Synthesis and Anticancer and Antiviral Activities of New 2-Pyrazoline-Substituted 4-Thiazolidinones

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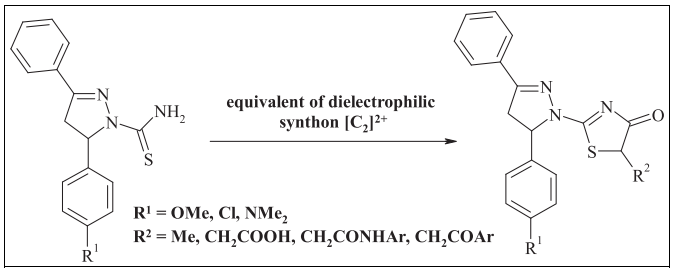

2-(4,5-Dihydropyrazol-1-yl)-thiazol-4-ones (**2–5**) have been synthesized starting from 3-phenyl-5-aryl-1-thiocarbamoyl-2-pyrazolines via [2+3]-cyclization with 2-bromopropionic acid, maleic anhydride, *N*-aryl-maleimides, and aroylacrylic acids. The *in vitro* anticancer activity of **2a**, **3a**, **4a**, **5b**, and **5c** were tested by the National Cancer Institute. Compounds **4a**, **5b**, and **5c** demonstrated selective inhibition of leukemia cell lines growth at a single concentration (10^{-5} M). The screening of antiviral activity for a broad panel of viruses revealed that *N*-(4-methoxyphenyl)-2-{2-[5-(4-methoxyphenyl)-3-phenyl-4,5-dihydropyrazol-1-yl]-4-oxo-4,5-dihydrothiazol-5-yl}-acetamide **4a** was highly active against Tacaribe TRVL 11 573 virus strain (EC_{50} = 0.71 μg/mL, selectivity index = 130).

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INTRODUCTION

The combination of 4-thiazolidinone scaffold with other heterocycles is a widely applicable approach in a drug-like molecules buildup [1–4]. The confirmation of this assertion could be various noncondensed systems with thiazolidine, diazole (pyrazoline or pyrazole), and related moieties that display broad spectrum of biological activities including anti-inflammatory [5, 6], antinociceptive [7], antimicrobial [8–10], antifungal [11], anticonvulsant [12], antioxidant [13] effects, and so on.

A considerable interest has been focused on the anticancer activity of thiazolidinone and pyrazole derivatives. Among mentioned substances, some of heterocyclic substituted 4-thiazolidinones were described in literature as inhibitors of necroptosis (**I**) [14] (Fig. 1), Burkitt's lymphoma promotion (**II**) [15] or as promising agent, which possessed significant effect against breast carcinoma (MCF7) and cervix carcinoma (HELA) cell lines (**III**) [16]. The pyrazoline derivative **IV** demonstrated the most marked effects in the NCI's 60 human tumor cell line *in vitro* screen on leukemia cancer cell lines CCRF-CEM and RPMI-8226 with GI_{50} 2.23 and 2.76 μ*M*, respectively [17]. Recently, we have demonstrated that thiazolidinone derivatives with pyrazoline core **V** displayed promising anticancer activity on leukemia, melanoma, lung, colon, CNS, ovarian, renal, prostate, and breast cancers cell lines [3].

The antiviral research of 4-thiazolidinones and pyrazolines also received considerable attention. Among antecedent derivatives, some novel compounds have been identified to be active against vaccinia virus (**VI**) with EC_{50} of 7.0 μg/mL [18] and tabacco mosaic virus (**VII**) [19]. Compound **VIII** showed promising anti-HIV activity *in vitro* against IIIB (IC_{50} = 5.7 μ*M*) and ROD strains (IC_{50} = 7.0 μ*M*) [20].

In the present work, we described our continuous research effort in the synthesis of a series of new pyrazoline-substituted 4-thiazolidinones and characterization of these compounds for antitumor and antiviral activities. The synthesis of 4-thiazolidinone-pyrazoline conjugates can be achieved by [2+3]-cyclization of pyrazoline-1-carbothioic acid amides with equivalents of dielectrophilic synthon $[C_2]^{2+}$ [1]. Following literature data, only the derivatives of α-halocarboxylic acids, phenacyl bromides, and

N-arylmaleimides [18, 21, 22, 23] have been used in the reactions with mentioned compounds. Therefore, we tried to enlarge a scope of using of 1-thiocarbamoyl pyrazoline derivatives as *N*,*S*-binucleophiles in [2+3]-cyclization.

RESULTS AND DISCUSSION

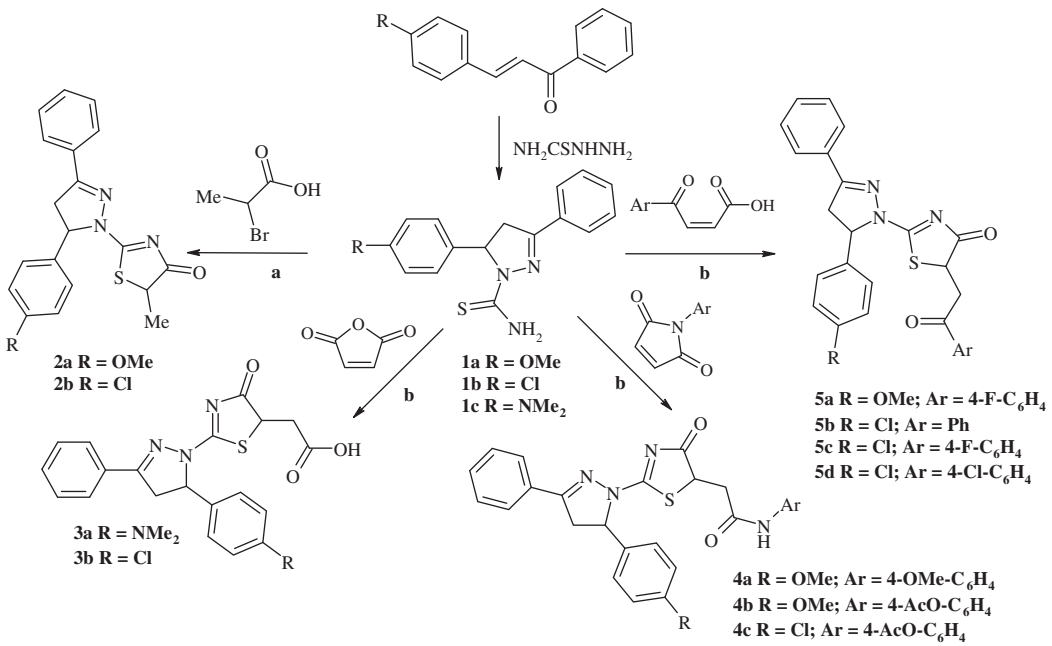
Chemistry. The general methods for synthesis of target pyrazoline substituted 4-thiazolidinones are depicted in Scheme 1.

