Bioorganic & Medicinal Chemistry Letters 23 (2013) 6223–6227

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

The sulfamide moiety affords higher inhibitory activity and oral bioavailability to a series of coumarin dual selective RAF/MEK inhibitors

Toshihiro Aoki [a], Ikumi Hyohdoh [a], Noriyuki Furuichi [a], Sawako Ozawa [a], Fumio Watanabe [a], Masayuki Matsushita [a], Masahiro Sakaitani [a], Kazutomo Ori [a], Kenji Takanashi [a], Naoki Harada [a], Yasushi Tomii [a], Mitsuyasu Tabo [b], Kiyoshi Yoshinari [a], Yuko Aoki [a], Nobuo Shimma [a], Hitoshi Iikura [a,b,*]

[a] Research Division, Chugai Pharmaceutical Co., Ltd, 200 Kajiwara, Kamakura, Kanagawa 247-8530, Japan
[b] Research Division, Chugai Pharmaceutical Co., Ltd, 1-135 Komakado, Gotemba, Shizuoka 412-8513, Japan

ARTICLE INFO

Article history:
Received 5 August 2013
Revised 27 September 2013
Accepted 1 October 2013
Available online 9 October 2013

Keywords:
MEK
Raf
Kinase inhibitor
Sulfamide
Anticancer

ABSTRACT

Introducing a sulfamide moiety to our coumarin derivatives afforded enhanced Raf/MEK inhibitory activity concomitantly with an acceptable PK profile. Novel sulfamide **17** showed potent HCT116 cell growth inhibition (IC_{50} = 8 nM) and good PK profile (bioavailability of 51% in mouse), resulting in high in vivo antitumor efficacy in the HCT116 xenograft (ED_{50} = 4.8 mg/kg). We confirmed the sulfamide moiety showed no negative impact on tests run on the compound to evaluate DMPK (PK profiles in three animal species, CYP inhibition and CYP induction) and the safety profile (hERG and AMES tests). Sulfamide **17** had favorable properties that warranted further preclinical assessment

The Ras/Raf/MEK/ERK pathway is one of the most important signal transduction pathways in human cancer.[1–3] Oncogenic mutations of Ras or Raf contribute to the constitutive activation of this pathway. For example, Ras mutations are found in colon cancer (32–57%), lung cancer (15–50%) and pancreatic cancer (72–90%) while B-Raf has a high rate of mutation in certain cancers including melanoma (66%), papillary thyroid (35–70%) and ovarian (30%).

As drugs for blocking this pathway, MEK or Raf inhibitors have been tested in clinical trials for cancer (Chart 1).[4] The first selective MEK inhibitor in a clinical trial was CI-1040 (**1a**),[5,6] followed by its derivatives, including PD0325901(**1b**)[6] and CH4987655(**1c**).[7] GSK1120212 (**1d**), the most advanced MEK inhibitor, received FDA approval most recently in V600E or V600K BRAF-mutated melanoma patients.[8,9] These compounds are noncompetitive and exquisitely selective to MEK. Raf inhibitors have also entered into clinical trials. Of them, vemurafenib (**2**) (marketed as Zelboraf, PLX4032) received FDA approval for the treatment of $BRAF^{V600E}$ mutation-positive metastatic melanoma in 2011.[10]

We previously reported that compound CH5126766 (RO5126766) showed both Raf and MEK inhibitory activity of the Ras/Raf/MEK/ERK pathway.[11] The dual, tandem and exquisitely selective inhibition of a single signal pathway by a single compound was remarkable: MEK was inhibited by the direct binding to MEK enzyme, and Raf activity was derived, not from direct binding to Raf, but from Raf/MEK/drug complex stabilization after MEK/drug complex formation. Characterization of this compound showed superior antitumor effect compared with that of a pure MEK inhibitor in a mouse xenograft.[11]

CH5126766, bearing a sulfamide moiety, was identified[12] as a clinical compound in the hit-to-lead processing of our HTS hit compound **3** (Chart 1).[13,14] Coumarin derivative **3** showed highly selective RAF/MEK inhibition, but its potency was modest in vitro and in vivo. Moreover, an aniline moiety of the hit compound **3** could have caused potential issues when developing the drug, because anilines are known to be AMES-positive,[15] be easily metabolized, and have lower oral bioavailability. We found that incorporating a sulfamide moiety enhanced inhibitory activity and also afforded satisfactory PK profiles, resulting in high in vivo efficacy. Sulfamide

Abbreviations: ERK, extracellular signal-regulated kinase; hERG, human ether-a-go-go related gene; HPCD, 2-hydroxypropyl-β-cyclodextrin; LYSA, lyophilized solubility assay; MEK, mitogen-activated protein kinase; PAMPA, parallel artificial membrane permeability assay; PEG, polyethylene glycol; TGI, tumor growth inhibition.

