19}N_5O_7S$: C, 43.54; H, 4.62; N, 16.92. Found: C, 43.38; H, 4.59; N, 16.88.

Aldehydo-D-arabinose 2-{[5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl]sulfanyl}-N'-[2,3,4,5 tetrahydroxypentylidene]acetohydrazide (**11**) **:** .

Anal. Calcd. for $C_{14}H_{17}N_5O_6S$: C, 43.86; H, 4.47; N, 18.27. Found: C, 43.80; H, 4.45; N, 18.20.

Aldehydo-D-ribose 2-{[5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl]sulfanyl}-N'-[2,3,4,5-tetrahydroxypentylidene]acetohydrazide (**12**) :

Anal. Calcd for $C_{14}H_{17}N_5O_6S$: C, 43.86; H, 4.47; N, 18.27. Found: C, 44.01; H, 4.35; N, 18.59.

Aldehydo-D-xylose 2-{[5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl]sulfanyl}-N'-[2,3,4,5-tetrahydroxypentylidene]acetohydrazide (13) :

Anal. Calcd for $C_{14}H_{17}N_5O_6S$: C, 43.86; H, 4.47; N, 18.27. Found: C, 44.07; H, 4.45; N, 18.56.

Biological Activity

Antibacterial activity

The *in vitro* antibacterial activity against *S. aureus* and *E. coli*. was determined by cup-plate method at 100 and 200 µg/mL concentrations using ampicillin as standard. The tests were repeated thrice to confirm the findings and the average is reported in **Table 2.**

Anti-fungal activity

The *in vitro* antifungal activity of titled compounds (100 and 200 µg/mL) was carried out against *C. albicans* and *A. niger* using fluconazole as standard. The tests were repeated thrice to confirm the findings and the average is reported in **Table 3.**

Anti-viral activities

1) Anti HIV Activity

The anti-HIV activity of the titled was performed against wild-type HIV-1 strain IIIB and HIV-2 ROD in MT-4 cells by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay using nevirapine [26] as standard. These compounds were also subjected to Cytotoxicity studies in uninfected MT-4 cells by same assay.

The inhibitory concentration of compounds was expressed as the concentration that caused 50% inhibition of viral cytopathogenicity (IC50) without direct toxicity to the cells. Cytotoxicity of the compounds was evaluated in parallel with their anti-viral activity. The cytotoxic concentration (CC50) of the compounds was monitored based on the growth of non-infected cells by the trypan blue exclusion method and corresponded to the concentration required to cause 50% cell death. The results, expressed as CC50, IC50 and SI (selectivity, given by the CC50/IC50 ratio) values, are summarized in **Table 4.**

2) Other antiviral activities:

The antiviral potential of titled compounds against other viruses like Herpes simplex virus-1, Herpes simplex virus-2, Vaccinia virus, Vesicular stomatitis virus-1 and Para-influenza-3 virus, Reovirus-1, Sindbis virus, Coxsackie B4 virus, Punta Toro virus in human embryonic lung fibroblast (HEL) and African green monkey kidney (Vero) is reported in **Table 5** and **Table 6.**

References

[1] (a) Frank, P.V.; Girish, K.S.; Kalluraya, B. J. Chem. Sci., 2007, 119, 41. (b) Kadi, A.A.; El-Brollosy, N.R.; Al-Deeb, O.A.; Habib, E.E.; Ibrahim, T.M.; El-Emam, A.A. Eur. J. Med. Chem., 2007, 42, 235.

[2] (a) Somani, R.R.; Shirodkar, P.Y.; Kadam, V.J. Lett. Drug Desi. Disco., 2008, 5, 348.

(b) Ouyang, X.; Patnitski, E. etal. Bioorg. Med. Chem. Lett., 2006, 16, 1191.

[3] Bhandari, S. .; Bothara, K.G.; Raut, M.K.; Patil, A.A.; Sarkate, A.P.; Mokale, V.J. Bioorg. Med. Chem., 2008, 16, 1822.

