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Article

Synthesis of Novel 1-(4-Substituted pyridine-3-sulfonyl)-3-phenylureas with Potential Anticancer Activity

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Abstract: A series of novel 4-substituted-*N*-(phenylcarbamoyl)-3-pyridinesulfonamides **11**–**27** have been synthesized by the reaction of 4-substituted pyridine-3-sulfonamides **2**–**10** with the appropriate aryl isocyanates in presence of potassium carbonate. The *in vitro* anticancer activity of compounds **11**, **12**, **14**–**21** and **24**–**26** was evaluated at the U.S. National Cancer Institute and in light of the results, some structure-activity relationships were discussed. The most prominent compound, *N*-[(4-chlorophenyl)carbamoyl]-4-[4-(3,4-dichlorophenyl)piperazin-1-yl]pyridine-3-sulfonamide (**21**) has exhibited a good activity profile and selectivity toward the subpanels of leukemia, colon cancer and melanoma, with average GI_{50} values ranging from 13.6 to 14.9 μM.

Keywords: sulfonamides; pyridine-3-sulfonamides; sulfonylureas; diarylsulfonylureas; anticancer; antitumor activity

1. Introduction

Sulfonylureas have been used in pharmacotherapy since the 1950s when the first antidiabetic compound *carbutamide* was released to the market. Since then, several sulfonylureas have been commonly used as antihypoglycemic (e.g., *tolbutamide*, *glipizide*, *glimepiride*), diuretics (*torasemide*) or herbicides (*rimsulfuron*). Large numbers of sulfonylurea derivatives have also been tested in

preclinical studies among others towards histamine H_3 receptor antagonism [1,2], thromboxane A_2 receptor antagonism [3,4], antibacterial [5], antimalarial [6] or antifungal activity [7], and in particular, an important part of this research concerns antitumor activity [8–12].

Studies on the antineoplastic activity led to discovery of N^1,N^3-diarylsulfonylureas (DSUs): LY-181984, LY-186641 (*sulofenur*) and LY-295501 (Figure 1) which were recognized as a group of compounds with activity against a broad spectrum of syngeneic rodent solid tumors and human tumor xenografts [13].

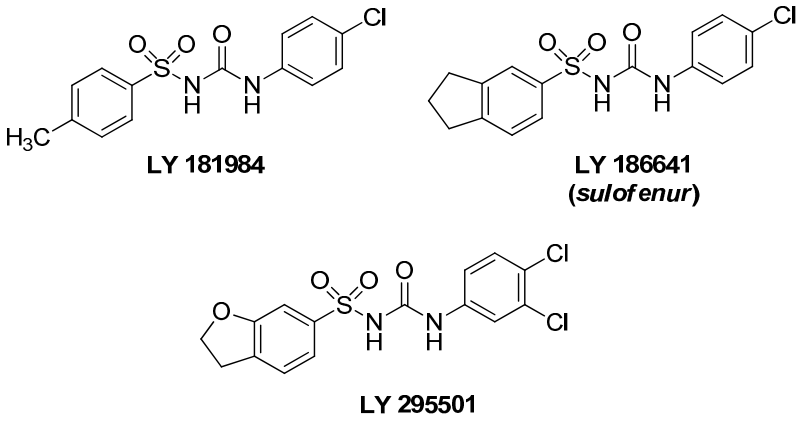


Figure 1. Anticancer diarylsulfonylureas (DSUs).

Due to the high *in vivo* activity in mouse models, *sulofenur* and LY-295501 have been evaluated in phase I or II clinical trials on patients with a non-small cell lung carcinoma (NSCLC), renal carcinoma. melanoma, and ovarian cancer [14]. Despite the disappointing results of the tests, mainly due to high hemotoxicity, novel sulfonylurea derivatives with anticancer activity are constantly being developed [15].

Recently, we have reported on the synthesis of a series of 4-substituted pyridine-3-sulfonamides bearing primary sulfonamide moieties [16,17] as an efficient and selective carbonic anhydrase inhibitors (types **I**–**III**, Figure 2), whereas 4-piperazin-1-yl-pyridine-3-sulfonamides of type **III** (Figure 2) exhibited also moderate anticancer activity [17]. It is also well known that selective hCA inhibitors have a proven ability to limit the growth and restrict metastasis in xenograft models of breast cancer [18,19], and therefore they are considered as novel type of anticancer drugs with novel mechanism of action [20–24].

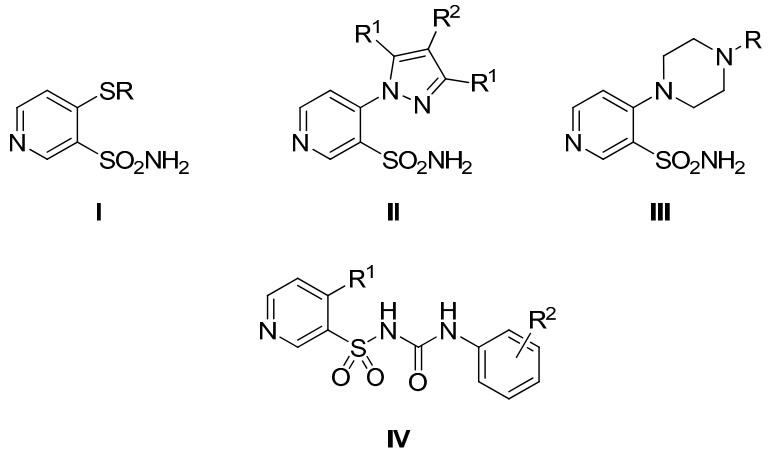


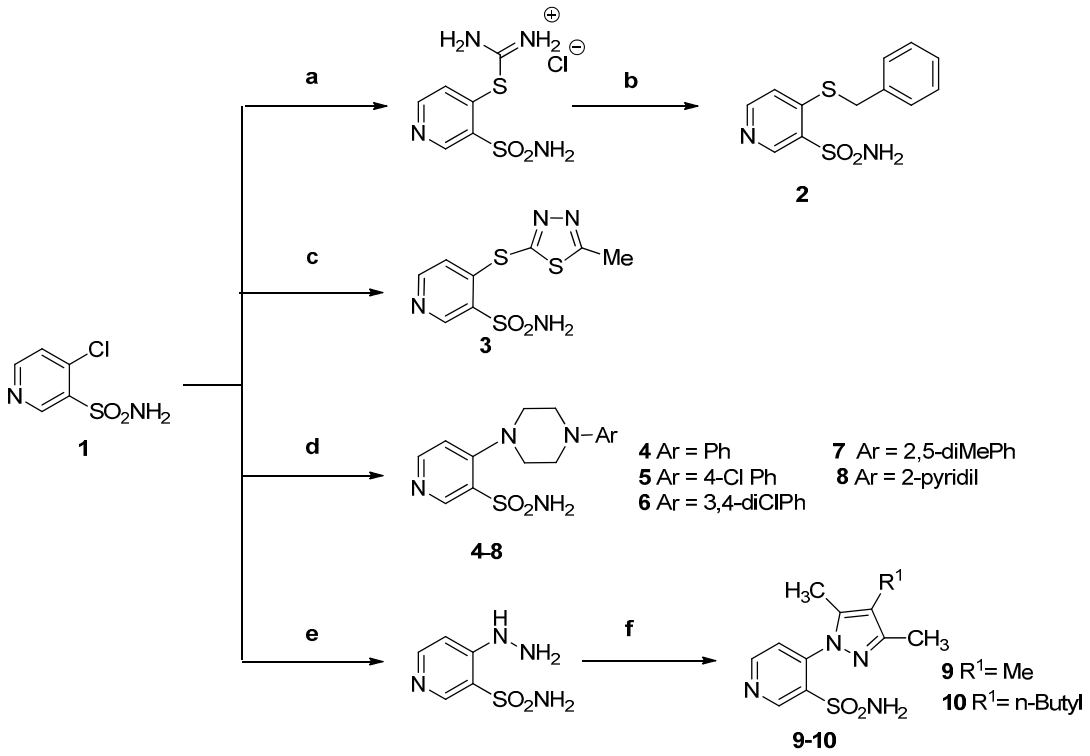
Figure 2. General structure of 4-substituted pyridine-3-sulfonamide derivatives.

