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Synthesis and antitubercular,antiviral and anticancer activity of 3-(3-mercaptoalkyl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]-thiadiazin-6-yl)chromen-2-one and its derivatives

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3-(3-Mercaptoalkyl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-6-yl)-chromen-2-one **3** have been prepared by the condensation of 3-(2-bromoacetyl)coumarin **1** and 4-amino-5-mercaptoalkyl-4*H*-[1,2,4]triazole-3-thiol **2** in anhydrous ethanol. Similarly the 7,8-benzo analagues of **1** on reaction with **2** resulted in the formation of 7,8-benzo derivatives of **3s-x**. Reaction of **3a** with phenacyl chloride in anhydrous ethanol gave corresponding 3-(3-(2-oxo-2-phenylethyl-sulphanylmethyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4] thiadiazin-6-yl]chromen-2-one **4**. The 7,8-benzo analogues of **3s-t** on treatment with phenacyl chloride in anhydrous ethanol under reflux gave **4g** and **4h**. The newly synthesized compounds are characterized on the basis of elemental analysis, IR, ^{1}H NMR and mass spectral data. Some of the compounds are screened for their antitubercular, antiviral and anticancer activities.

Keywords: Benzopyran-2-one, thiadiazine, 1,2,4-triazole, antitubercular, antiviral, anticancer.

Coumarin derivatives have been found to exhibit various remarkable activities such as fluorescent dyes[1,]CNS depressants[2],antitumor agents[3], HIV proliferator[4] and as powerful anticoagulents[5].Various 1,2,4-triazoles and N-bridged heterocycles derived from them are found to be associated with divers pharmacological activity[6-11]. The 1,2,4-triazole nucleus has recently been incorporated into a wide variety of therapeutically interesting drugs including H_1/H_2 histamine receptor blockers, choline esterase activity agents, CNS stumilants, antianxiety agents and sedatives[12].

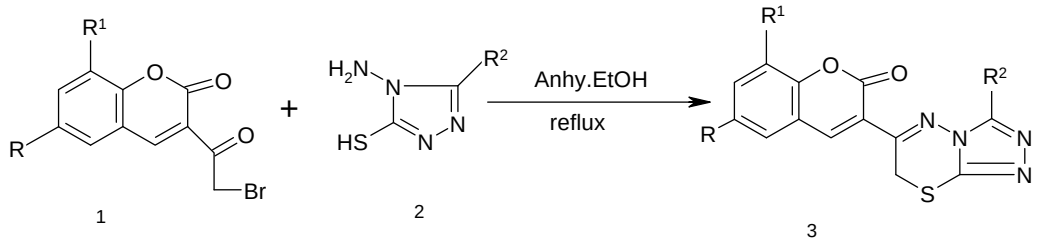
Prompted by the above observations and in continuation of our search for biologically active nitrogen and sulfur containing heterocycles[13-15]. It was decided to synthesize title compounds because many derivatives of 2*H*-1,3,5-thiadiazines have shown to be animal growth compounds[16]. They were also shown to possess varied biological activities like anti-microbial[17], antituberculatic[18.]

Synthesis of 3-(3-mercaptoalkyl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]-thiadiazine-6-yl)chromen-2-one **3** derivatives has been achieved by the condensation of 3-(2-bromoacetyl)coumarin **1** with 4-amino-5-mercaptoalkyl-4*H*-[1,2,4]triazole-3-thiol **2** in anhydrous ethanol under reflux for 3 to 4 hr (**Scheme I**). The 3-(3-mercaptoalkyl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine-6-yl)-chromen-2-one **3a** displayed strong absorption bands due to C=N and lactone carbonyl of coumarin at 1608 and 1722 cm^{-1}. The ^{1}H NMR spectrum of **3a** exhibited a characteristic singlet for -CH_2- of thiadiazine ring at δ 4.26. The acidic -SH proton appeared at δ 2.50. The remaining protons were observed in the usual regions.