Aiming the synthesis of new 4-thiazolidinones with pyrazoline moiety in position 2 of basic scaffold, we used an approach to obtaining of 4-thiazolidinone ring, which realizes on [2+3]-cyclization of 3-phenyl-5-aryl-1-thiocarbamoyl-2-pyrazolines **1a–c** with equivalents of dielectrophilic synthon $[C_2]^{2+}$ [1]. The target 2-[5-aryl-3-phenyl-4,5-dihydropyrazol-1-yl]-5-methylthiazol-4-ones **2a** and **b** were synthesized by reacting mentioned binucleophiles with 2-bromopropionic acid in the presence of fused sodium acetate in refluxing acetic acid. Reaction of 3-phenyl-5-aryl-1-thiocarbamoyl-2-pyrazolines with maleic anhydride, *N*-arylmaleimides, and aroylacrylic acids [22, 23] resulted in the formation of the corresponding compounds **3a** and **b**, **4a–c**, and **5a–d**, respectively.

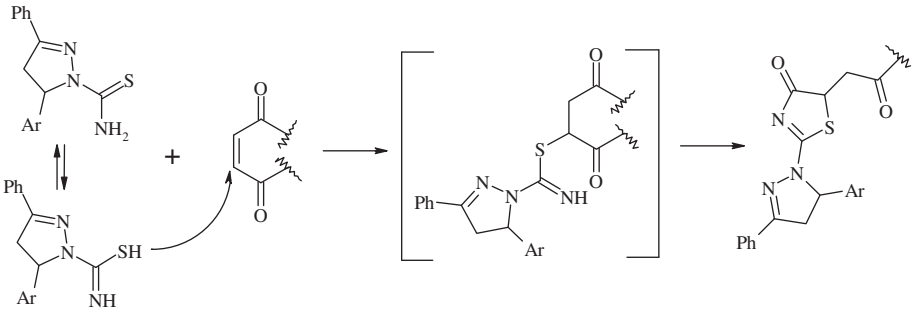
The [2+3]-cyclization of 3-phenyl-5-aryl-1-thiocarbamoyl-2-pyrazolines with equivalents of dielectrophilic synthon $[C_2]^{2+}$ consists of two steps: coupling of 3-phenyl-5-aryl-1-thiocarbamoyl-2-pyrazolines **1a–c** isoform to double bond of maleic anhydride, *N*-arylmaleimides, or aroylacrylic acids and following spontaneous cyclization of intermediate to 4-thiazolidone cycle [32] (Scheme 2).

The characteristic data of the new 4-thiazolidinones are presented in the experimental part. The analytical and spectral data (^{1}H- and ^{13}C-NMR) confirm the structure and purity of the synthesized compounds.

Scheme 1. Synthesis of 2-[5-aryl-3-phenyl-4,5-dihydropyrazol-1-yl]-thiazol-4-ones**.** Reagents, conditions and yields: (a) AcONa, AcOH, reflux 1 h, 68–75%; (b) AcOH, reflux 1 h, 63–78%.



Scheme 2. The mechanism of the [2+3]-cyclization of 3-phenyl-5-aryl-1-thiocarbamoyl-2-pyrazolines with equivalents of dielectrophilic synthon $[C_2]^{2+}$.



The compounds **2a** and **b** exist as a mixture of two diastereomers **I** and **II** in the ratio of 1:1. Probably, this phenomenon can be explained by keto-enol tautomerism of mentioned derivatives in positions 4–5 (Scheme 3). The diastereomeric equilibrium of these compounds was confirmed through the analysis of the ^{1}H-NMR spectral data. Thus, the protons of the methyl group in position 5 of thiazolidinone core were observed as two doublet at δ = 1.44–1.45 and δ = 1.47–1.48, and the proton at C5 forms a multiplet at δ = 4.13–4.21. Besides, in the ^{1}H-NMR spectra of compounds **2a** and **b**, the protons of the CH_2-CH moiety of the pyrazoline fragments showed the characteristic pattern of an AMX spin system [4]. The chemical shifts of the protons H_A, H_M, and H_X were determined to be δ = 3.43–3.46, δ = 4.07–4.13, and δ = 5.74–5.83, respectively, with coupling constants J_{AM} = 18.1–18.2, J_{AX} = 11.1–11.3, and J_{MX} = 4.5 Hz. Protons of two CH_2-CH groups of compounds **3a** and **b**, **4a–c**, and **5a–d** in the ^{1}H-NMR spectra showed characteristic patterns of two AMX systems. The chemical shifts of the protons H_A, H_M, and H_X for pyrazoline moiety were assigned to about δ ∼ 3.33–3.48, δ ∼ 4.09–4.17, and δ ∼ 5.66–5.85, respectively, and for 5-(2-oxoethyl)-4-thiazolidinone fragments to about δ ∼ 2.58–3.58, δ ∼ 3.05–3.97, and δ ∼ 4.24–4.45. The NH proton of compounds **4a–c** was found as singlet at δ ∼ 9.87–10.22.

Evaluation of anticancer activity *in vitro*. Synthesized pyrazoline-substituted 4-thiazolidinones (**2a**, **3a**, **4a**, **5b**, **5c**) were submitted and evaluated at single concentration of 10^{-5} M toward panel of approximately sixty cancer cell lines representing leukemia, melanoma, lung, colon, CNS, ovarian, renal, prostate, and breast cancers. Tested 2-[5-aryl-3-phenyl-4,5-dihydropyrazol-1-yl]-thiazol-4-ones demonstrated a moderate activity in the *in vitro* screen on the tested cell lines, as well as some distinctive patterns of selectivity (Table 1). Compound **2a** was moderate active on a nonsmall cell lung cancer HOP-92 sell line (GP = 59.48%), compounds **4a** and **5c**

Scheme 3. Diastereomers of compounds **2a** and **b**.

