Bioorganic & Medicinal Chemistry Letters 20 (2010) 679–683

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

2,3,5-Trisubstituted pyridines as selective AKT inhibitors. Part II: Improved drug-like properties and kinase selectivity from azaindazoles

Hong Lin [a,*], Dennis S. Yamashita [a], Jin Zeng [a], Ren Xie [a], Sharad Verma [a], Juan I. Luengo [a], Nelson Rhodes [b], Shuyun Zhang [b], Kimberly A. Robell [b], Anthony E. Choudhry [b], Zhihong Lai [b], Rakesh Kumar [b], Elisabeth A. Minthorn [c], Kristin K. Brown [d], Dirk A. Heerding [a]

[a] Oncology Medicinal Chemistry, GlaxoSmithKline,1250 S. Collegeville, Rd., Collegeville, PA 19426, United States
[b] Oncology Biology, GlaxoSmithKline,1250 S. Collegeville, Rd., Collegeville, PA 19426, United States
[c] Oncology Drug Metabolism and Pharmacokinetics, GlaxoSmithKline, 1250 S. Collegeville, Rd., Collegeville, PA 19426, United States
[d] Molecular Discovery Research, GlaxoSmithKline,1250 S. Collegeville, Rd., Collegeville, PA 19426, United States

ARTICLE INFO

Article history:
Received 25 September 2009
Revised 11 November 2009
Accepted 16 November 2009
Available online 20 November 2009

Keywords:
AKT kinase inhibitors
Selectivity
Azaindazole

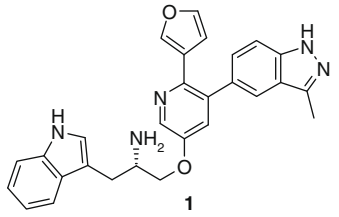
ABSTRACT

A novel series of AKT inhibitors containing 2,3,5-trisubstituted pyridines with novel azaindazoles as hinge binding elements are described. Among these, the 4,7-diazaindazole compound **2c** has improved drug-like properties and kinase selectivity than those of indazole **1**, and displays greater than 80% inhibition of GSK3β phosphorylation in a BT474 tumor xenograft model in mice.

Small-molecule protein kinase inhibitors have emerged as a promising class of cancer therapeutics. As most of these molecules target the relatively conserved ATP binding pocket, achieving kinase selectivity is a difficult task, especially among the kinases in the same superfamily.[1] The identification of more selective kinase inhibitors is an important step towards avoiding the potentially unintended biological consequences of an unselective kinase inhibitor. In addition, these selective agents can function as critical tools to facilitate our understanding of the signaling pathways regulated by these kinases.

Serine/threonine kinases AKT1/2/3 belong to the AGC superfamily and have been implicated as key mediators of cell proliferation, metabolism, survival and inhibition of apoptosis.[2] During the search for a potent, selective and novel kinase inhibitor of AKT, we identified compound **1**.[3] As shown in Table 1, compound **1** is a potent pan-AKT inhibitor that is selective against ROCK1, a close relative of AKT in AGC superfamily. Compound **1** was also potent in cellular mechanistic and proliferation assays,[4] displaying IC_{50} values of 0.34 μM and 0.19 μM respectively in proliferation assays in BT474 (breast) and LNCaP (prostate) cells, which harbor constitutively activated AKT, while showing greatly diminished potency in HFF cells, which do not contain constitutively active AKT.[5] Furthermore, compound **1** inhibited GSK3β phosphorylation in the BT474 cell line (IC_{50} = 0.50 μM), indicative of AKT inhibition. Although selective over ROCK1, compound **1** was still a potent

Table 1
Biological and developability data of compound **1**



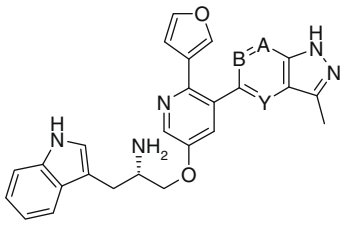
1

IC_{50}[a] (μM)							
Enzyme		Cellular activity		Kinase selectivity		CYP450	
AKT1	0.001	pGSK3β[b]	0.50	ROCK1	1.58	CYP1A2	50
AKT2	0.012	BT474[c]	0.34	P70S6K	0.007	CYP2C9	0.50
AKT3	0.001	LNCaP[c]	0.19	PAK1	0.031	CYP2C19	2.0
		HFF[c]	5.50	PDK1	0.050	CYP2D6	5.0
				PKA	0.001	CYP3A4	0.050
				RSK	0.025		

[a] $n \geqslant 2$.
[b] Inhibition of phosphorylation of GSK3β in BT474 cells.
[c] Inhibition of proliferation.