The compounds **4a-f** have been obtained by the reaction of various 3-(3-mercaptomethyl-7*H*-[1,2,4]-triazolo[3,4-*b*][1,3,4]thiadiazine-6-yl)chromen-2-one **3a** with phenacyl chloride in anhydrous ethanol. Similarly 7,8-benzo analogues of **4g** and **4h** have been prepared **Scheme II**. The ^{1}H NMR spectrum of **4a** exhibited a characteristic singlet for -CH_2-S-CO- at δ 3.7 while the -S-CH_2- of the thiadiazine ring appeared as singlet at δ 4.20. The triazole attached -CH_2-S- appeared as singlet at δ 4.7. The remaining protons were observed in the usual regions.

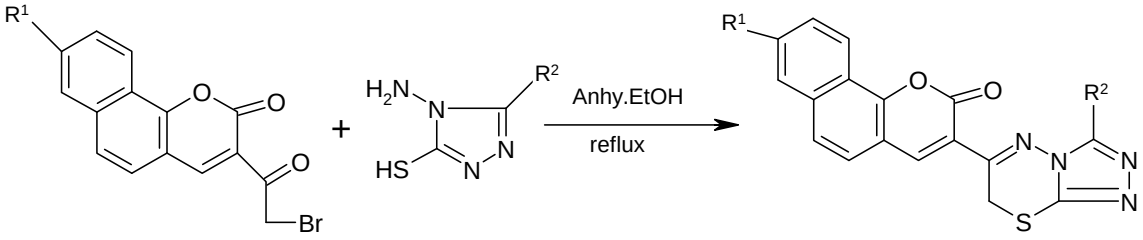
Experimental Section

All melting points were recorded on cintex melting point apparatus and are uncorrected. The purity of the compounds was checked by TLC. IR spectra were recorded on a Perkin-Elmer spectrum GX series FT-IR spectrophotometer. The ^{1}H NMR spectra on a



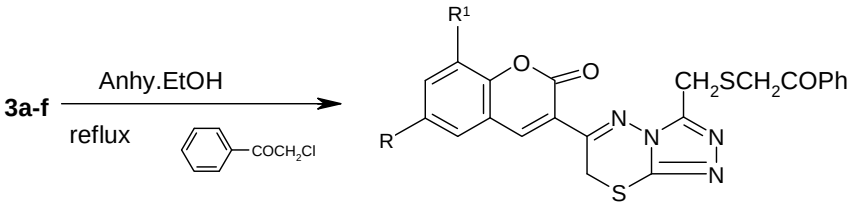
2a; $R^2 = CH_2$-SH
2b; R^2 = HS-CH-CH_3
2c; $R^2 = CH_2$-CH_2-SH

3a; R = R^1 = H, $R^2 = -CH_2$-SH
3b; $R^1 = OCH_3$, R = H, $R^2 = -CH_2$-SH
3c; R = Cl, R^1= H, $R^2 = -CH_2$-SH
3d; R = R^1 = Cl, $R^2 = -CH_2$-SH
3e; R = Br, R^1 = H, $R^2 = -CH_2$-SH
3f; R = R^1 = Br, $R^2 = -CH_2$-SH
3s; R^1 = H, $R^2 = -CH_2$-SH
3t; $R^1 = NO_2$,$R^2 = -CH_2$-SH
3g; R = R^1 = H, R^2 = HS-CH-CH_3
3h; $R^1 = OCH_3$, R = H, R^2 = HS-CH-CH_3
3i; R = Cl, R^1 = H, R^2 = HS-CH-CH_3
3j; R = R^1 = Cl, R^2 = HS-CH-CH_3
3k; R = Br, R^1 = H, R^2 = HS-CH-CH_3
3l; R = R^1 = Br, R^2 = HS-CH-CH_3
3u; R^1 = H, R^2= HS-CH-CH_3
3v; $R^1 = NO_2$,R^2 = HS-CH-CH_3
3m; R = R^1 = H, $R^2 = -CH_2$-CH_2-SH
3n; $R^1 = OCH_3$, R = H, $R^2 = -CH_2CH_2SH$
3o; R = Cl, R^1 = H, $R^2 = -CH_2$-CH_2-SH
3p; R = R^1 = Cl, $R^2 = -CH_2$-CH_2-SH
3q; R = Br, R^1 = H, $R^2 = -CH_2$-CH_2-SH
3r; R = R^1 = Br, $R^2 = -CH_2$-CH_2-SH
3w; R^1 = H, $R^2 = -CH_2$-CH_2-SH
3x; $R^1 = NO_2$, $R^2 = -CH_2$-CH_2-SH



