Contents lists available at ScienceDirect



Bioorganic & Medicinal Chemistry Letters

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



Discovery of *N*-methyl-4-(4-methoxyanilino)quinazolines as potent apoptosis inducers. Structure–activity relationship of the quinazoline ring

Nilantha Sirisoma^a, Azra Pervin^a, Hong Zhang^a, Songchun Jiang^a, J. Adam Willardsen^b, Mark B. Anderson^b, Gary Mather^b, Christopher M. Pleiman^b, Shailaja Kasibhatla^a, Ben Tseng^a, John Drewe^a, Sui Xiong Cai^{a,*}

^a EpiCept Corporation, 6650 Nancy Ridge Drive, San Diego, CA 92121, USA
^b Myriad Pharmaceuticals Inc., 320 Wakara Way, Salt Lake City, UT 84108, USA

ARTICLE INFO

Article history: Received 22 December 2009 Revised 22 January 2010 Accepted 27 January 2010 Available online 4 February 2010

Keywords: Apoptosis inducers Anticancer agents SAR

ABSTRACT

As a continuation of our efforts to discover and develop apoptosis inducing *N*-methyl-4-(4-methoxyanilino)quinazolines as novel anticancer agents, we explored substitution at the 5-, 6-, 7-positions of the quinazoline and replacement of the quinazoline by other nitrogen-containing heterocycles. A small group at the 5-position was found to be well tolerated. At the 6-position a small group like an amino was preferred. Substitution at the 7-position was tolerated much less than at the 6-position. Replacing the carbon at the 8-position or both the 5- and 8-positions with nitrogen led to about 10-fold reductions in potency. Replacement of the quinazoline ring with a quinoline, a benzo[d][1,2,3]triazine, or an isoquinoline ring showed that the nitrogen at the 1-position is important for activity, while the carbon at the 2-position can be replaced by a nitrogen and the nitrogen at the 3-position can be replaced by a carbon. Through the SAR study, several 5- or 6-substituted analogs, such as **2a** and **2c**, were found to have potencies approaching that of lead compound *N*-(4-methoxyphenyl)-*N*,2-dimethylquinazolin-4-amine (**1g**, EP128495, MPC-6827, Azixa[®]).

© 2010 Elsevier Ltd. All rights reserved.

Apoptosis is a well-controlled process for the elimination of excessive cells.¹ The mechanism of apoptosis involves a cascade of initiator and effector caspases that are activated sequentially.² Caspase-3 is one of the key effector caspases that cleaves multiple protein substrates in cells, leading to cell death.³ It has been determined that many clinically useful cytotoxic agents induce apoptosis in cancer cells.⁴ Among them, the proapoptotic chemotherapeutic agents that target tubulin, including taxanes such as Taxol and Taxotere and vinca alkaloids such as vincristine, vinblastine and vinorelbine are among the most successful anticancer therapies.⁵ Compounds that induce apoptosis in cancer cells by targeting the clinically validated tubulin/microtubule system while retaining activity in multi-drug-resistant tumors, exemplified by the recent approval of the epothilone analog ixabepilone,⁶ should provide new treatment options for cancers.⁷ In addition, since there are few treatments for neurologic cancers due to the blood-brain barrier (BBB) that prevents many traditional and newer anticancer drugs from entering the brain parenchyma,⁸ there is an urgent need for effective anticancer drugs with good BBB penetration.

* Corresponding author at present address: IMPACT Therapeutics, 10 Xinghuo Road, Floor 9, High and New Technology Zone, Nanjing, Jiangsu 210061, China. Tel.: +86 25 58619055.

E-mail address: s.cai@impacttherapeutics.com (S.X. Cai).