These findings prompted us to explore further series of DSUs possessing 1-(4-substituted pyridine-3-sulfonyl)-3-phenylureas core of type **IV** (Figure 2), and to investigate their anticancer properties.

2. Results and Discussion

2.1. Chemistry

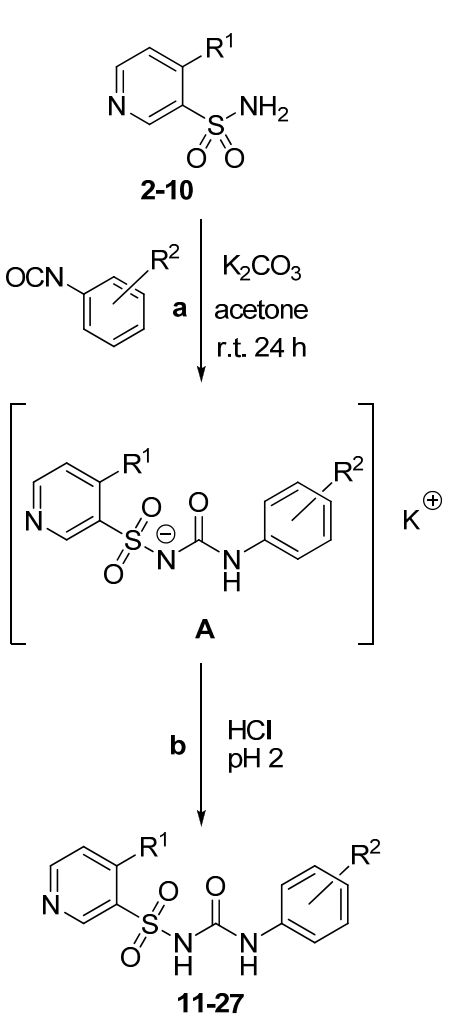
The starting 4-substituted pyridine-3-sulfonamides **2**, **4**–**10** were prepared according to the known methods [16,17], while the novel compound 4-[(5-methyl-1,3,4-thiadiazol-2-yl)thio]-3-pyridine-sulfonamide (**3**) was synthesized by the reaction of aromatic nucleophilic substitution of chlorine atom of **1** with 5-methyl-1,3,4-thiadiazole-2-thiol, under forcing conditions of elevated pressure and temperature (Scheme 1).

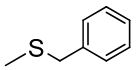
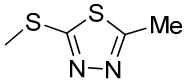
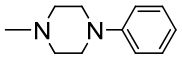
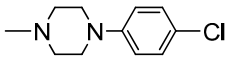
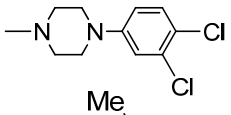
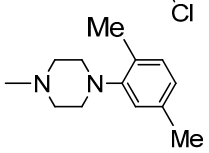
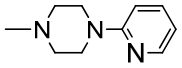
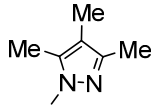
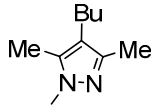


Reagents and conditions: (**a**) thiourea (1.02 eq.), MeCN, reflux, 3 h, [16]; (**b**) NaOH (2.14 eq.) water/THF 5 °C, 0.5 h, r.t. 5 h [16]; (**c**) 5-methyl-1,3,4-thiadiazole-2-thiol (1.2 eq.), MeCN r.t. 2 h, 100 °C 24 h, elevated pressure; (**d**) 4-Ar-piperazine (2 eq.), MeOH, r.t. 28 h, or 4-Ar-piperazine hydrochloride (1.2 eq.), Et_3N (2.25 eq.), MeOH r.t. 72 h [17]; (**e**) $H_2NNH_2 \times H_2O$ (6 eq.), MeOH r.t. 16 h, reflux, 4 h [16]; (**f**) 3-R^1-2,4-pentanedione (1.1 eq.), AcOH, reflux, 2 h [17].

Scheme 1. Facile synthesis of the starting 4-substituted 3-pyridinesulfonamide derivatives **2**–**10**.

The desired, 4-substituted *N*-(phenylcarbamoyl)pyridine-3-sulfonamides **11**–**27** were obtained by treatment for 24 h of primary sulfonamides **2**–**10** with the appropriate aryl isocyanates (*i.e.*, phenyl isocyanate, 4-chlorophenyl isocyanate or 3,4-dichlorophenyl isocyanate) in dry acetone at room temperature in the presence of anhydrous potassium carbonate (Scheme 2). Then, the initially formed intermediate potassium salts of type **A** were acidified with dilute hydrochloric acid to pH 2, to afford expected diarylsulfonylurea products in moderate to good yields (47%–80%).



Compd	R^1	R^2
2, 11		H
2, 12		4-Cl
2, 13		3,4-diCl
3, 14		4-Cl
4, 15		H
4, 16		4-Cl
4, 17		3,4-diCl
5, 18		H
5, 19		4-Cl
6, 20		H
6, 21		4-Cl
7, 22		4-Cl
8, 23		4-Cl
9, 24		H
9, 25		4-Cl
9, 26		3,4-diCl
10, 27		4-Cl

Reagents and conditions: (**a**) arylisocyanate (1.2 eq.), anhydrous K_2CO_3 (1.0 eq.), dry acetone, r.t. 24 h; (**b**) H_2O 5 mL, 4% HCl pH 2 r.t. 16 h.

Scheme 2. Synthesis of 4-substituted-*N*-(R^2-phenylcarbamoyl)-3-pyridinesulfonamides **11**–**27**.

The final compounds were characterized by IR and NMR spectroscopy as shown in the Experimental Section. Elemental analyses (C,H,N) were in accordance with the proposed structures. In detail, IR absorption bands corresponding to the stretching vibration of the carbonyl group in -NH(C=O)NH- appeared for compounds **11**–**14** and **24**–**27** in the range of 1716–1732 cm^{-1}, and was shifted to 1630–1648 cm^{-1} for compounds **15**–**23** possessing a piperazine ring attached at the 4 position. Inspection of the ^{1}H-NMR spectra revealed the characteristic resonance signals of pyridine ring protons appeared as two doublets of H-5 and H-6 at 7.18–7.64 and 8.27–8.96 ppm, respectively, as well as a singlet signal of H-2 at 8.71–9.26 ppm. In turn, the singlet signals attributable to the NH protons of the urea moieties were observed at 8.9–9.4 ppm, whereas a broad singlet of the SO_2NH proton was found downfield in the wide region of 9.7–13.4 ppm.

2.2. Anticancer Activity

Compounds **11**, **12**, **14**–**21** and **24**–**26** were tested *in vitro* at the U.S. National Cancer Institute (Bethesda, MD, USA) at single high concentration of 10 μM against the NCI panel of 60 cell lines

derived from nine different human cancer types: leukemia, non-small-cell lung cancer (NSCLC), colon, central nervous system (CNS), melanoma, ovarian, renal, prostate and breast cancer. Inhibition growth percent (IGP) data compared to no-drug control, obtained for each of the cell lines, are shown in Table 1.