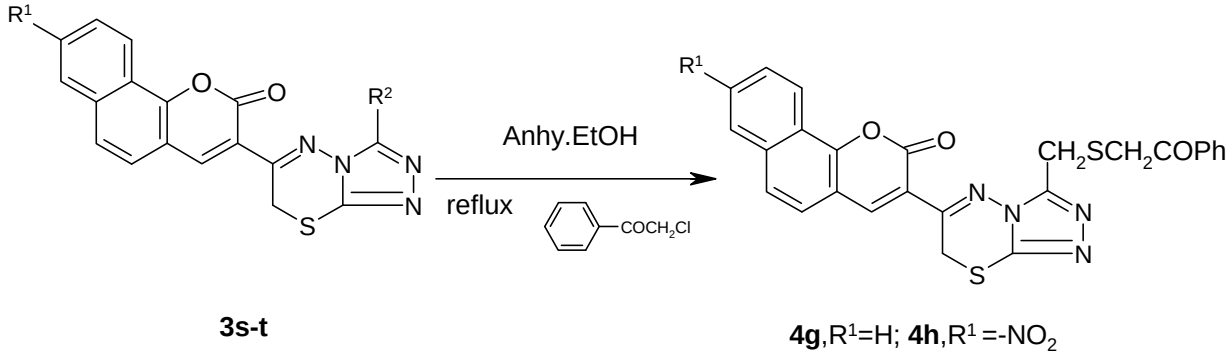
3s, 3t, 3u, 3v, 3w, 3x.

Scheme I



(4)

4a; R = R^1 = H
4b; $R^1 = OCH_3$,R = H
4c; R = Cl, R^1 = H
4d; R = R^1 = Cl
4e; R=Br, R^1 = H
4f; R = R^1 = Br



3s-t

4g,R^1=H; **4h**,$R^1 = -NO_2$

Scheme II

Varian dpx 200 MHz spectrometer using TMS as internal standard (chemical shifts in δ, ppm) and mass spectra on a Jeol-JMS-300 spectrometer at 70 eV.

The various 3-(2-bromoacetyl)coumarins were prepared according to our earlier procedure[19]. 4-Amino-5-mercaptomethyl-4*H*-[1,2,4]triazole-3-thiol has been prepared by the condensation of thiocarbohydrazide with mercaptoacetic acid[20-22].

Preparation of 4-amino-5-(1-mercaptoethyl)-4*H*-[1,2,4]triazole-3-thiol 2b
General Procedure

A mixture of thiocarbohydrazide (0.01 mole) and 2-mercapto propionic acid (0.01 mole) was refluxed for 3 hr on a heating mantle. The reaction-mixture was cooled and was filtered, washed with water and recrystallised from methanol to give **2b**. m.p. 95-97°C.

4-Amino-5-(1-mercaptoethyl)-4*H*-[1,2,4]triazole-3-thiol 2b: IR (KBr): 1612 (C=N), 2541 (-SH) and 3267 (-NH_2); ^{1}H NMR (DMSO-d_6): δ 1.59 (d, 3H, -CH_3), 2.51 (s, 1H, alkyl SH), 3.33 (s, 1H, SH, D_2O exchangeable), 4.21 (q, 1H, -CH), 5.57 (s, 2H, NH_2, D_2O exchangeable); MS: *m/z* 176.

Preparation of 4-amino-5-(2-mercapto-ethyl)-4*H*-[1,2,4]triazole-3-thiol 2c. It has been prepared by the condensation of thiocarbohydrazide with excess 3-mercaptopropionic acid as per procedure described in the literature[23-26].

Preparation of 3-(3-mercapto-alkyl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]-thiadiazin-6-yl)chromen-2-one 3. **General procedure**

A mixture of 3-(2-bromoacetyl)coumarin **1a-f** (1.33g, 0.005 mole) and 4-amino-5-mercaptoalkyl-4*H*-[1,2,4]triazole-3-thiol **2a-c** (0.740g, 0.005 mole) in anhydrous ethanol (10 mL) was refluxed for about 3-4 hr. The solid separated was collected by filtration dried and recrystallised from methanol to give **3a** (**Table I**). All the other compounds (**3b-x**) were prepared similar procedure.