* Corresponding author.
E-mail address: hong.2.lin@gsk.com (H. Lin).

0960-894X/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2009.11.060



A = N, B = Y = CH, **2a**;
A = B = CH, Y = N, **2b**;
A = Y = N, B = CH, **2c**;
A = CH, B = Y = N, **2d**;
A = Y = CH, B = N, **2e**

Figure 1. Azaindazole compounds.

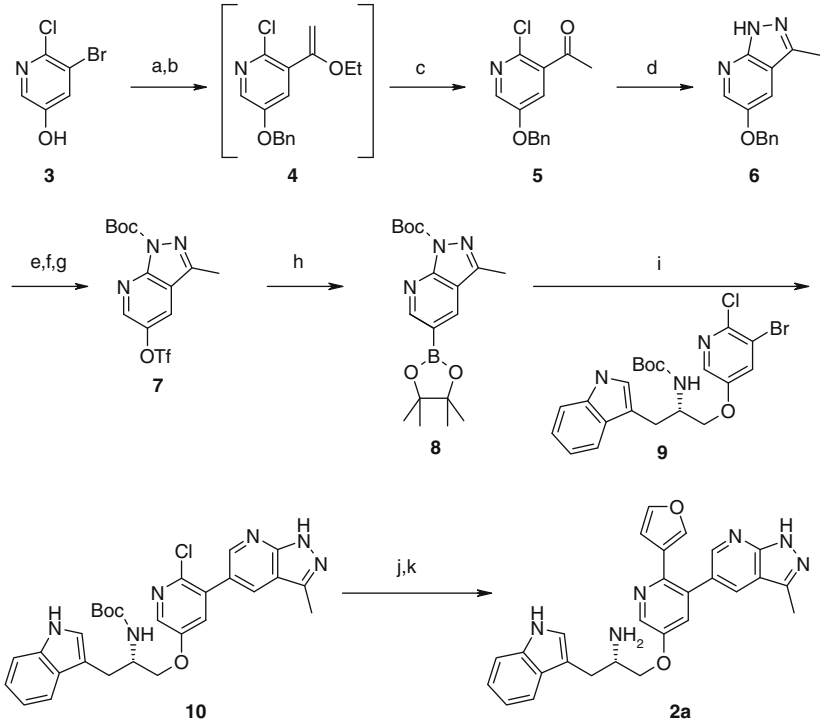
inhibitor of many other kinases in the AGC superfamily, such as p70S6K, PDK1, PKA and RSK. It was also observed to be a potent inhibitor of PAK1, a kinase in the STE superfamily. Furthermore, compound **1** was observed to be a very potent CYP3A4 inhibitor, displaying <100 nM potency.

Based on its observed AKT potency, compound **1** was profiled in an in vivo pharmacodynamic assay using a BT474 tumor xenograft model in mice, measuring the inhibition of GSK3β phosphorylation as the marker for intracellular AKT activity. However, compound **1** failed to show a pharmacodynamic effect in this experiment despite having significant drug concentrations in tumor samples (data not shown). We speculated that the absence of a pharmcodynamic effect could be explained by the poor physical properties, such as the high lipophilicity and high protein binding of compound **1**,[6] thereby preventing it from reaching the target proteins in vivo. We herein report our discovery of a series of azaindazole analogs[7] with improved drug-like properties and kinase selectivity that displayed greater than 80% inhibition of GSK3β phosphorylation in BT474 tumor xenografts.