Table 1. Inhibition growth percent (IGP [%]) for tested compounds (**11**, **12**, **14**–**21**, **24**–**26**) against selected NCI-60 cancer cell lines at single concentration 10^{-5} M.[a]

Panel	Cell Line	IGP [%] of Compound												
		11	**12**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**24**	**25**	**26**
Leukemia	CCRF-CEM	1	4	27	30	7	–	2	11	*	85	27	19	–
	K-562	6	67	–	45	–	7	12	70	20	95	42	72	*
	MOLT-4	7	21	–	27	–	6	5	18	9	85	9	20	8
	RPMI-8226	*	*	–	70	–	*	1	7	*	93	72	10	*
	SR	–	15	–	16	–	12	–	–	–	95	1	29	19
NSCLC	HOP-92	*	*	–	53	–	*	*	2	*	131	28	*	–
	NCI-H522	7	25	*	43	*	8	9	19	5	110	28	12	8
Colon cancer	HCC-2998	11	1	*	1	*	*	11	9	2	73	*	2	*
	HCT-15	*	39	37	*	31	9	*	28	*	41	*	53	4
	KM12	*	43	*	25	4	7	–	24	14	89	27	49	*
	SW-620	*	24	30	10	21	*	*	30	*	82	12	40	*
CNS cancer	SF-268	*	18	3	1	6	*	*	19	6	71	*	26	*
	SF-295	11	13	6	43	13	10	*	10	–	147	48	*	1
Melanoma	LOX IMVI	7	-	59	10	56	–	3	47	4	96	10	59	–
	MALME-3M	9	1	*	58	*	3	6	6	5	101	44	2	*
	M14	*	17	16	27	17	*	*	9	0	77	25	29	*
	MDA-MB-435	*	9	16	11	12	*	*	*	*	93	15	23	*
	UACC-62	*	57	51	33	38	*	*	32	*	73	31	42	10
Ovarian cancer	OVCAR-3	*	*	*	42	*	*	*	*	*	75	50	*	*
Renal cancer	A498	15	19	33	4	42	5	17	13	12	80	7	6	0
	ACHN	*	31	22	25	21	*	*	24	*	93	26	25	*
	CAKI-1	2	33	29	*	28	11	*	23	*	65	5	17	2
	UO-31	12	18	17	27	19	9	5	21	10	110	20	29	16
Prostate cancer	PC-3	11	6	14	54	17	*	6	21	16	101	51	12	*
	DU-145	*	16	5	*	7	*	*	18	*	67	1	32	*
Breast cancer	MDA-MB-468	*	7	–	59	–	3	*	*	*	109	57	*	*
	T-47D	2	20	21	33	17	6	10	27	9	92	26	18	7

[a] Data obtained from NCI-60 DTP human tumor cell line screening [25–29], * IGP ≤ 0%; – not tested.

The most important conclusion based on this preliminary anticancer assay is the finding that substitution patterns of the urea phenyl ring (R^2), has a crucial impact on the cytotoxic activity potency:

(a) All compounds with 4-chlorophenylcarbamoyl (R^2 = 4-Cl) moieties (**12**, **14**, **16**, **19**, **21** and **25**) are characterized by moderate to high activity with IGP range from 17 to 96% against the common cancer cell lines: leukemia (K-562, MOLT-4), colon cancer (HCT-15 and SW-620,) melanoma (LOX IMVI and UACC-62), and renal cancer (ACHN, CAKI-1) (Table 1), as well exhibit high overall activity with the average IGP for the whole panel in the range from 7 to 90%.

(b) Apparently the introduction of a second chlorine atom in position 3 of the 4-chloro-phenylcarbamoyl moiety (R^2 = 3,4-diCl) in compounds **17** and **26** definitely causes a loss of

activity. In this case the highest IGP values of 12 and 19% are observed only for the leukemia SR cell line.

(c) From among of the compounds with unsubstituted phenylcarbamoyl moieties (R^2 = H; *i.e.*, **11**, **15**, **18**, **20** and **24**) only compounds **15** and **24** exhibit high antiproliferative activity against certain cell lines: leukemia RPMI-8226 (IGP = 70 and 72%), NSCLC HOP-92 (IGP = 53 and 28%), CNS cancer (IGP = SF-295 43 and 48%), melanoma MALME-3M (IGP = 58 and 44%), ovarian cancer OVCAR-3 (IGP = 42 and 50%), prostate cancer PC-3 (IGP = 54 and 51%) or breast cancer MDA-MB-468 (IGP = 59 and 57%), respectively (Table 1). It should be noted that the mentioned cell lines, which are highly susceptible for compounds **15** and **24**, do not exhibit significant sensitivity for their 4-chlorophenylurea (R^2 = 4-Cl) analogs **16** and **25**.

It was stated that among a series of 4-chlorophenylureas (**12**, **14**, **16**, **19**, **21** and **25**) replacement of the benzylthio moiety (R^1) at the 4 position of the pyridine ring (compound **12**) by a 5-methyl-1,3,4-thiadiazole-2-thiol group in **14** led to a decrease of the susceptibility of NCI-H522 (from 25 to 0%), KM-12 (from 43 to 0%), however the cell lines CCRF-CEM, HCT-116 remain more sensitive to compound **12** (increase from 0 to 25% and from 0 to 43%, respectively). On the other hand removal of the sulfur atom and introduction of a pyrazole moiety in **25** leads to higher activity towards the majority of cell lines, especially for HCT-15, KM 12, SF-268, UO-31 and DU-145 (Table 1).

Additionally, introduction of a chlorine atom in **19** to the phenylpiperazinyl substituent of **16** results in a slight increase of antiproliferative activity towards the NSCLC cell line NCI-H522 (from 0 to 19%), colon cancer HCC-2998 (from 0 to 9%), KM12 (from 4 to 24%), SW-620 (from 21 to 30%), CNS cancer SF-268 (from 6 to 19%), prostate cancer PC-3 (from 17 to 21%), DU-145 (from 7 to 18%) breast cancer T-47D (from 17 to 27%), however it also resulted in loss of activity against renal cancer A498 (from 42 to 13%) melanoma M14 (from 17 to 9%) and MDA-MB-435 (from 12 to 0%) (Table 1). Nevertheless introducing of second chlorine atom at position 3 of the 4-chlorophenylpiperazin-1-yl in **21** causes a huge increase of activity since all mentioned lines demonstrate IGPs over 66%. The average IGP for all cell lines reached 90% and furthermore a cytotoxic effect (IGP > 100%) was observed for sixteen cell lines representing all nine cancer types.

Thus, the most active compound *N*-[(4-chlorophenyl)carbamoyl]-4-[4-(3,4-dichlorophenyl)-piperazin-1-yl]pyridine-3-sulfonamide (**21**) was further tested at the NCI five-dose assay (in the range of 0.01–100 μM) (Table 2). A relatively highest sensitivity to this compound was found for the subpanels of leukemia, colon cancer and melanoma, which the average GI_{50} values range from 13.6 to 14.9 μM (*sulofenur* (NSC-642684) 25.5–37.5 μM [30]).

Thus, the lowest GI_{50} was found for the cell lines of melanoma UACC-62 (1.5 μM) and M14 (8.9 μM), leukemia K-562 (3 μM) and CCRF-CEM (8.2 μM), and colon cancer HCT-15 (6.4 μM) as well as for the renal cancer CAKI-1 (6.28 μM) and UO-31 (9.8 μM) cell lines. Furthermore the GI_{50} values for the most sensitive cell lines (GI_{50} < 20 μM) for compound **21** are of the same order of magnitude and generally lower than for clinically tested *sulofenur* (Table 2).

