Available online at www.sciencedirect.com
SCIENCE DIRECT
European Journal of Medicinal Chemistry 41 (2006) 611–615
EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY
http://france.elsevier.com/direct/ejmech

Original article

Synthesis, structure and anticancer activity of novel alkenyl-1,3,5-triazine derivatives

F. Sączewski [a,*], A. Bułakowska [b]

[a] Department of Chemical Technology of Drugs, Medical University of Gdańsk, 80-416 Gdańsk, Poland
[b] Department of Organic Chemistry, Medical University of Gdańsk, 80-416 Gdańsk, Poland

Received 7 October 2005; received in revised form 2 December 2005; accepted 5 December 2005
Available online 15 March 2006

Abstract

A series of novel 4-(*E*)-ethenyl-6-alkylamino-1,3,5-triazin-2-ylamine derivatives **9**–**17** have been synthesized by a Wittig reaction of corresponding alkyltriphenylphosphonium bromides **5**–**8** with (hetero)aromatic aldehydes. The *E* configuration of these alkenes was confirmed by ^{1}H NMR spectroscopic data. All the compounds prepared were screened at the National Cancer Institute (NCI) for their activity against a panel of 56 tumor cell lines and relationship between structure and in vitro antitumor activity is discussed. The most active compounds **14** and **17** showed 50% growth inhibitory activity in low micromolar concentrations against renal cancer A498 cell line and colon cancer cell line COLO 205, respectively.

Keywords: 4-(*E*)-ethenyl-6-alkylamino-1,3,5-triazin-2-ylamines; Synthesis; Structure; Antitumor activity

1. Introduction

Recently, 1,3,5-triazine derivatives bearing amino groups at position 2 and 4 have attracted considerable attention due to their chemotherapeutic potential [1–6] and antiangiogenic properties which result in anticancer effect of these compounds [7,8].

Our continuous interest in the synthesis of diaminotriazines led to the discovery of novel agents comprising acrylonitrile (structure **A**, Fig. 1) and iminoacetonitrile (structure **B**, Fig. 1) moieties at position 6, which, depending on their structure, exhibited potent activity against some cell lines of leukemia, CNS cancer, breast cancer or melanoma [9–11]. The most active (1,3,5-triazin-6-yl)acrylonitrile **A-1** (Fig. 1) possessing 5-nitrothiophene ring at position 3 of acrylonitrile moiety and 3,5,5-trimethylpyrazoline moiety at position 6 of triazine ring showed growth inhibitory activity in nanomolar concentrations against leukemia K-562, RPMI-8226 and SR cell lines [10]. In order to explore further the structure–activity relationships for this class of compounds we synthesized a new series of 6-alkenyl derivatives of type **C** lacking the cyano group (Fig. 1). The possibility that these compounds would be active stems from the fact that the previously described alkenyl heterocycles exhibited pronounced anticancer activity [12–14].

2. Results and discussion

The approach to the synthesis of target compounds **9**–**17** was based on a Wittig olefination of aldehydes. Thus, as shown in Scheme 1, the reaction of the previously described [10,15] bromomethyltriazine derivatives **1**–**4** with triphenylphosphine afforded corresponding alkyltriphenylphosphonium bromides **5**–**8**. These salts were subsequently used in a Wittig reaction with suitable aldehydes carried out in methanol in the presence of sodium methoxide. The intermediary formed ylides of type **D** (Scheme 2) were readily detected by their dark-red color, which began to fade upon reaction with aldehyde.

The configuration of the resulting olefins **9**–**17** was affirmed to be *E* by ^{1}H NMR spectroscopy ($J_{trans\ CH=CH} \sim 16$ Hz).

It is well known that the stereochemistry of the alkene product in Wittig reaction arises from the intermediary formed oxaphosphetane which breaks-down by way of a concerted *syn*-elimination [16]. Therefore, of the two possible diastereomeric oxaphosphetanes, the *cis* isomer leads to the *Z*-alkene, and *trans* isomer to the *E* alkene. Apparently, in this case the thermodynamically more stable *trans* oxaphosphetane is formed exclusively, which subsequently breaks down to the *E*-alkene products **9**–**17** (Scheme 2).

