

## Design and Synthesis of Orally Bioavailable Benzimidazoles as Raf Kinase Inhibitors

Savithri Ramurthy,\* Sharadha Subramanian, Mina Aikawa, Payman Amiri, Abran Costales, Jeff Dove, Susan Fong, Johanna M. Jansen, Barry Levine, Sylvia Ma, Christopher M. McBride, Jonah Michaelian, Teresa Pick, Daniel J. Poon, Sandhya Girish, Cynthia M. Shafer, Darrin Stuart, Leonard Sung, and Paul A. Renhowe

Novartis Institutes for Biomedical Research,  
4560 Horton Street, Emeryville, California 94608

Received August 20, 2008

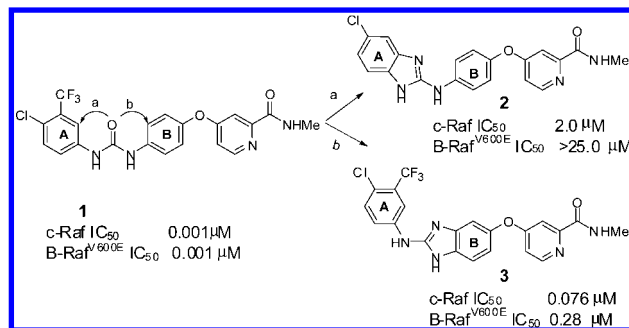
**Abstract:** A series of arylaminobenzimidazoles was designed and synthesized as Raf kinase inhibitors. Exploration of the structure–activity relationship resulted in compounds that are potent in vitro and show desirable in vivo properties.

The Ras-mitogen activated protein kinase (MAPK<sup>a</sup>) signaling pathway was the first signaling pathway elucidated from the cell membrane to the nucleus.<sup>1</sup> The MAPK signaling path consists of the Ras/Raf/MEK/ERK signal transduction cascade which is a vital mediator of a number of cellular fates including growth, proliferation, survival, and other aspects of cellular behavior that can contribute to the transformed phenotype, making it an attractive pathway to target in several cancer types. The three Raf isoforms (Raf-1 or c-Raf, A-Raf, and B-Raf) are all able to interact with Ras and activate the MAP kinase pathway.<sup>2–5</sup>

Inhibition of the Raf/MEK/ERK pathway at the level of Raf kinases is expected to be effective against tumors driven by this pathway. It has been shown that B-Raf mutation V600E in skin nevi is a critical step in the initiation of melanocytic neoplasia.<sup>6</sup> Furthermore, activating mutations in the kinase domain of B-Raf occur in roughly 66% of malignant melanomas, 40–70% of papillary thyroid carcinomas and 12% of colon carcinomas.<sup>5,7–9</sup> The many effects of Raf kinases on cancer cell growth and survival, together with the high prevalence of mutation in melanoma, for which there is no good treatment, make Raf a very attractive target for anticancer therapy.

Raf kinase inhibitors have been reported previously, and the most advanced small molecule inhibitor, **1** (BAY43-9006, Sorafenib), has been developed and launched for the treatment of renal cell carcinoma.<sup>10–14</sup> However, its lack of activity in tumors expressing mutant B-Raf, for example, melanoma, may be because the mechanism of action is through inhibition of VEGFR rather than Raf.<sup>15,16</sup> In this communication, we describe the discovery of a series of the arylaminobenzimidazole amides that potently inhibit Raf kinase. The structure–activity relationship for c-Raf and B-Raf<sup>V600E</sup>, PK, and efficacy for this scaffold will also be discussed.

At the time our program began, **1**, a potent biochemical inhibitor of Raf was in clinical trials. However, the poor



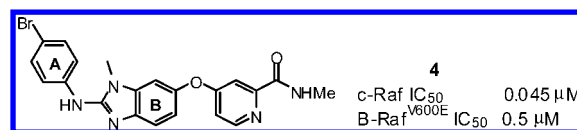
**Figure 1.** Evolution of the 2-arylamino benzimidazole scaffold.

physicochemical properties and the lack of downstream modulation on the MAP kinase axis on cells persuaded us to pursue a program to identify Raf kinase inhibitor(s) with an improved profile. Our initial effort involved trying to improve the physicochemical properties of **1** by eliminating the urea while retaining Raf kinase activity. Tying the urea back onto ring A (Figure 1, path a) led to **2** with lower affinity for Raf kinase,<sup>17</sup> while closing the urea onto the B ring gave **3** which, while less potent than **1**, still potently inhibited C and mutant B isoforms of Raf. Further SAR exploration centered on this series.

