Bioorganic & Medicinal Chemistry Letters 19 (2009) 2305–2309

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Discovery of substituted 4-anilino-2-arylpyrimidines as a new series of apoptosis inducers using a cell- and caspase-based high throughput screening assay. 2. Structure–activity relationships of the 2-aryl group

Nilantha Sirisoma, Azra Pervin, Bao Nguyen, Candace Crogan-Grundy, Shailaja Kasibhatla, Ben Tseng, John Drewe, Sui Xiong Cai *

EpiCept Corporation, 6650 Nancy Ridge Drive, San Diego, CA 92121, USA

ARTICLE INFO

Article history:
Received 30 January 2009
Revised 17 February 2009
Accepted 19 February 2009
Available online 23 February 2009

Keywords:
Apoptosis inducers
Anticancer agents
HTS
SAR

ABSTRACT

As a continuation of our efforts to discover and develop the apoptosis inducing 4-anilino-2-(2-pyridyl)pyrimidines as potential anticancer agents, we explored replacing the 2-pyridyl group by other aryl groups. SAR studies showed that the 2-pyridyl group can be replaced by a 3-pyridyl, 4-pyridyl and 2-pyrazinyl group, and that the SAR for the anilino group was similar to that of the 2-pyridyl series. However, replacement of the 2-pyridyl group by a phenyl group, a 3,5-dichloro-4-pyridyl group, or a saturated ring led to inactive compounds. Several potent compounds, including **2f**, **3d, 3j** and **4a**, with EC_{50} values of 0.048–0.024 μM in the apoptosis induction assay against T47D cells, were identified through the SAR studies. In a tubulin polymerization assay, compound **2f**, which was active against all the three cell lines tested (T47D, HTC116 and SNU398), inhibited tubulin polymerization with an IC_{50} value of 0.5 μM, while compound **2a**, which was active against T47D cells but not active against HTC116 and SNU398 cells, was not active in the tubulin assay at up to 50 μM.

Apoptosis, also called programed cell death, is a highly regulated process of cellular suicide and is known to play a vital role for the elimination of damaged or excess cells. Inadequate apoptosis is one of the hallmarks of cancers that result in excessive tumor cell growth and tumor resistance to chemotherapeutic treatment.[1] The pathways of apoptosis involve the activation of a family of cysteine proteases called caspases that is essential for the initiation as well as execution of apoptosis.[2] Caspase-3 is the main executioner of apoptosis and cleaves many protein substrates leading to cell death.[3] Since it is known that many chemotherapeutics induce apoptosis in cancer cells,[4] targeting apoptosis regulators to promote apoptosis is a promising strategy for anticancer drug discovery.[5] We have therefore developed a cell-based Anti-cancer Screening Apoptosis Program (ASAP) for the discovery of apoptosis inducers,[6] utilizing HTS assays with our proprietary fluorescent caspase-3 substrate.[7]

Applying this assay, we have discovered several series of novel apoptosis inducers including *N*-phenyl nicotinamide (**1a**),[8] 4-aryl-4*H*-chromenes (**1b**),[9] gambogic acid (**1c**),[10] 3-aryl-5-aryl-1,2,4-oxadiazoles (**1d**)[11] and 4-anilinoquinazolines (**1e**)[12] (Chart 1). More recently, we have reported the discovery and SAR study of 4-anilino-2-(2-pyridyl)pyrimidines (**1f**) as potent apoptosis inducers.[13] SAR studies of the anilino group showed that a small and electron-donating group, such as an OMe and OH group, at the *meta*-position is important for apoptosis inducing activity. An anilino substituted with small groups at the 2,5-positions, such as 2,5-dimethoxy (**1g**), was found to increase the potency >10-fold versus the mono-*meta*-substituted analogs.[13] Herein we report the SAR of the 2-aryl group of 4-anilino-2-arylpyrimidines as apoptosis inducers.

