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Balancing oral exposure with Cyp3A4 inhibition in benzimidazole-based IGF-IR inhibitors

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ABSTRACT

3-(Benzimidazol-2-yl)-pyridine-2-one-based ATP competitive inhibitors of Insulin-like Growth Factor 1 Kinase (IGF-IR) were optimized for reduced Cyp3A4 inhibition and improved oral exposure. The use of malonate as methyl anion synthon via S_NAr reaction and double decarboxylation under mild conditions is demonstrated.

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The Insulin-like Growth Factor-1 (IGF-I) receptor[1,2] (IGF-IR) is a member of the receptor tyrosine kinase family. Signaling through IGF-IR kinase results in activation of both the RAS/Raf/MAP Kinase pathway, which is primarily responsible for mitogenesis, the PI-3/Akt kinase pathway, which has an anti-apoptotic role.[1–3] Inhibition of both of these pathways makes IGF-IR kinase a promising target for cancer therapy. Epidemiological studies have also highlighted the importance of IGF-IR signaling in major tumor types by correlating elevated IGF-I levels with increased risk of developing colon, breast, prostate, and lung tumors.[4–8] Recent publications report pyrrolo-pyrimidines,[9] tryphostine analogs,[10] picropodophylin,[11] and 3-(benzimidazol-2-yl)-pyridine-2-ones[3,12–16] to have IGF-IR inhibitory and anti-tumor activity in animal models.

Initial results from our laboratories resulted in the discovery of morpholino-benzimidazole **1**, a potent IGF-IR kinase inhibitor, but also a strong Cyp3A4 inhibitor (see Table 1).[12,13] In this letter, we report the discovery of several compounds within the same benzimidazole chemotype with reduced Cyp inhibition, balanced with high oral exposure.

Cocrystallization of a number of inhibitors from this class with a truncated IGF-IR protein containing the kinase domain revealed that the 'top left part' of the molecule (morpholine in **1**) is solvent exposed and therefore offers an opportunity to optimize the pharmacokinetic properties and reduce Cyp inhibition, without much influence on kinase potency.[12]

Replacement of the morpholine of **1** with bioisosteres (4-hydroxypiperidine **2**, alkoxypiperidines **3**, **4** and **5**, piperidin-4-one spiroketal **6**) resulted in potent IGF-IR kinase inhibitors but little improvement with respect to Cyp3A4 inhibition (see Table 1). The 4-amino-piperidines (**7, 8**, and **9**) stood out with their 5- to 10-fold reduced Cyp3A4 inhibition, compared to **1** (Table 1), but their oral exposure is extremely low.

Replacing these basic amines with amides or carbamates (**10** and **11**) resulted in compounds with significantly increased oral exposure and improved cell potency, higher predicted log$D_{6.5}$ values (Table 1), but stronger Cyp3A4 inhibition.

Among these early compounds, examples **1**–**11**, we observed a good correlation between calculated log$D$ (at pH 6.5) and Cyp3A4

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Table 1
Kinase inhibition IC_{50}s of compounds **1–25**, selected PK data and calculated physical properties

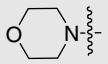
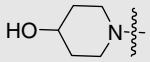
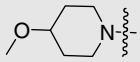
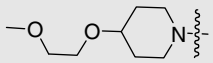
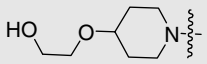
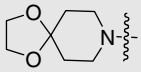
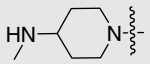
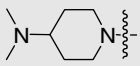
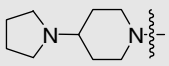
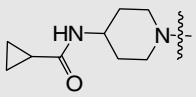
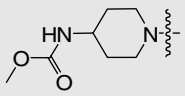
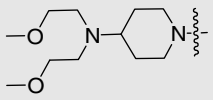
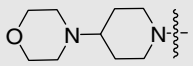
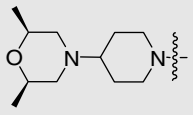
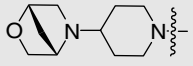
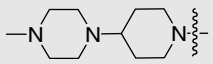
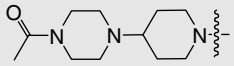
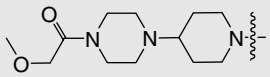
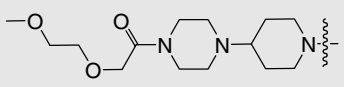
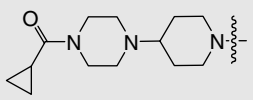
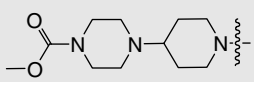
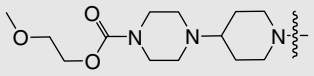
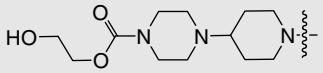
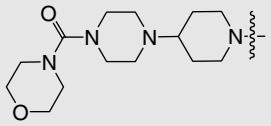
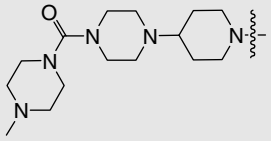
Compound	R^1	IGF-IR[a] (nM)	IGF-IR Sal[b] (nM)	Cyp3A4[c] (μM)	AUC[d] (μMh)	pK_a[e]	logD^f (6.5)
1		100	110	0.5	51		1.72
2		29	79	0.4	0.5		1.48
3		220	155	1	4.5		2.12
4		150	99	0.9			1.76
5		45	55	1.3	6.9		1.4
6		75	121	0.7	18.5		1.92
7		14	108	2.6	0	10.26	−1.19
8		33	92	3.9	0.2	9.34	−0.35
9		27	107	4.5	0	10.27	0.01
10		50	66	0.7	7.4		1.51
11		69	39	0.5	29		2.08
12		39	80	1	0	7.6	−0.49
13		45	108	4.1	3.3	7.69	0.76
14		49	83	3.1	6.9	7.76	1.67
15		29	86	0.5	0.5	9.27	−0.78
16		28	88	2.4	0	7.66 5.22	−0.08
17		32	105	0.8	0.6	5.79	1.65
18		12	145	5.6	1.4	5.49	1.57
19		40	193	3.0	2.6	5.47	1.51
20		100	139	1.7	4.5	5.72	2.04
21		82	77	3.5	11.3	5.67	2.33

