



Discovery and optimization of 2-(4-substituted-pyrrolo[2,3-*b*]pyridin-3-yl)methylene-4-hydroxybenzofuran-3(2*H*)-ones as potent and selective ATP-competitive inhibitors of the mammalian target of rapamycin (mTOR)

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ABSTRACT

We discovered 2-(4-substituted-pyrrolo[2,3-*b*]pyridin-3-yl)methylene-4-hydroxybenzofuran-3(2*H*)-ones as potent and selective ATP-competitive inhibitors of the mammalian target of rapamycin (mTOR). Since phenolic OH groups pose metabolic liability, one of the two hydroxyl groups was selectively removed. The SAR data showed the structural features necessary for subnanomolar inhibitory activity against mTOR kinase as well as selectivity over PI3K α . An X-ray co-crystal structure of one inhibitor with the mTOR-related PI3K γ revealed the key hydrogen bonding interactions.

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The mammalian target of rapamycin (mTOR) is a key component of the phosphoinositide 3-kinase (PI3K) pathway that plays an important role in regulating cell growth, metabolism and angiogenesis.^{1,2} mTOR, the founding member of a family of unconventionally high molecular mass serine/threonine protein kinases,³ is frequently dysregulated in human malignancy,^{4–6} making it an attractive target for cancer therapy.⁷ In fact, rapamycin analogs such as CCI-779 (temsirolimus)⁸ and RAD001 (everolimus)⁹ have been approved as first-in-class mTOR inhibitors for cancer therapy. However, they are allosteric inhibitors, only inhibiting mTOR complex 1 (mTORC1), but not mTOR complex 2 (mTORC2).^{10,11} The selective mTORC1 inhibitors can elicit a complex negative feedback mechanism, causing stimulation of PI3K/AKT signaling in some tumors, thereby minimizing the anticancer effect of mTORC1 inhibition.⁵ Intensive efforts have been underway to discover small-molecule ATP-competitive inhibitors of mTOR kinase as anticancer agents that target both mTOR complexes.

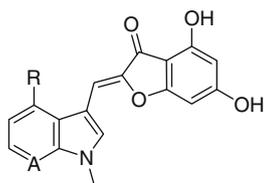
A majority of reported ATP-competitive inhibitors of mTOR are not selective, but rather pan-PI3K/mTOR inhibitors.^{7,12,13} PI3K is located upstream in the PI3K-AKT-mTOR signaling pathway. Relative to pan-PI3K/mTOR inhibitors, selective mTOR inhibitors may be

better tolerated, with the opportunity to achieve a higher therapeutic index for enhanced clinical efficacy. The ATP binding sites of mTOR and PI3Ks (specifically PI3K γ) show a high sequence similarity of 68%, making the search for selective mTOR inhibitors more challenging. Nevertheless, quite a few selective mTOR inhibitors have been reported recently.^{14–24} Herein, we report the discovery and optimization of a new series of potent and selective mTOR inhibitors.

Through high-throughput screening, we identified the indole-bearing 4,6-dihydroxybenzofuranone **1** as an early lead. Introducing a 4-phenyl substituent on the indole gave **2** with improved mTOR potency and higher selectivity over PI3K α . 7-Azaindole **3**, an analog of **1**, did not have improved selectivity, but exhibited enhanced mTOR potency (Table 1). We anticipated that combining the features of **2** and **3** would create analogs with higher mTOR potency while maintaining selectivity. That was indeed what we observed in **9a**, with mTOR potency (IC₅₀ = 0.46 nM) and selectivity (137-fold) superior over **2** and **3**. Since phenol is known for metabolic liability via glucuronidation and sulfation of the phenolic OH groups,²⁵ we decided to eliminate one of the two OH groups. As shown in Table 2, the 4-OH group (**9b**) is more important than the 6-OH group (**9c**) for mTOR potency, selectivity and cellular activity. Therefore, our analoging efforts were directed at the 4-hydroxybenzofuranones.

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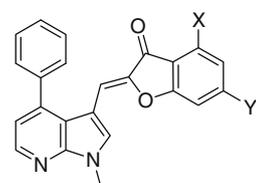
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Table 1
Early leads

Compd	R	A	IC ₅₀ ^a (nM)			IC ₅₀ ^a (μM) LNCap
			mTOR	PI3Kα	Sel ^b	
1	H	CH	800	1106	1.4	na
2	Ph	CH	33	1478	45	1.4
3	H	N	42	77	1.7	6.5

^a Determinations were done in duplicate and repeat values agreed, on average, with a mean twofold difference.