Removing the substituents on the aryl ring of **3** (ring A) to give the unadorned aryl ring (**5**, Table 1) led to a dramatic loss of affinity, indicating substitution on the aryl ring is needed for potent Raf inhibition. Systematic evaluation of various substituents at the 2-, 3- and 4-positions on ring A indicated that substitution on the 3- and 4-positions of the ring led to higher affinity for Raf than substitution on the 2-position (e.g., **7** and **8** vs **6**; **10** and **11** vs **9**). In particular, a bromine at the 4-position (**8**) improved affinity nearly 200-fold in B-Raf<sup>V600E</sup> compared to **5** while a trifluoromethyl group (**11**) further improved potency 770-fold over **5**. Incorporating a *tert*-butyl group at C-4 of ring A (**13**), while still quite potent, began to show some erosion of activity compared to **11**. In this case, moving the substituent to the meta position gave improved affinity (**12**).

Overall, it was concluded that incorporation of lipophilic substituents was needed for potent Raf inhibition. Further investigation of ring A arenes indicated that neither heteroatoms in the ring nor polar substituents on the ring were tolerated.<sup>17</sup>

At this point, introduction of a methyl on the benzimidazole NH was explored giving **18** and the regioisomer **4**<sup>25</sup> where the methyl is on the nitrogen meta to the oxygen linker of the pyridine. Compound **18** exhibited 45-fold better affinity in c-Raf over the other regioisomer **4**. Compared to the unmethylated analogues, the majority of the methylated analogues (**14**–**23**) exhibited significantly improved enzymatic potency (5- to 60-fold) against both isoforms of Raf. Compound **18** with a 4-bromo substituent exhibited an affinity for B-Raf<sup>V600E</sup> that was 5-fold better than **1**. However, further extending the methyl on the benzimidazole nitrogen to an ethyl (**28**) significantly decreased potency against both Raf isoforms.

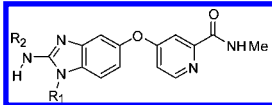


In addition to evaluating the SAR of aromatic A rings, aliphatic groups were also assessed. Replacing the aryl ring with

\* To whom correspondence should be addressed. Phone: 510-923-7767. Fax: 510-923-3360. E-mail: savithri.ramurthy@novartis.com.

<sup>a</sup> Abbreviations: MAPK, Ras-mitogen activated protein kinase; VEGFR, Vascular endothelial growth factor receptor; PDGFR platelet-derived growth factor receptor; CSF1R, colony stimulating factor-1 receptor; RTKs, receptor tyrosine kinases; STKs, serine threonine kinases; Lck, leukocyte specific protein tyrosine kinase.

**Table 1.** SAR Evaluating R<sub>1</sub> and R<sub>2</sub>



R<sub>2</sub> = Phenyl analogs **3-24, 28**  
R<sub>2</sub> = Cyclohexyl **25**  
R<sub>2</sub> = Cyclohexylmethyl **26**  
R<sub>2</sub> = 3-(4-pyridyl) **27**