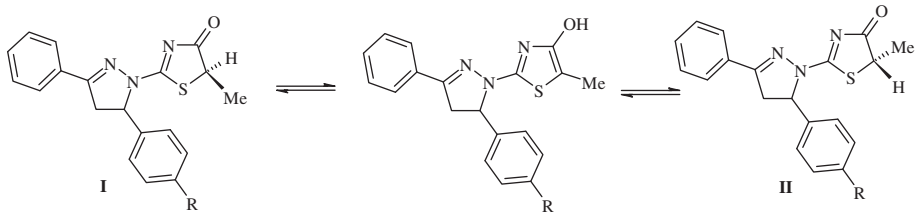


Table 1

Anticancer screening data in concentration $10^{-5}M$.

	60 cell lines assay in 1 dose 10^{-5} M conc			
Compounds	Mean growth %	Range of growth %	The most sensitive cell lines	Growth % of the most sensitive cell lines
2a	101.48	59.48–160.51	HOP-92 (Non-Small Cell Lung Cancer)	59.48
			UO-31 (Renal Cancer)	69.89
3a	101.34	77.31–115.90	UO-31 (Renal Cancer)	77.31
4a	78.60	32.76–142.11	RPMI (Leukemia)	32.76
			K-562 (Leukemia)	53.77
			MOLT-4 (Leukemia)	55.39
			RCF-7 (Breast cancer)	40.76
			HCT-15 (Colon cancer)	57.46
			EKVX (Non-small cell lung cancer)	49.76
			A549/ATCC (Non-small cell lung cancer)	54.56
			NCI-H460 (Non-small cell lung cancer)	59.21
			PC-3 (Prostate cancer)	58.91
5b	92.19	57.68–137.51	RXF 393 (Renal Cancer)	57.68
			RPMI (Leukemia)	60.70
			K-562 (Leukemia)	63.54
			MOLT-4 (Leukemia)	60.01
5c	96.04	63.60–132.43	RPMI (Leukemia)	63.60
			UO-31 (Renal cancer)	68.76

were active on a leukemia RPMI cell line (GP = 32.76 and 63.60%, respectively) and **5b**—on a renal cancer RXF 393 cell line (GP = 57.68%). In general, the compounds **4a**, **5b**, **5c**, selectively inhibit the growth of leukemia cell lines, what correspond to the previous observation of 4-thiazolidinones antitumor activity [33–37].

Evaluation of antiviral activity. Antiviral activity of **4a** and **5c** was determined aganinst corona viruses (SARS CoV), influenza types A and B viruses (Flu A, Flu B), arenavirus (Junin), and biodefense viruses (Tacaribe, Pichinde) using standart AACF screening assay protocols [28–30]. The obtained results are summarized in Table 2.

The compound **5c** showed low activity against strains of influenza viruses (SI = ~ 1.3/3.6). Especially, noteworthy antiviral activity of compounds **4a**, which possessed insignificant activity against Candid 1 strain of Junin virus (SI = 4/6) and Pichinde virus (SI = 9) but characterized by a high effect (EC_{50} = 0.71 μg/mL, SI = 130) on Tacaribe TRVL 11 573 virus strain by NR test. The results of a repeated test by the VYR-method (virus yield reduction) confirmed the considerable activity of the compound **5c** (SI = 15) against Tacaribe TRVL 11 573 virus strain.

Obtained results are seemed as promised regarding further investigations of *N*-aryl-[2-(4,5-dihydropyrazol-1-yl)-4-oxo-4,5-dihydrothiazol-5-yl]-acetamides as perspective antiviral agents.

CONCLUSIONS

New hybrid compounds combining 4-thiazolidinones with 4,5-dihydropyrazoles have been synthesized with high yields via [2+3]-cyclization using 3-phenyl-5-aryl-1-thiocarbamoyl-2-pyrazolines and bromopropionic acid, maleic anhydride, *N*-arylmaleimides, or aroylacrylic acids as a starting compounds. Five of synthesized compounds were tested and displayed moderate antitumor activity against leukemia, lung, renal, prostate, and breast cancers cell lines. The preliminary results of antiviral activity allowed to identify the active compound **4a**, which has shown the best antiviral activity against Tacaribe TRVL 11 573 virus strain (EC_{50} = 0.71 μg/mL; SI = 130).

EXPERIMENTAL

The starting 3-phenyl-5-aryl-1-thiocarbamoyl-2-pyrazolines **1a–c** [21] were obtained according to the known synthetic method.

Physical measurement. Melting points were measured in open capillary tubes on a BUCHI B-545 melting point apparatus and are uncorrected. Elemental analyses (C, H, N) were performed using the Perkin-Elmer 2400 CHN analyzer. The analyses indicated by the symbols of the elements or functions were within ±0.4% of the theoretical values. The ^{1}H-NMR spectra were recorded using the Varian Gemini 300 MHz and ^{13}C-NMR spectra using Varian Mercury-400 100 MHz in

Table 2

Antiviral activity of synthesized 2-[5-aryl-3-phenyl-4,5-dihydropyrazol-1-yl]-thiazol-4-one derivatives (**4a**, **5c**).

Compounds	Assay	Virus	Virus Strain	Cell Line	EC_{50}, or EC_{90}* μg/mL	CC_{50}, μg/mL	SI[a] (CC_{50}/EC_{50})	Comment[b]
4a	Neutral Red	Flu A (H3N2)	Wisconsin/67/2005	MDCK	35	>100	>2.9	NA
	Neutral Red	Flu A (H5N1)	Vietnam/1203/2004H	MDCK	33	>100	>3	NA
	Neutral Red	Flu B	Malaysia/2506/2004	MDCK	45	>100	>2.2	NA
	Neutral Red	SARS	Urbani	Vero-76	49	49	1	NA
	Neutral Red	Tacaribe	TRVL 11573	Vero-76	0,71	89	130	HA
	Viral CPE	Tacaribe	TRVL 11573	Vero 76	0,86	28	32	MA
	VYR	Tacaribe	TRVL 11573	Vero 76	2.29*	34	15	MA
	Viral CPE	Pichinde	An 4763	Vero	2.1	18	9	SA
	Neutral Red	Junin	Candid 1	Vero	7.2	27	4	SA
	Viral CPE	Junin	Candid 1	Vero	5.7	32	6	SA
5c	Neutral Red	Flu A (H3N2)	Wisconsin/67/2005	MDCK	37	>100	>2.7	NA
	Neutral Red	Flu A (H5N1)	Vietnam/1203/2004H	MDCK	77	>100	>1.3	NA
	Neutral Red	Flu B	Malaysia/2506/2004	MDCK	28	>100	>3.6	NA
	Neutral Red	SARS	Urbani	Vero 76	32	53	1,7	NA

[a]The table presents the results of antiviral activity against strains for which the selectivity index, SI ≥ 1.
[b]NA, not active; HA, highly active; MA, moderately active; SA, slightly active.