The 4-anilino-2-(3-pyridyl)-6-(trifluoromethyl)pyrimidines (**2a**–**n**) (Table 1) were synthesized as shown in Scheme 1, from reaction of 4-chloro-2-(3-pyridyl)-6-(trifluoromethyl)pyrimidine (**7**) with a substituted aniline.[13] Compound **7** was prepared following the literature procedure[14] from reaction of nicotinamidine (**8**) with ethyl 4,4,4-trifluorobut-2-ynoate (**9**) in the presence of KOH in EtOH to produce the intermediate 2-(3-pyridyl)-6-(trifluoromethyl)pyrimidin-4(3*H*)-one (**10**), followed by reaction with $POCl_3$ to convert the ketone to the chloride. The 4-anilino-2-(4-pyridyl)-6-(trifluoromethyl)pyrimidines (**3a**–**j**) (Table 2), 4-anilino-2-(2-pyrazinyl)-6-(trifluoromethyl)pyrimidines (**4a**–**d**) (Table 3) were prepared similar via reaction of 4-chloro-2-(4-pyridyl)-6-(trifluoromethyl)pyrimidine (**11**) and 4-chloro-2-(4-pyrazinyl)-6-(trifluoromethyl)pyrimidine (**12**) with a substituted aniline (Scheme 2). Similarly, compounds **5a**–**b** and **6a**–**d** (Table 4) were prepared via reaction of the corresponding substituted 4-chloropyrimidine with the corresponding substituted aniline. Compound **5c** was obtained from hydrogenation of **1f** under acidic conditions (Scheme 3).

* Corresponding author. Tel.: +1 858 202 4006; fax: +1 858 202 4000.
E-mail address: scai@epicept.com (S.X. Cai).

0960-894X/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2009.02.074

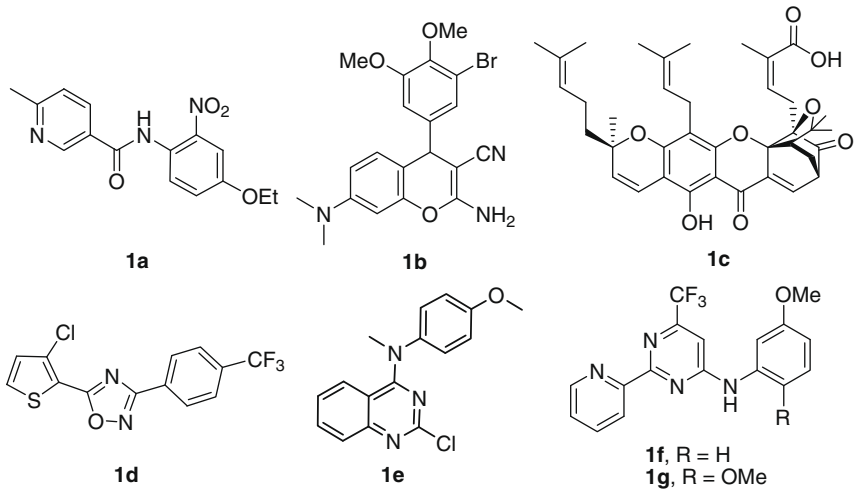
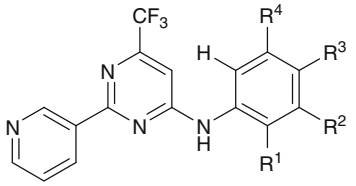


Chart 1.