^b Selectivity = (IC₅₀ PI3Kα)/(IC₅₀ mTOR).

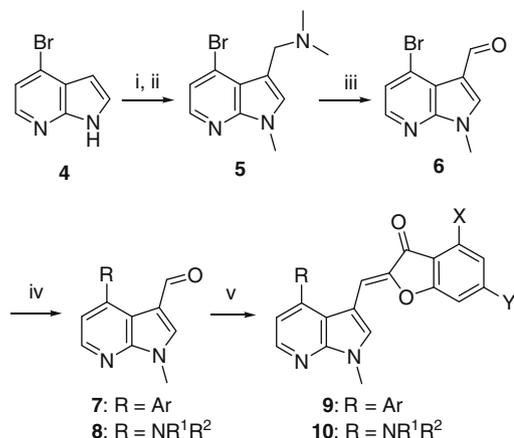
Table 2
Hydroxyl and dihydroxyl analogs

Compd	X	Y	IC ₅₀ ^a (nM)			IC ₅₀ ^a (μM) LNCap
			mTOR	PI3Kα	Sel ^b	
9a	OH	OH	0.46	63	137	0.077
9b	OH	H	3.45	89	25.8	0.2
9c	H	OH	19	219	11	1.8

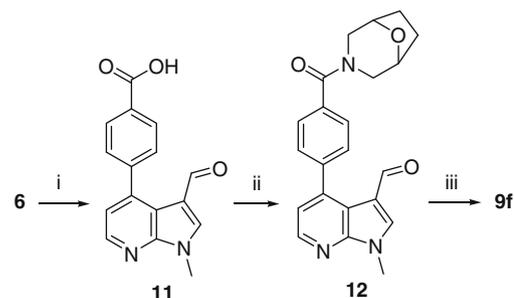
^a Determinations were done in duplicate and repeat values agreed, on average, with a mean twofold difference.

^b Selectivity = (IC₅₀ PI3Kα)/(IC₅₀ mTOR).

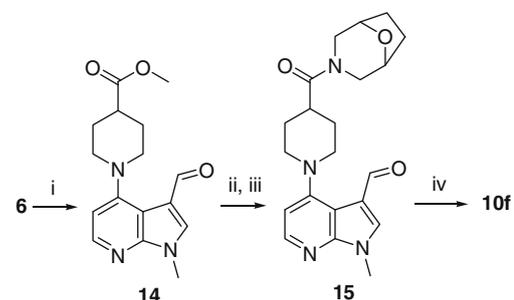
A key 4-bromo intermediate, **6**, was synthesized from 4-bromo-7-azaindole **4**²⁶ via N-methylation and Mannich reaction, followed by heating of **5** with hexamethylenetetramine.²⁷ A variety of 4-substituents were introduced via Suzuki or Buchwald coupling conditions to yield **7** or **8**, respectively. Subsequent coupling with hydroxybenzofuranones in acidic ethanol yielded **9** and **10**, respectively, as depicted in Scheme 1. 4,6-Dihydroxybenzofuranone was commercially available, but not 4-hydroxybenzofuranone, which was prepared from 2,6-dihydroxyacetophenone.²⁸ For **9f** where the benzamide boronic acid was not commercially available, the 4-benzamide was introduced via 4-benzoate followed by hydrolysis and then converting the resulting benzoic acid into amide as shown in Scheme 2. The corresponding piperidine amide **10f** was prepared similarly (Scheme 3). Compared to 4-phenyl compound **9b**, 4-benzamides **9d–h** and 4-piperidine amides **10d–h** were all more potent in inhibiting both mTOR kinase and cellular proliferation, as shown in Table 3. LNCap, a PTEN deficient prostate cancer cell line that showed hyperactive PI3K-AKT-mTOR signaling, was used to evaluate our analogs as mTOR inhibitors. Benzamides **9d–h** were slightly more potent than the corresponding piperidine amides **10d–h**, with IC₅₀ values at or below 1 nM. Both benzamides and piperidine amides showed excellent cellular activity with single digit nM IC₅₀ values. In terms of microsomal stability, 4,6-dihydroxy compounds **9a** had reasonable microsomal stability in phase I metabolism, but not in phase II metabolism, as expected. Unfortunately there is no phase II metabolism data for the corresponding 4-hydroxy compound **9b**. Nevertheless, both phase I and phase I/II data were determined for a group of benzamides and piperidinylla-