3-(3-Mercapto-methyl-7*H*-[1,2,4]triazolo[3,4-*b*]-[1,3,4]thiadiazin-6-yl)chromen-2-one 3a: IR (KBr): 1608 (C=N), 1722 (lactone-C=O) and 2451(-SH); ^{1}H NMR (DMSO-d_6): δ 2.50 (s, 1H, SH), 4.03 (s, 2H, -CH_2-SH), 4.26 (s, 2H, -S-CH_2- of thiadiazine ring), 7.46-7.55 (m, 4*H*, Ar-H), 8.66 (s, 1H, C_4 of coumarin); MS: *m/z* 330.

3-(3-Mercapto-methyl-7*H*-[1,2,4]triazolo[3,4-*b*]-[1,3,4]thiadiazin-6-yl)-8-methoxy-chromen-2-one 3b: IR (KBr): 1610 (C=N) and 1720 (lactone C=O), 2535 (-SH); ^{1}H NMR ($CDCl_3$): δ 1.70 (s, 1H, SH with D_2O exchangeable), 2.73 (s, 2H of -CH_2-),3.9 (s, 5H, 2H of -CH_2- and 3H of OCH_3),7.20-7.26 (m, 3H, Ar-H) and 8.48 (s, 1H, C_4 of Coumarin); MS: *m/z* 360.

3-[3-(1-Mercapto-ethyl)-7*H*-[1, 2, 4]triazolo[3, 4-*b*][1,3,4]thiadiazin-6-yl)-chromen-2-one 3g: IR (KBr): 1603 (C=N), 1724 (lactone -C=O) and 2545 (-SH); ^{1}H NMR (DMSO-d_6): δ 1.55 (s, 1H, SH), 1.66 (d, 3H, CH_3), 4.0-4.2 (m, 3H, 1H of -CH- and 2H of -S-CH_2-), 7.1-7.8 (m, 4*H*, Ar-H), 8.50 (s, 1H, C_4 of coumarin); MS: *m/z* 344.

3-[3-(2-Mercapto-ethyl)-7*H*-[1, 2, 4]triazolo[3, 4-b][1,3,4]thiadiazin-6-yl)-chromen-2-one 3m: IR (KBr): 1606 (C=N), 1720 (lactone C=O) and 2363 (-SH); ^{1}H NMR (DMSO-d_6): δ 1.08 (s, 1H, SH, D_2O exchangeable), 2.95 (t, 2H, -CH_2-), 3.15 (t, 2H, -CH_2-S- of side chain), 4.26 (s, 2H, -S-CH_2- of thiadiazine ring), 7.4-7.8 (m, 4*H*, Ar-H), 8.5 (s, 1H, C_4 of coumarin); MS: *m/z* 344.

Preparation of 3-[3-(2-oxo-2-phenyl-ethylsulfanylmethyl)-7*H*-[1,2,4] triazolo [3,4-*b*][1,3,4]thiadiazin-6-yl]chromen-2-one 4a, General procedure. A mixture of **3**-(3-mercaptomethyl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-6-yl)chromen-2-one. **3a** (0.001 mole) and phenacyl chloride (0.001 mole) in anhydrous ethanol (10 mL) was refluxed for about 3-4 hr. The solid separated was collected by filtration, washed with ethanol, dried and recrystallized from methanol to give **4a** (**Table I**). All the other compounds **4b-h** were prepared similar procedure.

3-(3-(2-Oxo-2-phenyl-ethylsulfanylmethyl)-7*H*-[1,2,4]triazolo[3,4-*b*]-[1,3,4]thiadiazin-6-yl]chromen-2-one 4a. IR (KBr): 1606 (-C=N), 1690 (Ketone C=O) and 1720 (lactone C=O); ^{1}H NMR (DMSO-d_6): δ 3.7 (s, 2H, -SCH_2-CO-), 4.2 (s, 2H, -SCH_2- of thiadiazine ring), 4.7 (s, 2H, -S-CH_2-), 7.3-7.95 (m, 9H, Ar-H), 8.50 (s, 1H, C_4 of coumarin); MS: *m/z* 448.