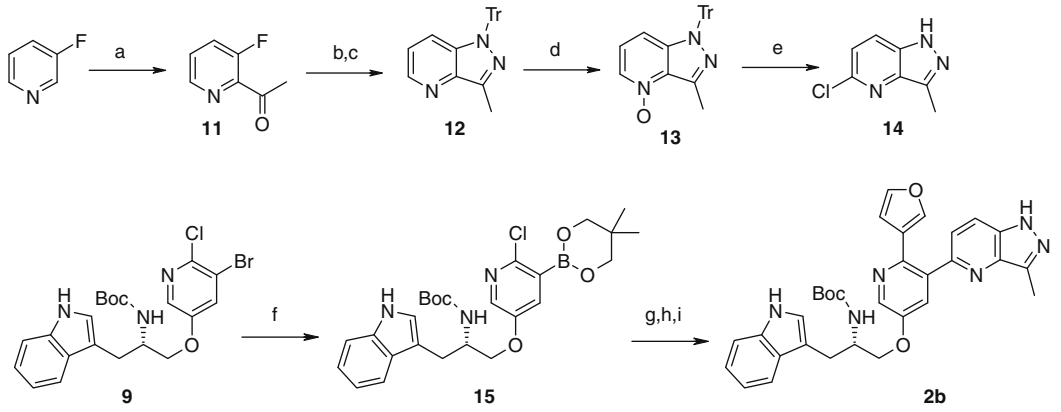
To improve the overall profile of compound **1**, we took a systematic approach to introduce one or two nitrogen atoms in the indazole ring to increase polarity of the molecule and to lower the *c* log P values. In particular, we were interested in making 7-azaindazole **2a**, 4-azaindazole **2b**, 4,7-diazaindazole **2c,** 4,6-diazaindazole **2d**, and 6-azaindazole **2e**[8] as illustrated in Figure 1.

The synthesis of compound **2a** is depicted in Scheme 1, and proceeded through boronate ester **8** as key step. Its preparation started from the trisubstituted pyridine **3**,[3] which we also used as the starting material for the preparation of compounds **2a**–**d**. Protection of the hydroxyl group of **3** with benzylbromide followed by a Stille coupling with 1-ethoxyvinyltin afforded intermediate **4**, which was hydrolyzed under acidic conditions in one pot to give acetylpyridine **5**. Cyclization of **5** with anhydrous hydrazine afforded 7-azaindazole **6**, which was converted to triflate **7** after Boc protection and debenzylation via hydrogenolysis. Triflate **7** was then converted to boronate pinacolate **8** under Pd(0) catalyzed conditions.[9] Both dppf and Cy_3P worked well as ligands for this reaction.[10] Bromopyridine **9**[3] was subjected to consecutive Suzuki coupling reactions with boronate ester **8** and 3-furanylboronate acid, followed by Boc deprotection under standard conditions to afford the final product **2a**.[11]

The synthesis of compound **2b** is depicted in Scheme 2 and required intermediate **14**. The preparation of this compound commenced with the introduction of an acetyl group onto 3-fluoropyridine, followed by cyclization with anhydrous hydrazine. Deprotonation of 3-fluoropyridine with *n*-BuLi, followed by quenching with *N*-methyl-*N*-(methyloxy)acetamide resulted in a 1:1 mixture of **11** and its 4-acetyl regio isomer. This mixture was treated with anhydrous hydrazine at 120 °C and compound **11** was converted to the desired 4-azaindazole, which was protected



Scheme 1. Synthesis of 7-azaindazole analog **2a**. Reagents and conditions: (a) BnBr, K_2CO_3, acetone, reflux, quant.; (b) Pd_2dba_3, 2%, Ph_3P, 8%, 1-ethoxyvinyltin, toluene, 110 °C, 2 h; in one pot (c) 3 N HCl, rt, overnight; (d) anhydrous NH_2NH_2, 120 °C, overnight, 67% over 3 steps; (e) Boc_2O, Et_3N, DMAP, DCM, 80%; (f) H_2 balloon, Pd/C, EtOH, rt, 2 h, 99%; (g) Tf_2NPh, Et_3N, DCM, rt, 2 h, 68%; (h) 4,4,4′,4′,5,5,5′,5′-octamethyl-2,2′-bi-1,3,2-dioxaborolane, Pd(dppf)Cl_2, KOAc, dioxane, 80 °C, overnight; (i) **9**, $Pd(Ph_3P)_4$, 2 N Na_2CO_3, microwave irradiation, 150 °C, 75% over 2 steps; (j) 3-furanylboronic acid, $Pd(Ph_3P)_4$, 2 N Na_2CO_3, microwave irradiation, 160 °C, 74%; (k) TFA, DCM, RP-HPLC purification, 53%.