Scheme 1. Reagents and conditions: (i) NaH, DMF, then MeI, room temperature; (ii) (CHO)_n, Me₂NHCl, *n*-BuOH, heat; (iii) hexamethylenetetramine, 66% propionic acid, heat; (iv) for **7**: ArB(OH)₂, Pd(PPh₃)₄, Na₂CO₃, DME, heat, 36–68% yield; for **8**: NHR¹R², Pd₂(dba)₃, 2'-(dicyclohexylphosphino)-*N,N*-dimethylbiphenyl-2-amine, K₂HPO₄, DME, heat, 38–80% yield; (v) substituted benzofuranone, EtOH, HCl, heat; for **9**, 49–82% yield; for **10**, 32–75% yield.

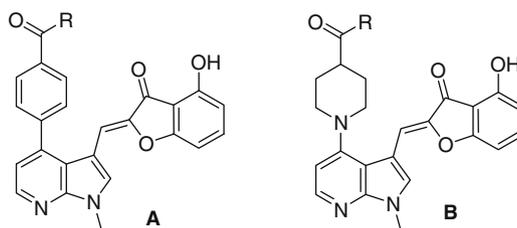


Scheme 2. Reagents and conditions: (i) methyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate, PS-Pd(PPh₃)₄, Na₂CO₃, DME, heat, 75% yield; then MeOH, 2 N NaOH, room temperature, 80% yield; (ii) DMF, THF, *N*-Me-morpholine, *i*-butylchloroformate, then add bridged morpholine, room temperature, 62% yield; (iii) 4-OH-benzofuranone, EtOH, HCl, heat, 70% yield.



Scheme 3. Reagents and conditions: (i) Pd₂(dba)₃, methyl isonipicotate, K₂HPO₄, 2'-(dicyclohexylphosphino)-*N,N*-dimethylbiphenyl-2-amine, DME, heat, 66% yield; (ii) 2 N NaOH, MeOH, 85% yield; (iii) *N*-Me-morpholine, *i*-butylchloroformate, THF, then bridged morpholine, 60% yield; (iv) 4-OH-benzofuranone, EtOH, HCl, heat, 60% yield.

midates as shown in Table 3. Amides bearing bulky amines exhibited more favorable phase II metabolic stability (**9h** > **9g** > **9e**; **10g**, **10e** > **10d**) with exceptions of **10h** bearing a hydroxyethylpiperazine and **9f** and **10f** bearing a 2,6-bridged morpholine.²³ In microsomal stability studies, piperidinyllamides appeared to be more stable than the corresponding benzamides, presumably because piperidine is more bulky and/or more polar than a phenyl ring. One exception lies in the pairs of **9h** (benzamide) and **10h**

Table 3
Benzamides and piperidylamides

Compd	R	IC ₅₀ ^a (nM)			IC ₅₀ (μM) ^a LNCap	Micros ^c	
		mTOR	PI3Kα	Sel ^b		I	I/II
9a		0.46	63	137	0.077	20	2
9b		3.45	89	25.8	0.2	22	—
9d		A	0.55	36	65	0.004	—
10d		B	0.67	30	46	0.001	>30
9e		A	0.5	49	97	0.001	>30
10e		B	1.4	63	45	<0.001	>30
9f		A	0.56	57	103	0.008	6
10f		B	2	52	26	0.001	>30
9g		A	1	70	70	0.009	28
10g		B	3.1	39	12	<0.001	>30
9h		A	0.39	100	256	0.001	>30
10h		B	1.85	25	13	0.001	>30

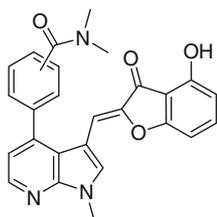
^a Determinations were done in duplicate and repeat values agreed, on average, with a mean twofold difference.

^b Selectivity = (IC₅₀ PI3Kα)/(IC₅₀ mTOR).