[4] Kucukguzel, S.G.; Kucukguzel, I.; Tatar, E.; Rollas, S.; Sahin, F.; Gulluce, M.; De Clercq, E.; Kabasakal, L. Eur. J. Med. Chem., 2007, 42, 893.

[5] Muhammad, Z.; Rashid, I.; Najim, A.A.; Javid, H. Z.; Muhammad, A. ChemInform, 2007, 38, Published Online.

[6] Kim, R.M.; Rouse, E.A.; Chapman, K.T.; Schleif, W.A.; Olsen, D.B.; Stahlhut, M.; Rutkowski, C.A.; Emini, E.A.; Tata, J.R. Bioorg. Med. Chem. Lett., 2004, 14, 4651.

[7] Navarrete-Vazquez, G.; Molina-Salinas, G.M.; Duarte-Fajardo, Z.V.; Vargas-Villarreal, J.; Estrada-Soto, S.; Gonzalez-Salazar, F.; Hernandez-Nunez, E.; Said-Fernandez, S. Bioorg. Med. Chem. Lett., 2007, 15, 5502.

[8] Kiselyov, A.S.; Semenova, M.; Semenov, V.V.; Milligan, D. Bioorg. Med. Chem. Lett., 2006, 16, 1913.

[9] Khan, M.T.H.; Choudhary, M.I.; Khan, K.M.; Rani, M.; Rahman, A. Bioorg. Med. Chem., 2005, 13, 3385.

[10] Xiaohu, O.; Piatnitski, E.; Pattaropong, V.; Xiaoling, C., Hai-Ying, He.; etal. Bioorg. Med. Chem. Lett., 2006, 16, 1191.

[11] Hu, G. Q.; etal. Chinese Chem. Lett., 2006, 17, 19.

[12] Hearn, M.J.; Cynamon, M.H. J. Antimicro. Chemothe., 2004, 53, 185.

[13] Somani R.R.; Agrawal A.G.; Bhanushali, U.V.; Kalantri P.P.; Clercq, E. D. Int. J. Drug Des. & Discov. 2010, in press.

[14] Sheban, M. A. E. Adv. Heterocycl. Chem., 1998, 70, 163.

[15] Gervay, J.; Flaherrty, T.M.; Holmes, D. Tetrahedron, 1997, 53, 16355.

[16] El Ashry, E.; El Kilany, Y. H. Adv. Heterocycl. Chem., 1998, 69, 129.

[17] Mohd, A.; Kumar, S. Eur. J. Med. Chem., 2004, 39, 535.

[18] Liu, K. Ch.; Hu, M.K.; Arch. Pharm.**,** 1987, 320(2), 166; *Chem. Abstr*. 1987, 107,198229 a.

[19] Asati, K.C.; Srivastava, S.K.; Srivastava, S.D. Ind. J. Chem., 2006, 45B, 526.

[20] Kidwai, M.; Kumar, P.; Goel, Y.; Kumar, K. *Ind. J. Chem*. **1997**, *36B*, 175.

[21] Kucukguzel, S.G.; Mazi, A.; Sahin, F.; Ozturk, S.; Stables, J. P. Eur. J. Med. Chem., 2003, 38, 1005.

[22] El-Khawass, S.M.; Habib, N.S. J. Heterocyclic. Chem., 1989, 26, 177.

[23] Bedia, K.; Elcin, O.; Seda, U.; Fatma, K.; Nathlay, S.; Sevim, R.; Dimalgo, A. Eur. J. Med. Chem., 2006, 41, 1253.

[24] Taoa, J.; Caoab, L.; Wanga, C.; Wanga, D. J. Chin. Chem. Soc., 2006, 53(5), 1193.

[25] El-Essawy F.A.; Khattab, A.F.; Abdel-Rahman, A. Monatshefte fur Chemie, 2007, 138, 777.

[26] Pauwels, R.; Balzarini, J.; Baba, M.; Snoeck, R.; Clercq, E.D. J. Virol.Methods, 1988, 20, 309.