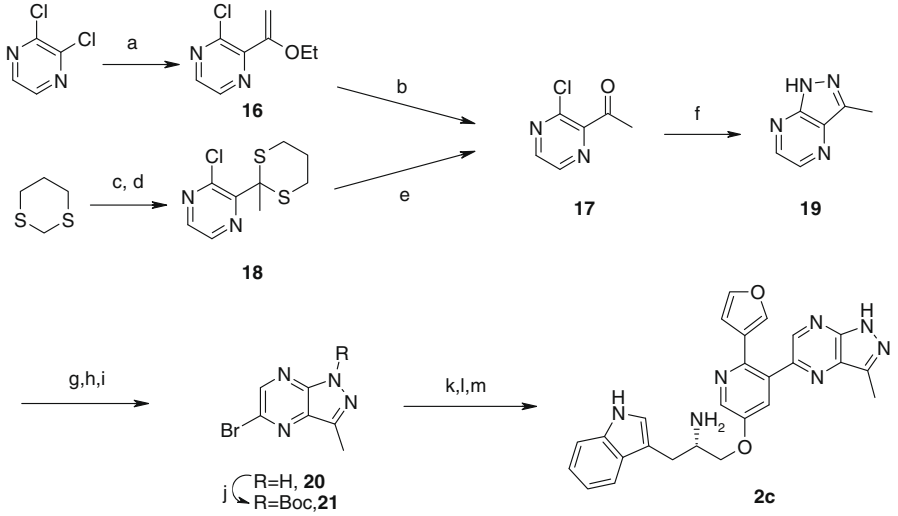
Scheme 2. Synthesis of 4-azaindazole analog **2b**. Reagents and conditions: (a) BuLi, then *N*-methyl-*N*-(methyloxy)acetamide, THF, −78 °C, 84%, 1:1 mix. of **11** and regioisomer; (b) anhydrous NH_2NH_2, 120 °C, overnight, 43%; (c) NaH, DMF, 0 °C, then TrCl, rt, 45%; (d) *m*CPBA, DCM, 0 °C to rt, 12 h, 98%; (e) $POCl_3$, 120 °C, 1 h, 86%; (f) 5,5,5′,5′-tetramethyl-2,2′-bi-1,3,2-dioxaborinane, $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$, KOAc, dioxane, 80 °C, overnight; (g) **14**, $Pd(Ph_3P)_4$, 2 N Na_2CO_3 aq, microwave irradiation, 150 °C, 40%; (h) 3-furanylboronate acid, $Pd(Ph_3P)_4$, 2 N Na_2CO_3, microwave irradiation, 160 °C, 97%; (i) TFA, DCM, RP-HPLC purification, 43%.

with a trityl group to give intermediate **12**. The 5-Cl group was introduced by oxidation of the nitrogen atom on the pyridine ring with *m*CPBA, and chlorination of *N*-oxide **13** with $POCl_3$ to give 5-Cl-4-azaindazole **14**.[12,13] Compound **9** was converted into boronate ester **15** with 5,5,5',5'-tetramethyl-2,2′-bi-1,3,2-dioxaborinane under Pd(0) catalyzed conditions.[14,15] Two successive microwave-assisted Suzuki coupling reactions followed by Boc deprotection gave compound **2b**.

The preparation of 4,7-diazaindazole **2c** is shown in Scheme 3. The synthesis required compound **19**, which in turn was prepared from chloropyrazine **17**. The acetyl group of **17** was introduced either by a Stille reaction of 2,3-dichloropyrazine and 1-ethoxyvinyltin followed by the hydrolysis under acidic conditions, or, by a *tele*-substitution of 2,6-dichloropyrazine with dithiane anion followed by $AgNO_3$ assisted oxidative cleavage of dithiane **18**.[16] The advantage of the latter method is that it avoids the use of highly toxic organo stannane reagents. Cyclization of compound **17** to 4,7-diazaindazole **19** was accomplished by heating compound **17** with 1 equiv of hydrazine in pyridine (0.05 M concentration to avoid intermolecular side reactions). The 5-bromo group was installed following the same sequence that was used to introduce 5-Cl group on 4-azaindazole core of compound **14** except that $POBr_3$ was used instead of $POCl_3$. Compound **20** was then protected with Boc_2O to give **21**, which was subjected to consecutive microwave-mediated Suzuki coupling reactions with deprotection and reverse phase HPLC purification to afford the final 4,7-diazaindazole derivative **2c**.

Table 2 summarizes some biological and developability properties of the novel azaindazole analogs (**2a**–**e**) in comparison to indazole containing compound **1**. Except for 4-azaindazole **2b**, the other azaindazole analogs **2c–e** were equally potent against AKT1, but less potent against AKT2/3. In both cellular proliferation and mechanistic assays, compound **2c** appeared to be most potent and selective in tumor cells (LnCAP, BT474) containing constitutively activated AKT versus normal cells (HFF) lacking activated AKT.