* Corresponding author. Tel.: +81 550 87 8597; fax: +81 550 87 5326.
E-mail address: iikurahts@chugai-pharm.co.jp (H. Iikura).

0960-894X/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.bmcl.2013.10.001

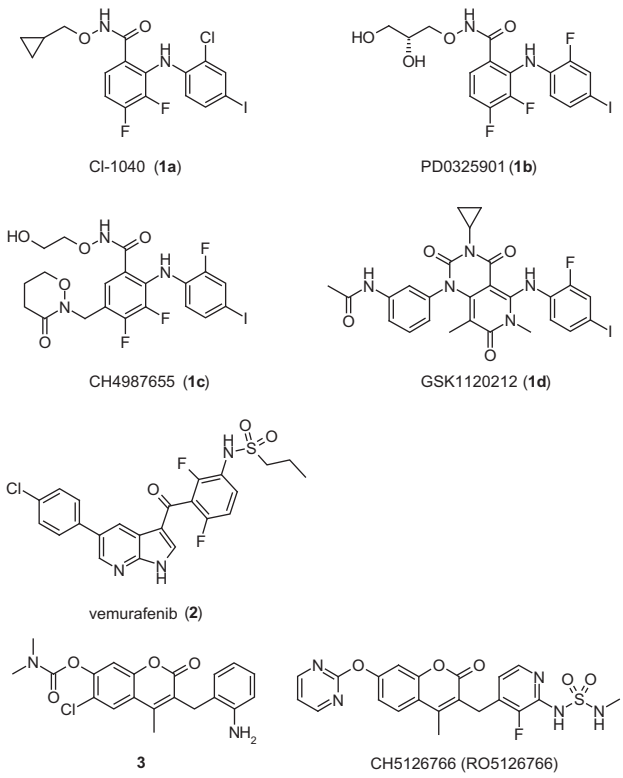


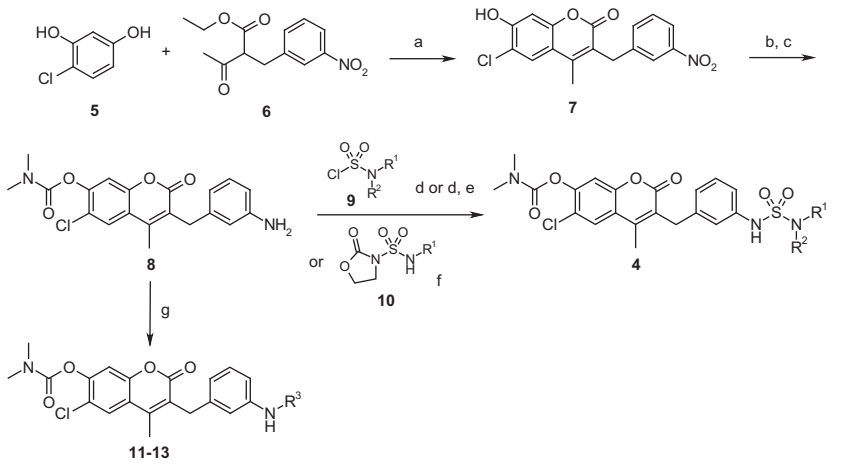
Chart 1. Structures of representative MEK inhibitors (**1**), a RAF inhibitor (**2**), HTS hit compound **3**, and CH5126766 (RO5126766).

moieties have attracted attention for their unique electronic and steric properties.[16,17] However, only a small number of reports have focused on the potential of sulfamide moieties for clinical usage, and the distinguishing advantages of sulfamide over isosteres, such as urea or sulfonamide.[18,19] Here we report a SAR study of the Raf/MEK inhibitory activity of coumarins with a sulfamide and its isosteres. We also report a physicochemical and a preliminary safety study of sulfamide compounds as oral drugs.

