Bioorganic & Medicinal Chemistry Letters 20 (2010) 4308–4312

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

BMCL Digest

Allosteric and ATP-competitive kinase inhibitors of mTOR for cancer treatment

Carlos García-Echeverría

Oncology Drug Discovery, Sanofi-Aventis, 13 Quai Jules Guesde, 94400 Vitry-sur-Seine, France

ARTICLE INFO

Article history:
Received 16 April 2010
Revised 25 May 2010
Accepted 26 May 2010
Available online 1 June 2010

Keywords:
Kinase inhibitors
mTOR
Anticancer agents

ABSTRACT

Over the past few years a number of components of the PI3K/mTOR pathway have been the subject of intense drug discovery activities both in pharmaceutical companies and in academia. This review article summarizes progress made in the identification and development of allosteric and ATP-competitive kinase inhibitors of mTOR and their potential therapeutic use in oncology.

The mammalian target of rapamycin (mTOR) is a member of the phosphatidylinositol 3-kinase (PI3K) related kinases (PIKKs) and a component of the PI3K signaling pathway. The PI3K/mTOR cascade plays an important role in controlling cell growth, proliferation and survival.[1] Through various mechanisms, this pathway is frequently dysregulated in human cancers, suggesting the use of pathway modulators as novel targeted anticancer agents.[2] To this end, substantial drug discovery efforts have been devoted both in pharmaceutical companies and in academia to identify and develop therapeutic agents able to specifically downregulate the Ser/Thr kinase activity of mTOR.[3] This protein is found in two structurally and functionally distinct multiprotein complexes known as mTOR complex **1** (mTORC1) and **2** (mTORC2), which have different subunit composition, downstream substrates and biological effects.[4] mTORC1 contains raptor, mLST8, PRAS40 and mTOR, while mTORC2 consists of rictor, mSIN1, mLST8 and mTOR.

This Letter reviews salient achievements in the identification and development of modulators of mTOR in oncology, updating recent reviews on this therapeutic target and pathway.[3,5–8] As shown herein, compounds with different mechanisms of action have been exploited to specifically inhibit the mTOR complexes, and some of these modulators have already provided proof-of-concept in cancer clinical settings.

A well-known mTOR inhibitor is rapamycin (sirolimus; compound **1**, Fig. 1), which is a macrocyclic antibiotic produced by *Streptomyces hygroscopicus.* This natural product inhibits mTOR kinase activity by forming a complex with the immunophilin FK506-binding protein of 12 kDa (FKBP12), which binds a region in the C-terminus of mTOR termed FRB (FKBP12-rapamycin binding) that it is adjacent to the catalytic site.[9] The formation of this protein–protein interaction interferes exclusively with the kinase activity of the mTORC1 complex, but it does not inhibit all the functions of mTOR, nor do they block the kinase activity of the mTORC2 complex.[10]

The limited pharmacological properties of rapamycin, mainly its poor bioavailability and aqueous insolubility in water, prompted the preparation of synthetic analogs. Currently, several of these derivatives, which are also known as 'rapalogs' (e.g., CCI-779 (temsirolimus), compound **2**; RAD001 (everolimus), compound **3**; and AP-23573 (deforolimus), compound **4**; Fig. 1), are being evaluated in cancer clinical trials.[11] Different approaches were followed to address the pharmacological limitations of the parent compound. Thus, the hydroxyl function at C-40, which is unrelated to both the mTOR and FKBP12-binding sites, was modified to introduce a solubilizing moiety –hydroxyethyl–, a pro-drug synthon –acylation with 2,2-bis(hydroxymethyl)propionyl– or a polar moiety –dimethylphosphinate–. These modifications do not significantly affect the mTORC1 inhibitory activity of the allosteric inhibitors, but seem to slightly improve their human pharmacokinetic properties in comparison to rapamycin.[12]

Overall, the preceding rapamycin derivatives are well tolerated in cancer patients and, although non-stratified clinical trials with these compounds have turned out to be less successful than predicted, induction of prolonged stable disease and increase time to progression has been observed in a subset of cancer patients. In particular, promising activity has been reported in patients with advanced renal cell carcinomas (RCCs) who have failed prior therapy,[13,14] and tubero-sclerosis patients who harbor renal angiomyolipomas or subependymal giant cell astrocytomas.[15] Following the positive results of phase III clinical trials,[14] temsirolimus and everolimus have been approved by the US Food and Drug Administration (FDA) for the treatment of advanced kidney cancer.