Since azaindazole derivatives **2a**, **2c** and **2d** displayed lower clogP values than that of indazole **1** in a range of 3.3–3.8, it was not surprising to see these compounds displayed improved drug-like properties. In general, they displayed reduced CYP450



Scheme 3. Synthesis of 4,7-diazaindazole analog **2c**. Reagents and conditions: (a) Pd_2dba_3, 2 mol %, Ph_3P, 8 mol %, 1-ethoxyvinyltin, toluene, 110 °C, 2 h; (b) 2 N HCl, acetonitrile, rt, overnight, 72% over 2 steps; (c) BuLi, −20 °C, MeI, −50 °C to rt, THF; (d) in one pot, BuLi, −20 °C, 2,6-dichloropyrazine, −50 °C to rt, 98%; (e) NCS, $AgNO_3$, acetonitrile/H_2O 4:1; (f) NH_2NH_2 hydrate, pyridine, 0.05 M, 120 °C, overnight, 62% over two steps; (g) NaH, DMF, 0 °C, then TrCl, rt, 62%; (h) *m*CPBA, DCM, 0 °C to rt, 12 h, 92%; (i) $POBr_3$, 90 °C, 2.5 h, 52%; (j) Boc_2O, Et_3N, DMAP, DCM, 68%; (k) **15**, $Pd(Ph_3P)_4$, 2 N Na_2CO_3 aq, microwave irradiation, 150 °C, 88%; (l) 3-furanylboronate acid, $Pd(Ph_3P)_4$, 2 N Na_2CO_3, microwave irradiation, 160 °C, 92%; (m) TFA, DCM, RP-HPLC purification, 53%.

Table 2
Some biological and developability data of azaindazole analogs

Compound	1	2a	2b	2c	2d[19]	2e[20]
AKT1 IC_{50}[a] (μM)	0.001	0.001	0.012	0.002	0.001	0.001
AKT2 IC_{50}[a] (μM)	0.012	ND	ND	0.039	0.031	0.006
AKT3 IC_{50}[a] (μM)	0.001	ND	ND	0.010	0.015	0.001
LnCAP IC_{50}[b] (μM)	0.19	0.085[c]	0.83[c]	0.096[c]	0.54[c]	0.23
BT474 IC_{50}[b] (μM)	0.34	0.30[c]	2.1[c]	0.37[c]	0.64[c]	0.75
HFF IC_{50}[b] (μM)	5.5	6.6[c]	30[c]	14.3[c]	30[c]	6.5
pGSK3β IC_{50}[c] (μM)	0.50	0.26	3.86	0.16	0.67	0.064
CYP450 3A4 IC_{50} (μM)	0.050	0.20	0.10[d]	0.40	1.3	0.016
HT solubility μM	52	108	225	200	205	NT
Protein binding%	95.9	95.3	93.1	90.9	84.5	94.3
c log *p*	4.45	3.75	4.17	3.31	3.31	3.96

[a] $n \geqslant 2$.
[b] Inhibition of cell proliferation.
[c] Inhibition of phosphorylation of GSK3β. Data were collected in methylene blue (MEB) format.[22]
[d] DEF = diethoxyfluorescein was used as CYP3A4 probe substrate.

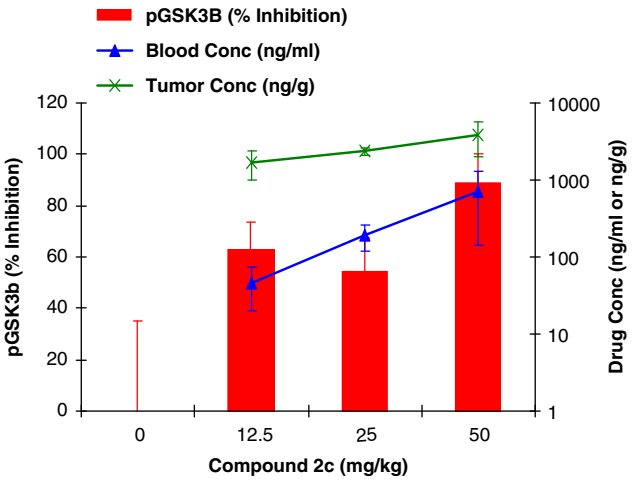


Figure 3. Dose response PD effect of **2c** on GSK3β phosphorylation in BT474 tumors in female SCID mice.

inhibition compared to indazole **1**, especially versus the 3A4 isozyme.[17,18] The azaindazole analogs also had increased solubility, which was particularly important for the development of an intravenous (iv) administrated agent, due to the lack of oral exposure in this chemotype. Furthermore, the azaindazole analogs displayed reduced protein binding (e.g., compound **2c** vs **1**), a factor that we suspected to be responsible for compound **1** not showing a pharmacodynamic effect in the mouse xenograft tumor model.