compd	R <sub>1</sub>	R <sub>2</sub>	IC <sub>50</sub> (μM) <sup>19</sup>		EC <sub>50</sub> (μM)	
			B-Raf <sup>V600E</sup>	c-Raf	SK-MEL-28	p-Erk
<b>1</b>			0.011	0.001	1.3	4.3
<b>5</b>	H	phenyl	7.7	3.5		
<b>3</b>	H	4-Cl-3-CF <sub>3</sub>	0.28	0.076		> 10
<b>6</b>	H	2-Br	2.4	0.49		
<b>7</b>	H	3-Br	1.3	0.21		
<b>8</b>	H	4-Br	0.039	0.019		
<b>9</b>	H	2-CF <sub>3</sub>	9.0	0.95		
<b>10</b>	H	3-CF <sub>3</sub>	0.30	0.056		
<b>11</b>	H	4-CF <sub>3</sub>	0.011	0.020		
<b>12</b>	H	3- <i>t</i> -Bu	0.026	0.008	7.1	5.9
<b>13</b>	H	4- <i>t</i> -Bu	0.063	0.015		
<b>14</b>	Me	phenyl	0.13	0.048		> 10
<b>15</b>	Me	4-Cl-3 CF <sub>3</sub>	0.028	0.015	> 10	7.3
<b>16</b>	Me	2-Br	0.039	0.010	> 10	9.8
<b>17</b>	Me	3-Br	0.025	0.004		> 5.0
<b>18</b>	Me	4-Br	0.002	0.001	4.6	1.9
<b>19</b>	Me	2-CF <sub>3</sub>	1.9	0.15		
<b>20</b>	Me	3-CF <sub>3</sub>	0.008	0.006	1.3	2.7
<b>21</b>	Me	4-CF <sub>3</sub>	0.088	0.009		
<b>22</b>	Me	2- <i>t</i> -Bu		0.15		
<b>23</b>	Me	3- <i>t</i> -Bu	0.045	0.004	0.89	0.28
<b>24</b>	Me	4- <i>t</i> -Bu	0.14	0.009	3.0	0.45
<b>25</b>	Me	cyclohexyl	4.4	1.1		
<b>26</b>	Me	cyclohexylmethyl	0.14	0.028	> 10	> 10
<b>27</b>	Me	3-(4-pyridyl)	0.014	0.010	2.3	5.9
<b>28</b>	Et	4-Br	0.068	0.018		

a cyclohexyl ring (**25**) led to an analogue with similar affinity as the unsubstituted aryl ring (**5**). Interestingly, extending the cyclohexyl ring by a methylene unit significantly increased B-Raf<sup>V600E</sup> affinity (**26**).

The inhibition of cellular proliferation in SK-MEL-28 cells (B-Raf<sup>V600E</sup>, melanoma cell line) was evaluated for a number of compounds and compared to **1**. In addition, inhibition of the p-Erk signal was measured in SK-MEL-28 cells to determine whether the compounds are acting via inhibition of Raf. **1** inhibited the proliferation of cellular growth and the p-Erk signal but with much lower potency compared to its biochemical activity. Compound **20** with a 3-trifluoromethyl moiety, however, exhibited cell inhibition and p-Erk modulation with similar activity as **1**. The discrepancy between biochemical and cell potency could be explained, that in the biochemical assay purified kinase domain of Raf is being tested compared to the cellular assay in which Raf exists as a complex with chaperons, cytoskeleton, phosphatases, and kinases.<sup>18</sup> Compound **23** with the 3-*tert*-butyl exhibited the most impressive inhibition of cell proliferation (0.89 μM) and inhibition of Erk phosphorylation (0.28 μM) in this series.

As mentioned earlier, only lipophilic groups on the arene gave good enzymatic potency, but they had limited solubility. The pyridyl end of the molecule was explored as an opportunity to modify the scaffold's physicochemical properties. The initial evaluation of the effect of amide substituents larger than methyl revealed no improvement (Table 2). For example, ethyl (**30**) gave similar potency as methyl (**18**). Modification of the secondary amide (**18**) to a tertiary amide (**34**) was detrimental, suggesting the importance of a hydrogen bond donor in this portion of the molecule. Incorporating a solubilizing group connected by a linker led to a slight loss in potency (**31–33**) and reduced inhibition of Erk phosphorylation. Interestingly,

**Table 2.** SAR of Amide

compd	R <sub>3</sub>	R <sub>4</sub>	IC <sub>50</sub> (μM)		EC <sub>50</sub> (μM)	
			B-Raf <sup>V600E</sup>	c-Raf	SK-MEL-28	p-Erk
<b>29</b>	H	H		0.001		2.8
<b>18</b>	H	Me	0.002	0.001	4.6	1.9
<b>30</b>	H	Et	0.013	0.014		>10
<b>31</b>	H	2-morpholinoethyl	0.031	0.017	>10	>10
<b>32</b>	H	2-hydroxyethyl	0.011	0.004		
<b>33</b>	H	2-propylpiperidine	0.007	0.041	0.61	7.4
<b>34</b>	Me	Me	2.7	0.78		

replacement of the methyl group with the polar primary carboxamide (**29**) retained Raf potency.