^c Nude mouse microsomes T_{1/2} (min). Phase I: Substrate half-life (min) when incubated at 37 °C for 15 min with nude mouse microsomes (0.5 mg/mL protein) and NADPH cofactor. Phase I/II: Substrate half-life (min) when incubated at 37 °C for 15 min with nude mouse microsomes (0.5 mg/mL protein), NADPH, and UDPGA cofactors.

(piperidinylamide), where **10h** was less stable than **9h** in phase II metabolism.

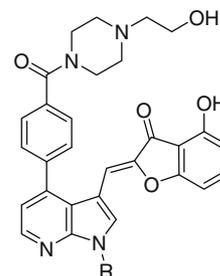
The effect of the amide group position on mTOR activity was also explored. It is clear from Table 4 that the amide substituent is best situated at the *para*-position rather than the *meta*- or *ortho*-position. As for substitution at N-1 of the azaindole, the methyl analog **9h** showed better mTOR potency and selectivity than **13** which bears the larger ethyl group (Table 5). Aminomethylpiperidine **17a** and aminopiperidine **17b** were prepared from the corresponding BOC-protected intermediates **16**, as shown in Scheme 4. Amines **17a** and **17b** were much less potent mTOR inhibitors than amides **10d** and **10i** (Table 6). The tertiary amide **10d** exhibited higher cellular potency than the primary amide

Table 4
Effect of the position of substitution

Compd	Position	IC ₅₀ ^a (nM)			IC ₅₀ ^a (μM) LNCap
		mTOR	PI3Kα	Sel ^b	
9d	<i>p</i> -	0.55	36	65	0.004
9i	<i>m</i> -	18	369	20.5	0.6
9j	<i>o</i> -	180	5895	32.8	>60

^a Determinations were done in duplicate and repeat values agreed, on average, with a mean twofold difference.

^b Selectivity = (IC₅₀ PI3Kα)/(IC₅₀ mTOR).

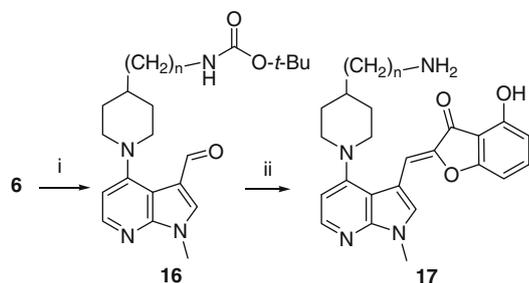
Table 5
N-1 Substitution

Compd	R	IC ₅₀ ^a (nM)			IC ₅₀ ^a (μM) LNCap
		mTOR	PI3Kα	Sel ^b	
9h	Me	0.39	100	256	0.001
13	Et	4.55	455	98	0.004

^a Determinations were done in duplicate and repeat values agreed, on average, with a mean twofold difference.

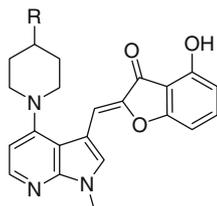
^b Selectivity = (IC₅₀ PI3Kα)/(IC₅₀ mTOR).

10i. Other 4-substituted amines, **10j–m**, which showed good mTOR potency and cellular activity were also prepared (Table 7). Compared to 4-morpholine **10j**, analog **10k** bearing a bulky 2,6-bridged morpholine had enhanced mTOR activity (IC₅₀ = 0.38 nM) and selectivity (274-fold). However, analog **10l**, bearing a 3,5-bridged morpholine, was less selective than **10j**, although the two compounds were equipotent versus mTOR and in LNCap cells. Compound **18**, a 4,6-dihydroxy analog of **10m** (Table 7), was slightly more potent (3-fold) than the 4-hydroxy compound **10m**. However, unlike the pair of **9a** (4,6-dihydroxy) and **9b** (4-hydroxy), where **9a** was more selective and more potent in cells than **9b**, **18**



Scheme 4. Reagents and conditions: (i) 4-substituted piperidine, $\text{Pd}_2(\text{dba})_3$, K_2HPO_4 , 2'-(dicyclohexylphosphino)-*N,N*-dimethylbiphenyl-2-amine, DME, heat, 43% yield; (ii) 4-OH-benzofuranone, EtOH, HCl, heat, 60% yield.