Compound **2c** not only had an improved overall profile in terms of cellular potency and drug-like properties, but also displayed improved kinase selectivity compared to indazole **1** (Fig. 2).

While maintaining AKT potency, compound **2c** displayed greater than 10-fold decreased potency against PKA, and almost 100-fold decreased potency against MSK1. These two kinases are close relatives of AKT in the AGC superfamily. Although it is not completely clear to us why 4,7-diazaindazole **2c** would be more selective than indazole **1**, we suspect that 4,7-diazaindazole might be a weaker H-bond acceptor due to the electronic effect of the N atoms in the six-member ring.[23] Therefore, the AKT potency of **2c** might be driven more by the specific interactions with other parts of the protein, and less by the H-bond interactions with the hinge, which are common for all kinases. As a consequence, an ATP competitive inhibitor, such as compound **2c** with a 'weaker' hinge binder, may be slightly less potent against AKT than indazole **1**, while being more selective over other kinases.

Since compound **2c** had the best overall profile in terms of potency, selectivity and drug-like properties among other azaindazole analogs, it was characterized in a BT474 xenograft pharmacodynamic study. As shown in Figure 3, compound **2c** demonstrated greater than 80% inhibition of GSK3β phosphorylation at a dose of 50 mg/kg (intraperitoneal administration). This pharmacodynamic effect mirrows well with the pharmacokinetic results.[24] The level of inhibition (89%) of GSK3β phosphorylation is consistent with cellular potency (160 nM IC_{50}) and drug concentration (3798 ng/mL) in tumor after correction protein binding for the free drug fraction.

In summary, we have described the synthesis and biological activities of novel azaindazole analogs as potent AKT inhibitors. Compound **2c** showed improved drug-like properties and kinase selectivity with respect to indazole **1**, and demonstrated an in vivo pharmacodynamic effect in BT474 tumor xenografts.

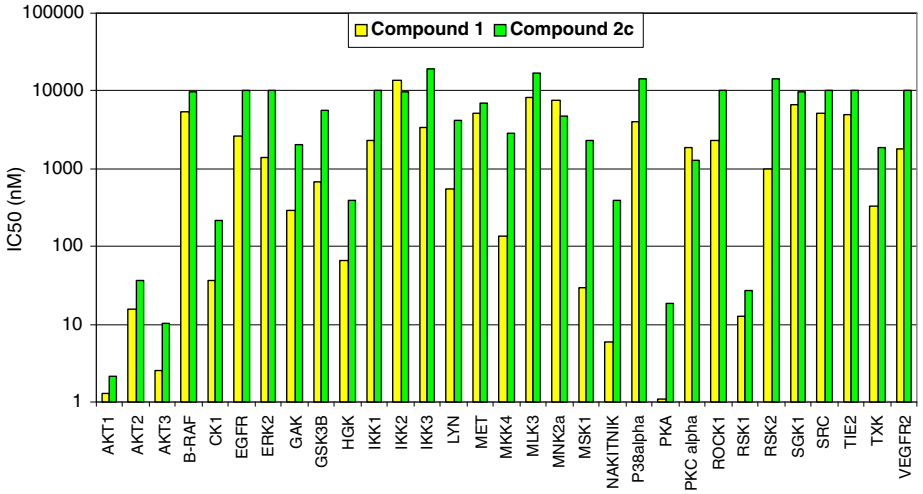


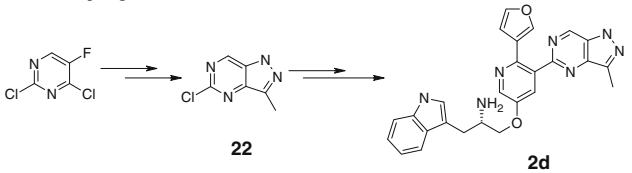
Figure 2. Comparison of the kinase selectivity between compound **1** and 4,7-diazaindazole analog **2c**.