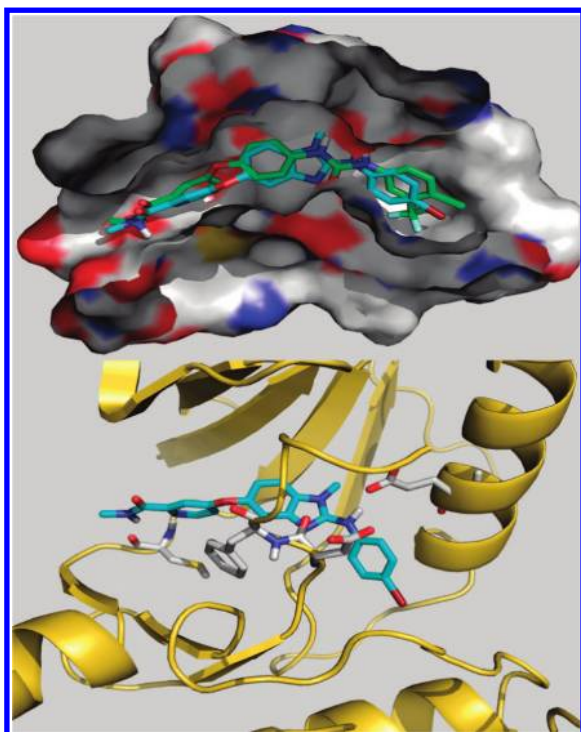
One of the goals of our program was to remove the urea in **1** while retaining potent Raf kinase activity and improving the physicochemical properties, in particular solubility. The solubility of our compounds was measured and compared to **1**, which had a solubility of <0.005 μg/mL at pH 7. The solubility of **18** at pH 7 was 4.9 μg/mL, significantly better than **1**. Incorporation of a solubilizing group on the amide like the 2-morpholinoethyl group of **31** resulted in further improved aqueous solubility of 7.3 μg/mL at pH 7 and 29 μg/mL at pH 5.5.

The benzimidazole amides in general have a narrow kinase profile. Example **23** was tested against 50 kinases including receptor tyrosine kinases (RTKs), serine/threonine kinases (STKs), and tyrosine kinases (TKs). Compound **23**, in addition to being a pan-Raf inhibitor, inhibits four RTKs, CSF1R kinase, VEGFR kinase, c-Kit, and PDGFRβ with IC<sub>50</sub> values of 19, 18, 10, and 10 nM, respectively. Additionally, **23** inhibits two members of Src family of kinases, cAbl and Lck, with IC<sub>50</sub> values of 80 and 60 nM, respectively. However, the compound was not tested in the respective cell based assays.

To rationalize the observed SAR from a 3D structural perspective, **18** was docked in the active site of the public domain crystal structure published for B-Raf (PDB accession code 1UWH).<sup>20</sup> Figure 2 (top) shows the overlay of that docking model with the cocrystallized conformation of **1**. The model suggests a very similar binding mode for both compounds, with matching occupancy of hydrophobic pockets and matching hydrogen bonds to the hinge domain (the backbone NH and C=O of Cys532) and to the Asp594/Glu501 pair in the catalytic region; selected residues interacting with **18** are shown in a cartoon representation in Figure 2 (bottom).

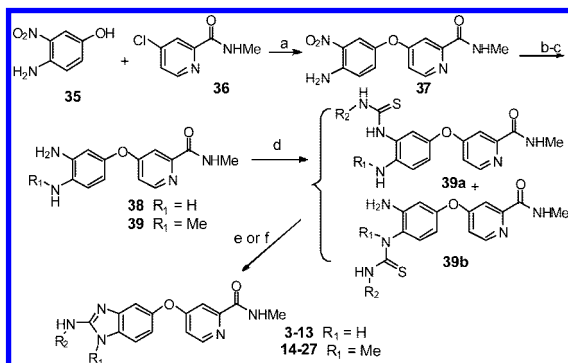
The *N*-methyl group of **18** occupies a hydrophobic subpocket of the selectivity pocket, rationalizing the increased affinity for this substitution. The observed preference for phenyl with lipophilic substituents as ring A is explained by the fact that the model places that ring in the pocket that is normally occupied by the phenylalanine from the DFG motif (Phe593) in the active, "DFG-in", conformation. Binding of **1** has been shown to induce the "DFG-out" conformation where the substituted phenyl takes the place of Phe593 in this hydrophobic environment.<sup>20</sup> The modeling work on **18** suggests that it too binds to the protein in the "DFG-out" conformation. The fact that solubilizing groups are tolerated on the pyridyl end of the scaffold is explained by the model, which places the solubilizing groups in the solvent-exposed part of the binding site.