The apoptosis inducing activity of these 4-anilino-2-arylpyrimidines was measured by our cell- and caspase-based HTS assay[8] in human breast cancer cells T47D, human colon cancer cells HCT116 and hepatocellular carcinoma cancer cells SNU398 and the results are summarized in Tables 1–4. Since it has been found that a small and electron-donating group at the 3-position of the anilino ring was important for the apoptosis inducing activity of 4-anilino-2-(2-pyridyl)pyrimidines,[13] we first explored the SAR of substituents at the 3-position of the anilino ring of 4-anilino-2-(3-pyridyl)-6-(trifluoromethyl)pyrimidines (Table 1). Table 1 shows that the 3-OMe analog **2a** had an EC_{50} value of 0.34 μM for caspase activation in T47D, and is inactive up to 10 μM against HCT116 and SNU398 cells, showing that **2a** is selective against certain cancer cell lines. The 3-OH analog **2b** is about threefold less active than **2a**. With an electron-withdrawing group or a large group at the 3-position, analogs **2c** (3-Cl) and **2d** (3-Ph) were inactive up to 10 μM. Similarly, the 4-methoxy analog **2e** also was inactive. These data indicate that the SAR of the anilino group for the 3-pyridyl compounds is similar to the previously reported SAR of 2-pyridyl compounds.[13]

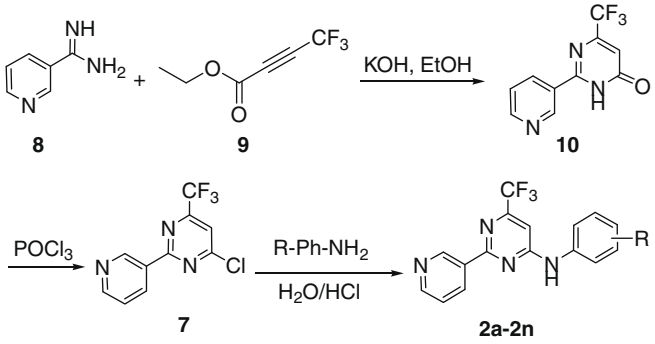
We then explored 2,5-disubstituted-anilino analogs of **2a**. Similar to what was observed previously for 4-anilino-2-(2-pyridyl)pyrimidines,[13] 2,5-disubstituted analogs of **2a** in general

Table 1
SAR of 4-anilino-2-(3-pyridyl)-6-(trifluoromethyl)pyrimidines in the caspase activation assay



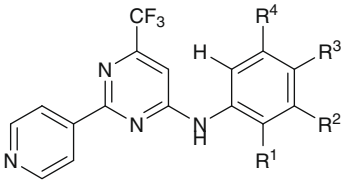
Entry	R^1	R^2	R^3	R^4	EC_{50} (μM)[a]		
					T47D	HCT116	SNU398
1f[b]	H	OMe	H	H	0.36 ± 0.17	6.0 ± 0.2	3.7 ± 0.7
1g[b]	OMe	H	H	OMe	0.018 ± 0.001	0.19 ± 0.03	0.11 ± 0.02
2a	H	OMe	H	H	0.34 ± 0.01	>10	>10
2b	H	OH	H	H	0.97 ± 0.02	>10	>10
2c	H	Cl	H	H	>10	>10	>10
2d	H	Ph	H	H	>10	>10	>10
2e	H	H	OMe	H	>10	>10	>10
2f	OMe	H	H	OMe	0.024 ± 0.005	0.17 ± 0.03	0.13 ± 0.01
2g	OMe	H	H	Me	0.096 ± 0.009	0.13 ± 0.01	0.13 ± 0.03
2h	OMe	H	H	Cl	0.36 ± 0.02	0.61 ± 0.05	0.44 ± 0.04
2i	Cl	H	H	OMe	0.14 ± 0.01	0.93 ± 0.23	0.82 ± 0.22
2j	OMe	H	H	OPh	1.5 ± 0.1	3.3 ± 0.3	5.0 ± 0.5
2k		H	H	OMe	>10	>10	>10
2l	Me	H	H	OH	0.087 ± 0.010	>10	5.5 ± 0.1
2m	Cl	H	H	OH	0.23 ± 0.04	>10	>10
2n	H	OMe	H	OMe	0.082 ± 0.003	2.9 ± 0.6	1.4 ± 0.1

[a] Cells were treated with the test compounds for 48 h, data are the mean of three or more experiments and are reported as mean ± standard error of the mean (SEM).
[b] 2-Pyridyl compounds, please see Chart 1 for structure.