Table 2. Anticancer *in vitro* data for compound **21** for the most sensitive cell lines (GI_{50} < 20 μM) [a], and comparative data for *sulofenur* (NSC-642684) [b] [30].

Panel	Cell line	21			Sulofenur [b]		
		GI_{50} [c]	TGI [d]	LC_{50} [e]	GI_{50} [c]	TGI [d]	LC_{50} [e]
Leukemia	CCRF-CEM	8.2	43.6	>100	29.8	>100	>100
	K-562	3.0	>100	>100	10.2	77.1	>100
	MOLT-4	19.9	68.1	>100	26.4	98.2	>100
	RPMI-8226	14.7	54.2	>100	24.4	85.7	>100
	SR	11.8	51.6	>100	57.0	>100	>100
NSCLC	A-549/ATCC	14.7	62.8	>100	32.7	97.7	>100
	HOP-62	18.8	43.5	>100	32.2	>100	>100
	NCI-H226	13.4	57.9	>100	37.9	77.8	>100
	NCI-H23	19.9	51.9	>100	28.1	56.0	90.8
	NCI-H322M	18.3	>100	>100	34.2	95.5	>100
	NCI-H460	17.2	69.4	>100	38.3	100	>100
	NCI-H522	14.1	49.4	>100	27.9	94.2	>100
Colon cancer	COLO 205	16.8	33.0	65.0	29.8	60.8	90.2
	HCC-2998	15.5	31.6	64.3	31.6	77.6	98.4
	HCT-116	15.1	34.4	78.2	26.2	67.3	85.1
	HCT-15	6.4	68.3	>100	35.6	90.2	>100
	HT29	15.9	45.7	>100	61.1	>100	>100
	KM12	13.0	>100	>100	36.1	98.9	>100
	SW-620	14.4	>100	>100	35.3	>100	>100
CNS cancer	SF-295	12.2	37.9	>100	46.7	>100	>100
	SF-539	13.1	29.0	64.4	28.3	69.2	>100
	SNB-19	19.1	57.6	>100	40.9	>100	>100
	U251	13.0	36.5	>100	30.7	77.4	>100
Melanoma	M14	8.9	53.4	>100	37.8	97.5	>100
	MDA-MB-435	18.9	>100	>100	17.6	48.3	>100
	SK-MEL-5	10.9	36.7	>100	26.8	74.0	98.2
	UACC-62	1.5	15.5	>100	23.9	84.7	>100
Ovarian cancer	IGROV1	16.3	68.1	>100	12.3	94.4	>100
	OVCAR-3	16.6	36.7	81.1	24.3	73.8	>100
	OVCAR-8	18.6	>100	>100	40.8	>100	>100
	NCI/ADR-RES	18.4	>100	>100	–	–	–
Renal cancer	786-0	16.1	43.7	>100	35.3	>100	>100
	A498	15.2	63.1	>100	45.0	>100	>100
	ACHN	11.6	>100	>100	29.4	>100	>100
	CAKI-1	6.3	>100	>100	42.8	>100	>100
	SN12C	18.4	>100	>100	39.2	>100	>100
	UO-31	9.8	27.3	75.0	25.1	76.4	>100
Prostate cancer	PC-3	14.4	71.1	>100	19.0	47.2	>100
	DU-145	17.3	55.7	>100	24.0	92.0	>100
Breast cancer	MCF7	19.7	97.4	>100	24.1	81.8	>100
	MDA-MB-231/ATCC	14.6	63.3	>100	–	–	–
	BT-549	16.1	44.7	>100	32.6	>100	>100
	T-47D	13.9	87.6	>100	16.4	74.6	>100
	MDA-MB-468	18.9	>100	>100	–	–	–

[a] Data obtained from NCI-60 DTP human tumor cell line screening [25–29]; [b] Sulofenur (NSC-642684): NCI cancer screen; September 2014 [30]; [c] GI_{50}: molar concentration [μM] that inhibits 50% net cell growth; [d] TGI: molar concentration [μM] giving total growth inhibition; [e] LC_{50}: molar concentration [μM] causing 50% net cell death; – not tested.

3. Experimental Section

3.1. General Procedures

The following instruments and parameters were used: melting points Boetius HMK apparatus; IR spectra: KBr pellets, 400–4000 cm^{-1} Thermo Mattson Satellite FTIR spectrophotometer; ^{1}H- and ^{13}C-NMR: Varian Gemini 200 apparatus at 200 MHz (^{1}H-NMR) and 50 MHz (^{13}C-NMR), Varian Unity 500 Plus apparatus at 500 MHz (^{1}H-NMR) and 125 MHz (^{13}C-NMR); chemical shifts are expressed in parts per million (ppm) relative to TMS as an internal standard. Elemental analyses were performed on PerkinElmer 2400 Series II CHN Elemental Analyzer, and they were in agreement with the theoretical values within ±0.4% range. The starting 4-chloro-3-pyridinesulfonamide (**1**) was commercially available (Alfa Aesar, Karlsruhe, Germany), while 4-substituted 3-pyridinesulfonamide **2**, **4**–**10** were obtained according to methods described previously: 4-benzylthio-3-pyridinesulfonamie (**2**) [16], 4-(4-substituted-piperazin-1-yl)-3-pyridinesulfonamides **4**–**8** [17], and 4-(1*H*-pyrazol-1-yl)-3-pyridine-sulfonamides **9**, **10** [17].

3.2. Synthesis

3.2.1. Procedure for the Preparation of 4-[(5-Methyl-1,3,4-thiadiazol-2-yl)thio]-3-pyridinesulfonamide (**3**)

In a closed glass pressure tube, a mixture of 4-chloro-3-pyridinesulfonamide (1.92 g, 10 mmol) and 5-methyl-1,3,4-thiadiazole-2-thiol (1.57 g, 12 mmol) in dry acetonitrile (16.5 mL) was stirred at room temperature for 2 h and then at 100 °C for 24 h. The precipitate of the hydrochloride was collected by filtration, washed with acetonitrile (3 × 2 mL) and dried, then suspended in water (8 mL) and slowly adjusted to pH 8 with 1% solution of NaOH. After stirring at room temperature for 3 h, the precipitate was filtered off, washed with water (2 × 1 mL), and dried. Yield 2.49 g (86%); mp 132–135 °C; IR (KBr) ν_{max} 3546, 3344 (NH), 1572 (C=C), 1330, 1163 (SO_2) cm^{-1}; ^{1}H-NMR (DMSO-d_6, 200 MHz) δ: 2.83 (s, 3H, CH_3); 7.09 (d, 1H, H-5 pyrid.); 8.00 (s, 2H, NH_2); 8.56 (d, 1H, H-6 pyrid.); 8.95 (s, 1H, H-2 pyrid.) ppm; anal. C 33.32, H 2.80, N 19.43% calcd. for $C_8H_8N_4O_2S_3$ C 33.02, H 2.84, N 19.33%.