The benzimidazole core was easily constructed beginning with the commercially available aminonitrophenol (**35**) (Scheme 1).



**Figure 2.** Docking model of **18** in B-Raf active site. Top: a surface representation of the active site colored by atom-type (oxygen = red, nitrogen = blue, sulfur = yellow, carbon and hydrogen = white), showing the overlay of **18** (cyan) with the co-crystallized conformation of **1** in green.<sup>20</sup> Bottom: a cartoon representation of the kinase with selected residues in stick model (Glu501, Cys532, Phe593, Asp594) and **18** in cyan.

#### Scheme 1<sup>a</sup>

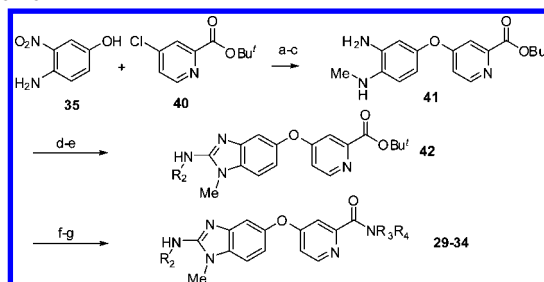


<sup>a</sup> Reagents and conditions: (a) KHMDS, K<sub>2</sub>CO<sub>3</sub>, DMF, 90°C, 16 h; (b) TFAA, (CH<sub>3</sub>)<sub>2</sub>SO<sub>4</sub>, NaOH, CH<sub>3</sub>CN, 16 h, room temp; (c) H<sub>2</sub>, 10% Pd/C, MeOH; (d) R<sub>2</sub>NCS, MeOH, room temp, 16 h; (e) MeI, MeOH, 16 h, room temp; (f) EDCI, THF, 16 h, room temp.

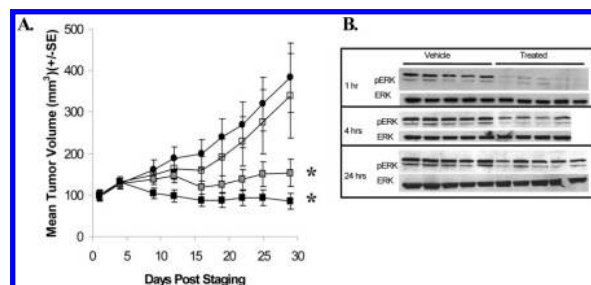
Our key intermediate (**37**) was obtained by O-arylation of chloropyridylacetamide (**36**) with **35**.<sup>21</sup> The nitro group was then reduced to give **38**. Alternatively, the amino of **37** could first be methylated and then reduced to give **39**.<sup>22,23</sup> The phenylenediamine (**38** or **39**) was then treated with an isothiocyanate to afford thioureas **39a** and **39b**. Ring closure of thioureas was affected by sulfur activation with methyl iodide<sup>24</sup> or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI) to give the 2-arylamino benzimidazoles **3–13** and **14–27**.<sup>25,26</sup>

To incorporate a variety of amides on the pyridyl ring, the aminonitrophenol (**35**) was coupled with *tert*-butyl 4-chloropyridine-2-carboxylate (**40**) (Scheme 2). The remainder of the synthesis followed that of the methylamide series shown in Scheme 1 until the end when the ester (**42**) was deprotected

#### Scheme 2<sup>a</sup>



<sup>a</sup> Reagents and conditions: (a) K<sub>2</sub>CO<sub>3</sub>, *t*-BuOK, DMAC; (b) CH<sub>3</sub>I, 10% aqueous NaOH, TBAB, CH<sub>2</sub>Cl<sub>2</sub>; (c) H<sub>2</sub>, 10% Pd/C, MeOH; (d) 4-bromophenyl isothiocyanate, MeOH, room temp, 16 h; (e) EDCI, HF, 16 h, room temp; (f) TFA, CH<sub>2</sub>Cl<sub>2</sub>; (g) HNR<sub>3</sub>R<sub>4</sub>, HBTU, DIEA, THF, room temp.