* Corresponding author.
E-mail address: saczew@amg.gda.pl (F. Sączewski).

0223-5234/$ - see front matter © 2006 Elsevier SAS. All rights reserved.
doi:10.1016/j.ejmech.2005.12.012

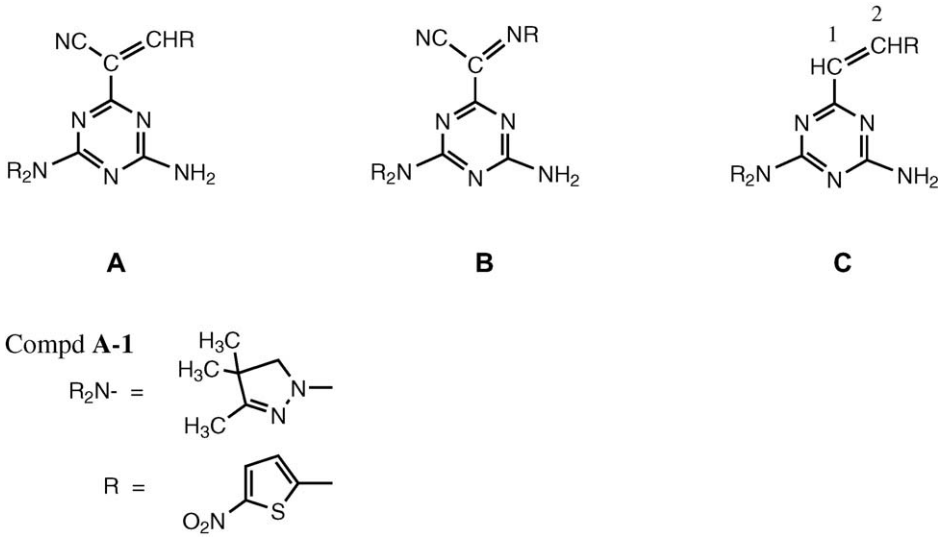
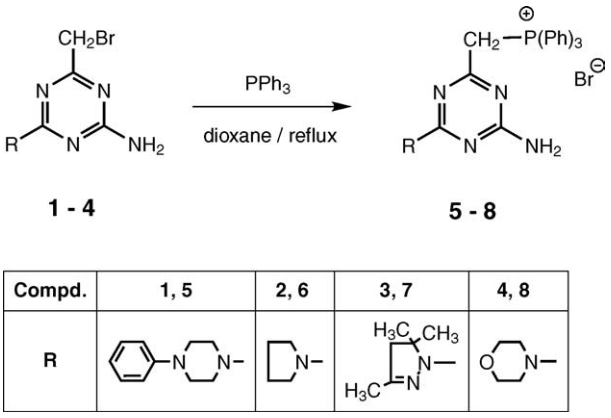


Fig. 1.



Scheme 1.

For the series of 6-alkenyl-1,3,5-triazine derivatives obtained, the effects of structural modifications on antitumor activity were explored within two structural domains: (hetero) aromatic ring R^2 at C-1 of alkenyl group and alkylamino substituents R_2N– at position 4′ of the triazine ring (Scheme 2).

First, it was found that incorporation of aromatic ring (R^2 = phenyl or 4-nitrophenyl) resulted in inactive compound **10** or afforded compounds **9**, **11** and **12** with weak to moderate activity (log MG_MID GI_{50} values between –4.49 and –5.18 (Table 1). As expected, the most potent compound **11** in this series incorporated 3,5,5-trimethylpyrazoline moiety at position 4′.

The heteroaromatic analogues **13**–**17** with 5-nitrofuryl and 5-nitrothienyl group exerted weak to fairly high activity (log MG_MID GI_{50} values ranged between –4.04 and –5.62). Interestingly, the least active in this series was compound **16** bearing a 3,5,5-trimethylpyrazoline moiety, while the most active compound was pyrrolidine analogue **17**, indicating that combination of R^2 = 5-nitrothienyl and R_2N– = pyrrolidinyl attached to alkenyl moiety results in compound with optimal properties.

From the pattern of mean graph it is evident that compound **14** demonstrates a greater than average selectivity towards some cell lines of renal cancer (A 498) and melanoma (SK MEL-5), whereas compounds **15** and **17** were selective against colon cancer cell line COLO 205 and melanoma cell line LOX-IMVI (Tables 1 and 2).