E-mail address: Carlos.Garcia-Echeverria@sanofi-aventis.com

0960-894X/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2010.05.099

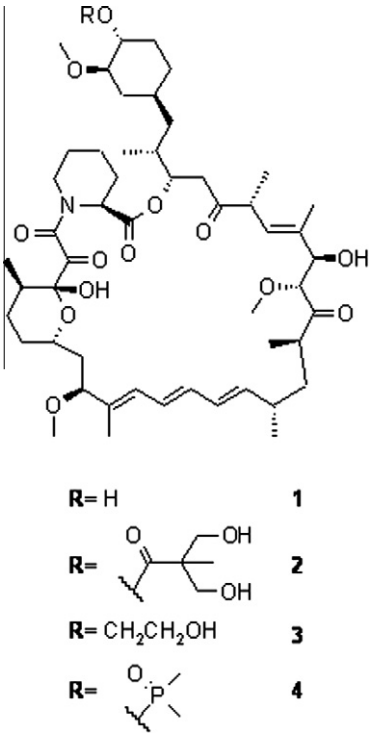

Figure 1. Allosteric inhibitors of mTORC1.

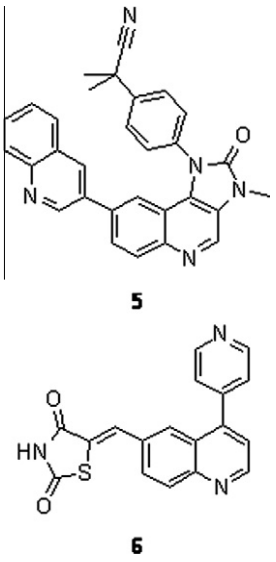

Figure 2. Representative examples of dual ATP-competitive inhibitors of PI3K and mTOR.

Temsirolimus has also received marketing approval for the treatment of mantle cell lymphoma (for a recent review on clinical data for rapalogs, see Ref. 16).

Parallel to the advancement of mTORC1 allosteric modulators in the clinic, several mechanisms of potential resistance to this type of drug have been identified. Among them, a negative feed-back loop mechanism in which mTORC1 inhibition can lead to phosphorylation and activation of Akt has been reported in preclinical and clinical settings.[17] Although it is unclear to which extent this or other feed-back mechanisms[18] may limit the therapeutic benefit of mTORC1 inhibitors as single agents, these findings have provided the rationale for combination studies with other anticancer drugs (e.g., IGF-IR, PI3K, Hsp90, Raf or Mek modulators)[16] to block such feed-back loops or the identification of ATP-competitive mTOR modulators. As shown in the next section, medicinal chemistry efforts have identified and developed compounds with different levels of selectivity against protein and lipid kinases. These mTOR modulators represent not only a new wave of potential targeted anticancer agents, but also useful pharmacological tools for deciphering the complexity of mTOR biological network.

Early reported ATP-competitive kinase inhibitors of mTOR also block the enzymatic activity of PI3K and related PIKKs, but show good selectivity over the rest of the human kinome. The kinase selectivity profile of these dual PI3K/mTOR modulators is consistent with the high sequence homology and identity in the ATP-catalytic cleft of these kinases, especially with the p110γ isoform. The mTOR activity of these non-selective mTOR modulators—for example, NVP-BEZ235 (compound **5**), NVP-BGT226, XL765, SF1126 and GSK1059615 (compound **6**), Figure 2; for a cross-comparison of the biological activity of these inhibitors, see Ref. 19—was found retrospectively, and their multitarget kinase profile was probably not part of the medicinal chemistry optimization strategy for these or related analogues. These dual PI3K/mTOR modulators contain 'classical hinge kinase binders' and docking studies performed with homology models suggest that the interactions mediated by the core scaffold are similar to the ones described for other ATP-competitive modulators (e.g., canonical H-bond interactions with residues in the hinge region of the lipid kinase).[5] These dual PI3K/mTOR modulators have demonstrated significant, concentration-dependent cell growth inhibition and induction of apoptosis in a variety of tumor cancer cells, particularly for those harboring p110α mutations and/or over-expressing erbB2.[20] In spite of their high lipophilicity and limited water solubility, the pharmacological, biological and preclinical safety profiles of these early dual PI3K/mTOR inhibitors supported their clinical development and a few of them are currently undergoing phase I/II clinical trials in cancer patients.