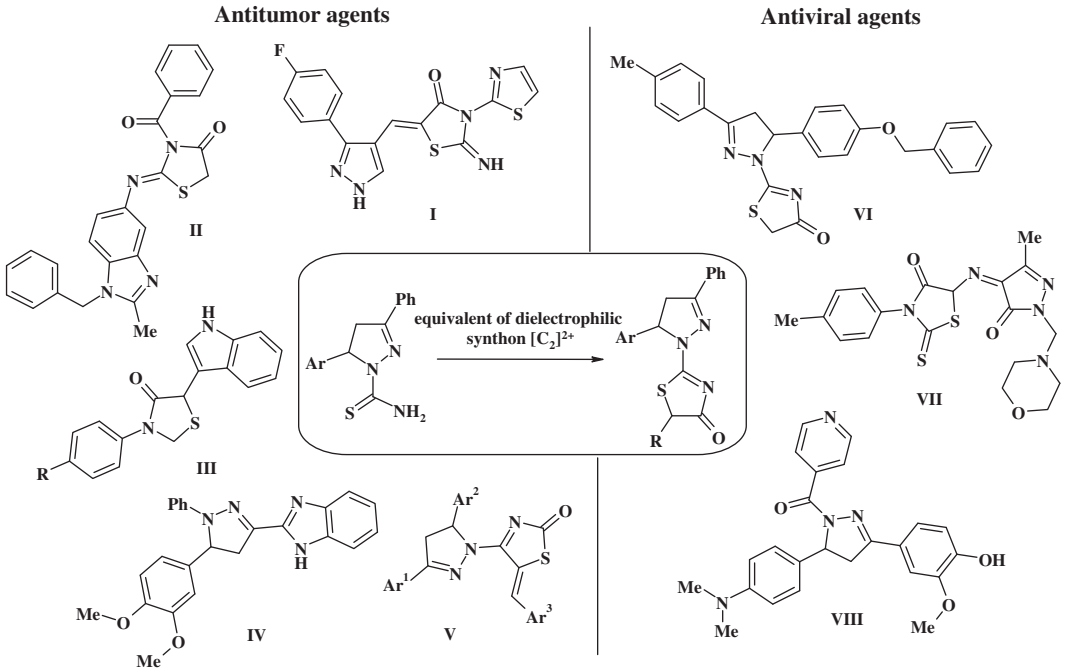


Figure 1. Structures of 4-thiazolidinones and diazoles with anticancer and antiviral activities.

DMSO-d_6 or DMSO-d_6 + CCl_4 mixture using tetramethylsilane as an internal standard. Chemical shifts are reported in ppm units using δ scale.

Chemistry. ***Synthesis of 2-(5-aryl-3-phenyl-4,5-dihydropyrazol-1-yl)-5-methylthiazol-4-one (2a, 2b).*** A mixture of pyrazoline-1-carbothioic acid amide (5 mmol), sodium acetate (5 mmol), and 2-bromopropionic acid (5 mmol) was refluxed for 1 h in 10 mL of acetic acid. After cooling, the reaction mixture was poured into cold water. A solid material that precipitated out was filtered, dried, and recrystallized with DMF:ethanol mixture (1:2).

*2-[5-(4-Methoxyphenyl)-3-phenyl-4,5-dihydropyrazol-1-yl]-5-methylthiazol-4-one (**2a**).* Yield 75%, mp 136–137°C. ^{1}H-NMR (300 MHz, DMSO-d_6 + CCl_4): 7.85 (d, 2H, J = 7.1 Hz, arom.); 7.56–7.50 (m, 3H, arom.); 7.16 (d, 2H, J = 8.4 Hz, arom.); 6.92 (d, 2H, J = 7.1 Hz, arom.); 5.74 (dd, 1H, J = 11.3, 4.5 Hz, $CH_2\underline{CH}$); 4.21–4.13 (m, 1H, $\underline{CH}CH_3$); 4.07 (dd, 1H, J = 18.2, 11.3 Hz, $\underline{CH_2}CH$); 3.72 (s, 3H, $\overline{OCH_3}$); 3.43 (dd, 1H, J = 18.2, 4.5 Hz, $\underline{CH_2}CH$); 1.47, 1.44 (d, d, 3H, CH_3). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 190.1 (C=O), 176.4 (C=N, thiaz.), 161.1 (C=N, pyraz.), 159.4, 132.9, 131.9, 130.3, 129.5, 127.8, 127.7, 126.7, 114.7, 63.7 ($\underline{C}HCH_2$), 55.6 (O-CH_3), 49.3 ($\underline{C}HCH_3$), 43.9 ($CH\underline{C}H_2$), 19.2 ($CH\underline{C}H_3$). Calcd. for $C_{20}H_{19}N_3O_2S$: C, 65.73; H, 5.24; N, 11.50; Found: C, 65.89; H, 5.13; N, 11.69%.