Scheme 1.

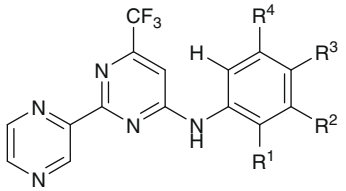
Table 2
SAR of 4-anilino-2-(4-pyridyl)-6-(trifluoromethyl)pyrimidines in the caspase activation assay



Entry	R^1	R^2	R^3	R^4	EC_{50} (μM)[a]		
					T47D	HCT116	SNU398
3a	H	OMe	H	H	1.3 ± 0.8	>10	>10
3b	H	OH	H	H	0.68 ± 0.01	3.1 ± 0.7	ND[b]
3c	H	H	OMe	H	>10	>10	>10
3d	Me	H	H	OMe	0.025 ± 0.004	0.12 ± 0.01	ND
3e	Cl	H	H	OMe	0.10 ± 0.01	0.96 ± 0.26	ND
3f	OMe	H	H	Me	0.076 ± 0.01	0.16 ± 0.03	ND
3g	Me	H	H	Me	0.12 ± 0.01	0.61 ± 0.39	ND
3h	Me	H	H	OH	0.048 ± 0.008	2.0 ± 0.2	ND
3i	Cl	H	H	OH	0.077 ± 0.007	1.1 ± 0.3	ND
3j	H	OMe	H	OMe	0.034 ± 0.016	0.24 ± 0.09	ND

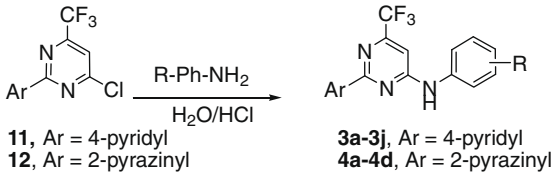
[a] Cells were treated with the test compounds for 48 h, data are the mean of three or more experiments and are reported as mean ± standard error of the mean (SEM).
[b] ND, not determined.

Table 3
SAR of 4-anilino-2-(2-pyrazinyl)-6-(trifluoromethyl)pyrimidines in the caspase activation assay



Entry	R1	R^2	R^3	R^4	EC_{50} (μM)[a]		
					T47D	HCT116	SNU398
4a	OMe	H	H	OMe	0.048 ± 0.006	0.41 ± 0.19	0.28 ± 0.03
4b	Me	H	H	OH	0.19 ± 0.01	>10	>10
4c	Cl	H	H	OH	0.56 ± 0.22	>10	>10
4d	H	OMe	H	OMe	0.13 ± 0.01	>10	>10

[a] Cells were treated with the test compounds for 48 h, data are the mean of three or more experiments and are reported as mean ± standard error of the mean (SEM).



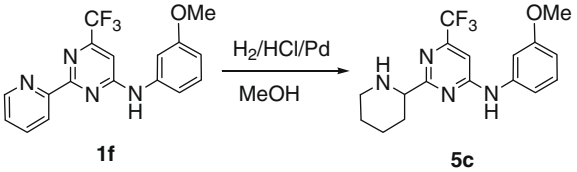
Scheme 2.

were found to be more potent than 3-substituted analogs. The 2,5-dimethoxy compound **2f** was the most potent analog, with an EC_{50} value of 0.024 μM at T47D cells, and was >10-fold more potent than **2a**. Compounds **2g**, **2h** and **2i** also were highly active with EC_{50} values of 0.096–0.36 μM at T47D cells. Interestingly, these 2,5-disubstituted analogs were active in all the three cell lines tested, suggesting that the 2,5-disubstituted analogs and the 3-substituted analogs may not have the same mechanism of action. 2,5-Disubstituted analogs with a large group at the 5-position (**2j**, OPh) or 2-position (**2k**, piperidino) were >50-fold less active than **2f**. Interestingly, compounds **2l** and **2m**, with a 5-OH group and a 2-Me or 2-Cl group, respectively, were highly active in T47D cells but had very low activity in HCT116 and SNU398 cells, indicating that they were selective against certain cancer cells similar to that of **2a**. The 3,5-dimethoxy compound **2n** also was highly active in the T47D cells with an EC_{50} value of 0.082 μM. Interestingly, it was >15-fold less active in the other two cell lines tested, indicating that it was selective against certain cancer cells.