We have been interested in the discovery and development of apoptosis inducers as potential anticancer agents, and have developed a cell-based Anticancer Screening Apoptosis Platform (ASAP) using our novel fluorescent caspase-3 substrates.⁹ We have reported the discovery and structure-activity relationship (SAR) studies of several novel series of apoptosis inducers as well as the identification of their molecular targets.¹⁰ These include gambogic acid (**1a**)¹¹ and the transferrin receptor as its molecular target,¹² 3-aryl-5-aryl-1,2,4-oxadiazoles (e.g., **1b**)¹³ and tail interacting protein (TIP47), an insulin growth factor II (IGF II) receptor binding protein as its molecular target,¹⁴ 4-aryl-4H-chromenes (e.g., 1c) as potent apoptosis inducers¹⁵ and vascular disrupting agents,¹⁶ as well as 4-aryl-3-(3-aryl-1-oxo-2-propenyl)-2(1H)quinolinones (e.g., 1d) that activate apoptosis in cancer cell lines with deregulated Myc¹⁷ (Chart 1). More recently, we have reported the discovery of N^4 -(4-methoxyphenyl)- N^4 -methyl- N^2 -((E)-3,7dimethylocta-2,6-dienyl)quinazoline-2,4-diamine (1e) as a potent apoptosis inducer using our cell- and caspase-based HTS assay, and SAR studies that led to the identification of 2-chloro-N-(4methoxyphenyl)-*N*-methylquinazolin-4-amine $(\mathbf{1f})^{18}$ and *N*-(4methoxyphenyl)-*N*,2-dimethylquinazolin-4-amine (**1g**, EP128495, MPC-6827, Azixa[®])¹⁹ as potent apoptosis inducers with activity in multi-drug-resistant cancer cell lines, high BBB penetration, good pharmacokinetics and high efficacies in in vivo anticancer xenograft models.²⁰ Utilizing a tritium labeled photoaffinity ana-

⁰⁹⁶⁰⁻⁸⁹⁴X/ $\$ - see front matter @ 2010 Elsevier Ltd. All rights reserved. doi:10.1016/j.bmcl.2010.01.155





log, the primary molecular target of these *N*-methyl-4-anilinoquinazolines has been identified as tubulin and compound **1g** was found to inhibit tubulin polymerization via binding at or near the colchicine site.²⁰ Compound **1g** is currently under clinical development as an novel anticancer agent.

We have reported the SAR study of *N*-methyl-4-anilinoquinazolines that showed that a small alkyl group at the nitrogen of the anilino group is essential for apoptosis inducing activity. A small and electron-donating group like methoxy or ethoxy at the 4-position of the anilino ring is important for activity and a small group such as chloro, methyl, methoxy, fluoromethyl or hydroxymethyl is preferred at the 2-position of the quinazoline. Substitution at the 6- and 7-positions of the quinazoline results in reduced activity. These data showed that the SAR of 4-anilinoquinazolines as apoptosis inducers is significantly different from the reported SAR of 4-anilinoquinazolines as EGFR kinase inhibitors such as Iressa and Tarceva.^{18,19} As a continuation of our efforts to optimize the apoptosis inducing *N*-methyl-4-(4-methoxyanilino)quinazolines as potential anticancer therapeutics, herein, we report further modification of the quinazoline ring.

Compounds 2a-2b, 2f and 3a-3b were prepared as shown in Scheme 1 using previously reported procedures.^{18,19} 4-Chloro-5methoxy-2-methylquinazoline (7a) was prepared via reaction of 2-amino-6-methoxybenzoic acid (5a) and acetyl chloride in the presence of 4-N,N-dimethylaminopyridine (DMAP) and triethylamine followed by treatment with ammonium acetate to produce 2-methyl-5-methoxyquinazolin-4-ol (6a), followed by the reaction of **6a** with freshly distilled POCl₃ in anhydrous toluene and diisopropylethylamine (DIPEA). 4-Chloro-2-methylpyrido[2,3-d]pyrimidine (7b) was prepared similarly from reaction of 2-aminonicotinic acid (5b). 4-Chloro-6-nitro-2-methylquinazoline (7c) was prepared via reaction of 2-amino-5-nitrobenzoic acid (5c) with acetic anhydride followed by treatment of the intermediate with ammonia in dioxane to produce 2-methyl-6-nitroquinazolin-4-ol (6c), which was subsequently treated with POCl₃. 4-Chloro-7-nitro-2-methylquinazoline (7d) was prepared similarly to 7c starting from 2-amino-4-nitrobenzoic acid (5d). 4-Chloro-2-methylpteridine (7e) was prepared from condensation of 6-chloro-2-methylpyrimidine-4,5-diamine (5e) with 1,4-dioxane-2,3-diol. Reaction of 7a-7e with N-methyl-4-methoxyaniline (8) in anhydrous isopropanol (IPA) in the presence of concentrated HCl produced compounds 2a-2b, 2f and 3a-3b (Scheme 1).