In conclusion, the readily available analogues of highly active (1,3,5-triazin-6-yl)acrylonitriles **A**, lacking the cyano group, retain the antitumor activity. However, they are less potent (compound **17** versus **A-1**) and a marked disparity in tumor cell specificity between these series is observed (Table 1). From the structure–activity point of view, these results may suggest that mechanisms by which acrylonitriles of type **A** and 6-alkenyltriazines **13**–**17** exert their antitumor effects are different.

3. Experimental protocols

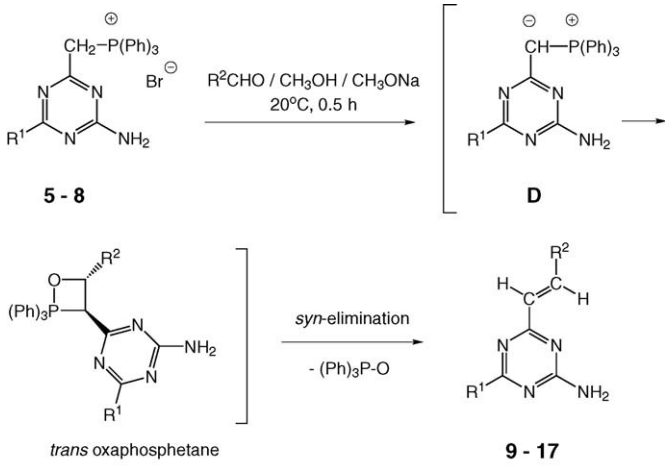
Melting points are not corrected and were recorded on a Buchi apparatus. IR spectra, KBr pellets, 400–4000 cm^{-1}, were recorded on a SATELLITE FTIR spectrophotometer (Mattson). ^1H and ^{13}C NMR spectra were recorded on a Varian Gemini 200 instrument at 200 and 50 MHz, respectively (chemical shifts are expressed as δ values relative to Me_4Si as standard). Elemental analyses of C, H, N were within ± 0.4% of the theoretical values.

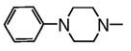
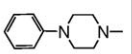
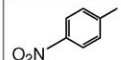
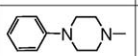
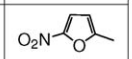
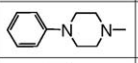
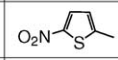
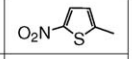
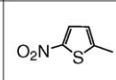
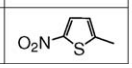
3.1. Synthesis

3.1.1. General procedure for the synthesis of (4-amino-6-alkylamino-[1,3,5]triazin-2-ylmethyl)-triphenyl-phosphonium, bromides *5, 7 and 8*

A mixture of the appropriate 6-bromometylytriazine **1**, **3** or **4** (1.4 mmol) and triphenylphosphine (0.37 g, 1.4 mmol) in dry dioxane (6 ml) was refluxed for 1 h. After cooling to room temperature, the solid that precipitated was collected by filtration, washed dioxane and dried.

*3.1.1.1. [4-Amino-6-(4-phenylpiperazin-1-yl)-[1,3,5]triazin-2-ylmethyl]-triphenyl-phosphonium, bromide **5***. Yield: 80%, m.p.



Compd.	R^1	R^2
5, 9		
6, 10		
7, 11		
5, 12		
5, 13		
5, 14		
8, 15		
7, 16		
6, 17		

Scheme 2.

157–160 °C; IR (KBr): 3324, 3057, 2806, 1658, 1567, 1438, 1335, 1107, 862, 772, 692, 515 cm $^{-1}$.

3.1.1.2. [4-Amino-6-(3,5,5-trimethyl-4,5-dihydro-pyrazol-1-yl)-[1,3,5]triazin-2-ylmethyl]-triphenyl-phosphonium, bromide 7. Yield: 76%, m.p. 104–108 °C; IR (KBr): 3337, 2965, 2870, 1645, 1558, 1437, 1340, 1107, 855, 719, 690, 513 cm $^{-1}$.