We then explored the SAR of 4-anilino-2-(4-pyridyl)-6-(trifluoromethyl)pyrimidines (Table 2). Similar to what is observed for the 2-pyridyl and 3-pyridyl analogs, the 3-OMe analog **3a** and 3-OH analog **3b** were active in the T47D cells while the 4-methoxy analog **3c** was inactive. 2,5-Disubstituted analogs (**3d**–**g**) were found to be highly potent, with **3d** the most potent one with an EC_{50} value of 0.025 μM. Similar to what was observed for compounds **2l** and **2m**, analogs 3 h and **3i**, with an OH group at the 5-position, were highly active in T47 D cells but had low activity in HCT116 cells. The 3,5-dimethoxy compound **2j** also was highly active in the T47D cells with an EC_{50} value of 0.034 μM.

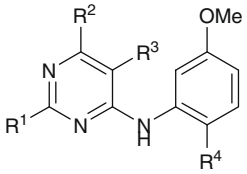
The 4-anilino-2-(2-pyrazinyl)-6-(trifluoromethyl)pyrimidines (Table 3) were found to have a similar SAR as the pyridyl-pyrimidines (Table 1 and 2). 2,5-Di-methoxy analog **4a** was highly potent, with an EC_{50} value of 0.048 μM. Compounds **4b** and **4c**, with a OH group at the 5-position, were highly active in T47 D cells but had low activity in HCT116 and SNU398 cells. The 3,5-dimethoxy compound **4d** also was highly active in the T47D cells but inactive in HCT116 and SNU398 cells up to 10 μM.

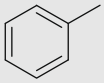
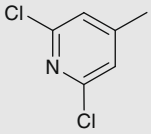
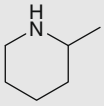
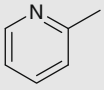
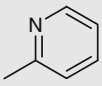
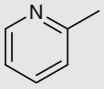
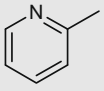
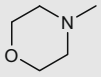
We then explored the replacement of the 2-pyridyl group in **1f** by other ring systems (Table 4). Compound **5a**, with the 2-pyridyl group in **1f** replaced by a phenyl group, was inactive up to 10 μM, indicating that the nitrogen in **1f**, as well as in **2a** and **3a**, is important for the apoptosis inducing activity. Replacing the 4-pyridyl group in **3e** by a 3,5-dichloro-4-pyridyl group also led to an inactive compound (**5b**), suggesting that substitutions in this ring are not preferred. Compound **5c**, with a saturated 2-piperidyl group



Scheme 3.

Table 4
SAR of substituted 4-anilinopyrimidines in the caspase activation assay



Entry	R^1	R^2	R^3	R4	EC_{50} (μM)[a]		
					T47D	HCT116	SNU398
5a		CF_3	H	H	>10	>10	>10
5b		CF_3	H	Cl	>10	>10	>10
5c		CF_3	H	H	>10	>10	>10
6a			H	OMe	0.42 ± 0.12	0.33 ± 0.21	0.16 ± 0.04
6b		H	OMe	H	>10	>10	>10
6c		H	OMe	OMe	>10	>10	>10
6d		Me	H	Cl	>10	>10	>10

[a] Cells were treated with the test compounds for 48 h, data are the mean of three or more experiments and are reported as mean ± standard error of the mean (SEM).

replacing the 2-pyridyl group in **1f**, was inactive up to 10 μM, indicating that a plainer aromatic ring is needed for activity.