**Figure 3.** Efficacy and pathway inhibition of **27** in the HT29 (B-RafV600E) human colorectal carcinoma xenograft model: (A) 10 (mg/kg)/day (open squares), 30 (mg/kg)/day (gray squares), or 100 (mg/kg)/day (black squares). Circles represent vehicle treatment. \* indicates  $p < 0.05$  (one-way ANOVA). (B) HT29 tumors from mice dosed with **27** at 100 mg/kg for 5 days were harvested 1, 4, and 24 h after the final dose, and tumor lysates were analyzed by Western blot for phospho-ERK (pERK) and total ERK (ERK).

and the carboxylic acid was coupled with amines to give the desired products (**29–33**).

The PK parameters of **18** and **27** were examined. Following a single 20 mg/kg oral administration to female mice in 5% captisol, **18** exhibited a low clearance (0.4 mL/min/kg), low volume of distribution (183 mL/kg), long half-life (325 min), and almost complete oral bioavailability. Compound **27** exhibited a higher clearance (7.1 mL/min/kg), slightly higher volume of distribution (406 mL/kg), and shorter half-life (105 min) than **18** but also had almost complete oral bioavailability, suggesting the compounds of this class were suitable for further in vivo evaluation.

Compound **27** was selected for evaluation in a mouse tumor xenograft model because of better solubility over other compounds in this series. The SK-MEL-28 cell line could not be grown in vivo in nude mice, and therefore, the HT29 (B-Raf<sup>V600E</sup>) human colorectal tumor xenograft model was used to test the effect of the compound on tumor growth in vivo. Subcutaneous tumors were established to a size of approximately 100 mm<sup>3</sup> before oral dosing commenced. HT29 human colon carcinoma tumor cells were harvested from in vitro cultures and implanted subcutaneously into female nu/nu mice (2 × 10<sup>6</sup> cells/mouse). Ten days after implant, mice were randomized by tumor volume (~100 mm<sup>3</sup>) into four groups (10/group) and then treated by oral gavage with vehicle (10% Captisol) or **27** at 10, 30, or 100 mg/kg daily for 28 days. Tumor volume and body weight were measured twice weekly ( $n = 10$ /group). Compound **27** demonstrated significant antitumor activity (Figure 3A) at doses of 30 (mg/kg)/day ( $\Delta T/\Delta C = 19\%$ ) and 100 (mg/kg)/day (15% tumor regression) over the course of 28 days of treatment. The compound was very well-tolerated at



30 (mg/kg)/day; however, in the 100 mg/kg/day group there was an average 10% body weight loss and one mortality. The compound showed time dependent inhibition of pERK consistent with inhibition of B-Raf<sup>V600E</sup> in tumors (Figure 3B). On the other hand, as this compound has similar profile as **23**, we cannot discount the contribution of VEGFR/other kinase inhibition to efficacy. These data simply demonstrate the efficacy of the novel, orally active 2-aminobenzimidazole **27** in human colorectal xenografts.

In conclusion, we developed a novel series of potent Raf inhibitors that significantly improved the solubility compared to the urea **1**. In addition, favorable pharmacokinetics was demonstrated for **18** and **27**, which was indicative of the series. Further work on this scaffold to improve the inhibition of cellular proliferation and Erk phosphorylation was done to identify compound Raf-265, which is in phase I clinical trials with results to be communicated in due course.

**Acknowledgment.** The authors acknowledge Ahmad Hashash and Keshi Wang for formulation and bioanalytics done on these compounds.

**Supporting Information Available:** Experimental details for the synthesis and characterization of all compounds; procedure on biochemical and cellular assay. This material is available free of charge via the Internet at <http://pubs.acs.org>.