*3.1.1.3. (4-Amino-6-morpholin-4-yl-[1,3,5]triazin-2-ylmethyl)-triphenyl-phosphonium, bromide **8***. Yield: 64%, m.p. 238–242 °C; IR (KBr): 3463, 3248, 3131, 2848, 1618, 1576, 1437, 1110, 995, 853, 756, 691, 515 cm $^{-1}$.

*3.1.1.4. (4-Amino-6-pyrrolidin-1-yl-[1,3,5]triazin-2-ylmethyl)-triphenyl-phosphonium, bromide **6***. A suspension of triazine **2** (0.36 g, 1.4 mmol) and triphenylphosphine (0.37 g, 1.4 mmol) in dry dioxane (6 ml) was heated under reflux for 1 h. After cooling to room temperature, the solvent was evaporated under reduced pressure to dryness. The oily residue thus obtained was triturated thoroughly with dry diethyl ether. The product **6** that precipitated was separated by suction and dried: 94% yield, m.p. 180–184 °C; IR (KBr): 3399, 3057, 2847, 1660, 1543, 1437, 1335, 1107, 774, 719 cm $^{-1}$.

*3.1.2. General procedure for the preparation of 4-[(E)-2-phenylethenyl]-6-alkylamino-1,3,5-triazin-2-ylamines **9–17***

To a stirred solution of phosphonium salt **5–8** (1 mmol) and the corresponding aldehyde (1 mmol) in dry methanol (5 ml), was added drop-wise at 25 °C methanolic solution of sodium methoxide (1 mmol). After heating under reflux for 30 min., the reaction mixture was cooled to room temperature and the precipitate thus obtained was filtered off, washed with cold methanol and dried. Recrystallization from DMF or acetonitrile afforded the desired alkenyl derivatives **9–17**.

*3.1.2.1. 4-[(E)-2-phenylethenyl]-6-(4-phenylpiperazin-1-yl)-1,3,5-triazin-2-ylamine **9***. Yield: 46%, m.p. 139–143 °C (acetonitrile); IR (KBr): 3318, 3175, 2921, 2828, 1637, 1527, 1446, 1392, 1328 cm $^{-1}$; ^{1}H NMR ($CDCl_3$) δ: 3.26 (t, 4H, CH_2, $J = 5$ Hz, $J = 5.1$ Hz), 4.07 (s, 4H, CH_2), 5.49 (br. s, 2H, NH_2), 6.82–7.0 (m, 4H, CH), 7.31–7.45 (m, 5H, CH), 7.6–7.65 (m, 2H, CH), 8.05 (d, 1H, CH, $J = 16$ Hz) ppm. ^{13}C NMR ($CDCl_3$) δ: 43.76, 49.95, 117.17, 120.92, 125.96, 128.51, 129.31, 129.74, 130.14, 135.95, 141.14, 151.65, 164.92, 165.99, 170.11 ppm.

*3.1.2.2. 4-[(E)-2-phenylethenyl]-6-pyrrolidin-1-yl-1,3,5-triazin-2-ylamine **10***. Yield: 66%, m.p. 180–183 °C (acetonitrile); IR (KBr): 3329, 3171, 2971, 2870, 1665, 1642, 1533, 1451, 1340 cm $^{-1}$; ^{1}H NMR ($CDCl_3$) δ: 1.94–2.07 (m, 4H, CH_2), 3.55–3.72 (m, 4H, CH_2), 5.58 (s, 2H, NH_2), 6.88 (d, 1H, CH, $J = 16$ Hz), 7.3–7.46 (m, 3H, CH), 7.6–7.66 (m, 2H, CH), 8.04 (d, 1H, CH, $J = 16$ Hz) ppm. ^{13}C NMR ($CDCl_3$) δ: 25.49, 46.44, 46.66, 126.93, 128.09, 128.97, 129.48, 136.03, 139.62, 163.62, 166.51, 170.38 ppm.