3.2.2. General Procedure for the Preparation of 4-Substituted-*N*-(R^2-phenylcarbamoyl)-3-pyridine-sulfonamides

A mixture of 4-substituted-3-pyridinesulfonamide **2**–**10** (1 mmol), the appropriate phenyl isocyanate (1.2 mmol) and anhydrous potassium carbonate (0.14 g, 1 mmol) in dry acetone (15 mL) was stirred at room temperature for 24 h. The precipitate containing potassium salt of type **A** (Scheme 2) and inorganic salts was collected by filtration and washed with acetone (2 × 5 mL). The solid thus obtained was suspended in water (5 mL), slowly acidified with 4% hydrochloric acid to pH 2, and stirred overnight. The precipitate was filtered off washed with water (2 × 2 mL), and dried. In this manner the following compounds were obtained:

4-(Benzylthio)-N-(phenylcarbamoyl)-3-pyridinesulfonamide (**11**). Starting from 4-benzylthio-3-pyridinesulfonamide (**2**, 0.28 g), and phenyl isocyanate (0.14 g), the title compound **11** was obtained (0.32 g, 80%): mp 198–201 °C; IR (KBr) ν_{max} 3369 (NH), 3081 (C_{Ar}-H) 2928, 2853 (C-H), 1727

(C=O), 1600, 1579, 1547 (C=C, C=N), 1350, 1160 (SO_2) cm^{-1}; ^{1}H-NMR (DMSO-d_6, 200 MHz) δ 4.51 (s, 2H, CH_2), 7.03 (t, 1H, H-4′ Ph), 7.18–7.34 (m, 7H, H_{Ar}), 7.47 (m, 2H, H_{Ar}), 7.64 (d, J = 5.5 Hz, 1H, H-5 pyrid.), 8.58 (d, J = 5.5 Hz, 1H, H-6 pyrid.), 8.71 (s, 1H, H-2 pyrid.), 8.91 (s, 1H, NH), 11.0 (br.s, 1H, NH) ppm; ^{13}C-NMR (DMSO-d_6, 125 MHz) δ 35.52, 119.47, 121.45, 124.06, 128.31, 129.29, 129.61, 129.87, 131.89, 135.62, 138.43, 149.58, 149.67, 150.95, 152.89 ppm; anal. C 57.12, H 4.29, N 10.52% calcd for $C_{19}H_{17}N_3O_3S_2$ C 56.77, H 4.26, N 10.48%.

4-(Benzylthio)-N-[(4-chlorophenyl)carbamoyl]-3-pyridinesulfonamide (**12**). Starting from 4-benzylthio-3-pyridinesulfonamide (**2**, 0.28 g), and 4-chlorophenyl isocyanate (0.18 g), the title compound **12** was obtained (0.25 g, 58%): mp 204–207 °C; IR (KBr) ν_{max} 3391 (NH), 3107 (C_{Ar}-H) 2851 (C-H), 1725 (C=O), 1599, 1581, 1539, 1494 (C=C, C=N), 1347, 1153 (SO_2) cm^{-1}; ^{1}H-NMR (DMSO-d_6, 200 MHz) δ 4.50 (s, 2H, CH_2), 7.24 (m, 3H, H_{Ar}), 7.33 (s, 4H, H_{Ar}), 7.46 (m, 2H, H_{Ar}), 7.64 (d, J = 5.0 Hz, 1H, H-5 pyrid.), 8.58 (d, J = 5.0 Hz, 1H, H-6 pyrid.), 8.85 (s, 1H, H-2 pyrid.), 8.90 (s, 1H, NH), ppm; ^{13}C-NMR (DMSO-d_6, 125 MHz) δ 35.52, 121.13, 121.47, 127.57, 128.32, 129.28, 129.43, 129.89, 131.98, 135.61, 137.53, 149.85, 150.74, 152.68 ppm; anal. C 52.59, H 3.72, N 9.68% calcd for $C_{19}H_{16}ClN_3O_3S_2$ C 52.21, H 3.60, N 9.78%.

4-(Benzylthio)-N-[(3,4-dichlorophenyl)carbamoyl]-3-pyridinesulfonamide (**13**). Starting from 4-benzylthio-3-pyridinesulfonamide (**2**, 0.28 g), and 3,4-dichlorophenylisocyanate (0.23 g), the title compound **13** was obtained (0.27 g, 57%): mp 205–208 °C; IR (KBr) ν_{max} 3377 (NH), 3093 (C_{Ar}-H), 2924, 2852 (C-H), 1732 (C=O), 1599, 1578, 1532, 1477 (C=C, C=N), 1352, 1155 (SO2) cm^{-1}; ^{1}H-NMR (DMSO-d_6, 200 MHz) δ 4.50 (s, 2H, CH_2), 7.24–7.30 (m, 4H, H_{Ar}), 7.44–7.52 (m. 3H, H_{Ar}), 7.66–7.68 (m, 2H, H_{Ar}, H-5 pyrid.), 8.58 (d, 1H, H-6 pyrid.), 8.89 (s, 1H, H-2 pyrid.), 9.03 (s, 1H, NH), ppm; ^{13}C-NMR (DMSO-d_6, 50 MHz) δ 35.20, 119.32, 120.27, 121.15, 124.83, 127.90, 128.87, 129.49, 130.91, 131.34, 132.13, 135.20, 138.62, 149.71, 150.11, 150.32, 151.49 ppm; anal. C 48.73, H 3.23, N 8.97% calcd for $C_{19}H_{15}Cl_2N_3O_3S_2$ C 48.17, H 3.00, N 8.85%.

N-[(4-Chlorophenyl)carbamoyl]-4-[(5-methyl-1,3,4-thiadiazol-2-yl)thio]-3-pyridinesulfonamide (**14**). Starting from 4-[(5-methyl-1,3,4-thiadiazol-2-yl)thio]-3-pyridinesulfonamide (**3**, 0.29 g), and 4-chlorophenyl isocyanate (0.18 g), the title compound **14** was obtained (0.28 g, 63%): mp 167–171 °C; IR (KBr) ν_{max} 3297, 3201 (NH), 3076 (C_{Ar}-H), 2924, 2855 (C-H), 1716 (C=O), 1610, 1547, 1492 (C=C, C=N), 1350, 1159 (SO_2) cm^{-1}; ^{1}H-NMR (DMSO-d_6, 200 MHz) δ 2.80 (s, 3H, CH_3), 7.18 (d, 1H, H-5 pyrid.), 7.30–7.39 (m, 4H, Ph), 8.63 (d, 1H, H-6 pyrid.), 9.07 (s, 2H, H-2 pyrid. NH), 8.90 (s, 1H, NH), ppm; ^{13}C-NMR (DMSO-d_6, 125 MHz) δ 16.47, 121.36, 123.44, 127.60, 129.39, 133.28, 137.61, 145.94, 151.21, 153.96, 157.83, 172.56 ppm; anal. C 40.77, H 2.74, N 15.85% calcd for $C_{15}H_{12}ClN_5O_3S_3$ C 40.65, H 2.60, N 16.08%.

N-(Phenylcarbamoyl)-4-(4-phenylpiperazin-1-yl)-3-pyridinesulfonamide (**15**). Starting from 4-(4-phenylpiperazin-1-yl)-3-pyridinesulfonamide (**4**, 0.32 g), and phenyl isocyanate (0.14 g), the title compound **15** was obtained (0.32 g, 73%): mp 154–156 °C; IR (KBr) ν_{max} 3466 (NH), 3059 (C_{Ar}-H), 2826 (C-H), 1640 (C=O), 1599, 1524, 1504 (C=C, C=N), 1314 1138 (SO_2) cm^{-1}; ^{1}H-NMR (DMSO-d_6, 200 MHz) δ 3.33 (s, 4H, 2 × CH_2), 3.82 (s, 4H, 2 × CH_2), 6.77–7.06 (m, 4H, H_{Ar}), 7.12–7.40 (m, 7H, H_{Ar}, H-5 pyrid.), 8.39 (d, 1H, H-6 pyrid.), 8.77 (s, 1H, H-2 pyrid.), 8.92 (s, 1H, NH), 12.10 (br.s, 1H,

NH), ppm; ^{13}C-NMR (DMSO-d_6, 50 MHz) δ 48.14, 51.06, 114.35, 115.68, 118.31, 119.34, 121.61, 128.72, 129.15, 129.29, 140.59, 150.82, 156,69 ppm; anal. C 60.39, H 5.30, N 16.01%. calcd for $C_{22}H_{23}N_5O_3S$, C 60.26, H 5.36, N 15.68%.