The synthesis of sulfamide compound **4** is outlined in Scheme 1. The benzylation of ethyl acetoacetate afforded derivative **6**, which was then converted to coumarin **7** via Pechmann reaction with 4-chlororesorcinol **5** in a manner similar to reported procedures.[13] After carbamoylation of the phenoic hydroxyl group by *N*,*N*-dimethylcarbamoyl chloride, reduction of a nitro group by $SnCl_2$ afforded aniline derivative **8**. Sulfamide **4** was obtained by the reaction of **8** with sulfamoyl chloride **9**[20,21] or sulfamoyl oxazolizinone **10**.[22] Amide (**11**), urea (**12**) and sulfonamide (**13**) derivatives were prepared by the coupling of aniline **8** by the usual procedure.

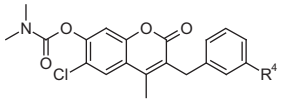
Our SAR study to modify aniline moiety of hit compound **3** showed that compound **4b** with a sulfamide group afforded the strongest inhibition of Raf and MEK (Table 1). A set of compounds with a functional group at R^4 position were evaluated, because moving the amino group to R^4 (amine **8**) gave better MEK inhibition (IC_{50} = 56 nM) and HCT116 cell growth inhibition (IC_{50} = 290 nM) than the original hit (**3**, IC_{50}'s of 210 and 1200 nM, respectively). Introduction of an amide (**11**) or urea (**12**) did not enhance the Raf or MEK inhibitory activity of amine **8**. On the other hand, introduction of a sulfonamide (**13a**, **b**) or a sulfamide (**4a**–**c**) afforded stronger inhibitory activity on Raf/MEK enzyme and cell growth of HCT116 and HT29. Sulfamide **4a**, which is a derivative after nitrogen substitution of sulfonamide **13a**, showed similar bioactivity to sulfonamide **13a** with an IC_{50} value around 30 nM. Sulfamide **4b**, which is a derivative after nitrogen substitution of sulfonamide **13b**, demonstrated about 10-fold superior cell growth inhibition over **13b**. Sulfamide **4c**, which has two methyl groups at terminal nitrogen also has strong bioactivity with an IC_{50} value around 10 nM. Compound **4b** has exquisite selectivity to Raf and MEK inhibitions. No kinases with IC_{50} < 5 μM in our panel (29 kinases) were observed except Raf and MEK (see Supplementary data). We achieved a reduced risk of mutagenicity (see below) by modifying the aniline moiety, and to increase the HCT116 activity up to 300-fold by introducing sulfamide.

Evaluation of sulfamide compounds **4a**–**c** as oral drugs for water solubility, metabolic stability and membrane permeability showed comparable or superior values to sulfonamide compounds **13a** or **13b** (Table 1). Solubility was evaluated by the LYSA method,[23] and solubility of sulfamide **4a** (19 μg/ml) was higher than that of the corresponding sulfonamide **13a** (8 μg/ml). Sulfamide **4b** also has better solubility than sulfonamide **13b**. This increase in solubility could be explained by the effect of introducing a hetero atom (nitrogen). Sulfamide **4c** has lower solubility than sulfamide **4a** or **4b**, which is a reflection of higher lipophilicity. Metabolic stability was evaluated using human and mouse liver microsomes, and metabolic stability of sulfamide **4a** showed better values (CL: 7 μL/min/mg in human, 8 μL/min/mg in mouse) than sulfonamide **13a** (CL: 11 μL/min/mg in human,



Scheme 1. Synthesis of compounds **4**, **11**–**13**. Reagents and conditions: (a) 70% H_2SO_4 aq, rt, 12 h; (b) *N*,*N*-dimethylcarbamoyl chloride (1.5 equiv), NaH (1.1 equiv), DMF, rt, 2 h; (c) $SnCl_2{\cdot}2H_2O$ (4.0 equiv), DMF, rt, 12 h; (d) compound **9**, pyridine or Et_3N, CH_2Cl_2; (e) 50% HCl aq, THF, 40 °C; (f) compound **10** (3.0 equiv), Et_3N (3.0 equiv), CH_3CN, reflux; (g) R^3X, Et_3N, CH_2Cl_2.