*2-[5-(4-Chlorophenyl)-3-phenyl-4,5-dihydropyrazol-1-yl]-5-methylthiazol-4-one (**2b**).* Yield 68%, mp 199–200°C. ^{1}H-NMR (300 MHz, DMSO-d_6 + CCl_4): 7.85 (d, 2H, J = 7.1 Hz, arom.); 7.57–7.51 (m, 3H, arom.); 7.45 (d, 2H, J = 6.9 Hz, arom.); 7.28 (d, 2H, J = 8.2 Hz, arom.); 5.83 (dd, 1H, J = 11.1, 4.9 Hz, $CH_2\underline{CH}$); 4.21–4.15 (m, 1H, $\underline{CH}CH_3$); 4.13 (dd, 1H, J = 18.1, 11.1 Hz, $\underline{CH_2}CH$); 3.46 (dd, 1H, J = 18.1, 4.9 Hz, $\underline{CH_2}CH$); 1.48, 1.45 (d, d, 3H, CH_3). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 189.9 (C=O), 176.5 (C=N, thiaz.), 161.0 (C=N, pyraz.), 139.8, 132.9, 132.1, 130.2 129.5, 128.3, 128.2, 127.8, 63.5 ($\underline{C}HCH_2$), 49.4 ($\underline{C}HCH_3$), 43.8 ($CH\underline{C}H_2$), 19.2 ($CH\underline{C}H_3$). Calcd. for $C_{19}H_{16}ClN_3OS$: C, 61.70; H, 4.36; N, 11.36; Found: C, 61.82; H, 4.50; N, 11.21%.

General procedure for synthesis of [2-(5-aryl-3-phenyl-4,5-dihydropyrazol-1-yl)-4-oxo-4,5-dihydrothiazol-5-yl]-acetic acids (3a, 3b), N-aryl-2-[2-(5-aryl-3-phenyl-4,5-dihydropyrazol-1-yl)-4-oxo-4,5-dihydrothiazol-5-yl]-acetamides (4a–c) and 2-(5-aryl-3-phenyl-4,5-dihydropyrazol-1-yl)-5-(2-oxo-2-arylethyl)-thiazol-4-ones (5a–d). A mixture of pyrazoline-1-carbothioic acid amide (5 mmol) and maleic anhydride or appropriate *N*-arylmaleimide (5 mmol), or β-aroylacrylic acid (5 mmol) was refluxed for 1 h in 10 mL of acetic acid. After cooling to the room temperature, precipitated white powder was filtered off, washed with water and methanol, and recrystallized with DMF:ethanol mixture (1:2).

*{2-[5-(4-Dimethylaminophenyl)-3-phenyl-4,5-dihydropyrazol-1-yl]-4-oxo-4,5-dihydrothiazol-5-yl}-acetic acid (**3a**).* Yield 76%, mp 200–202°C. ^{1}H-NMR (300 MHz, DMSO-d_6 + CCl_4): 12.68 (brs, 1H, COOH); 7.87 (d, 2H, J = 8.1 Hz, arom.); 7.57–7.52 (m, 3H, arom.); 7.05 (d, 2H, J = 7.5 Hz, arom.); 6.89 (d, 2H, J = 8.1 Hz, arom.); 5.66 (dd, 1H, J = 10.9, 2.4 Hz, $CH_2\underline{CH}$, pyraz.); 4.34 (dd, 1H, J = 11.2, 2.3 Hz, $CH_2\underline{CH}$, thiaz.); 4.10 (dd, 1H, J = 17.9, 10.9 Hz, $\underline{CH_2}CH$, pyraz.); 3.43 (dd, 1H, J = 17.9, 2.4 Hz, $\underline{CH_2}CH$, pyraz.); 3.05 (dd, 1H, J = 18.1, 11.2 Hz, $\underline{CH_2}CH$, thiaz.); 2.87 (s, 6H, $N(CH_3)_2$); 2.73 (dd, 1H, J = 18.1, 2.3 Hz, $\underline{CH_2}CH$, thiaz.). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 188.1 (C=O), 176.9 (C=N, thiaz.), 172.8 (C=O), 161.4 (C=N, pyraz.), 150.5, 133.5, 131.9, 130.4, 129.1, 128.4, 127.8, 112.9, 63.9 ($\underline{C}HCH_2$), 50.5 ($\underline{C}HCH_2$), 45.2 (N- $(CH_3)_2$), 43.8 ($CH\underline{C}H_2$), 38.1 ($CH\underline{C}H_2$). Calcd. for $C_{22}H_{22}N_4O_3S$: C, 62.54; H, 5.25; N, 13.26; Found: C, 62.41; H, 5.38; N, 13.12%.

*{2-[5-(4-Chlorophenyl)-3-phenyl-4,5-dihydropyrazol-1-yl]-4-oxo-4,5-dihydrothiazol-5-yl}-acetic acid (**3b**).* Yield 66%, mp 205–207°C. ^{1}H-NMR (300 MHz, DMSO-d_6 + CCl_4): 12.75 (brs, 1H, COOH); 7.86 (d, 2H, J = 6.8 Hz, arom.); 7.57–7.51 (m, 3H, arom.); 7.44 (d, 2H, J = 7.1 Hz, arom.); 7.27 (d, 2H,

J = 7.3 Hz, arom.); 5.83 (dd, 1H, J = 10.9, 2.7 Hz, $CH_2\underline{CH}$, pyraz.); 4.36 (dd, 1H, J = 10.3, 3.4 Hz, $CH_2\underline{CH}$, thiaz.); 4.17 (dd, 1H, J = 18.1, 10.9 Hz, $\underline{CH_2}CH$, pyraz.); 3.45 (dd, 1H, J = 18.1, 2.7 Hz, $\underline{CH_2}CH$, pyraz.); 3.05 (dd, 1H, J = 16.4, 10.3 Hz, $\underline{CH_2}CH$, thiaz.); 2.73 (dd, 1H, J = 16.4, 3.4 Hz, $\underline{CH_2}CH$, thiaz.). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 188.0 (C═O), 177.3 (C═N, thiaz.), 172.8 (C═O), 161.1 (C═N, pyraz.), 139.8, 132.8, 132.1, 130.2, 129.5, 128.4, 128.2, 127.8, 63.4 ($\underline{C}HCH_2$), 50.8 ($\underline{C}HCH_2$), 43.8 ($CH\underline{C}H_2$), 37.8 ($CH\underline{C}H_2$). Calcd. for $C_{20}H_{16}ClN_3O_3S$: C, 58.04; H, 3.90; N, 10.15; Found: C, 58.15; H, 3.78; N, 10.27%.