The potential synergistic effect of concomitant inhibition of PI3K and mTOR has also been exploited by preparing hybrid molecules.[21] 17-Hydroxywortmannin analogues have been conjugated to rapamycin derivatives via a pro-drug linker (e.g., diester bond; structure not shown). Conjugation resulted in enhanced water solubility relative to the parent compounds and better tolerability in preclinical efficacy studies. However, and due to the limited available public information on this type of compounds, it is difficult to evaluate the potential advantages that these hybrid molecules may provide over the existing dual PI3K/mTOR inhibitors.

Although most biologically active low molecular mass kinase inhibitors have a degree of promiscuity, and such unexpected activity against other therapeutic targets has proven useful for some kinase inhibitors (e.g., imatinib or sunitinib),[22,23] it is still too early to know if the concomitant inhibition of PI3K and mTOR is going to translate into effective clinical cancer agents with an acceptable safety profile. This uncertainty has triggered drug discovery efforts directed to identify mTOR inhibitors with more stringent protein kinase selectivity profiles.

PP242 (compound **7**, Fig. 3) has been one of the first selective mTOR catalytic inhibitor described in the literature.[24] The unexpected mTOR activity (IC_{50} = 8 nM) of this pyrazolopyrimidine derivative was identified by an extensive kinome-level biochemical profiling of a chemical library intended to target tyrosine and lipid kinases. The compound shows a relative good selectivity profile against protein kinases (1–2 log units) and has been used as a biological tool to interrogate mTOR signaling.[25] These studies, which complement the ones performed with shRNA approaches, have shown that a catalytic mTOR inhibitor can block the proliferation of tumor cells and the phosphorylation of the mTORC1 substrate 4EBP1 more effectively than rapamycin. Moreover, the

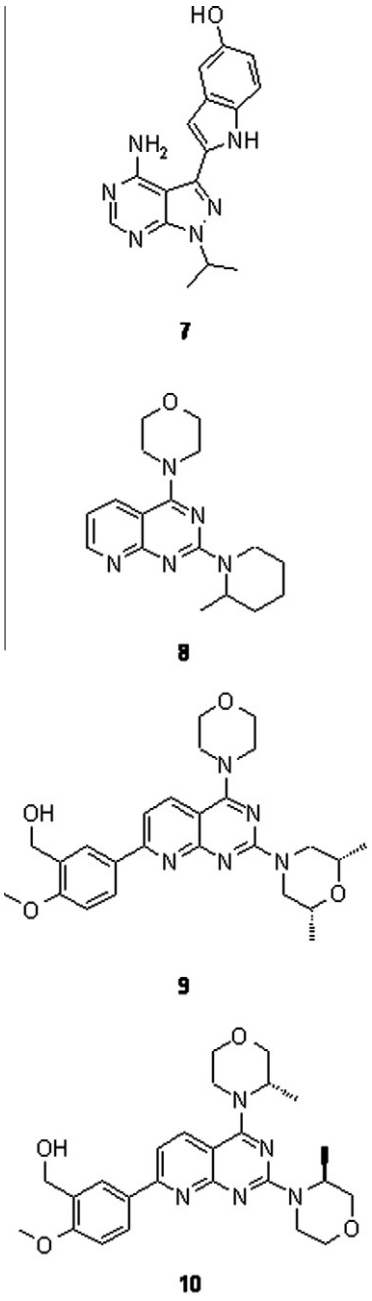

Figure 3. Representative examples of ATP-competitive mTOR inhibitors: PP242 and optimization of pyrido[2,3-*d*]pyrimidine-2,4-diamine derivatives.

compound also inhibits the mTORC2 complex and its downstream signaling (e.g., phosphorylation of Ser473 and Thr450-Akt). These initial findings, which have also been confirmed with other early ATP-competitive mTOR inhibitors (e.g., Torin1[26] and WYE-354[27]), hold promise that compounds with this mechanism of action will be more effective at blocking the PI3K pathway, and suppressing protein synthesis required for growth and proliferation of cancer cells than rapamycin derivatives. In this context, the antitumor activity of PP242 in combination with bcr-abl modulators has been recently illustrated in models of acute leukemia harboring the Philadelphia chromosome (Ph) translocation.[28]