## References

- (1) Dumaz, N.; Marais, R. Protein kinase A blocks Raf-1 activity by stimulating 14-3-3 binding and blocking Raf-1 interaction with Ras. *J. Biol. Chem.* **2003**, *278*, 29819–29813.
- (2) Weber, C. K.; Slupsky, J. R.; Herrmann, C.; Schuler, M.; Rapp, U. R.; Block, C. Mitogenic signaling of Ras is regulated by differential interaction with Raf isozymes. *Oncogene* **2000**, *19*, 169–176.
- (3) Pritchard, C. A.; Samuels, M. L.; Bosch, E.; McMahon, M. Conditionally oncogenic forms of the A-Raf and B-Raf protein kinases display different biological and biochemical properties in NIH 3T3 cells. *Mol. Cell. Biol.* **1995**, *15*, 6430–6432.
- (4) Minamoto, T.; Mai, M.; Ronai, Z. e. K-ras mutation: early detection in molecular diagnosis and risk assessment of colorectal, pancreas, and lung cancers—a review. *Cancer Detect. Prev.* **2000**, *24*, 1–12.
- (5) Yuen, S. T.; Davies, H.; Chan, T. L.; Ho, J. W.; Bignell, G. R.; Cox, C.; Stephens, P.; Edkins, S.; Tsui, W. W.; Chan, A. S.; Futreal, P. A.; Stratton, M. R.; Wooster, R.; Leung, S. Y. Similarity of the phenotypic patterns associated with BRAF and KRAS mutations in colorectal neoplasia. *Cancer Res.* **2002**, *62*, 6451–6455.
- (6) Pollock, P. M.; Harper, U. L.; Hansen, K. S.; Yudt, L. M.; Stark, M.; Robbins, C. M.; Moses, T. Y.; Hostetter, G.; Wagner, U.; Kakareka, J.; Salem, G.; Pohida, T.; Heenan, P.; Duray, P.; Kallioniemi, O.; Hayward, N. K.; Trent, J. M.; Meltzer, P. S. High frequency of BRAF mutations in nevi. *Nat. Genet.* **2003**, *33*, 19–20.
- (7) Davies, H.; Bignell, G. R.; Cox, C.; Stephens, P.; Edkins, S.; Clegg, S.; Teague, J.; Woffendin, H.; Garnett, M. J.; Bottomley, W.; Davis, N.; Dicks, E.; Ewing, R.; Floyd, Y.; Gray, K.; Hall, S.; Hawes, R.; Hughes, J.; Kosmidou, V.; Menzies, A.; Mould, C.; Parker, A.; Stevens, C.; Watt, S.; Hooper, S.; Wilson, R.; Jayatilake, H.; Gusterson, B. A.; Cooper, C.; Shipley, J.; Hargrave, D.; Pritchard-Jones, K.; Maitland, N.; Chenevix-Trench, G.; Riggins, G. J.; Bigner, D. D.; Palmieri, G.; Cossu, A.; Flanagan, A.; Nicholson, A.; Ho, J. W. C.; Leung, S. Y.; Yuen, S. T.; Weber, B. L.; Seigler, H. F.; Darrow, T. L.; Paterson, H.; Marais, R.; Marshall, C. J.; Wooster, R.; Stratton, M. R.; Futreal, P. A. Mutations of the BRAF gene in human cancer. *Nature* **2002**, *417*, 949–954.
- (8) Kimura, E. T.; Nikiforova, M. N.; Zhu, Z.; Knauf, J. A.; Nikiforov, Y. E.; Fagin, J. A. High prevalence of BRAF mutations in thyroid cancer: genetic evidence for constitutive activation of the RET/PTC-RAS-BRAF signaling pathway in papillary thyroid carcinoma. *Cancer Res.* **2003**, *63*, 1454–1457.
- (9) Brose, M. S.; Volpe, P.; Feldman, M.; Kumar, M.; Rishi, I.; Gerrero, R.; Einhorn, E.; Herlyn, M.; Minna, J.; Nicholson, A.; Roth, J. A.; Albelda, S. M.; Davies, H.; Cox, C.; Brignell, G.; Stephens, P.; Futreal, P. A.; Wooster, R.; Stratton, M. R.; Weber, B. L. BRAF and RAS mutations in human lung cancer and melanoma. *Cancer Res.* **2002**, *62*, 6997–7000.
- (10) Smith, R. A.; Barbosa, J.; Blum, C. L.; Bobko, M. A.; Caringal, Y. V.; Dally, R.; Johnson, J. S.; Katz, M. E.; Kennure, N.; Kingery-Wood, J.; Lee, W.; Lowinger, T. B.; Lyons, J.; Marsh, V.; Rogers, D. H.; Swartz, S.; Walling, T.; Wild, H. Discovery of heterocyclic ureas as a new class of raf kinase inhibitors: identification of a second generation lead by a combinatorial chemistry approach. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2775–2778.