Acknowledgment

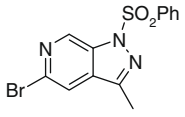
The authors thank Dr. Arthur Shu for preparing 7-azaindazole **6** and 4,7-diazaindazole **20** in large scale to support the SAR study.

References and notes

1. (a) Karaman, M. W.; Herrgard, S.; Treiber, D. K.; Gallant, P.; Atteridge, C. E.; Campbell, B. T.; Chan, K. W.; Ciceri, P.; Davis, M. I.; Edeen, P. T.; Faraoni, R.; Floyd, M.; Hunt, J. P.; Lockhart, D. J.; Milanov, Z. V.; Morrison, M. J.; Pallares, G.; Patel, H. K.; Pritchard, S.; Wodicka, L. M.; Zarrinkar, P. P. *Nat. Biotechnol.* **2008**, *26*, 127; (b) Buchanan, S. G. *Targets* **2003**, *2*, 101.
2. (a) Lindsley, C. W.; Barnett, S. F.; Layton, M. E.; Bilodeau, M. T. *Curr. Cancer Drug Targets* **2008**, *8*, 7; (b) Li, Q. *Expert Opin. Ther. Patents* **2007**, *17*, 1077; (c) Bellacosa, A.; Kumar, C. C.; Cristofano, A. D.; Testa, J. R. *Adv. Cancer Res.* **2005**, *94*, 29.
3. Lin, H.; Yamashita, D.; Zeng, J.; Xie, R.; Wang, W.; Nidarmarthy S.; Luengo, J. I.; Rhodes, N.; Knick, V. B.; Choudhry, A. E.; Lai, Z.; Minthorn, E. A.; Strum, S. L.; Wood, E. R.; Elkins, P. A.; Concha, N. O.; Heerding, D. A. Bioorg. Med. Chem. Lett., doi:10.1016/j.bmcl.2009.11.061.
4. For details of in vitro kinase inhibition assays and cellular assays to measure proliferation and inhibition of GSK3β phosphorylation, see: Rhodes, N.; Heerding, D. A.; Duckett, D. R.; Eberwein, D. J.; Knick, V. B.; Lansing, T. J.; McConnell, R. T.; Gilmer, T. M.; Zhang, S. Y.; Robell, K.; Kahana, J. A.; Geske, R. S.; Kleymenova, E. V.; Choudhry, A. E.; Lai, Z. V.; Leber, J. D.; Minthorn, E. A.; Strum, S. L.; Wood, E. R.; Huang, P. S.; Copeland, R. A.; Kumar, R. *Cancer Res.* **2008**, *68*, 2366.
5. A compound that is less potent against HFF in proliferation assay is considered to be less cytotoxic and to have a cleaner selectivity profile in general.
6. The cellular potency of compound **1** in BT474 proliferation assay shifted sixfold to be less potent when protein was added.
7. For easy comparison with the indazole, the pyrazolopyridine, pyrazolopyrazine or pyrazolopyrimidine analogs are all called azaindazoles instead. For example, 4-azaindazole is 1*H*-pyrazolo[4,3-*b*]pyridine, 4,7-diazaindazole is 1*H*-pyrazolo[3,4-*b*]pyrazine and 4,6-diazaindazole is 1*H*-pyrazolo[4,3-*d*]pyrimidine.
8. The 6-azaindazole was described in Abbott's publication on 2,3-disubstituted pyridine AKT inhibitors: Zhu, G.-D.; Gandhi, V. B.; Gong, J.; Thomas, S.; Woods, K. W.; Song, X.; Li, T.; Diebold, R. B.; Luo, Y.; Liu, X.; Guan, R.; Klinghofer, V.; Johnson, E. F.; Bouska, J.; Olson, A.; Marsh, K. C.; Stoll, V. S.; Mamo, M.; Polakowski, J.; Campbell, T. J.; Martin, R. L.; Gintant, G. A.; Penning, T. D.; Li, Q.; Rosenberg, S. H.; Giranda, V. L. *J. Med. Chem.* **2007**, *50*, 2990.
9. Boronate ester **8** is very stable. It can be purified on silica gel column and stored as a white solid.
10. Ishiyama, T.; Ishida, K.; Miyaura, N. *Tetrahedron* **2001**, *57*, 9813.
11. These two Suzuki reactions worked well under thermal conditions, but for efficiency, microwave conditions were used often on mg to g scales.
12. Ohi, N.; Sato, N.; Soejima, M.; Doko, T.; Terauchi, T.; Naoe, Y.; Motoki, T. PCT Int. Appl. WO2003101968, 2003.
13. Transformation of **14** to its stannane reagent or boronate ester for coupling with bromopyridine **9**, was not successful.
14. 4,4,4′,4′,5,5,5′,5′-Octamethyl-2,2′-bi-1,3,2-dioxaborolane did not give the corresponding boronate pinacolate under the same condition.
15. Boronate ester **15** can either be used as a crude reaction mixture or purified on silica gel for storage.
16. Torr, J. E.; Large, J. M.; Horton, P. N.; Hursthouse, M. B.; McDonald, E. *Tetrahedron Lett.* **2006**, *47*, 31.
17. Furan, indole and pyridine are all canonical CYP450 culprits. Modification of indole and replacement of furan (compounds in Ref. 3, CYP450 data not shown) did not result in improvement of CYP450 profile. Modification of pyridine is addressed in a separate publication: Lin, H.; Yamashita, D. S.; Xie, R.; Zeng, J.; Wang, W.; Leber, J.; Safonov, I. G.; Verma, S.; Li, M.; LaFrance, L; Venslavsky, J.; Takata, D.; Luengo, J. I.; Kahana, J. A.; Zhang, S.; Robell, K. A.; Levy, D.; Kumar, R.; Choudhry, A. E.; Schaber, M.; Lai, Z.; Brown, B. S.; Donovan, B. T.; Minthorn, E. A.; Brwon, K. K.; Heerding, D. A. Bioorg. Med. Chem. Lett., doi:10.1016/j.bmcl.2009.11.064.
18. Replacement of indazole with thienopyrazole did not reduce CYP450 3A4 inhibition (data not shown). For preparation of thienopyrazole derivatives, see: Yamashita, D. S.; Lin, H.; Wang, W. PCT Int. Appl. WO2005085227, 203, 2005.
19. The 4,6-diazaindazole analog **2d** was prepared similarly to the above mentioned azaindazole analogs. A regio selective Stille coupling reaction of 2,4-dichloro-5-fluoropyrimidine and 1-ethoxyvinyltin followed by acidic hydrolysis of the vinyl ether and subsequent cyclization with 1 equiv of hydrazine hydrate afforded 5-chloro-4,6-diazaindazole **22**. Two consecutive microwave-assisted Suzuki coupling reactions of **22** with boronate ester **15** and 3-furanylboronate acid followed by acidic deprotection and reverse phase HPLC purification furnished final target molecule **2d**. Although this synthetic route was suitable for preparing analogs in small scale, it was not optimized for gram-scale synthesis due to low yields during formation of **22** and subsequent Suzuki coupling reactions.