We also explored other substitutions in the pyrimidine ring. Previously, we found that the trifluoromethyl group in **1f** and **1g** can be replaced by a methyl group.[13] Compound **6a**, with the trifluoromethyl group in **1g** replaced by a 2-pyridyl group, was >10-fold less active than **1g** in T47D cells, but had similar activity in the HCT116 and SNU398 cells, indicating that the relatively large 2-pyridyl group is tolerated at the 6-position of the pyrimidine ring. Compounds **6b** and **6c**, with the 6-trifluoromethyl group in **1f** and **1g** replaced by a 5-methoxy group, were not active up to 10 μM, suggesting that substitution in the 5-position is not preferred. Compound **6d**, with a morpholino group at the 2-position of pyrimidine, also was inactive up to 10 μM, confirming the above observation with **5c** that a saturated ring is not tolerated at that position.

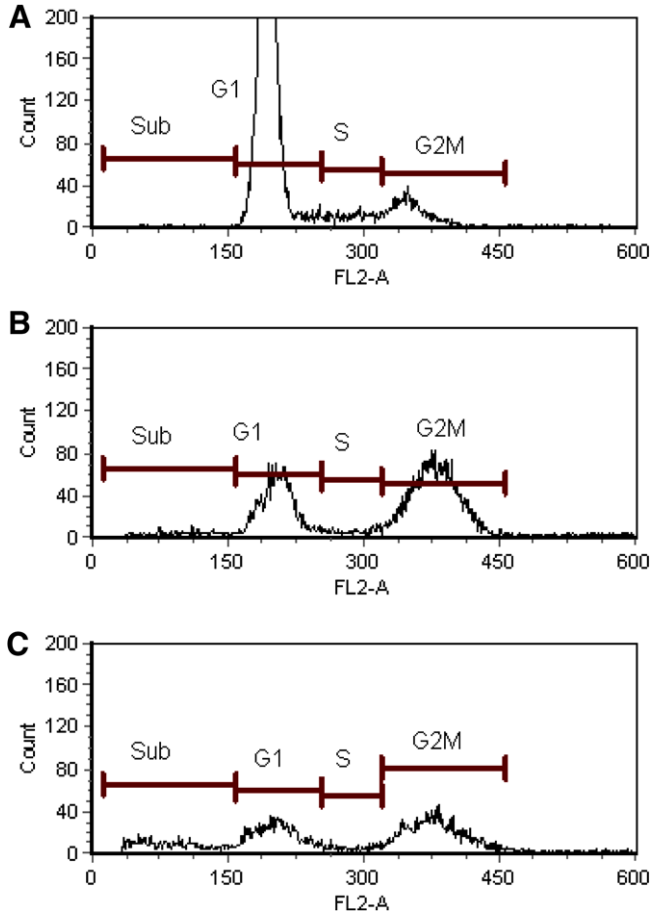
Selected compounds were also tested by the traditional inhibition of cell growth (GI_{50}) assay to confirm that the active compounds can inhibit tumor cell growth. The growth inhibition assays in T47D, HCT116 and SNU398 cells were run in a 96-well microtiter plate as described previously[6] and the data are summarized in Table 5. Compound **2a** was found to be highly active with a GI_{50} value of 0.094 μM in T47D cells, and was >50-fold less active against HCT116 and SNU398 cells, confirming that **2a** was selective against certain cancer cells. Compounds **2n** and **3j**, found to be selective in the caspase assay, were also selective in the growth inhibition assay. In comparison, compounds **2f** and **6a** were equipotent in all three cell lines, confirming that they are broadly active.