Table 6
Substitution on the piperidine ring

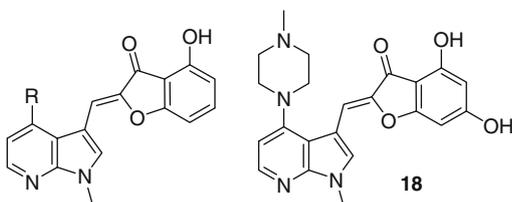


Compd	R	IC_{50}^a (nM)			IC_{50}^a (μM) LNCap
		mTOR	PI3K α	Sel ^b	
10d		0.63	38	60	0.001
10i		0.72	29	41	0.01
17a		17	155	9	0.075
17b		19	119	6	0.24

^a Determinations were done in duplicate and repeat values agreed, on average, with a mean twofold difference.

^b Selectivity = $(\text{IC}_{50} \text{ PI3K}\alpha)/(\text{IC}_{50} \text{ mTOR})$.

Table 7
Effect of the amine substitution



Compd	R	IC_{50} (nM) ^a			IC_{50} (μM) ^a LNCap
		mTOR	PI3K α	Sel ^b	
10j		2.2	53	24	0.005
10k		0.38	104	274	0.002
10l		2.1	19	9	0.002
10m		2.75	173	63	0.003
18		0.94	43	46	0.11

^a Determinations were done in duplicate and repeat values agreed, on average, with a mean twofold difference.

^b Selectivity = $(\text{IC}_{50} \text{ PI3K}\alpha)/(\text{IC}_{50} \text{ mTOR})$.

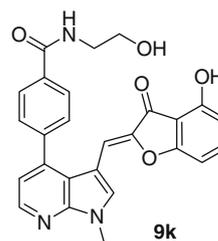
(4,6-dihydroxy) was less selective and less potent (by 37-fold) in cells, compared to **10m** (4-hydroxy). One compound **9k** was evaluated for its ability to inhibit a panel of protein kinases, as shown

in Table 8. It is clear that **9k** was quite potent ($\text{IC}_{50} = 1.6 \text{ nM}$) and selective for mTOR versus 23 other protein kinases.

Compound **18** was successfully co-crystallized with PI3K γ protein, which was utilized as a surrogate for crystallography studies based on its high similarity to mTOR at the ATP binding sites. The X-ray structures (PDB code 3LJ3) and the predicted binding mode with the mTOR homology model showed the 7-N forms a hydrogen bond to Val2240 in the hinge region at the ATP binding site of the protein (Fig. 1). This helps explain why the 7-azaindoles are more potent mTOR inhibitors than the corresponding indoles. The 4-hydroxy group in the benzofuranone portion of **18** makes a hydrogen bonding interaction with Lys2187. In addition, the 6-hydroxy group forms a hydrogen bond to Asp2195 and the backbone-NH of Phe2358. These hydrogen bond interactions may explain the contribution of the 4- and 6-hydroxy groups to mTOR binding affinity. It is clear that there is a lot of room to accommodate substituents at the C-4 position of the azaindole core, although the X-ray structure does not reveal structural requirements for selectivity for mTOR over PI3K α .

In summary, we discovered a series of 4-substituted 7-azaindoles as potent and selective mTOR inhibitors. Since phenolic OH

Table 8
Inhibitory activity of **9k** against a panel of protein kinases



Kinase	IC_{50} (nM)	Kinase	IC_{50} (nM)	Kinase	IC_{50} (μM)
mTOR	0.0016	VEGFR2	50	SRC	50
PI3K α	0.016	RSK1	45.9	ROCK1	50
PKC α	50	PKA	50	PDGFR α	50
P38 α	50	MK2	6.5	MET	50
LYN A	27.7	IKK α	50	HCK	27.1
GSK3 β	5.9	GSK3 α	10.6	GCK	50
FGFR1	50	ERK2	50	CK1 γ	50
CDK2	35.5	CDK1	39.2	Aurora B	22.2
ABL1	9.7				