Table 1
Enzymatic and cellular activities and pharmaceutical properties of coumarin derivatives



Compd	R^4	IC_{50} (nM)				Solubility (μg/mL)	CL (μL/min/mg)		PAMPA (10^{-6} cm/s)	AUC_{po}[b] (μM h)	TGI[f] (%)
		C-Raf	MEK1	HCT116	HT-29		Human	Mouse			
3		100	210	1200	250	ND	29	49	ND[a]	ND	34
8		120	56	290	370	ND	27	59	6	29	38
4a		26	28	39	15	19	7	8	5	70	107
4b		8	7	4	1	13	23	21	4	51[c,e]	105[g]
4c		5	11	12	9	6	32	52	4	3[d]	78
11		170	96	360	75	ND	ND	ND	ND	ND	33
12		570	500	4600	480	ND	ND	ND	ND	ND	ND
13a		56	29	30	26	8	11	41	3	41[c]	64
13b		50	21	36	33	9	ND[a]	ND[a]	3	30[c]	ND

[a] Data not obtainable due to low solubility.
[b] Compounds were evaluated in 24-h exposure studies in mice at 200 mg/kg and formulated as solutions of 5% DMSO, 5% Cremophor EL, 15% PEG400, 15% HPCD, and 60% water.
[c] At 100 mg/kg.
[d] At 50 mg/kg.
[e] Sodium salt of **4b** was used.
[f] Tumor growth inhibition in the HCT116 human colon cancer xenograft model at 200 mg/kg/day for 11 days.
[g] At 100 mg/kg/day for 11 days.

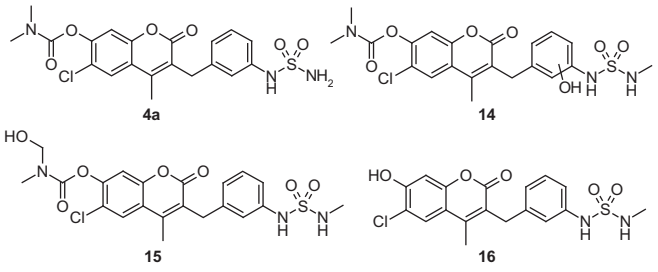


Chart 2. Metabolites of **4b** using human liver microsome.

41 μL/min/mg in mouse). Though no comparison between sulfamide **4b** and sulfonamide **13b** was available (solubility of **13b** is too low to evaluate stability), the metabolic stability of sulfamide **4b** itself was in the acceptable ranges. Metabolites analysis of terminal mono-substituted sulfamide **4b** using human liver microsomes yielded **4a** (de-methylation of the sulfamide terminal nitrogen), in addition to compounds **14**–**16** (Chart 2). This result suggested that the reduced stability of the sulfamides with a modified terminal nitrogen atom was due to metabolism from de-methylation. There could be a difference in the metabolic stability of the *N*-aryl and *N*-alkyl sulfamides. In addition, no hydrolysis of sulfamide moiety (N–S dissociation) was observed. Because aniline was not detected after microsomes treatment, the risk for AMES positive by aniline metabolites could be considered low (see below). Permeability was evaluated by PAMPA, and was maintained or even increased in the sulfamide compounds in spite of a higher hydrophilicity compared with sulfonamide compounds.

A brief study on drug formulation and mouse PK confirmed that drugs with a sulfamide group could form salts, as does a sulfonamide, and therefore higher bioavailability (BA), AUC and dose could possibly be achieved by forming the salt rather than the free form. A Na salt of **4b** was prepared by reacting with NaOH. The BA of mouse at 100 mg/kg administered as a Na salt was 31% (AUC: 51 μM h), which is an improvement over the 10% (AUC: 17 μM h) of the free form. The major metabolite **4a** (de-methylation) was detected 1/10 in AUC to the parent compound.

Oral administrations of sulfamides **4a** and **4b** showed high in vivo antitumor effects on xenograft HCT-116 at a dose of 200 and 100 mg/kg once daily, respectively (the experimental procedure was similar to that explained in Fig. 1). The TGI of sulfamides **4a** (107%) and **4b** (105%) was superior to that of sulfonamide **13a** (64%), aniline **8** (38%) and amide **11** (33%), and was attributed to their higher cell growth inhibition and/or better physicochemical properties. A TGI of 78% for di-substituted sulfamide **4c** is reflected in its AUC, which was lower than those of compounds **4a** and **4b**.