*3.1.2.3. 4-[(E)-2-phenylethenyl]-6-(3,5,5-trimethyl-4,5-dihydro-1H-pyrazolin-1-yl)-1,3,5-triazin-2-ylamine **11***. Yield: 32%, m.p. 237–240 °C (DMF); IR (KBr): 3302, 3169, 2961, 1639, 1519, 1450, 1378, 1331, 1233 cm $^{-1}$, ^{1}H NMR ($CDCl_3$) δ: 1.73 (s, 6H, CH_3), 2.14 (s, 3H, CH_3), 2.85 (s, 2H, CH_2), 5.89 (br. s, 2H, NH_2), 6.85 (d, 1H, CH, $J = 15.8$ Hz), 7.36–7.61 (m, 5H, CH), 7.97 (d, 1H, CH, $J = 15.8$ Hz) ppm.

*3.1.2.4. 4-[(E)-2-(4-nitrophenyl)ethenyl]-6-(4-phenylpiperazin-1-yl)-1,3,5-triazin-2-ylamine **12***. Yield: 73%, m.p. 258–262 °C (DMF); IR (KBr): 3403, 3316, 3158, 2825, 1639, 1518, 1441, 1390, 1336 cm $^{-1}$; ^{1}H NMR (DMSO-d_6) δ: 3.25 (m, 4H, CH_2), 3.95 (m, 4H, CH_2), 6.8–7.09 (m, 6H, CH + NH_2), 7.26 (m, 2H, CH), 7.92–8.02 (m, 3H, CH, $J = 15.9$ Hz), 8.26 (d, 2H, CH, $J = 8.8$ Hz) ppm.

*3.1.2.5. 4-[(E)-2-(5-nitro-2-furyl)ethenyl]-6-(4-phenylpiperazin-1-yl)-1,3,5-triazin-2-ylamine **13***. Yield: 88%, m.p. 215–217 °C (acetonitrile); IR (KBr): 3516, 3400, 3148, 2820, 1612, 1555, 1440, 1348, 1288 cm $^{-1}$; ^{1}H NMR ($CDCl_3$) δ: 3.28 (t,

Table 1
Overview of the results of the in vitro antitumor screening for compounds **9** and **11**–**17**[a]

Compound.	No. of the cell lines giving positive log GI_{50}[b] [M], log TGI[c] [M] and log LC_{50} [M][d]						MG_MID[e] and Δ[f] for		Most sensible cell lines
	log GI_{50}[M][b]		log TGI [M[c]]		log LC_{50} [M][d]				
	Number	Range	Number	Range	Number	Range	log GI_{50}	log TGI	
9	56	–4.21 to –4.79	35	–4.50 to –4.02	4	–4.13 to –4.09	–4.57 0.37	–4.13 0.37	Renal cancer 786.0
11	56	–5.80 to –4.68	56	–5.15 to –4.11	44	–4.47 to –4.01	–5.18 0.62	–4.61 0.54	Breast cancer MDA-MB-435, melanoma LOXIMVI
12	53	–4.88 to –4.01	27	–4.48 to –4.02	3	–4.22 to –4.03	–4.49 0.25	–4.09 0.39	Melanoma SK-MEL-5
13	56	–5.56 to –4.60	46	–5.00 to –4.06	7	–4.18 to –4.01	–5.08 0.5	–4.36 0.64	Colon cancer COLO 205, renal cancer CAKI-1
14	56	–7.13 to –4.14	51	5.0 to –4.01	22	–4.50 to –4.01	–4.78 2.35	–4.32 0.68	Renal cancer A 498, melanoma SK Mel-5
15	55	–5.68 to –4.44	51	–5.29 to –4.25	43	–4.70 to –4.03	–5.01 0.67	–4.55 0.74	Colon cancer COLO 205, melanoma LOXIMVI
16	6	–4.52 to –4.11	0	> –4.00	0	> –4.00	–4.04 0.48	> –4.00 0.00	CNS cancer SNB-75
17	56	–7.02 to –4.72	56	–5.84 to –4.38	48	–5.30 to –4.02	–5.62 1.4	–4.88 0.96	Colon cancer COLO 205, melanoma LOXIMVI
A-1 [g]	60	–8.00 to –5.10	56	–7.24 to –4.16	43	–6.53 to –4.09	–6.59 1.72	–5.89 1.79	Leukemia RPMI-8226 Non small lung cancer NCI

[a] Data obtained from the NCI's in vitro disease-oriented human tumor cells screen (see Refs 5–7 for details). Compounds **11**–**18** and **20** were inactive (log GI_{50} [M] > 4.00).
[b] The log of the molar concentration that inhibits 50% net cell growth.
[c] The log of the molar concentration leading to total growth inhibition.
[d] The log of the molar concentration leading to 50% net cell death.
[e] MG_MID = mean graph midpoint = arithmetical mean value for all tested cell lines. If the indicated effect was not attainable within the used concentration interval, the highest tested concentration was used for the calculation.
[f] The reported data represent the logarithmic difference between the parameter value referred to the most sensible cell line and the same mean parameter. Delta is considered low if < 1, moderate > 1 and < 3, high if > 3.
[g] see Ref. [10].