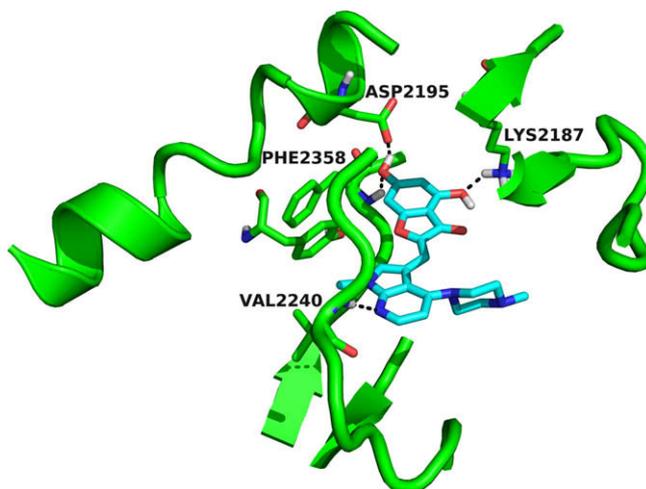


Figure 1. Predicted binding mode of **18** with mTOR based on co-crystallization with PI3K γ . Close-up of interactions of **18** with the mTOR binding site. Hydrogen bonds are shown with black dashed lines and residue numbers are indicated for hydrogen bonding partners.

groups pose metabolic liability, one of the two hydroxyl groups was selectively removed. Lead optimization generated subnanomolar, ATP-competitive mTOR kinase inhibitors with low nanomolar cellular activity. An X-ray structure of our inhibitor with PI3K γ revealed the important hydrogen bonding interactions, which suggested the basis for the high mTOR potency of this new series of inhibitors.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.01.135.