6-Amino compound **2c** was prepared from hydrogenation of the 6-nitro analog **2b**. Reaction of **2c** with formaldehyde in the presence of sodium cyanoborohydride produced the 6-dimethylamino



Scheme 1. Reagents: (a) (1) $ACCI/Et_3N/DMAP/DMF$; (2) NH_4Ac ; (b) (1) $(AcO)_2O$; (2) $NH_3/dioxane$; (c) 1,4-dioxane-2,3-diol/EtOH; (d) $POCl_3$, DIPEA, toluene; (e) 4-MeO-PhNHMe (8), IPA, HCl.

analog **2d**. The 6-acetamide analog **2e** was prepared from reaction of **2c** with acetyl chloride (Scheme 2). 7-Amino analog **2g** was similarly prepared from hydrogenation of 7-nitro analog **2f**. The azido analog **2h** was prepared via reaction of **2g** with sodium nitrite in aqueous HCl followed by treatment with sodium azide. The corresponding tritium labeled analog **2k** was prepared similarly from the dibromo analog **2i**, which was prepared from reaction of



Scheme 2. Reagents: (a) H₂, Pd/C, EtOH; (b) HCHO, NaBH₃CN; (c) AcCl.

4-chloro-7-nitro-2-methylquinazoline (**7d**) with 3,5-dibromo-*N*-methyl-4-methoxyaniline. Treatment of **2i** with tritium gas under hydrogenation conditions produced the ditritium analog **2j**. Diazotization of **2j** followed by treatment with sodium azide, using procedures similar to the preparation of the cold azido analog **2h** produced tritium analog **2k** (Scheme 3). Compound **2k** was synthesized as a photoaffinity agent for target identification.

1-(4-Methoxyanilino)-*N*-methylisoquinoline (**4a**) was prepared via reaction of a mixture of 1-chloroisoquinoline with *N*-methyl-4-methoxyaniline (**8**) in a sealed tube heated to 140 °C overnight. 4- (4-Methoxyanilino)-*N*-methylquinoline **4b** was prepared similarly from reaction of 4-chloroquinaline with *N*-methyl-4-methoxyaniline (**8**) (Scheme 4). 4-Chlorobenzo[*d*][1,2,3]triazine (**7f**) was prepared from benzo[*d*][1,2,3]triazin-4-ol via reaction with phosphorus oxychloride in toluene and diisopropylethylamine. Reaction of **7f** with *N*-methyl-4-methoxyaniline (**8**) in isopropanol produced 4-(4-methoxyanilino)-*N*-methylbenzo[*d*][1,2,3]triazine **4c** (Scheme 5).

The apoptosis inducing activity of N-methyl-4-(4-methoxyanilino)quinazolines and related compounds was measured in our celland caspase-based HTS assay²¹ in two cell lines, human breast cancer cells T47D and human non-small cell lung cancer cells H1299, the results are summarized in Table 1. Starting from compound 1g, we explored the effects of various substituents at the 5,6,7-positions of the quinazoline ring. The 5-methoxy analog 2a was found to be slightly less active than 1g, suggesting that substitution at the 5-position by a small group might be tolerated. The 6-nitro analog 2b was 200-fold less active than 1g, while the 6-amino analog 2c was fourfold less active than 1g indicating that a small hydrophilic group but not a strong electron withdrawing group is tolerated at the 6-position. The 6-dimethylamino (2d) and 6-acetamide (2e) analogs were more than 200-fold less active than 1g, suggesting that the pocket around the 6-position may have size limitations. The 7-nitro analog **2f** was not active at up to $10 \,\mu$ M, which is >5000-fold less active than 1g, and the 7-amino analog 2g was about 200-fold less active than the 6-amino analog **2c**, indicating substitution at the 7-position is less tolerated than the 6-position. These data are in agreement with our previously reported SAR around 1e which showed that substitution at the 6-position is more tolerated than 7-position.¹⁸ The 7-azido analog **2h** was about 50-fold less active than 1g but still had reasonable activity with an EC₅₀ value of 110 nM against T47D cells. Compound 2k, a tritium



Scheme 3. Reagents: (a) IPA, HCI; (b) H_2 , Pd/C, EtOH; or T_2 , Pd/C, EtOH; (c) NaNO₂, HCI, then NaN₃.