- (11) Khire, U. R.; Bankston, D.; Barbosa, J.; Brittelli, D. R.; Caringal, Y.; Carlson, R.; Dumas, J.; Gane, T.; Heald, S. L.; Hibner, B.; Johnson, J. S.; Katz, M. E.; Kennure, N.; Kingery-Wood, J.; Lee, W.; Liu, X.-G.; Lowinger, T. B.; McAlexander, I.; Monahan, M.-K.; Natero, R.; Renick, J.; Riedl, B.; Rong, H.; Sibley, R. N.; Smith, R. A.; Wolanin, D. Omega-carboxypyridyl substituted ureas as Raf kinase inhibitors: SAR of the amide substituent. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 783–786.
- (12) Wood, J. E.; Wild, H.; Rogers, D. H.; Lyons, J.; Katz, M. E.; Caringal, Y. V.; Dally, R.; Lee, W.; Smith, R. A.; Blum, C. L. Preparation of Urea Derivatives as raf Kinase Inhibitors. Patent Application WO 9852559, 1998.
- (13) Lyons, J. F.; Wilhelm, S.; Hibner, B.; Bollag, G. Discovery of a novel Raf kinase inhibitor. *Endocr.-Relat. Cancer* **2001**, *8*, 219–225.
- (14) Kumar, C. C.; Madison, V. Drugs targeted against protein kinases. *Expert Opin. Emerging Drugs* **2001**, *6*, 303–315.
- (15) Wilhelm, S. M.; Carter, C.; Tang, L.; Wilkie, D.; McNabola, A.; Rong, H.; Chen, C.; Zhang, X.; Vincent, P.; McHugh, M.; Cao, Y.; Shujath, J.; Gawlak, S.; Eveleigh, D.; Rowley, B.; Liu, L.; Adnane, L.; Lynch, M.; Auclair, D.; Taylor, I.; Gedrich, R.; Voznesensky, A.; Riedl, B.; Post, L. E.; Bollag, G.; Trail, P. BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. *Cancer Res.* **2001**, *64*, 7099–7109.
- (16) Eisen, T.; Ahmad, T.; Flaherty, K. T.; Gore, M.; Kaye, S.; Marias, R.; Gibebns, I.; Hackett, S.; James, M.; Schuster, L. M.; Nathanson, K. L.; Xia, C.; Simantov, R.; Schwartz, B.; Poulin-Costello, M.; O'Dwyer, P. J.; Ratain, M. J. Sorafenib in advanced melanoma: a phase II randomised discontinuation trial analysis. *Br. J. Cancer* **2006**, *95* (5), 581–586.
- (17) Unpublished results.
- (18) Kolch, W. Meaningful relationships: the regulation of the Ras/Raf/MEK/ERK pathway by protein interactions. *Biochem. J.* **2000**, *351* (2), 289–305.
- (19) Information on biochemical and cellular assays is included in the Supporting Information.
- (20) Wan, P. T. C.; Garnett, M. J.; Roe, S. M.; Lee, S.; Niculescu-Duvaz, D.; Good, V. M.; Jones, C. M.; Marshall, C. J.; Springer, C. J.; Barford, D.; Marais, R. Mechanism of activation of the RAF-ERK signaling pathway by oncogenic mutations of B-RAF. *Cell* **2004**, *116*, 855–867.
- (21) Bankston, D.; Dumas, J.; Natero, R.; Riedl, B.; Monahan, M.-K.; Sibley, R. A scaleable synthesis of BAY 43-9006: a potent Raf kinase inhibitor for the treatment of cancer. *Org. Process Res. Dev.* **2002**, *6*, 777–781.
- (22) Brown, S. A.; Rizzo, C. J. A “one-pot” phase transfer alkylation/hydrolysis of *o*-nitrotrifluoroacetanilides. A convenient route to *N*-alkyl *o*-phenylenediamines. *Synth. Commun.* **1996**, *26*, 4065–4080.
- (23) McKillop, A.; Fiaud, J. C.; Hug, R. P. Phase-transfer catalysis for the synthesis of phenol ethers. *Tetrahedron* **1974**, *30*, 1379–1382.
- (24) Hamley, P.; Tinker, A. C. 1,2-Diaminobenzimidazoles: selective inhibitors of nitric oxide synthase derived from aminoguanidine. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1573–1576.
- (25) Krchnak, V.; Smith, J.; Vagner, J. A solid-phase traceless synthesis of 2-arylamino benzimidazoles. *Tetrahedron Lett.* **2001**, *42*, 1627–1630.
- (26) Synthetic methodology and characterization data for compounds including **4**, **18**, **23**, **27** are included in the Supporting Information.

JM801050K