Biological evaluation

Antitubercular activity. Primary antitubercular screening is conducted at 6.25 μg/mL (or molear equivalent of highest molecular weight compound in a series of congeners) against *Mycobacterium tuberculosis* H_{37} R_V (ATCC 27294) in BACTEC 12B medium using a broth microdilution assay, the Microplate Alamar Blue Assay[27] (MABA). Compounds effecting <90% inhibition in the primary screen (i.e., MIC > 6.25 μg/mL) are not generally

Table I — Analytical Data of Compounds **3a-x** and **4a-h**

Compd	M.p. (°C)	Yield (%)	Mol.Formula (Mol.wt.)	Found (Calcd)% C	H	N	Compd	M.p. (°C)	Yield (%)	Mol.Formula (Mol.wt.)	Found (Calcd)% C	H	N
3a	220-22	82	$C_14H_{10}N_4S_2O_2$ (330)	59.90 (50.92	3.03 3.05	16.92 16.96)	**3q**	194-96	86	$C_{15}H_{11}N_4O_2S_2Br$ (423)	42.51 (42.56	2.60 2.62	13.21 13.24)
3b	138-40	80	$C_{15}H_{12}N_4O_3S_2$ (360)	49.94 (49.99	3.30 3.36	15.45 15.50)	**3r**	210-12	80	$C_{15}H_{10}N_4O_2S_2Br_2$ (502)	35.84 (35.87	2.00 2.02	11.13 11.16)
3c	250-52	84	$C_14H_9N_4O_2S_2Cl$ (364)	46.04 (46.09	2.44 2.49	15.34 15.36)	**3s**	170-72	88	$C_{18}H_{12}N_4O_2S_2$ (380)	56.80 (56.83	3.15 3.18	14.70 14.73)
3d	258-60	86	$C_14H_8N_4O_2S_2Cl_2$ (399)	42.10 (42.11	2.00 2.02	14.00 14.03)	**3t**	175-77	84	$C_{18}H_{11}N_5O_4S_2$ (425)	50.80 (50.82	2.58 2.61	16.44 16.46)
3e	182-84	90	$C_14H_9N_4O_2S_2Br$ (409)	41.06 (41.09	2.20 2.22	13.65 13.69)	**3u**	265-67	90	$C_{19}H_{14}N_4O_2S_2$ (394)	57.80 (57.87	3.54 3.58	14.18 14.20)
3f	188-90	92	$C_14H_8N_4O_2S_2Br_2$ (488)	34.40 (34.45	1.61 1.64	11.44 11.48)	**3v**	>280	81	$C_{16}H_{13}N_5O_5S_2$ (439)	51.90 (51.93	2.94 2.98	15.90 15.94)
3g	188-90	86	$C_{15}H_{12}N_4O_2S_2$ (344)	52.31 (52.34	3.48 3.51	16.25 16.27)	**3w**	234-36	84	$C_{19}H_{14}N_4O_2S_2$ (394)	57.81 (57.85	3.54 3.58	14.18 14.20)
3h	202-04	85	$C_{16}H_{14}N_4O_3S_2$ (374)	51.30 (51.32	3.74 3.77	14.94 14.96)	**3x**	243-45	88	$C_{19}H_{13}N_5O_4S_2$ (439)	51.90 (51.93	2.94 2.98	15.90 15.94)
3i	176-78	80	$C_{15}H_{11}N_4O_2S_2Cl$ (378)	47.50 (47.55	2.90 2.93	14.76 14.79)	**4a**	115-17	90	$C_{22}H_{16}N_4O_3S_2$ (448)	58.89 (58.91	3.57 3.60	12.44 12.49)
3j	184-86	88	$C_{15}H_{10}N_4O_2S_2Cl_2$ (412)	43.54 (43.59	2.40 2.44	13.54 13.56)	**4b**	198-200	92	$C_{23}H_{18}N_4O_4S_2$ (478)	57.70 (57.73	3.75 3.79	11.68 11.71)
3k	215-17	89	$C_{15}H_{11}N_4O_2S_2Br$ (423)	42.51 (42.56	2.60 2.62	13.20 13.24)	**4c**	204-06	90	$C_{22}H_{15}N_4O_3S_2Cl$ (482)	54.71 (54.74	3.10 3.13	11.56 11.60)
3l	224-26	92	$C_{15}H_{10}N_4O_2S_2Br_2$ (502)	35.84 (35.87	2.00 2.01	11.12 11.16)	**4d**	215-17	88	$C_{22}H_{14}N_4O_3S_2Cl_2$ (517)	51.04 (51.07	2.70 2.73	10.81 10.83)
3m	165-67	80	$C_{15}H_{12}N_4O_2S_2$ (344)	52.39 (52.41	3.48 3.51	16.25 16.27)	**4e**	210-12	86	$C_{22}H_{15}N_4O_3S_2Br$ (527)	50.07 (50.10	2.84 2.87	10.60 10.62)
3n	135-37	82	$C_{16}H_{14}N_4O_3S_2$ (374)	51.30 (51.32	3.74 3.77	14.94 14.96)	**4f**	225-27	90	$C_{22}H_{14}N_4O_3S_2Br_2$ (606)	43.54 (43.58	2.30 2.33	9.22 9.24)
3o	166-68	78	$C_{15}H_{11}N_4O_2S_2Cl$ (378)	47.51 (47.55	2.90 2.93	14.75 14.79)	**4g**	194-96	82	$C_{26}H_{18}N_4O_3S_2$ (498)	62.60 (62.64	3.60 3.64	11.20 11.24)
3p	174-76	82	$C_{15}H_{10}N_4O_2S_2Cl_2$ (412)	43.54 (43.59	2.40 2.44	13.54 13.56)	**4h**	202-04	84	$C_{26}H_{17}N_5O_5S_2$ (543)	57.40 (57.45	3.12 3.15	12.86 12.88)