Modifications of the sulfamide at the terminal nitrogen afforded a set of potent Raf/MEK inhibitors (Table 2). Sulfamide **4e** or **4g** with an electron withdrawing group, sulfamide **4h** with a hydroxyl group, and sulfamide **4i** with an ether group have potent Raf/MEK inhibition and HCT116 cell growth inhibition. Sulfamide **4d** with an oxygen located next to the terminal nitrogen, sulfamide **4f** with

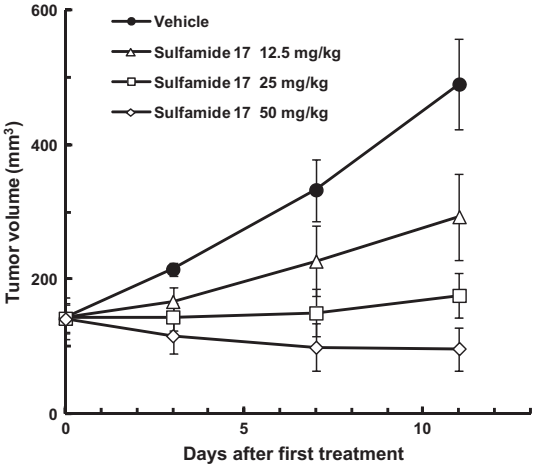
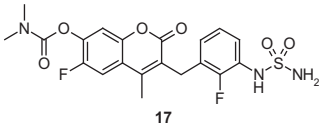


Figure 1. In vivo efficacy of sodium salt of **17** in the HCT116 human colon cancer xenograft model. HCT116 cells were inoculated subcutaneously into the right flank of BALB-nu/nu mice. Tumors were allowed to establish growth after implantation before start of treatment. Sulfamide **17** was administered orally once daily for 11 days, from day 0 to 10. Tumor size was measured twice per week. Values are mean ± SD, $n = 4$.

another nitrogen attached to the terminal nitrogen via ethylene linker, and sulfamide **4j** of dialkyl version also showed potent Raf/MEK inhibition, but poorer HCT116 cell growth inhibitory activity, mainly because of poorer permeability. The AUC's of sulfamides **4d** and **4e** showed comparable or superior values to that of sulfamide **4b**, while the AUC's of sulfamide **4h** and **4i** showed smaller values than that of sulfamide **4b**. De-alkylated metabolism could be a reason for smaller AUC (in PK study of **4i**, metabolite **4a** was detected at 14 μM h, which was higher than that of the parent **4i** (9 μM h)). Because modification of the terminal nitrogen with various groups was acceptable, such modification could be used to adjust the physicochemical properties, such as solubility.

Table 3
In vitro profile of sulfamide **17**



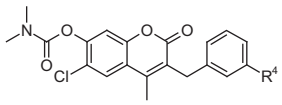
17

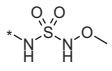
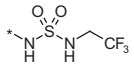
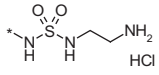
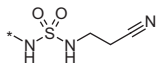
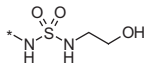
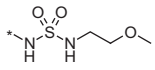
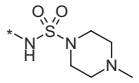
IC_{50} (nM)			CYP inhibition: IC_{50}[a] (μM)	
C-Raf	MEK1	HCT116	2C9 (−/+)	3A4 (−/+)
5	9	8	12/12	14/18

[a] IC_{50} (−) and IC_{50} (+) values were determined after a 30-min pre-incubation without and with NADPH, respectively.

While optimization of the carbamate part (points for metabolism, Chart 2) could be a choice, changing carbamate to another group resulted in decreasing the bioactivity by one order or worse in our preliminary SAR. To elucidate the potential of this lead and sulfamide group as a clinical candidate earlier, we utilized a result of fluorine scan[24] to afford sulfamide **17** with keeping carbamoyl group. Compound **17** demonstrated favorable properties that warrant further preclinical assessment (Tables 3 and 4). Sulfamide **17** has potent Raf/MEK inhibitory activity, HCT116 cell growth inhibitory activity, and showed relatively weak CYP inhibitory activity (IC_{50}'s of CYP/HCT116 >1000) and weak CYP induction activity (see Supplementary data) and thus small or negligible drug–drug