4H, CH_2), 4.08 (br. s, 4H, CH_2), 5.43 (br. s, 2H, NH_2), 6.8 (d, 1H, CH, J = 3 Hz), 6.92–7.12 (m, 4H, CH), 7.33–7.41 (m, 3H, CH), 7.86 (d, 1H, CH, J = 15.8 Hz) ppm.

3.1.2.6. 4-[(E)-2-(5-nitro-2-thienyl)ethenyl]-6-(4-phenylpiperazin-1-yl)-1,3,5-triazin-2-ylamine ***14***. Yield: 91%, m.p. 240–242 °C (DMF); IR (KBr): 3443, 3307, 3159, 2821, 1625, 1544, 1512, 1436, 1356 cm $^{-1}$; ^{1}H NMR (DMSO-d_6) δ: 3.2 (br. s, 4H, CH_2), 3.94 (br. s, 4H, CH_2), 6.8–7.04 (m, 6H, CH + NH_2), 7.26 (m, 2H, CH), 7.63 (d, 1H, CH, J = 4.4 Hz), 8.0 (d, 1H, CH, J = 15.7 Hz), 8.15 (d, 1H, CH, J = 4.4 Hz) ppm.

3.1.2.7. 6-[(E)-2-(5-nitro-2-thiophenyl)ethenyl]-4(-morpholin-4-yl)-1,3,5-triazin-2-ylamine ***15***. Yield: 71%, m.p. 240–243 °C (DMF); IR (KBr): 3457, 3304, 3131, 2861, 1630, 1513, 1432, 1328, 1281 cm $^{-1}$; ^{1}H NMR (DMSO-d_6) δ: 3.63 (t, 4H, CH_2), 3.76 (br. s, 4H, CH_2), 6.85 (d, 1H, CH, J = 16.1 Hz), 7.07 (br. s, 2H, NH_2), 7.6 (d, 1H, CH, J = 4 Hz), 8.0 (d, 1H, CH, J = 16.1 Hz), 8.13 (d, 1H, CH, J = 4 Hz) ppm.

3.1.2.8. 4-[(E)-2-(5-nitro-2-thienyl)ethenyl]-6-(3,5,5-trimethyl-4,5-dihydro-1H-pyrazolin-1-yl)-1,3,5-triazin-2-ylamine ***16***. Yield: 76%, m.p. 277–280 °C (DMF); IR (KBr): 3509, 3271, 3136, 2912, 1675, 1626, 1513, 1431, 1329 cm $^{-1}$; ^{1}H NMR (DMSO-d_6) δ: 1.61 (s, 6H, CH_3), 1.98 (s, 3H, CH_3), 2.83 (s, 2H, CH_2), 6.88 (d, 1H, CH, J = 16.1 Hz), 7.1 (s, 2H, NH_2), 7.61 (d, 1H, CH, J = 4.4 Hz), 7.86 (d, 1H, CH, J = 15.6 Hz), 8.12 (d, 1H, CH, J = 4.4 Hz) ppm.

3.1.2.9. 4-[(E)-2-(5-nitro-2-thienyl)ethenyl]-6-pyrrolidin-1-yl-1,3,5-triazin-2-ylamine ***17***. Yield: 73%, m.p. 247–249 °C (DMF); IR (KBr): 3473, 3324, 3127, 2973, 2874, 1668, 1642, 1558, 1508 cm $^{-1}$; ^{1}H NMR (DMSO-d_6) δ: 1.89 (s, 4H, CH_2), 3.5 (d, 4H, CH_2), 6.85 (d, 1H, CH, J = 15.6 Hz), 7.03 (br. s, 2H, NH_2), 7.59 (d, 1H, CH, J = 4.4 Hz), 7.95 (d, 1H, CH, J = 15.6 Hz), 8.11 (d, 1H, CH, J = 4.4 Hz) ppm.