N-(4-Methoxyphenyl)-2-{2-[5-(4-methoxyphenyl)-3-phenyl-4,5-dihydropyrazol-1-yl]-4-oxo-4,5-dihydrothiazol-5-yl}-acetamide ***(4a)***. Yield 65%, mp 224–225°C. ^{1}H-NMR (300 MHz, DMSO-d_6 + CCl_4): 9.87 (s, 1H, NH); 7.83 (d, 2H, J = 6.8 Hz, arom.); 7.46–7.51 (m, 5H, arom.); 7.17 (d, 2H, J = 8.4 Hz, arom.); 6.88 (d, 2H, J = 8.4 Hz, arom.); 6.80 (d, 2H, J = 8.8 Hz, arom.); 5.75 (dd, 1H, J = 11.2, 3.6 Hz, $CH_2\underline{CH}$, pyraz.); 4.29 (dd, 1H, J = 7.8, 4.0 Hz, $CH_2\underline{CH}$, thiaz.); 4.14 (dd, 1H, J = 18.4, 11.2 Hz, $\underline{CH_2}CH$, pyraz.); 3.75 (s, 3H, OCH_3); 3.73 (s, 3H, OCH_3); 3.36 (dd, 1H, J = 18.4, 3.6 Hz, $\underline{CH_2}CH$, pyraz.); 3.19 (dd, 1H, J = 16.4, 7.8 Hz, $\underline{CH_2}CH$, thiaz.); 2.58 (dd, 1H, J = 16.4, 4.0 Hz, $\underline{CH_2}CH$, thiaz.). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 188.5 (C═O), 177.4 (C═N, thiaz.), 168.5 (C═O), 161.2 (C═N, pyraz.), 159.4, 155.8, 133.0, 132.5, 132.0, 130.3, 129.5, 127.8, 127.5, 121.2, 114.7, 114.4, 63.4 ($\underline{C}HCH_2$), 55.6 (O-CH_3), 55.2 (O-CH_3), 50.9 ($\underline{C}HCH_2$), 43.9 ($CH\underline{C}H_2$), 40.3 ($CH\underline{C}H_2$). $C_{28}H_{26}N_4O_4S$: C, 65.35; H, 5.09; N, 10.89; Found: C, 65.57; H, 5.18; N, 10.67%.

N-(4-Acetoxyphenyl)-2-{2-[5-(4-methoxyphenyl)-3-phenyl-4,5-dihydropyrazol-1-yl]-4-oxo-4,5-dihydrothiazol-5-yl}-acetamide ***(4b)***. Yield 72%, mp 230–232°C. ^{1}H-NMR (300 MHz, DMSO-d_6 + CCl_4): 10.21 (s, 1H, NH); 7.82 (d, 2H, J = 7.8 Hz, arom.); 7.59–7.44 (m, 5H, arom.); 7.15 (d, 2H, J = 8.7 Hz, arom.); 7.05 (d, 2H, J = 8.9 Hz, arom.); 6.90 (d, 2H, J = 8.4 Hz, arom.); 5.75 (dd, 1H, J = 11.1, 3.6 Hz, $CH_2\underline{CH}$, pyraz.); 4.36 (dd, 1H, J = 11.4, 3.5 Hz, $CH_2\underline{CH}$, thiaz.); 4.09 (dd, 1H, J = 18.3, 11.1 Hz, $\underline{CH_2}CH$, pyraz.); 3.72 (s, 3H, OCH_3); 3.33 (dd, 1H, J = 18.3, 3.6 Hz, $\underline{CH_2}CH$, pyraz.); 3.24 (dd, 1H, J = 16.4, 11.4 Hz, $\underline{CH_2}CH$, thiaz.); 2.67 (dd, 1H, J = 16.4, 3.5 Hz, $\underline{CH_2}CH$, thiaz.); 2.23 (s, 3H, $COCH_3$). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 188.5 (C═O), 177.4 (C═N, thiaz.), 169.8 (C═O), 169.1 (C═O), 161.3 (C═N, pyraz.), 159.4, 146.5, 136.9, 132.9, 132.0, 130.3, 129.5, 127.8, 127.7, 122.5, 120.5, 114.7, 63.7 ($\underline{C}HCH_2$), 55.6 (O-CH_3), 50.8 ($\underline{C}HCH_2$), 43.9 ($CH\underline{C}H_2$), 40.3 ($CH\underline{C}H_2$), 21.3 (CO-$\underline{C}H_3$). Calcd. for $C_{29}H_{26}N_4O_5S$: C, 64.19; H, 4.83; N, 10.33; Found: C, 64.31; H, 4.68; N, 10.20%.

N-(4-Acetoxyphenyl)-2-{2-[5-(4-chlorphenyl)-3-phenyl-4,5-dihydropyrazol-1-yl]-4-oxo-4,5-dihydrothiazol-5-yl}-acetamide ***(4c)***. Yield 78%, mp 235–237°C. ^{1}H-NMR (300 MHz, DMSO-d_6 + CCl_4): 10.22 (s, 1H, NH); 7.86 (d, 2H, J = 7.3 Hz, arom.); 7.60–7.50 (m, 5H, arom.); 7.45 (d, 2H, J = 8.1 Hz, arom.); 7.29 (d, 2H, J = 5.9 Hz, arom.); 7.08 (d, 2H, J = 8.6 Hz, arom.); 5.84 (dd, 1H, J = 11.1, 3.6 Hz, $CH_2\underline{CH}$, pyraz.); 4.24 (dd, 1H, J = 10.1, 3.0 Hz, $CH_2\underline{CH}$, thiaz.); 4.13 (dd, 1H, J = 16.5, 11.1 Hz, $\underline{CH_2}CH$, pyraz.); 3.48 (dd, 1H, J = 16.5, 3.6 Hz, $\underline{CH_2}CH$, pyraz.); 3.26 (dd, 1H, J = 16.4, 10.0 Hz, $\underline{CH_2}CH$, thiaz.); 2.73 (dd, 1H, J = 16.4, 3.0 Hz, $\underline{CH_2}CH$, thiaz.); 2.25 (s, 3H, $COCH_3$). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 188.5 (C═O), 177.6 (C═N, thiaz.), 169.8 (C═O), 169.0 (C═O), 161.1 (C═N, pyraz.), 146.5, 139.9, 136.9, 132.9, 132.0, 129.5, 129.4, 128.4, 128.3, 127.8, 122.5, 120.5, 63.5 ($\underline{C}HCH_2$), 50.8 ($\underline{C}HCH_2$), 43.8 ($CH\underline{C}H_2$), 43.7 ($CH\underline{C}H_2$), 21.3 (CO-$\underline{C}H_3$). Calcd. for $C_{28}H_{23}ClN_4O_4S$: C, 61.48; H, 4.24; N, 10.24; Found: C, 61.32; H, 4.48; N, 10.40%.