Scheme 4. Reagents and conditions: (a) 4-MeO-PhNHMe (8), 140 °C, overnight.



Scheme 5. Reagents: (a) POCl₃, DIPEA, toluene; (b) 4-MeO-PhNHMe (8), IPA.

version of **2h**, was prepared and used in the target identification study to confirm that the molecular target of the apoptosis inducing *N*-methyl-4-(4-methoxyanilino)quinazolines is tubulin.²⁰

We then explored introduction of nitrogen into the benzo moiety of the quinazoline ring. The 8-aza analog **3a** was found to be about sevenfold less active than **1g** and the 5,8-aza analog **3b** was about 14-fold less active than **1g**. Aza analogs still maintained relatively good potency, but the quinazoline ring structure is preferred over other nitrogen-containing heterocycles.

We also explored the replacement of the pyrimidine moiety of the quinazoline ring by other nitrogen-containing rings. The isoquinoline analog **4a** was 100-fold less active than the corresponding quinazoline analog **1h**,¹⁸ indicating that the nitrogen at the 1position of the quinazoline structure is important for the apoptosis inducing activity. The quinoline analog **4b** was about threefold less active than **1h**, suggesting that the nitrogen at the 3-position is less important for activity. The benzo[*d*][1,2,3]triazine analog **4c** was about twofold less active than **1h**, indicating that the 2-position carbon of quinazoline can be replaced by a nitrogen.

The potencies of all reported compounds towards the human non-small cell lung cancer cell line H1299 were roughly parallel to their activity towards T47D cells. In general, H1299 cells were slightly less sensitive (about 2–4-fold less sensitive as measured by the EC_{50} value) to the compounds than T47D cells in this assay.

We have found that compound **1g** and related compounds are tubulin inhibitors that bind at or close to the colchicine site of β -tubulin.²⁰ Compounds **2a** and **4b**, which were highly active in the caspase activation assay, were tested in the tubulin polymerization assay.²² Both compounds were found to inhibit tubulin polymerization with IC₅₀ values of about 0.4 μ M, which is similar to that of compound **1g**. Compound **2g**, which was less active in the caspase activation assay, was also less active in the tubulin assay with IC₅₀ value of 2 μ M. Therefore these modifications to the quinazo-line structure do not change the mechanism of action of these compounds.

We have reported that compound **1g** has high BBB penetration.¹⁹ The brain/plasma AUC (area under the concentration–time curves) ratios of several compounds related with **1g** were measured after a single intravenous (iv) dose of 2.5 mg/kg in mice and determined via LC–MS/MS using plasma from blood samples and homogenized whole brain samples as reported previously.¹⁹ As summarized in Table 2, all compounds have brain/plasma AUC ratio of >1, indicating significant BBB penetration. These data are in

Table 1

Caspase activation activity of N-methyl-4-(4-methoxyanilino)quinazolines and related compounds