3.2. Biology

Compounds **9** and **11**–**17** which passed the preliminary screening on three tumor cell lines were tested in the framework of the in vitro Anticancer Screen Program of the National Cancer Institute (Bethesda, USA) on a panel of 56 human tumor cell lines derived from nine different cancer types: leukemia, lung, colon, CNS, melanoma, ovarian, renal, prostate and breast. Details of the system and the information which is encoded by the activity pattern over all cell lines, have been published [17–19]. The antitumor activity of a test compound is given by the parameters for each cell line: log GI_{50} value (GI_{50} = molar concentration of the compound that inhibits 50% net cell growth), log TGI value (TGI = molar concentration of compound leading to total growth inhibition), and LC_{50} value (LC_{50} = molar concentration of the compound leading to

Table 2
Inhibition of in vitro colon cancer, melanoma and renal cancer cell lines by selected compounds **14**, **15** and **17**[a]

Panel cell line	Compound **14**			Compound **15**			Compound **17**		
	log GI_{50}[b] [M]	log TGI[c] [M]	log LC_{50}[d] [M]	log GI_{50}[b] [M]	log TGI[c] [M]	log LC_{50}[d] [M]	log GI_{50}[b] [M]	log TGI[c] [M]	log LC_{50}[d] [M]
Colon cancer									
COLO 205	–4.81	–4.49	–4.17	–5.68	–5.29	–4.70	–7.02	–5.84	–5.26
HCC-2998	–4.65	–4.35	–4.04	–5.29	–4.78	–4.39	–5.48	–5.09	–4.56
HCT-116	–4.77	–4.50	–4.24	–5.53	–4.96	–4.48	–6.30	–5.69	–5.30
HCT-15	–4.83	–4.55	–4.26	–	–	–	–	–	–
HT29	–4.56	–4.15	a	–	–	–	–	–	–
KM12	–4.78	–4.41	–4.05	–5.46	–4.78	–4.26	–6.47	–5.61	–4.82
SW-620	–5.20	–4.55	–4.09	–4.86	a	a	–5.95	–4.75	a
Melanoma									
LOX IMVI	–4.80	–4.54	–4.27	–5.67	–5.02	–4.47	–6.70	–5.62	–4.83
MALME-3M	–4.60	–4.22	a	–	–	–	–	–	–
M 14	–4.71	–4.41	–4.10	–4.98	–4.61	–4.24	–5.71	–4.83	–4.42
SK-MEL-2	–4.67	–4.31	a	–4.76	–4.35	a	–4.93	–4.56	–4.19
SK-MEL-28	–4.60	–4.33	–4.05	–4.75	–4.42	–4.09	–4.93	–4.58	–4.24
SK-MEL-5	–5.80	–5.00	–4.50	–5.23	–4.72	–4.33	–5.11	–4.68	–4.33
UACC-257	–4.68	–4.35	–4.03	–4.97	–4.64	–4.30	–5.83	–5.02	–4.51
UACC-62	–4.87	–4.51	–4.15	–5.15	–4.71	–4.35	–5.84	–5.06	–4.52
Renal cancer									
786-0	–4.52	–4.31	–4.01	–4.80	–4.52	–4.24	–4.97	–4.63	–4.29
A498	–7.13	–4.81	–4.09	–5.05	–4.64	–4.28	–	–5.04	–4.40
ACHN	–4.72	–4.38	–4.05	–5.30	–4.75	–4.38	–5.13	–4.96	–4.48
CAKI-1	–4.74	–4.41	–4.07	–4.71	–4.40	–4.10	–4.97	–4.51	–4.06
RXF-393	–4.73	–4.43	–4.13	–4.95	–4.58	–4.21	–5.53	–4.85	–4.38
SN12C	–4.84	–4.45	–4.08	–4.88	–4.58	–4.27	–5.57	–4.60	–4.08
TK-10	–4.14	a	a	–4.66	–4.33	a	–5.58	–5.03	–4.11
UO-31	–4.73	–4.35	a	–4.83	–4.52	–4.22	–5.16	–4.64	–4.24

[a] The values of log GI_{50}, log TGI or log $LC_{50} > 4.00$.
[b] The log of the molar concentration that inhibits 50% net cell growth.
[c] The log of the molar concentration leading to total grown inhibition.
[d] The log of the molar concentration leading to 50% net cell death.