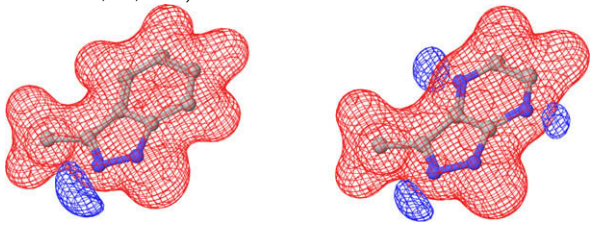


22 **2d**



23

20. The 6-azaindazole analog **2e** was prepared in a similar manner to the synthesis of **2b** except for the use of 5-bromo-6-azaindazole **23** as a coupling partner with boronate ester **15**.[21] Basic conditions are required to deprotect the benzenesulfonamide on the 6-azaindazole ring.
21. Verma, S. K.; LaFrance, L. V. *Tetrahedron Lett.* **2009**, *50*, 383.
22. Rusnak, D. W.; Lackey, K.; Affleck, K.; Wood, E. R.; Alligood, K. J.; Rhodes, N.; Ketih, B. R.; Murray, D. M.; Knight, W. B.; Mullin, R. J.; Gilmer, T. M. *Mol. Cancer Ther.* **2001**, *1*, 85.
23. Electrostatic potential of the two hinge binders indicate that 4,7-diazaindazole have weaker H-bond interaction to hinge (calculated using Density Function Theory with B3LYP/6-31G** basis set within *JAQUAR, Version 7.5*; Schrodinger, LLC: New York, NY, 2008).



24. Although the pharmacodynamic effect appeared to be inverted at the 12.5 and 25 mg/kg doses, the similar tumor concentrations at these two doses and the error bars indicated a lack of significant difference in pharmacodynamic effect between these two dose levels.