AZD8055, AZD2014, OSI-027 and INK-128 have been the first optimized ATP-competitive mTOR inhibitors to enter clinical trials. Although most of the structures of these clinical compounds have not yet been disclosed, they are probably derived from previously described protein kinase scaffolds. A case in point is the optimization of pyrido[2,3-*d*]pyrimidine-2,4-diamine derivatives that lead to the discovery of AZD8055.[29] The original hit (compound **8**, racemate; Fig. 3) was identified by high-throughput screening and the medicinal chemistry optimization was guided by using an homology model of mTOR derived from the X-ray crystal structure of p110γ.[30] Extensive substitutions were performed at C7 and, although this synthetic effort resulted in the identification of

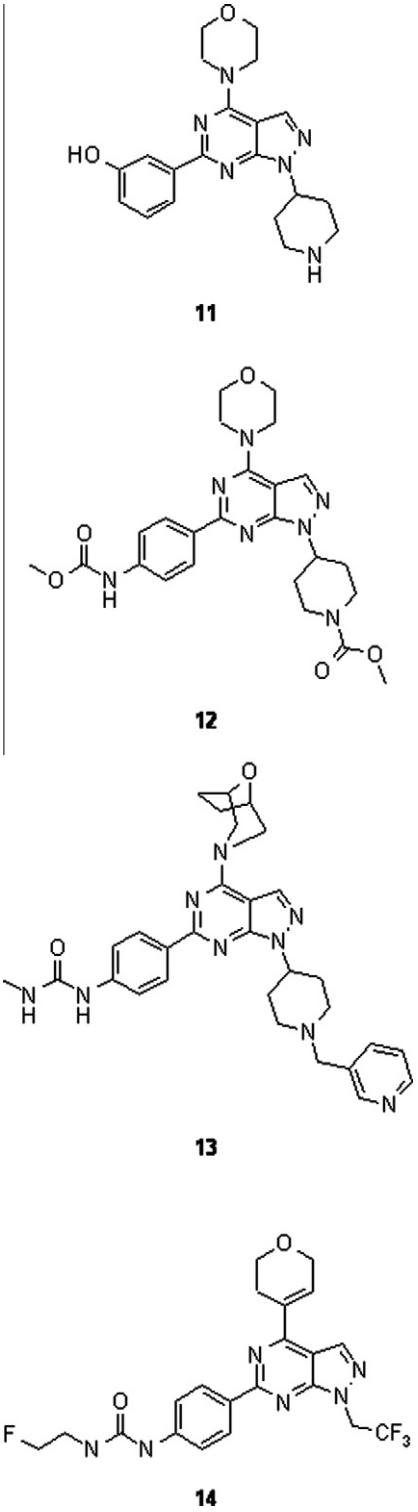

Figure 4. Representative examples of ATP-competitive mTOR inhibitors: optimization of pyrazolopyrimidine derivatives.

potent and selective compounds (e.g., IC_{50} = 16 nM and 8.9 μM, for mTOR and p110α, respectively; KU-0063794, compound **9**, Fig. 3),[31] the subtle SAR data generated from these modifications were not readily explained by the homology model. Further optimization of the pyridopyrimidine scaffold resulted in the identification of AZD8055 (compound **10**, Fig. 3). The compound inhibits the kinase activity of mTOR with an IC_{50} of 0.8 nM and shows significant selectivity against lipid (1000-fold) and protein kinases.[29] As expected from its mechanism-of-action, it induces a dose-dependent growth inhibition and/or regression in a broad range of human tumor xenografts at tolerated doses when administered orally.