Table 2
SAR of sulfamides with modified terminal nitrogen



Compd	R^4	IC_{50} (nM)			Solubility (μg/mL)	CL (μL/min/mg)		PAMPA (10^{-6} cm/s)	AUC_{po}[a] (μM h)
		C-Raf	MEK1	HCT1169		Human	Mouse		
4d		37	58	170	11	17	34	3	62[b]
4e		45	65	68	15	ND	ND	3	26[b]
4f		40	5	93	290	4	2	0.2	0.2
4g		4	36	23	10	40	31	5	25
4h		6	46	42	8	32	22	5	14
4i		4	47	36	9	51	51	4	9
4j		16	35	160	50	101	63	2	ND

[a] Compounds were evaluated in 24-h exposure studies in mice at 200 mg/kg and formulated as solutions of 5% DMSO, 5% Cremophor EL, 15% PEG400, 15% HPCD, and 60% water and administered as a free form (not sodium salt).
[b] At 100 mg/kg.

Table 4
PK profile of sodium salt of **17** in mouse, rat and monkey[a]

Parameter	Mouse	Rat	Monkey
iv/po dose (mg/kg)	10/20	5.0/10	2.5/5.0
AUC_{inf} (μM h), po	26	6.0	2.2
$t_{1/2}$ (h), iv	0.9	0.7	16
Cl (mL min^{-1} kg^{-1})	14	33	25
Bioavailability (%)	51	62	30

[a] Vehicle: 5% DMSO/5% Cremophor EL/15% PEG400/15% HPCD/60% water.

interactions. The hERG inhibition (24% at 10 μM) was also weak and an AMES test was negative (see above). The compound showed satisfactory PK data for mouse, rat and monkey (Table 4) with BA values of 51%, 62% and 30%, respectively.[25] High antitumor effect was observed in the HCT116 xenograft model: ED_{50} of 4.8 mg/kg and TGI of >100% at 50 mg/kg (Fig. 1). It showed no serious effects on body weight or clinical signs. On the other hand, sulfamides with a mono-substituted terminal nitrogen (like **4b**) showed BA of lower than 5% in monkey (several compounds tested, data not shown) even though good mouse BA was observed in mouse. The idea that species difference could be an issue is supported by the detection of de-methylated compounds (like **4a**) from monkey blood. Species difference in the metabolism of alkylated sulfamides might need to be considered when developing oral drugs.

In summary, compounds with a sulfamide group showed stronger inhibitory activity on the Raf/MEK enzyme and in a mouse xenograft than those with a sulfonamide. In our compounds, the sulfamide group itself had no negative impact on the compound as an oral drug, as shown by the PK of several species, CYP inhibition and induction activities, hERG inhibition activities and an AMES test. Physicochemical properties such as solubility and metabolic stability were comparable and/or superior to sulfonamides, which are often used as oral drugs. As a result, a highly potent and selective Raf/MEK inhibitor with a unique scaffold, **17**, was identified.

Acknowledgements

We thank Y. Tachibana-Kondoh, K. Sakata, and T. Fujii for biological assays, H. Suda for mass spectrometry measurement, and Chugai Editing Services for proofreading the manuscript.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl. 2013. 10.001.