The compounds **3a-x** and **4a-h** were recrystallized from methanol

evaluated further. From the **Table II** it is evident that none of the compounds **3a-c**, **3e-f**, **3s** and **3t** exhibited antitubercular activity.

Antiviral activity. The antiviral activities[28] of **4a-h** were also determined against HSV-1, HSV-2, VV, VSV and HSV-1, TK^- strains in HEL cell cultures. The compounds did not exhibit an appreciable antiviral activity (i.e., minimal antiviral by effective concentration $\geq$ 5 fold lower than minimal cytotoxic concentration). Similarly, they did not show any specific activity against other viruses (e.g., VSV, Coxasackie virus B_4 and respiratory syncytial virus in HeLa cell cultures. Also, the compounds did not show

Table II — Antitubercular activity of compounds (**3a-c, 3e-f, 3s** and **3t**)

Compd	Assay	MIC (μg/mL)	% Inhibition	Activity
3a	Alamar	> 6.25	0	--
3b	Alamar	> 6.25	0	--
3c	Alamar	> 6.25	0	--
3e	Alamar	> 6.25	0	--
3f	Alamar	> 6.25	6	--
3s	Alamar	> 6.25	4	--
3t	Alamar	> 6.25	4	--

Table III — Cytotoxicity and antiviral activity of compounds. HeLa cell cultures **4a-h**

Comp.	Minimum cytotoxic concentration[a] (μg/mL)	Minimum inhibitory concentration[b] (μg/mL)				
		Herpes simplex virus-1 (KOS)	Herpes simplex virus-2 (G)	*Vaccinia* virus	Vesicular *stomatitis* virus	*Herpes simplex* virus-1 TK KOS ACV^r
4a	80	> 16	> 16	> 16	> 16	> 16
4b	80	> 16	> 16	> 16	> 16	> 16
4c	80	> 16	> 16	> 16	> 16	> 16
4d	≥ 16	> 16	> 16	> 16	> 16	> 16
4e	≥ 16	> 16	> 16	> 16	> 16	> 16
4f	≥ 16	> 16	> 16	> 16	> 16	> 16
4g	80	> 16	> 16	> 16	> 16	> 16
4h	≥ 16	> 16	> 16	> 16	> 16	> 16
Brivudin	≥ 400	0.0256	400	16	> 400	> 400
Ribavirin	> 400	> 400	> 400	240	> 400	> 400
Acyclovir	> 400	0.0768	0.0768	> 400	> 400	48
Ganciclovir	> 100	0.0038	0.0192	> 100	> 100	0.48