OSI-027 (structure not available) is probably derived from the 8-amino-imidazopyrazine scaffold,[32,33] which was previously exploited for the identification of IGF-IR inhibitors (e.g., OSI-906). INK-128 (structure not available) is also an orally administered, mTOR inhibitor (IC_{50} = 1.6 nM) which is active against a broad range of human tumor cell lines (EC_{50} <20 nM).[34] The compound was discovered via a proprietary platform based on initial research at UCSF.[35,36]

Pyrazolopyrimidine derivatives with a wide variety of substituents and differential binding affinities for mTOR and PI3K have been covered in several seminal publications (for representative examples, see Refs. 27,37,38). The original hit (IC_{50} = 0.22 μM, mTOR; compound **11**, Fig. 4) was identified by high-throughput screening and it showed a modest selectivity (six-fold) over p110α.[39] Varying the phenolic group—a potential glucuronidation site—with indole or carbamate containing phenyl groups and introducing substituents in the piperidine ring resulted in more potent and selective mTOR inhibitors (e.g., IC_{50} = 5 nM and 1026 nM for mTOR and p110α, respectively; WYE-354, compound **12**, Fig. 4).[27] Of special note in some of these derivatives is the high level of mTOR activity and selectivity obtained by replacement of the morpholine group with bridged (chiral and achiral) synthons.[40,41] The suggested binding mode of these derivatives in an mTOR homology model based again on the X-ray structure of p110δ revealed that the morpholine moiety is involved in a H-bond interaction with Val-2240 in the hinge region of mTOR. The increased mTOR selectivity observed for the bridged morpholine-derivatives (e.g., IC_{50} = 0.48 nM and 677 nM for mTOR and p110α, respectively; compound **13**, Fig. 4) is caused by a single amino acid difference (Leu vs Phe) that creates a deeper pocket in mTOR. The side chain of Phe961 in p110α cannot accommodate properly the bridged-morpholine group and may cause a displacement of the morpholine oxygen away from its H-bonding partner. The 8-oxa-3-azabicyclo[3.2.1]octane synthon has also been used to optimize the mTOR inhibitory activity and selectivity over lipid kinases of thienopyrimidine derivatives,[42] which is a scaffold previously exploited to target PI3K (e.g., GDC-0941).[43] Recently, it has been shown that the interactions mediated by the morpholine group in the preceding compounds can also be mimicked with the 3,6-dihydro-2*H*-pyran moiety (compound **14**, Fig. 4).[44]

As briefly illustrated in this review, there is promise in considering mTOR as a node upon which to develop therapeutic approaches to target solid tumors and hematological malignancies. Convincing clinical activity has already been reported for the allosteric mTORC1 inhibitors in RCC, tubero-sclerosis and lymphoma patients, and a few of these compounds have already received marketing approval. In an effort to expand the antitumor activity of rapamycin and derivatives thereof, ATP-competitive mTOR kinase inhibitors with different levels of selectivity against lipid and protein kinases have been identified and optimized, and some of these compounds are in the early days of clinical evaluation. The current and future armamentarium of mTOR modulators will hopefully lead to more effective targeted anticancer treatments as well as a better understanding into the roles of the mTOR complexes and downstream effectors in human cancer biology.

Acknowledgments

I thank Gary McCort, Michael Teufel and Laurent Schio for their comments and suggestions during the preparation of this manuscript.