50% net cell death). Furthermore, a mean graph midpoint (MG_MID) is calculated for each of the mentioned parameters, giving an averaged activity parameter over all cell lines. For the calculation of the MG_MID, insensitive cell lines of the screen are included with the highest concentration tested. Selectivity of a compound with respect to one or more cell lines of the screen is characterized by a high deviation of the particular cell line parameter compared to the MG_MID value.

References

[1] M. Jarman, H.M. Coleg, I.R. Judson, T.J. Thornton, D.E.V. Wilman, J. Med. Chem. 36 (1993) 4195–4200.
[2] J. Soudon, M. Berlion, C. Lucas, P. Haddad, F. Calvo, Cancer Chemother. Pharmacol. 36 (1995) 195–199.
[3] J.P. Tassin, J. Dubois, M. Hancoq, G. Atassi, Talanta 42 (1995) 747–752.
[4] M. Ono, N. Kawahara, D. Goto, Y. Wakabayashi, S. Ushiro, Cancer Res. 56 (1996) 1512.
[5] R. Menicagli, S. Samaritani, G. Signore, F. Vaglini, L.D. Via, J. Med. Chem. 47 (2004) 4649–4652.
[6] N. Baindur, N. Chadha, B.M. Brandt, D. Asgari, R.J. Patch, C. Schalk-HiHi, T.E. Carver, I.P. Petrounia, C.A. Baumann, H. Ott, C. Manthey, B.A. Springer, M.H. Player, J. Med. Chem. 48 (2005) 1717–1720.
[7] M. Ono, N. Kawahara, D. Goto, Y. Wakabayashi, S. Ushira, S. Yoshida, H. Izumi, M. Kuwano, Y. Sato, Cancer Res. 56 (1996) 1512.
[8] S. Nozaki, M. Maeda, H. Truda, G.W. Sledze, Breast Cancer Res. Treat. 83 (2004) 195–199.
[9] Z. Brzozowski, F. Sączewski, M. Gdaniec, Eur. J. Med. Chem. 35 (2000) 1053–1064.
[10] Z. Brzozowski, F. Sączewski, Eur. J. Med. Chem. 37 (2002) 709–720.
[11] F. Sączewski, A. Bułakowska, P. Bednarski, R. Grunert, Eur. J. Med. Chem. (in Press).
[12] R.M. Abel-Rahman, J.M. Morsy, F. Hanafy, H.A. Amen, Pharmazie 54 (1999) 347–351.
[13] H. Naito, M. Sugimori, I. Mitsui, Y. Nakamura, M. Wahana, M. Ishii, K. Hirotani, E. Kumazawa, A. Jima, Chem. Pharm. Bull. (Tokyo) 47 (1999) 1679–1684.
[14] N. Demibras, R. Uguruoglu, A. Demibras, Bioorg. Med. Chem. 10 (2002) 3717–3723.
[15] F. Sączewski, A. Bułakowska, Pol. J. Chem. 79 (2005) 739–748.
[16] W. Carruthers, I. Oldham, in: "Modern methods of organic synthesis", Cambridge University Press, 2004, pp. 132–144.
[17] M.R. Boyd, Am. Assoc. Cancer Res. 30 (1989) 652–653.
[18] A.P. Monks, D.A. Scudiero, P. Skehan, R. Shoemaker, K.D. Poull, D. Vistica, C. Hose, J. Langley, P. Cronise, A. Vaigro-Wolff, J. Natl. Cancer Inst. 83 (1991) 757–776.
[19] J.N. Weinstein, T.G. Myers, P.M. O'Connor, S.H. Friend, A.J. Jr Fornance, K.W. Kohn, J.K. Buolamwini, W.W. van Osdol, A.P. Monks, D.A. Scudeiro, E.A. Sansville, D.W. Zaharevitz, R.E. Bunow, K.D. Paull, Science 275 (1997) 343–349.