Table IV — Cytotoxicity and antiviral activity of compounds HeLa cell cultures **4a-h**

Compd	Minimum cytotoxic concentration[a] (μg/mL)	Minimum inhibitory concentration[b] (μg/mL)		
		Vesicular stanatitis virus	*Coxsackie* virus B_4	Respiratory syncytial virus
4a	80	> 16	> 16	> 16
4b	400	> 80	> 80	> 80
4c	400	> 80	> 80	> 80
4d	80	> 16	> 16	> 16
4e	400	> 80	> 80	> 80
4f	400	> 80	> 80	> 80
4g	400	> 80	> 80	> 80
4h	≥ 80	> 80	> 80	> 80
Brivudin	≥ 400	> 400	> 400	> 400
(S)-DHPA	≥ 400	> 400	> 400	> 400
Ribavirin	≥ 400	48	400	16

[a]Required to cause a microscopically detectable alteration of normal cell morphology.
[b]Required to reduce virus-induced cytopathogencity by 50%

Table V — Cytotoxicity and antiviral activity of compounds Vero cell cultures **(4a-h)**

Compd	Minimum cytotoxic concentration[a] (μg/mL)	*Parainfluenza*-3 virus	Minimum inhibitory concentration[b] (μg/mL)			
			Reovirus-1	*Sindbis* virus	*Coxsackie* virus B_4	*Punta Taro* virus
4a	≥ 80	> 80	> 80	> 80	> 80	> 80
4b	80	> 16	> 16	> 16	> 16	> 16
4c	≥ 80	> 80	> 80	> 80	> 80	> 80
4d	≥ 80	> 80	> 80	> 80	> 80	> 80
4e	≥ 80	> 80	> 80	> 80	> 80	> 80
4f	≥ 80	> 80	> 80	> 80	> 80	> 80
4g	≥ 80	> 80	> 80	> 80	> 80	> 80
4h	80	> 16	> 16	>16	> 16	>16
Brivudin	> 400	> 400	> 400	> 400	> 400	>400
(S)-DHPA	> 400	> 400	> 400	> 400	> 400	> 400
Ribavirin	> 400	48	48	400	> 400	48

[a]Required to cause a microscopically detectable alteration of normal cell morphology.
[b]Required to reduce virus-induced cytopathogenicity by 50%.

any specific activity against other viruses like *Parainfluenza*, *Reovirus*-1, *Sindbis virus*, *Coxasackie virus* B_4 and *Punta Toro virus* in Vero cell cultures **Tables III, IV** and **V**. Compounds **3a-c, 3e-f, 3s** and **3t** were tested for their biological activities in various tumor cell lines[29-31]. The **Table VI** indicates the inhibitory effects on the growth of a variety of tumor cell virus, L 1210, Molt 4/C8 and CEM. When the

Table VI — Inhibitory effects of compounds. The proliferation of murine leukaemia cells (L 1210/0) and human T-lymphocyte cells (Molt 4/C8, CEM/0) **(3a-c, 3e-f, 3s** and **3t)**

Compd	IC_{50} (μg/mL)[a]		
	L 1210/0	Molt 4/C8	CEM/0
3a	58 ± 10	52 ± 6	25 ± 5
3b	73 ± 20	69 ± 16	52 ± 16
3c	73 ± 5	87 ± 4	46 ± 18
3e	76 ± 21	73 ± 12	34 ± 25
3f	108 ± 9	95 ± 15	69 ± 26
3s	61 ± 9	70 ± 8	17 ± 4
3t	17 ± 0	19 ± 1	12 ± 1

[a]50% inhibitory concentration.

compounds were tested for their cytotoxic by measuring the IC_{50} values in the proliferation of murine leukemia cells (L_{12} 10%) and human T-lymphocyte (Molt 4/L_8, CEM/0) cells. None of the compounds showed IC_{50} value less than 10 μg/mL on only one of the cell lines tested. **3t** is some what relatively having cytotoxic properties below 20 μg/mL on all the tested cells. In general these compounds are not having any cytotoxic activity.

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