References and notes

1. Carnero, A.; Blanco-Aparicio, C.; Renner, O.; Link, W.; Leal, J. F. M. *Curr. Cancer Drug Targets* **2008**, *8*, 187.
2. Garcia-Echeverria, C.; Sellers, W. R. *Oncogene* **2008**, *27*, 5511.
3. Guertin, D. A.; Sabatini, D. M. *Sci. Signalling* **2009**, *2*, 24.
4. Yang, Q.; Guan, L. *Cell Res.* **2007**, *17*, 666.
5. Maira, S. M.; Furet, P.; Stauffer, F. *Future Med. Chem.* **2009**, *1*, 137.
6. Brachmann, S.; Fritsch, C.; Maira, S.-M.; Garcia-Echeverria, C. *Curr. Opin. Cell Biol.* **2009**, *21*, 1.
7. Liu, P.; Cheng, H.; Roberts, T.; Zhao, J. J. *Nat. Rev.* **2009**, *8*, 627.
8. Engelman, J. A. *Nat. Rev.* **2009**, *9*, 550.
9. Choi, J.; Chen, J.; Schreiber, S. L.; Clardy, J. *Science* **1996**, *273*, 239.
10. Yonezawa, K.; Tokunaga, C.; Oshiro, N.; Yoshino, K. *Biochem. Biophys. Res. Commun.* **2004**, *313*, 437.
11. Fasolo, A.; Sessa, C. *Expert Opin. Invest. Drugs* **2008**, *17*, 1717.
12. Hartford, C. M.; Ratain, M. J. *Clin. Pharmacol. Ther.* **2007**, *82*, 381.
13. Motzer, R. J.; Escudier, B.; Oudard, S.; Hutson, T. E.; Porta, C.; Bracarda, S.; Grüunwald, V.; Thompson, J. A.; Figlin, R. A.; Hollaender, N.; Urbanowitz, G.; Berg, W. J.; Kay, A.; Lebwohl, D.; Rovaud, A. *Lancet* **2008**, *372*, 449.
14. Hudes, G.; Carducci, M.; Tomczak, P.; Dutcher, J.; Figlin, R.; Kapoor, A.; Staroslawaska, E.; Sosman, J.; McDermott, D.; Bodrogi, I.; Kovacevic, Z.; Lesovoy, V.; Schmidt-Wolf, I. G.; Babarash, O.; Gokmen, E.; O'Toole, T.; Lustgarten, S.; Mooren, L.; Motzer, R. J. *N. Eng. J. Med.* **2007**, *356*, 2271.
15. Bissler, J. J.; McCormack, F. X.; Young, L. R.; Elwing, J. M.; Chuck, G.; Leonard, J. M.; Schmithorsdt, V. J.; Laor, T.; Brody, A. S.; Bean, J.; Salisbury, S.; Franz, D. N. *N. Eng. J. Med.* **2008**, *358*, 140.
16. Meric-Bernstam, F.; Gonzalez-Angulo, A. M. *J. Clin. Oncol.* **2009**, *27*, 2278.
17. O'Reilly, K. E.; Rojo, F.; She, Q. B.; Solit, D.; Mills, G. B.; Smith, D.; Lane, H.; Hofmann, F.; Hicklin, D. J.; Ludwig, D. L.; Baselga, J.; Rosen, N. *Cancer Res.* **2006**, *66*, 1500.
18. Carracedo, A.; Ma, L.; Teruya-Feldstein, J.; Rojo, F.; Salmera, L.; Alimonti, A.; Egia, A.; Sasaki, A. T.; Thomas, G.; Kozma, S. C.; Papa, A.; Nardelia, C.; Cantley, L. C.; Baselga, J.; Pandolfi, P. P. *J. Clin. Invest.* **2008**, *118*, 3065.
19. Ihle, N. T.; Powis, G. *Mol. Cancer Ther.* **2009**, *8*, 1.
20. Brachmann, S. M.; Hofmann, I.; Schnell, C.; Fritsch, C.; Wee, S.; Lane, H.; Wang, S.; Garcia-Echeverria, C.; Maira, S. M. *Proc. Natl. Acad. Sci. U.S.A.* **2009**, *106*, 22299.
21. Ayral-Kaloustian, S.; Gu, J.; Cinque, M.; Gaydos, C.; Zask, A.; Chaudhary, I.; Wang, J.; Di, L.; Young, M.; Ruppen, M.; Mansour, T. S.; Gibbons, J. J.; Yu, K. *J. Med. Chem.* **2010**, *53*, 452.
22. Morphy, R. *J. Med. Chem.* **2010**, *53*, 1413.
23. Knight, Z. A.; Lin, H.; Shokat, K. M. *Nat. Rev. Cancer* **2010**, *10*, 130.
24. Apsel, B.; Blair, J. A.; Gonzalez, B.; Nazif, T. M.; Feldman, M. E.; Aizenstein, B.; Hoffman, R.; Williams, R. L.; Shokat, K. M.; Knight, Z. A. *Nat. Chem. Biol.* **2008**, *4*, 691.
25. Feldman, M. E.; Apsel, B.; Uotila, A.; Loewith, R.; Knight, Z. A.; Ruggero, D.; Shokat, K. M. *PLoS Biol.* **2009**, *7*, e38.
26. 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.
27. 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.; Ayral-Kaloustian, S.; Mansour, T. S.; Gibbons, J. J.; Abrahman, R. T.; Nowak, P.; Zask, A. *Cancer Res.* **2009**, *69*, 6232.
28. Janes, M. R.; Limon, J. J.; So, L.; Chen, J.; Lim, R. J.; Chavez, M. A.; Vu, C.; Lilly, M. B.; Mallya, S.; Ong, S. T.; Konopleva, M.; Martin, M. B.; Ren, P.; Liu, Y.; Rommel, C.; Fruman, D. A. *Nat. Med.* **2010**, *16*, 205.
29. Chresta, C. M.; Davies, B. R.; Hickson, I.; Harding, T.; Cosulich, S.; Critchlow, S. E.; Vincent, J. P.; Ellston, R.; Jones, D.; Sini, P.; James, D.; Howard, Z.; Dudley, P.; Hughes, G.; Smith, L.; Maguire, S.; Hummersone, M.; Malagu, K.; Menear, K.; Jenkins, R.; Jacobsen, M.; Smith, G. C. M.; Guichard, S.; Pass, M. *Cancer Res.* **2010**, *70*, 288.
30. Malagu, K.; Duggan, H.; Menear, K.; Hummersone, M.; Gomez, S.; Bailey, C.; Edwards, P.; Drzewiecki, J.; Leroux, F.; Jimenez Quesada, M.; Hermann, G.; Maine, S.; Molyneaux, C.-A.; Le Gall, A.; Pullen, J.; Hickson, I.; Smith, L.; Maguire, S.; Martin, N.; Smith, G.; Pass, M. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5950.
31. 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.
32. Castelhano, A. L.; Mulvihill, K. M.; Rechka, J. A. WO Patent 9,117,482, 2009.
33. Chen, X.; Coate, H.; Crew, A. P.; Dong, H.-Q.; Honda, A.; Mulvihill, M. J.; Tavares, P. A. R.; Wang, J.; Werner, D. S.; Mulvihill, K. M.; Siu, K. W.; Panicker, B.; Braradway, A.; Arnold, L. D.; Jin, M.; Volk, B.; Weng, Q.; Beard, J. D. U.S. Patent 7,112,005, 2007.
34. Rommel, C. *Abstracts of Papers, Oral presentation*, 100th Annu Meet Am Assoc Cancer Res (AACR), April 18–22, Denver 2009.
35. Liu, Y.; Ren, P.; Li, L.; Chan, K.; Wilson, T. E. WO Patent 9,114,870, 2009.