The apoptosis-inducing activity of the potent analog **2f** was also characterized by cell cycle analysis. T47D cells were treated with 0.05 μM of compound **2f** for 24 h or 48 h at 37 °C, then stained with propidium iodide and analyzed by flow cytometry (Fig. 1). An increase in G_2/M population (from 13% to 53%) was observed after 24 h treatment with **2f**, together with an increased apoptotic sub-G_1 population (from 1% to 7%). Sub-G_1 population was increased to 19% after 48 h treatment with **2f**, indicating that many

Table 5
Inhibition of cell growth of 4-anilino-2-(3-pyridyl)-6-(trifluoromethyl)pyrimidines

Entry	GI_{50} (μM)[a]		
	T47D	HCT116	SNU398
2a	0.094 ± 0.007	>10	6.4 ± 0.1
2f	0.095 ± 0.010	0.18 ± 0.04	0.068 ± 0.010
2n	0.061 ± 0.031	1.3 ± 0.2	1.0 ± 0.1
3j	0.036 ± 0.006	0.27 ± 0.02	0.27 ± 0.01
6a	0.24 ± 0.01	0.13 ± 0.02	0.41 ± 0.09

[a] Cells were treated with the test compounds for 48 h, data are the mean of three or more experiments and are reported as mean ± standard error of the mean (SEM).



Entry	Sub(%)	G_1(%)	S(%)	G_2/M(%)
1A	1	78	7	13
1B	7	32	6	53
1C	19	31	7	43

Figure 1. Drug-induced apoptosis in T47D cells as measured by flow cytometric analysis. The *x*-axis is the fluorescence intensity and the *y*-axis is the number of cells with that fluorescence intensity. (A) Control cells showing most of the cells in G_1 phase of the cell cycle. (B) Cells treated with 0.05 μM of compound **2f** for 24 h showing most of the cells arrested in G_2/M phase. (C) Cells treated with 0.05 μM of compound **2f** for 48 h showing a progression from G_2/M to cells with sub-diploid DNA content, which are apoptotic cells with fragmented nuclei.

cells were apoptotic. These data showed that compound **2f** arrested cancer cells in G_2/M, indicative of an antimitotic effect, followed by induction of apoptosis.

Since compound **2f** arrested cells at G_2/M followed by induction of apoptosis, which is similar to known tubulin inhibitors such as colchicine, we suspected that **2f** might be a tubulin inhibitor. In a tubulin polymerization assay,[9b] compound **2f** was found to inhibit polymerization of tubulin with an IC_{50} value of 0.5 μM, indicating that **2f** most probably induces apoptosis through inhibiting tubulin polymerization, which is in agreement with its broad activity against the three cancer cell lines tested. In comparison, compound **2a**, which was active against T47D cells but was inactive against colon cancer HCT116 and liver cancer SNU398 cells, was found not to inhibit tubulin polymerization at up to 50 μM, suggesting that **2a** should have a different mechanism of action from that of **2f**. Similarly, compounds **2l** and **2n**, both of which showed activity against T47D cells but were much less active against colon cancer HCT116 and liver cancer SNU398 cells, were found not to inhibit tubulin polymerization at up to 50 μM.

In conclusion, we have explored the SAR of the 2-aryl group of 4-anilino-2-arylpyrimidines as apoptosis inducers. Our studies showed that the 2-pyridyl group in our previously reported apoptosis inducing 4-anilino-2-(2-pyridyl)pyrimidines can be replaced by a 3-pyridyl, 4-pyridyl and 2-pyrazinyl group, and these compounds maintain similar SAR for the anilino group. However, replacement of the 2-pyridyl group by a phenyl group, or a 3,5-dichloro-4-pyridyl group, or a saturated 2-piperidyl or morpholino group, resulted in inactive compounds. In addition, replacement of the 6-trifluoromethyl group in the pyrimidine ring by a 6-(2-pyridyl) group was tolerated while its replacement by a 5-methoxy group led to inactive compounds. Through these studies, several low nanomolar compounds, both selective and nonselective were identified in the apoptosis induction assay against T47D cells. Compounds that were active against all the three cell lines (T47D, HCT116 and SNU398), such as **2f**, were found to be inhibitors of tubulin polymerization, which most probably is the mechanism of action in inducing apoptosis. Compounds that were selective against T47D cells, such as **2a**, **2l** and **2n**, were found to be inactive in the tubulin assay and the primary cellular target remains to be defined.