References and notes

1. Friday, B. B.; Adjei, A. A. *Biochim. Biophys. Acta* **2005**, *1756*, 127.
2. Sebolt-Leopold, J. S.; Herrera, R. *Nat. Rev. Cancer* **2004**, *4*, 937.
3. Downward, J. *Nat. Rev. Cancer* **2003**, *3*, 11.
4. Rusconi, P.; Caiola, E.; Broggini, M. *Curr. Med. Chem.* **2012**, *19*, 1164.
5. Sebolt-Leopold, J. S.; Dudley, D. T.; Herrera, R.; Becelaere, K. V.; Wiland, A.; Gowan, R. C.; Tecle, H.; Barrett, S. D.; Bridges, A.; Przybranowski, S.; Leopold, W. R.; Saltiel, A. R. *Nat. Med.* **1999**, *5*, 810.
6. Barrett, S. D.; Bridges, A. J.; Dudley, D. T.; Saltiel, A. R.; Fergus, J. H.; Flamme, C. M.; Delaney, A. M.; Kaufman, M.; LePage, S.; Leopold, W. R.; Przybranowski, S. A.; Sebolt-Leopold, J.; Becelaere, K. V.; Doherty, A. M.; Kennedy, R. M.; Marston, D., ; Howard, W. A., Jr.; Smith, Y.; Warmus, J. S.; Tecle, H. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6501.
7. Isshiki, Y.; Kohchi, Y.; Iikura, H.; Matsubara, Y.; Asoh, K.; Murata, T.; Kohchi, M.; Mizuguchi, E.; Tsujii, S.; Hattori, K.; Miura, T.; Yoshimura, Y.; Aida, S.; Miwa, M.; Saitoh, R.; Murao, N.; Okabe, H.; Belunis, C.; Janson, C.; Lukacs, C.; Schück, V.; Shimma, N. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1795.
8. Abe, H.; Kikuchi, S.; Hayakawa, K.; Iida, T.; Nagahashi, N.; Maeda, K.; Sakamoto, J.; Matsumoto, N.; Miura, T.; Matsumura, K.; Seki, N.; Inaba, T.; Kawasaki, H.; Yamaguchi, T.; Kakefuda, R.; Nanayama, T.; Kurachi, H.; Hori, Y.; Yoshida, T.; Kakegawa, J.; Watanabe, Y.; Gilmartin, A. G.; Richter, M. C.; Moss, K. G.; Laquerre, S. G. *ACS Med. Chem. Lett.* **2011**, *2*, 320.
9. Flaherty, K. T.; Robert, C.; Hersey, P.; Nathan, P.; Garbe, C.; Milhem, M.; Demidov, L. V.; Hassel, J. C.; Rutkowski, P.; Mohr, P.; Dummer, R.; Trefzer, U.; Larkin, J. M. G.; Utikal, J.; Dreno, B.; Nyakas, M.; Middleton, M. R.; Becker, J. C.; Casey, M.; Sherman, L. J.; Wu, F. S.; Ouellet, D.; Martin, A.-M.; Patel, K.; Schadendorf, D. N. *Engl. J. Med.* **2012**, *367*, 107.
10. Bollag, G.; Hirth, P.; Tsai, J.; Zhang, J.; Ibrahim, P. N.; Cho, H.; Spevak, W.; Zhang, C.; Zhang, Y.; Habets, G.; Burton, E. A.; Wong, B.; Tsang, G.; West, B. L.; Powell, B.; Shellooe, R.; Marimuthu, A.; Nguyen, H.; Zhang, K. Y. J.; Artis, D. R.; Schlessinger, J.; Su, F.; Higgins, B.; Iyer, R.; D'Andrea, K.; Koehler, A.; Stumm, M.; Lin, P. S.; Lee, R. J.; Grippo, J.; Puzanov, I.; Kim, K. B.; Ribas, A.; McArthur, G. A.; Sosman, J. A.; Chapman, P. B.; Flaherty, K. T.; Xu, X.; Nathanson, K. L.; Nolop, K. *Nature* **2010**, *467*, 596.
11. Ishii, N.; Harada, N.; Joseph, E. W.; Ohara, K.; Miura, T.; Sakamoto, H.; Matsuda, Y.; Tomii, Y.; Tachibana-Kondo, Y.; Iikura, H.; Aoki, T.; Shimma, N.; Arisawa, M.; Sowa, Y.; Poulikakos, P. I.; Rosen, N.; Aoki, Y.; Sakai, T. *Cancer Res.* **2013**, *73*, 4050.
12. Iikura, H. Abstract of Papers, 102nd National Meeting of American Association for Cancer Research, Orland, FL; American Association for Cancer Research: Philadelphia, PA, 2011, Abstract 2789.
13. Cheng, J.-F.; Chen, M.; Wallace, D.; Tith, S.; Arrhenius, T.; Kashiwagi, H.; Ono, Y.; Ishikawa, A.; Sato, H.; Kozono, T.; Sato, H.; Nadzan, A. M. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2411.