N-[(4-Chlorophenyl)carbamoyl]-4-(4-phenylpiperazin-1-yl)-3-pyridinesulfonamide (**16**). Starting from 4-(4-phenylpiperazin-1-yl)-3-pyridinesulfonamide (**4**, 0.32 g), and 4-chlorophenylisocyanate (0.18 g), the title compound **16** was obtained (0.27 g, 56%): mp 145–149 °C; IR (KBr) ν_{max} 3478, 3290 (NH), 3070 (C_{Ar}-H), 2836 (C-H), 1641 (C=O), 1603, 1519, (C=C, C=N), 1320, 1133 (SO_2) cm^{-1}; ^{1}H-NMR (DMSO-d_6, 200 MHz) δ 3.30 (s, 4H, 2 × CH_2), 3.96 (s, 4H, 2 × CH_2), 6.78 (t, 1H, H-4 Ph), 6.94 (d, 2H, H-2,6 Ph), 7.14–7.31 (m, 5H, H_{Ar} and H-5 pyrid.), 7.44 (d, 2H, H-2′,6′ Ph), 8.32 (d, 1H, H-6 pyrid.), 8.89 (s, 1H, H-2 pyrid.), 8.95 (s, 1H, NH), 13.0 (br.s, 1H, NH), ppm; ^{13}C-NMR (DMSO-d_6, 125 MHz) δ 48.57, 51.11, 116.09, 119.81, 128.83, 129.53, 129.71, 151.12, 156.82 ppm; anal. C 55.99, H 4.70, N 14.84%. calcd for $C_{22}H_{22}ClN_5O_3S$, C 55.78, H 4,96, N 14.71%.

N-[(3,4-Dichlorophenyl)carbamoyl]-4-(4-phenylpiperazin-1-yl)-3-pyridinesulfonamide (**17**). Starting from 4-(4-phenylpiperazin-1-yl)-3-pyridinesulfonamide (**4**, 0.32 g), and 3,4-dichlorophenyl isocyanate (0.23 g), the title compound **17** was obtained (0.24 g, 47%): mp 172–175 °C; IR (KBr) ν_{max} 3425 (NH), 3062 (C_{Ar}-H), 2919, 2855 (C-H), 1630 (C=O), 1599, 1577, 1540, 1506 (C=C, C=N), 1371, 1140 (SO_2) cm^{-1}; ^{1}H-NMR (DMSO-d_6, 200 MHz) δ 3.29 (s, 4H, 2 × CH_2), 4.02 (s, 4H, 2 × CH_2), 6.79 (t, 1H, H-4 Ph), 6.93 (d, 2H, H-2,6 Ph), 7.18–7.32 (m, 5H, H_{Ar} and H-5 pyrid.), 7.85 (s, 1H, H-2′ Ph), 8.27 (d, 1H, H-6 pyrid.), 8.88 (s, 1H, H-2 pyrid.), 9.12 (s, 1H, NH), 13.4 (br.s, 1H, NH), ppm; ^{13}C-NMR (DMSO-d_6, 125 MHz) δ 48.58, 50.89, 113.65, 116.10, 118.16, 118.95, 119.83, 121.83, 129.47, 129.71, 130.74, 131.24, 142.68, 146.01, 151.08, 156.64 ppm; anal. C 52.18, H 4.18, N 13.83%. calcd for $C_{22}H_{21}Cl_2N_5O_3S$, C 51.78, H 4.05, N 13.86%.

4-[4-(4-Chlorophenyl)piperazin-1-yl]-N-(phenylcarbamoyl)-3-pyridinesulfonamide (**18**). Starting from 4-[4-(4-chlorophenyl)piperazin-1-yl]-3-pyridinesulfonamide (**4**, 0.35 g), and phenyl isocyanate (0.14 g), the title compound **18** was obtained (0.36 g, 76%): mp 177–181 °C; IR (KBr) ν_{max} 3404, 3278 (NH), 3083 (C_{Ar}-H), 2923, 2855 (C-H), 1648 (C=O), 1650 1598, 1496 (C=C, C=N), 1311 1128 (SO_2) cm^{-1}; ^{1}H-NMR (DMSO-d_6, 200 MHz) δ 3.34 (s, 4H, 2 × CH_2), 3.81 (s, 4H, 2 × CH_2), 6.86 (t, 1H, H-4′ Ph), 6.98 (d, J = 8.9 Hz, 2H, H-2,6 Ph), 7.16 (t, 2H, H-3′5′ Ph), 7.26 (d, J = 8.9 Hz, 2H, H-3,5 Ph), 7.31 (d, 1H H-5 pyrid.), 7.38 (d, 2H, H-2′,6′ Ph), 8.40 (d, 1H, H-6 pyrid.), 8.77 (s, 1H, H-2 pyrid.), 8.92 (s, 1H, NH), ppm; ^{13}C-NMR (DMSO-d_6, 125 MHz) δ 48.32, 51.21, 117.52, 118.64, 123.22, 129.11, 129.37, 129.61, 150.02, 157.06 ppm; anal. C 55.99, H 4.70, N 14.84%. calcd for $C_{22}H_{22}ClN_5O_3S$, C 55.59, H 4.65, N 14.87%.

N-[(4-Chlorophenyl)carbamoyl]-4-[4-(4-chlorophenyl)piperazin-1-yl]pyridine-3-sulfonamide (**19**). Starting from 4-[4-(4-chlorophenyl)piperazin-1-yl]-3-pyridinesulfonamide (**5**, 0.35 g), and 4-chlorophenyl isocyanate (0.18 g), the title compound **19** was obtained (0.28 g, 56%): mp 178–182 °C; IR (KBr) ν_{max} 3427, 3180 (NH), 3050 (C_{Ar}-H), 2920, 2854 (C-H), 1642 (C=O), 1626, 1583, 1540, 1497 (C=C, C=N), 1278, 1153 (SO_2) cm^{-1}; ^{1}H-NMR (DMSO-d_6, 200 MHz) δ 3.32 (s, 4H, 2 × CH_2), 3.95 (s, 4H, 2 × CH_2), 6.96 (d, 2H, H-2,6 Ph), 7.17 (d, 2H, H-3,5 Ph′), 7.23–7.31 (m, 3H, H-3,5 Ph and H-5

pyrid.), 7.44 (d, 2H, H-2,6 Ph′), 8.33 (d, 1H, H-6 pyrid.), 8.90 (s, 1H, H-2 pyrid.), 8.93 (s, 1H, NH), ppm; anal. C 52.18, H 4.18, N 13.83%. calcd for $C_{22}H_{21}Cl_2N_5O_3S$, C 52.38, H 3.98, N 13.71%.