Entry	\mathbb{R}^1	R ²	R ³	EC ₅₀ ^a	EC_{50}^{a} (μM)		
				T47D	H1299		
1g 2a 2b 2c 2d 2e 2f 2g 2h	H OMe H H H H H	H H NH ₂ NHe ₂ NHAC H H H	H H H H H NO ₂ NH ₂ N ₃	$\begin{array}{c ccccc} H & 0.002 \pm 0.0001 & 0.007 \pm 0.001 \\ H & 0.004 \pm 0.001 & 0.008 \pm 0.002 \\ H & 0.40 \pm 0.04 & 0.13 \pm 0.03 \\ H & 0.008 \pm 0.001 & 0.014 \pm 0.001 \\ H & 0.45 \pm 0.07 & 1.4 \pm 0.1 \\ H & 0.96 \pm 0.16 & 1.4 \pm 0.1 \\ NO_2 & >10 & >10 \\ NH_2 & 0.78 \pm 0.04 & 0.57 \pm 0.03 \\ N_3 & 0.11 \pm 0.02 & 0.13 \pm 0.02 \\ \end{array}$			
		A B		<			
Entry	А	В		$EC_{50}^{a}(\mu M)$			
					111200		
				T47D	П1299		
3a 3b	CH N	N	[T47D 0.015 ± 0.001 0.029 ± 0.001	0.021 ± 0.002 0.036 ± 0.004		
3a 3b	CH N	N N		T47D 0.015 ± 0.001 0.029 ± 0.001	0.021 ± 0.002 0.036 ± 0.004		
3a 3b Entry	CH N A	B		$ \frac{\text{T47D}}{0.015 \pm 0.001} \\ 0.029 \pm 0.001 $ OMe $ \underbrace{\text{EC}_{50}^{a}} $	0.021 ± 0.002 0.036 ± 0.004		
3a 3b Entry	CH N A	M N B		$\frac{T47D}{0.015 \pm 0.001}$ 0.029 ± 0.001 OMe $\frac{CC_{50}^{a}}{T47D}$	<u>(µM)</u> H1299		

 $^{\rm a}$ Data are the mean of three or more experiments and are reported as mean \pm standard error of the mean (SEM).

^b Data from Ref. 18.

agreement with the suggested rules that compounds having hydrogen bond donor (HBD) of <3, Clog *P* of 2–5 and molecular weight (MW) of <500 are preferred for potential BBB penetration,²³ and that if the number of nitrogen plus oxygen (N+O) is five or less in a molecule, then it has a high chance of entering the brain.²⁴ For comparison, the BBB penetration of compound **2c**, with an amino group added (one nitrogen and two hydrogen bond donors) to **1g**, as measured by the brain/plasma AUC ratio was reduced from 16.0 to 3.6. Compounds **3a**, with one additional nitrogen, resulted in a brain/plasma AUC ratio reduction from 16.0 to 1.8. These data are in agreement with our previous observations that increases in the number of (N+O), or increases in the number of hydrogen bond donors (HBD) reduce BBB penetration.¹⁹

In conclusion, we have explored further the SAR of the apoptosis inducing *N*-methyl-4-(4-methoxyanilino)quinazolines as potential anticancer agents via modifications at the 5-, 6- and

Table 2	
---------	--

The brain/plasma ratio of AUC of 4-arylaminoquinazolines

Entry	Brain/plasma ratio of AUC	MW	# of HBA	# of HBD	# of N+O	Clog P ^a	EC ₅₀ (nM) T47D ^b
1g	16.0	279	4	0	4	4.18	2
2c	3.6	294	5	2	5	3.86	8
3a	1.8	280	5	0	5	3.14	15
3b	2.1	281	6	0	6	2.37	29
1h	3.1	265	4	0	4	3.68	6
4b	9.2	264	3	0	3	4.47	21

^a Calculated using ChemDraw.

^b Data from Table 1.

7-positions, and replacement of the guinazoline ring by other nitrogen-containing heterocycles. It was found that a small group such as methoxy at the 5-position led to a potent compound. At the 6-position, a small group like amino was preferred, while slightly larger groups such as dimethylamino or a strong electron withdrawing group like nitro resulted in significant reduction of apoptotic activity. Substitution at the 7-position was much less preferred than at the 6-position. Replacement of the carbon at the 8-position or both 5- and 8-positions by nitrogen led to 7-14-fold reduction in potency. Replacement of the quinazoline ring by an isoquinoline ring resulted in 100-fold reductions in activity while its replacement by a quinoline or benzo[d][1,2,3]triazine ring was well tolerated with 2-3-fold reduction in potency. Several 5and 6-substituted analogs, such as 2a and 2c, were found to have potencies approaching that of lead compound 1g. Additional studies of these 4-anilinoquinazolines, including in vivo study of compound 1g in brain tumor model, will be reported in future publications.