5-[2-(4-Fluorophenyl)-2-oxoethyl]-2-[5-(4-methoxyphenyl)-3-phenyl-4,5-dihydropyrazol-1-yl]-thiazol-4-one ***(5a)***. Yield 63%, mp 121–122°C. ^{1}H-NMR (300 MHz, DMSO-d_6 + CCl_4): 8.07 (dd, 2H, J = 8.8, 5.2 Hz, arom.); 7.82 (d, 2H, J = 6.8 Hz, arom.); 7.49–7.47 (m, 3H, arom.); 7.26 (t, 2H, J = 8.8 Hz, arom); 7.18 (d, 2H, J = 8.8 Hz, arom.); 6.86 (d, 2H, J = 8.4 Hz, arom.); 5.77 (dd, 1H, J = 11.2, 3.2 Hz, $CH_2\underline{CH}$, pyraz.); 4.32 (dd, 1H, J = 11.2, 4.0 Hz, $CH_2\underline{CH}$, thiaz.); 4.09 (dd, 1H, J = 18.8, 11.2 Hz, $\underline{CH_2}CH$, pyraz.); 3.90 (dd, 1H, J = 16.4, 11.2 Hz, $\underline{CH_2}CH$, thiaz.); 3.75 (s, 3H, OCH_3); 3.39 (dd, 1H, J = 18.8, 3.2 Hz, $\underline{CH_2}CH$, pyraz.); 3.32 (dd, 1H, J = 16.4, 4.0 Hz, $\underline{CH_2}CH$, thiaz.). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 196.9 (C═O), 188.7 (C═O), 177.5 (C═N, thiaz.), 165.8 (d, J_{CF} = 200.0 Hz, 1C), 161.2 (C═N, pyraz.), 139.5, 136.2, 134.2, 132.9, 131.8 (d, J_{CF} = 30.0 Hz, 2C), 130.3, 129.5, 128.4, 127.8, 116.3 (d, J_{CF} = 10.0 Hz, 2C), 114.7, 63.7 ($\underline{C}HCH_2$), 55.6 (O-CH_3), 49.7 ($\underline{C}HCH_2$), 43.9 ($CH\underline{C}H_2$), 42.9 ($CH\underline{C}H_2$). Calcd. for $C_{27}H_{22}FN_3O_3S$: C, 66.52; H, 4.55; N, 8.62; Found: C, 66.69; H, 4.38; N, 8.82%.

5-[2-Phenyl-2-oxoethyl]-2-[5-(4-chlorophenyl)-3-phenyl-4,5-dihydropyrazol-1-yl]-thiazol-4-one ***(5b)***. Yield 64%, mp 215–217°C. ^{1}H-NMR (300 MHz, DMSO-d_6 + CCl_4): 8.00 (d, 2H, J = 7.7 Hz, arom.); 7.85 (d, 2H, J = 7.2 Hz, arom.); 7.67 (t, 1H, J = 7.1 Hz, arom.); 7.56–7.52 (m, 5H, arom.); 7.44 (d, 2H, J = 7.9 Hz, arom.); 7.31 (d, 2H, J = 7.9 Hz, arom.); 5.85 (dd, 1H, J = 11.0, 3.3 Hz, $CH_2\underline{CH}$, pyraz.); 4.45 (dd, 1H, J = 10.5, 3.3 Hz, $CH_2\underline{CH}$, thiaz.); 4.16 (dd, 1H, J = 18.3, 11.0 Hz, $\underline{CH_2}CH$, pyraz.); 3.97 (dd, 1H, J = 18.7, 10.5 Hz, $\underline{CH_2}CH$, thiaz.); 3.54 (dd, 1H, J = 18.7, 3.3 Hz, $\underline{CH_2}CH$, thiaz.); 3.45 (dd, 1H, J = 18.3, 3.3 Hz, $\underline{CH_2}CH$, pyraz.). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 198.2 (C═O), 188.7 (C═O), 177.7 (C═N, thiaz.), 161.1 (C═N, pyraz.), 139.8, 136.2, 134.2, 132.9, 132.1, 130.2, 129.5, 129.4, 129.3, 128.6, 128.3, 127.8, 63.5 ($\underline{C}HCH_2$), 49.8 ($\underline{C}HCH_2$), 43.8 ($CH\underline{C}H_2$), 42.9 ($CH\underline{C}H_2$). Calcd. for $C_{26}H_{20}ClN_3O_2S$: C, 65.89; H, 5.25; N, 8.87; Found: C, 65.72; H, 5.40; N, 9.00%.

5-[2-(4-Fluorophenyl)-2-oxoethyl]-2-[5-(4-chlorophenyl)-3-phenyl-4,5-dihydropyrazol-1-yl]-thiazol-4-one ***(5c)***. Yield 69%, mp 200–202°C. ^{1}H-NMR (300 MHz, DMSO-d_6 +CCl_4): 8.09–8.06 (m, 2H, arom.); 7.85 (d, 2H, J = 6.8 Hz, arom.); 7.55–7.51 (m, 3H, arom.); 7.43 (d, 2H, J = 8.0 Hz, arom); 7.35–7.30 (m, 4H, arom.); 5.85 (dd, 1H, J = 11.1, 3.6 Hz, $CH_2\underline{CH}$, pyraz.); 4.44 (dd, 1H, J = 10.7, 2.6 Hz, $CH_2\underline{CH}$, thiaz.); 4.15 (dd, 1H, J = 18.1, 11.1 Hz, $\underline{CH_2}CH$, pyraz.); 3.95 (dd, 1H, J = 18.8, 10.7 Hz, $\underline{CH_2}CH$, thiaz.); 3.52 (dd, 1H, J = 18.8, 2.6 Hz, $\underline{CH_2}CH$, thiaz.); 3.44 (dd, 1H, J = 18.1, 3.6 Hz, $\underline{CH_2}CH$, pyraz.). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 196.8 (C═O), 188.7 (C═O), 177.6 (C═N, thiaz.), 165.8 (d, J_{CF} = 200.0 Hz, 1C), 161.1 (C═N, pyraz.), 139.8, 132.9, 131.9 (d, J_{CF} = 30.0 Hz, 2C), 131.6, 130.2, 129.5, 129.3, 128.3, 127.8, 116.3 (d, J_{CF} = 10.0 Hz, 2C), 63.5 ($\underline{C}HCH_2$), 49.8 ($\underline{C}HCH_2$), 43.8 ($CH\underline{C}H_2$), 42.9 ($CH\underline{C}H_2$). Calcd. for $C_{26}H_{19}ClFN_3O_2S$: C, 63.48; H, 3.89; N, 8.54; Found: C, 63.57; H, 3.70; N, 8.68%.