4-[4-(3,4-Dichlorophenyl)piperazin-1-yl]-N-(phenylcarbamoyl)-3-pyridinesulfonamide (**20**). Starting from 4-[4-(3,4-dichlorophenyl)piperazin-1-yl]-3-pyridinesulfonamide (**6**, 0.39 g), and phenyl isocyanate (0.14 g), the title compound **20** was obtained (0.40 g, 80%): mp 177–180 °C; IR (KBr) ν_{max} 3443 (NH), 3058 (C_{Ar}-H), 2837 (C-H), 1639 (C=O), 1595, 1526, 1510, 1485 (C=C, C=N), 1314, 1141 (SO_2) cm^{-1}; ^{1}H-NMR (DMSO-d_6, 200 MHz) δ 3.39 (s, 4H, 2 × CH_2), 3.79 (s, 4H, 2 × CH_2), 6.86 (t, 1H, H-4′ Ph), 6.96 (dd, J_{ortho} = 8.2 Hz, J_{meta} = 2.2 Hz, 1H, H-6 3,4-diClPh), 7.16 (m, 3H, H-5 3,4-diClPh and H-3,5 Ph), 7.30 (d,h 1H, H-5 pyrid.), 7.36–7.44 (m, 3H, H-2,6 Ph and H-2,3 4-diClPh), 8.40 (d, 1H, H-6 pyrid.), 8.77 (s, 1H, H-2 pyrid.), 8.91 (s, 1H, NH), ppm; anal. C 52.18, H 4.18, N 13.83%. calcd for $C_{22}H_{21}Cl_2N_5O_3S$, C 52.51, H 4.11, N 13.81%.

N-[(4-Chlorophenyl)carbamoyl]-4-[4-(3,4-dichlorophenyl)piperazin-1-yl]pyridine-3-sulfonamide (**21**). Starting from 4-[4-(3,4-dichlorophenyl)piperazin-1-yl]-3-pyridinesulfonamide (**6**, 0.39 g), and 4-chlorophenyl isocyanate (0.18 g), the title compound **21** was obtained (0.35 g, 65%): mp 164–168 °C; IR (KBr) ν_{max} 3469 (NH), 3095 (C_{Ar}-H), 2925, 2837 (C-H), 1641 (C=O), 1591, 1525, 1489 (C=C, C=N), 1306. 1141 (SO_2) cm^{-1}; ^{1}H-NMR (DMSO-d_6, 200 MHz) δ 3.38 (s, 4H, 2 × CH_2), 3.93 (s, 4H, 2 × CH_2), 6.94 (dd, 1H, H-6 3,4-diClPh), 7.17 (m, 3H, H-5 3,4-diClPh and H-3,5 Ph), 7.28 (d, 1H, H-5 pyrid.), 7.38–7.46 (m, 3H, H-2,6 Ph and H-2 3,4-diClPh), 8.33 (d, 1H, H-6 pyrid.), 8.89 (s, 1H, H-2 pyrid.), 8.92 (s, 1H, NH), ppm; ^{13}C-NMR (DMSO-d_6, 50 MHz) δ 47.32, 50.33, 113.71, 113.75, 115.44, 116.42, 119.47, 119.99, 124.43, 128.42, 129.28, 130.78, 131.82, 140.32, 150.41, 156.49 ppm. anal. C 48.86, H 3.73, N 12.95%. calcd. for $C_{22}H_{20}Cl_3N_5O_3S$, C 48.82, H 3.70, N 12.81%.

N-[(4-Chlorophenyl)carbamoyl]-4-[4-(2,5-dimethylphenyl)piperazin-1-yl]-3-pyridinesulfonamide (**22**). Starting from 4-[4-(2,5-dimethylphenyl)piperazin-1-yl]-3-pyridinesulfonamide (**7**, 0.35 g), and 4-chlorophenyl isocyanate (0.18 g), the title compound **22** was obtained (0.36 g, 72%): mp 171–174 °C; IR (KBr) ν_{max} 3302 (NH), 3023 (C_{Ar}-H), 2945, 2918, 2857 (C-H), 1642 (C=O), 1516 (C=C, C=N), 1320, 1129 (SO_2) cm^{-1}; ^{1}H-NMR (DMSO-d_6, 200 MHz) δ 2.24 (s, 6H, 2 × CH_3), 2.96 (br.s, 4H, 2 × CH_2), 3.93 (br.s, 4H, 2 × CH_2), 6.78 (d, 1H, H-4 Ph), 6.86 (s. 1H, H-6 Ph), 7.06 (d, 1H, H-3 Ph), 7.17 (d, 2H, H-3,5 Ph) 7.30 (d, 1H, H-5 pyrid.), 7.47 (d, 2H, H-2,6 Ph), 8.33 (d, 1H, H-6 pyrid.), 8.89 (s, 1H, H-2 pyrid.), 8.97 (s, 1H, NH), ppm; ^{13}C-NMR (DMSO-d_6, 125 MHz) δ 17.84, 21.48, 51.83, 51.93, 114.17, 115.86, 119.66, 120.46, 124.45, 128.77, 129.24, 130.32, 131.33, 136.27, 141.13, 146.81, 151.24, 156.94, 157.63 ppm; anal. C 57.65, H 5.24, N 14.01%. calcd for $C_{24}H_{26}ClN_5O_3S$, C 57.21, H 5.44, N 14.07%.

N-[(4-Chlorophenyl)carbamoyl]-4-[4-(pyridin-2-yl)piperazin-1-yl]-3-pyridinesulfonamide (**23**). Starting from 4-[4-(pyridin-2-yl)piperazin-1-yl]-3-pyridinesulfonamide (**8**, 0.32 g), and 4-chlorophenyl isocyanate (0.18 g), the title compound **23** was obtained (0.30 g, 64%): mp 187–193 °C; IR (KBr) ν_{max} 3307 (NH), 3073 (C_{Ar}-H), 2923, 2854 (C-H), 1638 (C=O), 1609, 1593, 1505, (C=C, C=N), 1315, 1149 (SO_2) cm^{-1}; ^{1}H-NMR (DMSO-d_6, 200 MHz) δ 3.67 (s, 4H, 2 × CH_2), 3.76 (s, 4H, 2 × CH_2), 6.66 (t, 1H, H-5′ pyrid.), 6.85 (d, 1H, H-3′ pyrid.), 7.13 (m, 3H, H-3,5 Ph, H-5 pyrid), 7.46 (d, 2H, H-2,6 Ph), 7.56 (t, 1H, H-4′ pyrid.), 8.13 (d, 1H, H-6′ pyrid.), 8.29 (d, 1H, H-6 pyrid.), 8.81 (s, 1H, H-2 pyrid.),

8.91 (s, 1H, NH), ppm; ^{13}C-NMR (DMSO-d_6, 125 MHz) δ 45.01, 50.73, 107.79, 113.70, 113.76, 119.61, 124.16, 128.70, 130.79, 138.30, 141.43, 145.69, 148.25, 149.24, 156.08, 158.07, 159.38 ppm; anal. C 53.33, H 4.48, N 17.77%. calcd for $C_{21}H_{21}ClN_6O_3S$, C 52.44, H 4.19, N 17.67%.

N-(Phenylcarbamoyl)-4-(3,4,5-trimethyl-1H-pyrazol-1-yl)-3-pyridinesulfonamide (**24**). Starting from 4-(3,4,5-trimethyl-1*H*-pyrazol-1-yl)-3-pyridinesulfonamide (**9**, 0.27 g), and phenyl isocyanate (0.14 g), the title compound **24** was obtained (0.33 g, 87%): mp 161–164 °C; IR (KBr) ν_{max} 3254, 3199 (NH), 3079, 3018 (C_{Ar}-H), 2927, 2860 (C-H), 1730 (C=O), 1583, 1499 (C=C, C=N), 1363, 1350, 1170 (SO_2) cm^{-1}; ^{1}H-NMR (DMSO-d_6, 200 MHz) δ 1.93 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.17 (s, 3H, CH_3), 7.04 (t, 1H, H-4 Ph), 7.28 (m, 4H, Ph), 7.57 (d, J = 5.2 Hz, 1H H-5 pyrid.), 8.96 (d, J = 5.2 Hz, 1H, H-6 pyrid.), 9.08 (s, 1H, H-2 pyrid.), 9.27 (s, 1H, NH), 9.7 (br.s, 1H, NH), ppm; ^{13}C-NMR (DMSO-d_6, 125 MHz) δ 8.56, 10.61, 12.64, 114.15, 119.43, 124.07, 124.21, 129.65, 132.08, 138.48, 144.97, 149.67, 150.12, 152.88, 155.93 ppm; anal. C 56.09, H 4.97, N 18.17%. calcd for $C_{18}H_{19}N_5O_3S$, C 55.78, H 4.89, N 18.18%.