14. Han, S.; Zhou, V.; Pan, S.; Liu, Y.; Hornsby, M.; McMullan, D.; Klock, H. E.; Haugen, J.; Lesley, S. A.; Gray, N.; Caldwell, J.; Gu, X.-J. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5467.
15. Kazius, J.; McGuire, R.; Bursi, R. *J. Med. Chem.* **2005**, *48*, 312.
16. Casini, A.; Winum, J.-Y.; Montero, J.-L.; Scozzafava, A.; Supuran, C. T. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 837.
17. Winum, J.-Y.; Scozzafava, A.; Montero, J.-L.; Supuran, C. T. *Med. Res. Rev.* **2006**, *26*, 767.
18. Parker, M. H.; Smith-Swintosky, V. L.; McComsey, D. F.; Huang, Y.; Brenneman, D.; Klein, B.; Malatynska, E.; White, H. S.; Milewski, M. E.; Herb, M.; Finley, M. F. A.; Liu, Y.; Lubin, M. L.; Qin, N.; Iannucci, R.; Leclercq, L.; Cuyckens, F.; Reitz, A. B.; Maryanoff, B. E. *J. Med. Chem.* **2009**, *52*, 7528.
19. After completion of our investigations (see Ref. 12), orally available sulfamide compounds have been reported: (a) Katz, J. D.; Jewell, J. P.; Guerin, D. J.; Lim, J.; Dinsmore, C. J.; Deshmukh, S. V.; Pan, B.-S.; Marshall, C. G.; Lu, W.; Altman, M. D.; Dahlberg, W. K.; Davis, L.; Falcone, D.; Gabarda, A. E.; Hang, G.; Hatch, H.; Holmes, R.; Kunii, K.; Lumb, K. J.; Lutterbach, B.; Mathvink, R.; Nazef, N.; Patel, S. B.; Qu, X.; Reilly, J. F.; Rickert, K. W.; Rosenstein, C.; Soisson, S. M.; Spencer, K. B.; Szewczak, A. A.; Walker, D.; Wang, W.; Young, J.; Zeng, Q. *J. Med. Chem.* **2011**, *54*, 4092; (b) Bolli, M. H.; Boss, C.; Binkert, C.; Buchmann, S.; Bur, D.; Hess, P.; Iglarz, M.; Meyer, S.; Rein, J.; Rey, M.; Treiber, A.; Clozel, M.; Fischli, W.; Weller, T. *J. Med. Chem.* **2012**, *55*, 7849; (c) Kim, S. H.; Bok, J. H.; Lee, J. H.; Kim, I. H.; Kwon, S. W.; Lee, G. B.; Kang, S. K.; Park, J. S.; Jung, W. H.; Kim, H. Y.; Rhee, S. D.; Ahn, S. H.; Bae, M. A.; Ha, D. C.; Kim, K. Y.; Ahn, J. H. *ACS Med. Chem. Lett.* **2012**, *3*, 88; (d) Wurz, R. P.; Liu, L.; Yang, K.; Nishimura, N.; Bo, Y.; Pettus, L. H.; Caenepeel, S.; Freeman, D. J.; McCarter, J. D.; Mullady, E. L.; Miguel, T. S.; Wang, L.; Zhang, N.; Andrews, K. L.; Whittington, D. A.; Jiang, J.; Subramanian, R.; Hughes, P. E.; Norman, M. H. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 5714; (e) Hartung, I. V.; Hitchcock, M.; Pühler, F.; Neuhaus, R.; Scholz, A.; Hammer, S.; Petersen, K.; Siemeister, G.; Brittain, D.; Hillig, R. C. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 2384.
20. Timberlake, J. W.; Ray, W. J., Jr.; Stevens, E. D.; Klein, C. L. *J. Org. Chem.* **1989**, *54*, 5824.
21. Berredjem, M.; Winum, J. Y.; Toupet, L.; Masmoudi, O.; Aouf, N. E.; Montero, J. L. *Synth. Commun.* **2004**, *34*, 1653.
22. Borghese, A.; Antoine, L.; Van Hoeck, J. P.; Mockel, A.; Merschaert, A. *Org. Process Res. Dev.* **2006**, *10*, 770.
23. Alsenz, J.; Kansy, M. *Adv. Drug Delivery Rev.* **2007**, *59*, 546.
24. Hyohdoh, I. Furuichi, N. Aoki, T. Itezono, Y. Shirai, H. Ozawa, S. Watanabe, F. Matsushita, M. Sakaitani, M. Ho, P.-S. Takanashi, K. Harada, N. Tomii, Y. Yoshinari, K. Ori, K. Tabo, M. Aoki, Y. Shimma, N. Iikura, H. ACS Med. Chem. Lett. published, online September 22, 2013; doi: 10.1021/ml4002419.
25. The PK test here utilized highly organic vehicles, which could not predict human PK (we have no PK data utilizing a clinical formulation). Further preformulation study would have been required if compound **17** had been selected as a clinical candidate.