References and notes

1. Reed, J. C.; Tomaselli, K. J. *Curr. Opin. Biotechnol.* **2000**, *11*, 586.
2. Leung, D.; Abbenante, G.; Fairlie, D. P. *J. Med. Chem.* **2000**, *43*, 305.
3. Thornberry, N. A. *Chem. Biol.* **1998**, *5*, R97.
4. Rich, T.; Allen, R. L.; Wyllie, A. H. *Nature* **2000**, *407*, 777.
5. Fesik, S. W. *Nat. Rev. Cancer* **2005**, *5*, 876.
6. Cai, S. X.; Drewe, J.; Kasibhatla, S. *Curr. Med. Chem.* **2006**, *13*, 2627.
7. Cai, S. X.; Zhang, H. Z.; Guastella, J.; Drewe, J.; Yang, W.; Weber, E. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 39.
8. Cai, S. X.; Nguyen, B.; Jia, S.; Herich, J.; Guastella, J.; Reddy, S.; Tseng, B.; Drewe, J.; Kasibhatla, S. *J. Med. Chem.* **2003**, *46*, 2474.
9. (a) Kemnitzer, W.; Kasibhatla, S.; Jiang, S.; Zhang, H.; Wang, Y.; Zhao, J.; Jia, S.; Herich, J.; Labreque, D.; Storer, R.; Meerovitch, K.; Bouffard, D.; Rej, R.; Denis, R.; Blais, C.; Lamothe, S.; Attardo, G.; Gourdeau, H.; Tseng, B.; Drewe, J.; Cai, S. X. *J. Med. Chem.* **2004**, *47*, 6299; (b) Kemnitzer, W.; Drewe, J.; Jiang, S.; Zhang, H.; Zhao, J.; Crogan-Grundy, C.; Xu, L.; Lamothe, S.; Gourdeau, H.; Denis, R.; Tseng, B.; Kasibhatla, S.; Cai, S. X. *J. Med. Chem.* **2007**, *50*, 2858; (c) Kemnitzer, W.; Drewe, J.; Jiang, S.; Zhang, H.; Crogan-Grundy, C.; Labreque, D.; Bubenick, M.; Attardo, G.; Denis, R.; Lamothe, S.; Gourdeau, H.; Tseng, B.; Kasibhatla, S.; Cai, S. X. *J. Med. Chem.* **2008**, *51*, 417.
10. Zhang, H.-Z.; Kasibhatla, S.; Wang, Y.; Herich, J.; Guastella, J.; Tseng, B.; Drewe, J.; Cai, S. X. *Bioorg. Med. Chem.* **2004**, *12*, 309.
11. Zhang, H.-Z.; Kasibhatla, S.; Kuemmerle, J.; Kemnitzer, W.; Oliis-Mason, K.; Qui, L.; Crogran-Grundy, C.; Tseng, B.; Drewe, J.; Cai, S. X. *J. Med. Chem.* **2005**, *48*, 5215.
12. Sirisoma, N.; Kasibhatla, S.; Pervin, A.; Zhang, H.; Jiang, S.; Willardsen, J. A.; Anderson, M.; Baichwal, V.; Mather, G. G.; Jessing, K.; Hussain, R.; Hoang, K.; Pleiman, C. M.; Tseng, B.; Drewe, J.; Cai, S. X. *J. Med. Chem.* **2008**, *51*, 4771.
13. Sirisoma, N.; Kasibhatla, S.; Nguyen, B.; Pervin, A.; Wang, Y.; Claassen, G.; Tseng, B.; Drewe, J.; Cai, S. X. *Bioorg. Med. Chem.* **2006**, *14*, 7761.
14. Brown, D. J.; Cowden, W. B.; Grigg, G. W.; Kavulak, D. *Aust. J. Chem.* **1980**, *33*, 2291.