N-[(4-Chlorophenyl)carbamoyl]-4-(3,4,5-trimethyl-1H-pyrazol-1-yl)-3-pyridinesulfonamide (**25**). Starting from 4-(3,4,5-trimethyl-1*H*-pyrazol-1-yl)-3-pyridinesulfonamide (**9**, 0.27 g), and 4-chlorophenyl isocyanate (0.18 g), the title compound **25** was obtained (0.31 g, 75%): mp 178–182 °C; IR (KBr) ν_{max} 3247, 3186 (NH), 3010, 3035 (C_{Ar}-H), 2992, 2862 (C-H), 1727 (C=O), 1588, 1552, 1496 (C=C, C=N), 1384, 1363, 1170 (SO_2) cm^{-1}; ^{1}H-NMR (DMSO-d_6, 200 MHz) δ 1.93 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.16 (s, 3H, CH_3), 7.35 (s, 4H, Ph), 7.57 (d, 1H H-5 pyrid.), 8.96 (d, 1H, H-6 pyrid.), 9.21 (s, 1H, H-2 pyrid.), 9.26 (s, 1H, NH), ppm; ^{13}C-NMR (DMSO-d_6, 50 MHz) δ 8.13, 10.19, 12.21, 113.75, 120.69, 123.83, 127.29, 129.11, 131.64, 137.07, 138.09, 144.56, 149.28, 149.72, 152.40, 155.57 ppm; anal. C 51.49, H 4.32, N 16.68%. calcd for $C_{18}H_{18}ClN_5O_3S$, C 51.22, H 4.20, N 16.57%.

N-[(3,4-Dichlorophenyl)carbamoyl]-4-(3,4,5-trimethyl-1H-pyrazol-1-yl)-3-pyridinesulfonamide (**26**). Starting from 4-(3,4,5-trimethyl-1*H*-pyrazol-1-yl)-3-pyridinesulfonamide (**9**, 0.27 g), and 3,4-dichlorophenyl isocyanate (0.23 g), the title compound **26** was obtained (0.25 g, 55%): mp 163–166 °C; IR (KBr) ν_{max} 3324 (NH), 3104 (C_{Ar}-H), 2924, 2856 (C-H), 1727 (C=O), 1599, 1581, 1477 (C=C, C=N), 1381 1169 (SO_2) cm^{-1}; ^{1}H-NMR (DMSO-d_6, 200 MHz) δ 1.92 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.14 (s, 3H, CH_3), 7.25 (dd, 1H, H-6 Ph), 7.55 (m, 2H, H-5 Ph, H-5 pyrid.), 7.69 (d, 1H H-2 Ph), 8.96 (d, 1H, H-6 pyrid.), 9.26 (s, 1H, H-2 pyrid.), 9.40 (s, 1H, NH), ppm; ^{13}C-NMR (DMSO-d_6, 125 MHz) δ 8.55, 10.60, 12.64, 114.16, 119.69, 120.63, 124.29, 125.50, 131.48, 131.85, 132.12, 138.51, 138.78, 144.96, 149.97, 150.13, 152.75, 156.00 ppm; anal. C 47.58, H 3.77, N 15.41% calcd for $C_{18}H_{17}Cl_2N_5O_3S$, C 47.45, H 3.81, N 15.38%.

4-(4-Butyl-3,5-dimethyl-1H-pyrazol-1-yl)-N-[(4-chlorophenyl)carbamoyl]-3-pyridinesulfonamide (**27**). Starting from 4-(4-butyl-3,5-dimethyl-1*H*-pyrazol-1-yl)-3-pyridinesulfonamide (**10**, 0.31 g), and 4-chlorophenyl isocyanate (0.18 g), the title compound **27** was obtained (0.35 g, 76%): m.p. (EtOAc/Et_2O). 138–142 °C ; IR (KBr) ν_{max} 3344 (NH), 3127, (C_{Ar}-H), 2947, 2865 (C-H), 1726 (C=O), 1602, 1579, 1541, 1495 (C=C, C=N), 1385, 1164 (SO_2) cm^{-1}; ^{1}H-NMR (DMSO-d_6, 200 MHz) δ 0.90 (t, 3H, CH_3), 1.36 (m, 4H, 2 × CH_2), 2.07 (s, 3H, CH_3), 2.19 (s, 3H, CH_3), 2.36 (t, 2H, CH_2), 7.36 (s, 4H, Ph), 7.60 (d, 1H H-5 pyrid.), 8.96 (d, 1H, H-6 pyrid.), 9.25 (s, 1H, H-2 pyrid.), 9.27 (s, 1H, NH),

ppm; ^{13}C-NMR (DMSO-d_6, 125 MHz) δ 10.61, 12.68, 14.55, 22.46, 23.22, 32.85, 119.09, 121.04, 124.19, 127.66, 129.51, 132.13, 137.50, 138.48, 144.91, 149.77, 149.79, 152.80, 155.88 ppm; anal. C 54.60, H 5.24, N 15.16% calcd for $C_{21}H_{24}ClN_5O_3S$, C 54.21, H 5.16, N 14.99%.

3.3. In Vitro Anticancer Screening

Antitumor evaluation of compounds **11**, **12**, **14**–**21** and **24**–**26** was performed at the National Cancer Institute according to NCI-60 DTP Human Tumor Cell Line Screen procedure [25–29].

4. Conclusions

We have obtained a novel series of 4-substituted *N*-(R^2-phenylcarbamoyl)-3-pyridinesulfonamide derivatives **11**–**27** by the reaction of 4-substituted pyridine-3-sulfonamides **2**–**10** with aryl isocyanates in the presence of potassium carbonate. The compounds **11**, **12**, **14**–**21** and **24-26** have been screened *in vitro* for their anticancer activity at the U.S. National Cancer Institute. We found that many of the investigated compounds exhibited structure-dependent moderate or weak anticancer activity. Considering the structure-activity relationships, we conclude that in general the presence of a 4-chlorophenylcarbamoyl moiety attached to the sulfonamide functionality exerts in most cases a favorable influence on anticancer activity and selectivity of the tested diarylsulfonylurea derivatives **12**, **14**, **16**, **19**, **21** and **25**. Thus, the most active compound, *N*-[(4-chlorophenyl)carbamoyl]-4-[4-(3,4-dichlorophenyl)piperazin-1-yl]pyridine-3-sulfonamide (**21**) exhibited a good activity profile and selectivity toward the subpanels of either leukemia and colon cancer, or melanoma, with average GI_{50} values ranging from 13.6 to 14.9 μM, and could be considered as a lead compound for further optimization.

Supplementary Materials

Supplementary materials can be accessed at: http://www.mdpi.com/1420-3049/20/07/12029/s1.

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Author Contributions

K.S. carried out the synthesis of all compounds, analyzed spectroscopic and biological data and participated in preparing the text of this manuscript. J.S. created the concept of this work, gained founds, coordinated biological tests and wrote the manuscript together with K.S.

Conflicts of Interest

The authors declare no conflict of interest.

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Sample Availability: Samples of the compounds **2**–**27** are available from the authors.