5-[2-(4-Chlorophenyl)-2-oxoethyl]-2-[5-(4-chlorophenyl)-3-phenyl-4,5-dihydropyrazol-1-yl]-thiazol-4-one ***(5d)***. Yield 74%, mp 203–205°C. ^{1}H-NMR (300 MHz, DMSO-d_6 + CCl_4): 8.02 (d, 2H, J = 8.3 Hz, arom.); 7.85 (d, 2H, J = 7.4 Hz, arom.); 7.62 (d, 2H, J = 8.3 Hz, arom.); 7.56–7.50 (m, 3H, arom); 7.45 (d, 2H, J = 7.9 Hz, arom.); 7.29 (d, 2H, J = 8.29 Hz, arom.); 5.85 (dd, 1H, J = 10.9, 3.2 Hz, $CH_2\underline{CH}$, pyraz.); 4.44 (dd, 1H, J = 10.7, 2.6 Hz, $CH_2\underline{CH}$, thiaz.); 4.15 (dd, 1H, J = 18.1, 10.9 Hz,

$\underline{CH_2}CH$, pyraz.); 3.97 (dd, 1H, J = 19.2, 10.7 Hz, $\underline{CH_2}CH$, thiaz.); 3.58 (dd, 1H, J = 19.2, 2.6 Hz, $\underline{CH_2}CH$, thiaz.); 3.47 (dd, 1H, J = 18.1, 3.2 Hz, $\underline{CH_2}CH$, pyraz.). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 196.7 (C═O), 188.7 (C═O), 177.4 (C═N, thiaz.), 161.2 (C═N, pyraz.), 139.7, 136.2, 133.0, 132.2, 131.8, 131.6, 130.2, 129.5, 129.4, 128.4, 128.2, 127.8, 63.4 ($\underline{C}HCH_2$), 49.7 ($\underline{C}HCH_2$), 43.8 ($CH\underline{C}H_2$), 42.7 ($CH\underline{C}H_2$). Calcd. for $C_{26}H_{19}Cl_2N_3O_2S$: C, 61.42; H, 3.77; N, 8.26; Found: C, 61.57; H, 3.60; N, 8.41%.

Pharmacology ***Primary anticancer assay.*** Primary anticancer assay was performed at ∼ 60 human tumor cell lines panel derived from nine neoplastic diseases (leukemia, melanoma, lung, colon, CNS, ovarian, renal, prostate, and breast cancers), in accordance with a protocol of the Drug Evaluation Branch, National Cancer Institute, Bethesda [24–28]. Tested compounds were added to the cultures at a single concentration (10^{-5} M), and the cultures were incubated for 48 h. End point determinations were made with a protein-binding dye, sulforhodamine B (SRB). Results for each tested compound were reported as a percent of growth of the treated cells when compared with the untreated control cells.

Methods for assay of antiviral activity. Primary antiviral assay was performed at a biodefense viruses panel (Tacaribe, Pichinde, Junin) and a respiratory viruses panel [Flu A (H3N2), Flu A (H5N1), Flu B, SARS] with a protocol of the NIAID's antimicrobial acquisition and coordinating [29–31]. Results for each tested compound were reported as virus-inhibitory concentration, 50% endpoint (EC_{50}), or 90% effective concentration (EC_{90}) and cell-inhibitory concentration, 50% endpoint (CC_{50}) were determined. A general selectivity index (SI) was calculated as a ration of (CC_{50})/(EC_{50}). An SI of 3 or greater indicates that confirmatory testing is needed.

Inhibition of viral cytopathic effect. This test, run in 96-well flat-bottomed microplates, was used for the initial antiviral evaluation of compounds. In this cytopathic effect (CPE) inhibition test, four log10 dilutions of each test compound (*e.g.*, 1000, 100, 10, 1 μg/mL) were added to three cups containing the cell monolayer; within 5 min. On the next step, the virus was added, and the plate was sealed and incubated at 37°C. CPE read microscopically when untreated infected controls develop a 3 to 4+ CPE (∼ 72–120 h). A known positive control drug was evaluated in parallel with test drugs in each test. This drug was ribavirin for influenza, Tacaribe, Pichinde, and Junin viruses and alferon for SARS virus. The data are expressed as 50% effective concentrations (EC_{50}).

Increase in neutral red dye uptake. This test was run to validate the CPE inhibition seen in the initial test, and utilized the same 96-well micro plates after the CPE has been read. When neutral red (NR) was added to the medium cells that were not damaged by virus take up a greater amount of dye, which is desplayed on a computerized microplate autoreader. An EC_{50} was determined from this dye uptake.

Decrease in virus yield assay (VYR-test). Compounds considered active by CPE inhibition and by NR dye uptake were retested on reduction of virus yield by assaying frozen and thawed eluates from each cup for virus titer by serial dilution onto monolayers of susceptible cells. Development of CPE in these cells is the indication of presence of infectious virus. The same as in the initial tests, a known active drug was run in parallel as a positive control. The 90% effective concentration (EC_{90}), which is drug concentration that inhibits virus yield by 1 log10, was determined from these data.

Methods for assay of cytotoxicity. In the CPE inhibition tests, two wells of uninfected cells treated with each concentration of tested compounds was run in parallel with the infected, treated wells. At the time CPE was determined microscopically. The toxicity control cells were also examined microscopically for any changes in cell appearance compared with normal control cells run in the same plate. These changes may be enlargement, granularity, cells with ragged edges, filmy appearance, rounding, detachment from the surface of the well, or other changes. These changes were given a designation of T (100% toxic), PVH (partially toxic–very heavy–80%), PH (partially toxic–heavy–60%), P (partially toxic–40%), Ps (partially toxic–slight–20%), or 0 (no toxicity–0%), conforming to the degree of cytotoxicity seen. A 50% cell inhibitory (cytotoxic) concentration (CC_{50}) was determined by regression analysis of these data.

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