Table 1 (*continued*)

Compound	R^1	IGF-IR[a] (nM)	IGF-IR Sal[b] (nM)	Cyp3A4[c] (μM)	AUC[d] (μM h)	pK_a[e]	log D[f] (6.5)
22		100	115	2.4	10.2	5.59	2.36
23		37	130	1.8	3.9	5.56	1.73
24		9	99	19	1.1	6.32	1.33
25		16	151	40	1.1	6.78 6.24	1.31

[a] IGF-IR kinase IC_{50}.
[b] Cellular IC_{50}, measured via thymidine incorporation.
[c] Cyp3A4 inhibition, 7-Benzyloxy-4-trifluoromethylcoumarin was used as probe molecule.
[d] Area under the curve for plasma concentration of compound versus time, interval 0–4 h, after oral administration of 20 mg/kg to mice.
[e] pK_a is the predicted pK_a value for the amine-nitrogen within R_1, calculated for R_1-phenyl as a simplified model. pK_a values were calculated using ACD/pK_a calculator, version 8.0, Advanced Chemistry Development, Inc., Toronto ON, Canada, www.acdlabs.com, 2003.
[f] Log D(6.5) values were calculated using ACD/LogD Sol Suite, version 7.0, Advanced Chemistry Development, Inc., Toronto ON, Canada, www.acdlabs.com, 2003.

inhibition, with more polar compounds showing less Cyp inhibition. Oral exposure also followed a good correlation with log D, more polar compounds having lower oral exposure. Differences in rate of metabolism cannot explain the higher oral exposure of more lipophilic compounds, since these displayed comparable or even higher rates of metabolism in mouse liver microsomes.[17] In an attempt to balance these two contrary trends we focused on moderating the pK_a of the amine-nitrogen of this type of 4-amino-piperidine compounds. β-Electron-withdrawing substituents are known to reduce the basicity of alkylamines.[18] Bis-methoxy-ethyl amine **12** had good IGF-IR potency, somewhat reduced Cyp inhibition (IC_{50} = 1.0 μM) but no oral exposure. It is known in the literature that the number of freely rotating bonds correlates inversely with oral bioavailability. Cyclizing (formally) the two methoxy-ethyl chains to a morpholine resulted in compound **13**, which has the same β-oxy-amine substructure as **12** and comparable basicity, but fewer freely rotating bonds. This compound has good potency (IC_{50} = 45 nM), reduced Cyp inhibition (Cyp3A4 IC_{50} = 4.1 μM) and improved oral exposure. Increasing log D by introduction of methyl substituents on the morpholine (e.g., **14**) only slightly improved oral exposure.

The addition of a methano-bridge over the morpholine results in a significantly more basic amine **15**, similar to the dimethyl amine **8**. This is due to a reduction of the above-mentioned β-oxygen effect because of unfavorable orbital geometry. This increased basicity (relative to **13**) is reflected in a lower calculated log D ($\Delta \log D_{6.5}$ = 1.54) and lower oral exposure (~6-fold, see Table 1). For this example Cyp3A4 inhibition does not follow the general trend. Replacing the morpholino-piperidine substructure with piperazino-piperidines results in compounds (e.g., **16**) with an additional basic-nitrogen atom, consequently a significantly lower calculated log D (~0.0), and (as predicted) low Cyp3A4 inhibition, and very low oral exposure.