36. Shokat, K. M.; Fruman, D.; Ren, O.; Wilson, T. E.; Li, L.; Hsieh, A.; Feldman, M.; Apsel, B.; Liu, Y.; Rommel, C.; Chan, K.; Ruggero, D.; Pearce, D.; Janes, M. WO 10,006,072, 2010.
37. Verheijen, J. C.; Richard, D. J.; Curran, K.; Kaplan, J.; Lefever, M.; Nowak, P.; Malwitz, D. J.; Brooijmans, N.; Toral-Barza, L.; Wei-Guo, Z.; Lucas, J.; Holander, I.; Ayral-Kaloustian, S.; Mansour, T. S.; Yu, K.; Zask, A. *J. Med. Chem.* **2009**, *52*, 8010.
38. 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.; Ayral-Kaloustian, S.; Mansour, T. S.; Yu, K. *J. Med. Chem.* **2009**, *52*, 5013.
39. Nowak, P.; Cole, D. C.; Brooijmans, N.; Bursavich, M. G.; Curran, K. J.; Ellingboe, J. W.; Gibbson, 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.
40. Zask, A.; Kaplan, J.; Verheijen, J. C.; Richard, D. J.; Curran, K.; Brooijmans, N.; Bennett, E. M.; Toral-Barza, L.; Hollander, I.; Ayral-Kaloustian, S.; Yu, K. *J. Med. Chem.* **2009**, *52*, 7942.
41. 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.
42. Verheijen, J. C.; Yu, K.; Toral-Barza, L.; Hollander, I.; Zask, A. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 375.
43. 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, L.; Sohal, S.; Ultsch, M. H.; Valenti, M.; Walweber, H. J.; Wan, N. C.; Wiesmann, C.; Workman, P.; Zhyvoloup, A.; Zuelebil, M. J.; Shuttleworth, S. J. *J. Med. Chem.* **2008**, *51*, 5522.
44. Kaplan, J.; Verheijen, J. C.; Brooijmans, N.; Toral-Barza, L.; Hollander, I.; Yu, K.; Zask, A. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 640.