References and notes

- 1. Henson, P. M.; Bratton, D. L.; Fadok, V. A. Curr. Biol. 2001, 11, R795.
- 2. Green, D. R.; Reed, J. C. Science 1998, 281, 1309.
- 3. Stennicke, H. R.; Ryan, C. A.; Salvesen, G. S. Trends Biochem. Sci. 2002, 27, 94.
- 4. Rich, T.; Allen, R. L.; Wyllie, A. H. Nature 2000, 407, 777.
- 5. Kingston, D. G.; Newman, D. J. Curr. Opin. Drug Discov. Devel. 2007, 10, 130.
- 6. Hunt, J. T. Mol. Cancer Ther. 2009, 8, 275.
- 7. Li, Q.; Sham, H.; Rosenburg, S. Annu. Rev. Med. Chem. 1999, 34, 139.
- Deeken, J. F.; Loscher, W. Clin. Cancer Res. 2007, 13, 1663.
 Cai, S. X.; Zhang, H.-Z.; Guastella, J.; Drewe, J.; Yang, W.; Weber, E. Bioorg. Med.
- Chem. Lett. 2001, 11, 39.
- 10. Cai, S. X.; Drewe, J.; Kasibhatla, S. Curr. Med. Chem. 2006, 13, 2627.
- Zhang, H.-Z.; Kasibhatla, S.; Wang, Y.; Herich, J.; Guastella, J.; Tseng, B.; Drewe, J.; Cai, S. X. *Bioorg. Med. Chem.* **2004**, *12*, 309.
- Kasibhatla, S.; Jessen, K.; Maliartchouk, S.; Wang, J.; English, N.; Drewe, J.; Qui, L.; Archer, S.; Ponce, A.; Sirisoma, N.; Jiang, S.; Zhang, H.-Z.; Gehlsen, K.; Cai, S. X.; Green, D. R.; Tseng, B. Proc. Natl. Acad. Sci. U.S.A. 2005, 102, 12095.
- 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.
- Jessen, K.; English, N.; Wang, J.; Qui, L.; Brand, R.; Maliartchouk, S.; Drewe, J.; Kuemmerle, J.; Zhang, H.-Z.; Gehlsen, K.; Tseng, B.; Cai, S. X.; Kasibhatla, S. *Mol. Cancer Ther.* 2005, 4, 761.
- (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.
- (a) Kasibhatla, S.; Gourdeau, H.; Meerovitch, K.; Drewe, J.; Reddy, S.; Qiu, L.; Zhang, H.; Bergeron, F.; Bouffard, D.; Yang, Q.; Herich, J.; Lamothe, S.; Cai, S. X.; Tseng, B. *Mol. Cancer Ther.* **2004**. *3*, 1365; (b) Gourdeau, H.; Leblond, L.; Hamelin, B.; Desputeau, C.; Dong, K.; Kianicka, I.; Custeau, D.; Bourdeau, C.; Geerts, L.; Cai, S. X.; Drewe, J.; Labrecque, D.; Kasibhatla, S.; Tseng, B. *Mol. Cancer Ther.* **2004**, *3*, 1375.
- Claassen, G.; Brin, E.; Crogan-Grundy, C.; Vaillancourt, M. T.; Zhang, H.-Z.; Cai, S. X.; Drewe, J.; Tseng, B.; Kasibhatla, S. *Cancer Lett.* **2009**, *274*, 243.
- 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.

- 19. Sirisoma, N.; Pervin, A.; Zhang, H.; Jiang, S.; Willardsen, A. J.; Anderson, M.; Mather, G. G.; Pleiman, C. M.; Kasibhatla, S.; Tseng, B.; Drewe, J.; Cai, S. X. J. Med. Chem. **2009**, *52*, 2341.
- Kasibhatla, S.; Baichwal, V.; Cai, S. X.; Roth, B.; Skvortsova, I.; Skvortsov, S.; Lukas, P.; English, N. M.; Sirisoma, N.; Drewe, J.; Pervin, A.; Tseng, B.; Carlson, R. O.; Pleiman, C. M. *Cancer Res.* **2007**, *67*, 5865.
- 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.
 Barron, D. M.; Chatterjee, S. K.; Ravindra, R.; Roof, R.; Baloglu, E.; Kingston, D. G.
 - I.; Bane, S. Anal. Biochem. 2003, 315, 49.
- Hitchock, S. A.; Pennington, L. D. J. Med. Chem. 2006, 49, 7559.
 Norinder, U.; Haeberlein, M. Adv. Drug Delivery Rev. 2002, 54, 291.