References and notes

- Guertin, D. A.; Sabatini, D. M. *Cancer Cell* **2007**, *12*, 9.
- Chiang, G. G.; Abraham, R. T. *Trends Mol. Med.* **2007**, *13*, 433.
- Abraham, R. T. *DNA Repair* **2004**, *3*, 883.
- Yuan, T. L.; Cantley, L. C. *Oncogene* **2008**, *27*, 5497.
- Carracedo, A.; Pandolfi, P. P. *Oncogene* **2008**, *27*, 5527.
- Inoki, K.; Corradetti, M. N.; Guan, K. L. *Nat. Genet.* **2005**, *37*, 19.
- Verheijen, J.; Yu, K.; Zask, A. *Annu. Rep. Med. Chem.* **2008**, *43*, 189.
- Hudes, G.; Carducci, M.; Tomczak, P.; Ditcher, J.; Figilin, R.; Kapoor, A.; Staroslawska, E.; Sosman, J.; McDermott, D.; Bodrogi, I.; Kovacevic, Z.; Lesovoy, V.; Schmidt-Wolf, I. G. H.; Barbarash, O.; Gokmen, E.; O'Toole, T.; Lustgarten, S.; Moore, L.; Motzer, R. J. *N. Eng. J. Med.* **2007**, *356*, 2271.
- Motzer, R. J.; Escudier, B.; Oudard, S.; Hutson, T. E.; Porta, C.; Bracarda, S.; Grunwald, V.; Thompson, J. A.; Figlin, R. A.; Hollaender, N.; Urbanowitz, G.; Berg, W. J.; Kay, A.; Lebwohl, D.; Ravaud, A. *Lancet* **2008**, *372*, 449.
- Choi, J.; Chen, J.; Schreiber, S. L.; Clardy, J. *Science* **1996**, *273*, 239.
- Liang, J.; Choi, J.; Clardy, J. *Acta Crystallogr., Sect. D.* **1999**, *55*, 736.
- Maira, S.-M.; Staffer, F.; Brueggen, J.; Furet, P.; Schnell, C.; Fritsch, C.; Brachmann, S.; Chene, P.; De Pover, A.; Schoemaker, K.; Fabbro, D.; Gabriel, D.; Simonen, M.; Murphy, L.; Finan, P.; Sellers, W.; Garcia-Echeverria, C. *Mol. Cancer Ther.* **2008**, *7*, 1851.
- Folkes, A. J.; Ahmadi, K.; Alderton, W. K.; Alix, S.; Baker, S. J.; Box, G.; Chuckowree, I. S.; Clarke, P. A.; Depledge, P.; Eccles, S. A.; Friedman, L. S.; Hayes, A.; Hancox, T. C.; Kugendradas, A.; Lensun, L.; Moore, P.; Olivero, A. G.; Pang, J.; Patel, S.; Pergl-Wilson, G. H.; Raynaud, F. I.; Robson, A.; Saghir, N.; Salphati, N. C.; Wiesmann, C.; Workman, P.; Zhyvoloup, A.; Zvelebil, M. J.; Shuttleworth, S. J. *J. Med. Chem.* **2008**, *51*, 5522.
- Feldman, M. E.; Apse, B.; Uotila, A.; Loewith, R.; Knight, Z. A.; Ruggero, D.; Shokat, K. M. *PLoS Biol.* **2009**, *7*, 371.
- Garcia-Martinez, J. M.; Moran, J.; Clarke, R. G.; Gray, A.; Cosulich, S. C.; Chresta, C. M.; Alessi, D. R. *Biochem. J.* **2009**, *421*, 29.
- Thoreen, C. C.; Kang, S. A.; Chang, J. W.; Liu, Q.; Zhang, J.; Gao, Y.; Reichling, L. J.; Sim, T.; Sabatini, D. M.; Gray, N. S. *J. Biol. Chem.* **2009**, *284*, 8023.
- Yu, K.; Toral-Barza, L.; Shi, C.; Zhang, W.-G.; Lucas, J.; Shor, B.; Kim, J.; Verheijen, J.; Curran, K.; Malwitz, D. J.; Cole, D. C.; Ellingboe, J.; Ayril-Kaloustian, S.; Mansour, T. S.; Gibbons, J. J.; Abraham, R. T.; Nowak, P.; Zask, A. *Cancer Res.* **2009**, *69*, 6232.
- Zask, A.; Verheijen, J. C.; Curran, K.; Kaplan, J.; Richard, D. J.; Nowak, P.; Malwitz, D. J.; Brooijmans, N.; Bard, J.; Svenson, K.; Lucas, J.; Toral-Barza, L.; Zhang, W.-G.; Hollander, I.; Gibbons, J. J.; Abraham, R. T.; Ayril-Kaloustian, S.; Mansour, T. S.; Yu, K. *J. Med. Chem.* **2009**, *52*, 5013.
- Meneer, K. A.; Gomez, S.; Malagu, K.; Bailey, C.; Blakburn, K.; Cockroft, X.-L.; Ewen, S.; Fundo, A.; Le Gall, A.; Hermann, G.; Sebastian, L.; Sunose, M.; Presnot, T.; Torode, E.; Hickson, I.; Martin, N. M. B.; Smith, G. C. M.; Pike, K. G. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5898.
- Richard, D. J.; Verheijen, J. C.; Curran, K.; Kaplan, J.; Toral-Barza, L.; Hollander, I.; Lucas, J.; Yu, K.; Zask, A. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6830.
- Nowak, P.; Cole, D. C.; Brooijmans, N.; Bursavich, M. G.; Curran, K. J.; Ellingboe, J. W.; Gibbons, J. J.; Hollander, I.; Hu, Y.; Kaplan, J.; Malwitz, D. J.; Toral-Barza, L.; Verheijen, J. C.; Zask, A.; Zhang, W.-G.; Yu, K. *J. Med. Chem.* **2009**, *52*, 7081.
- Verheijen, J.; Richard, D. J.; Curran, K.; Kaplan, J.; Lefever, M.; Nowak, P.; Malwitz, D. J.; Brooijmans, N.; Toral-Barza, L.; Zhang, W.-G.; Lucas, J.; Hollander, I.; Ayril-Kaloustian, S.; Mansour, T.; Yu, K.; Zask, A. *J. Med. Chem.* **2009**, *52*, 8010.
- Zask, A.; Kaplan, J.; Verheijen, J. C.; Richard, D. J.; Curran, K.; Brooijmans, N.; Bennett, E. M.; Toral-Barza, L.; Hollander, I.; Ayril-Kaloustian, S.; Yu, K. *J. Med. Chem.* **2009**, *52*, 7942.
- Kaplan, J.; Verheijen, J. C.; Brooijmans, N.; Toral-Barza, L.; Hollander, I.; Yu, K.; Zask, A. *Bioorg. Med. Chem. Lett.* **2009**, *20*, 640.
- Shangari, N.; Chan, T. S.; O'Brien, P. J. *Methods Enzymol.* **2005**, *400*, 342.
- Thibault, C.; L'Heureux, A.; Bhide, R. S.; Ruel, R. *Org. Lett.* **2003**, *5*, 5023.
- Robison, M. M.; Robison, B. L. *J. Am. Chem. Soc.* **1955**, *77*, 457.
- Li, W.-S.; Guo, Z.; Thornton, J.; Katipally, K.; Polniaszek, R.; Thottathil, J.; Vu, T.; Wong, M. *Tetrahedron Lett.* **2002**, *43*, 1923.