Acylating the piperazine moiety (**17** vs **16**) not only turns an amine-nitrogen into a non-basic moiety, but it also reduces, through an inductive effect, the basicity of the remaining central amine. Thus, amides (**17**, **18**, **19**, and **20**), carbamates (**21**, **22**, and **23**), and ureas (**24** and **25**) all have less basic central nitrogens (pK_a ~5.5–6.3) and favorable moderate polarity (log D between 1.5 and 2.5). The carbamates (**21**, **22**, and **23**) combine potent IGF-IR kinase inhibition, acceptable oral exposure, and reduced Cyp3A4 inhibition.

In conclusion, the current study demonstrates that oral bioavailability and Cyp3A4 inhibition of 3-(benzimidazol-2-yl)-pyridine-2-one-based IGF-IR kinase inhibitors can be balanced by careful tuning of the polarity and basicity of the C_5 substituent, although not separated. These compounds are (within the experimental limits) equipotent against IGF-IR and the Insulin Receptor Kinase (IR).[19] Further lead optimization efforts, including work toward compounds with improved selectivity against a wide variety of kinases, together with in-vivo data, will be subject of future disclosures.

An ideal synthesis for the series of compounds depicted in Table 1 would build up the core and right side of the molecule first and introduce diversity on the left side late in the synthesis. Attempts to carry a bromide (R_1 = Br in Fig. 1) through the synthesis to introduce various amines late in the synthesis failed. Buchwald reactions of 4-bromo-2-methyl-6-nitro-aniline with 4-substituted piperidines required separate optimization for every amine and gave unsatisfactory results, especially on scale-up.[12,20] Therefore we turned to the sequence shown in Scheme 1, three consecutive S_NAr reactions on commercially available 2,4,6-trifluoronitrobenzene **26**.

Trifluoronitrobenzene reacts with deprotonated malonate esters to give selectively the mono-ortho-substitution product **27** (ortho:para selectivity ~10:1, <5% bis-substitution). Treatment of **27** with an excess of ammonia in MeOH results in selective replacement of the other *ortho*-fluoride to give nitroaniline **28** in 80% yield over two steps. HCl-catalyzed hydrolysis of the bis-*tert*-butyl ester and mono-decarboxylation result in formation of acid **29**. The key step of the sequence shown in Scheme 1 is the second decarboxylation from **29** to **30**. We observed no conversion under the conditions reported by Toussaint[21] (0.1 equiv Cu_2O, 50 °C in CH_3CN). For our substrate this transformation required 2 equiv Cu_2O and 12 h refluxing in CH_3CN. Under these more forc-

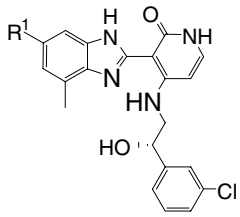
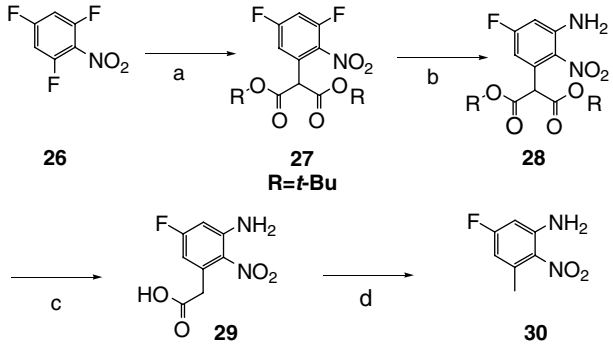


Figure 1. General structure of compounds **1**–**25**.

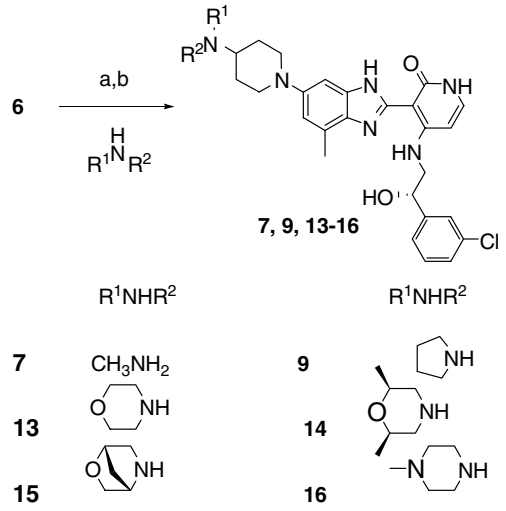


Scheme 1. Reagents and conditions: (a) NaH, DMF, bis-*tert*-butyl-malonate, 0–20 °C; (b) NH_3/MeOH, 85 °C, pressure flask, 80%; (c) 1 N HCl, dioxane, 40 °C; (d) Cu_2O, CH_3CN, reflux 12 h, 80%.

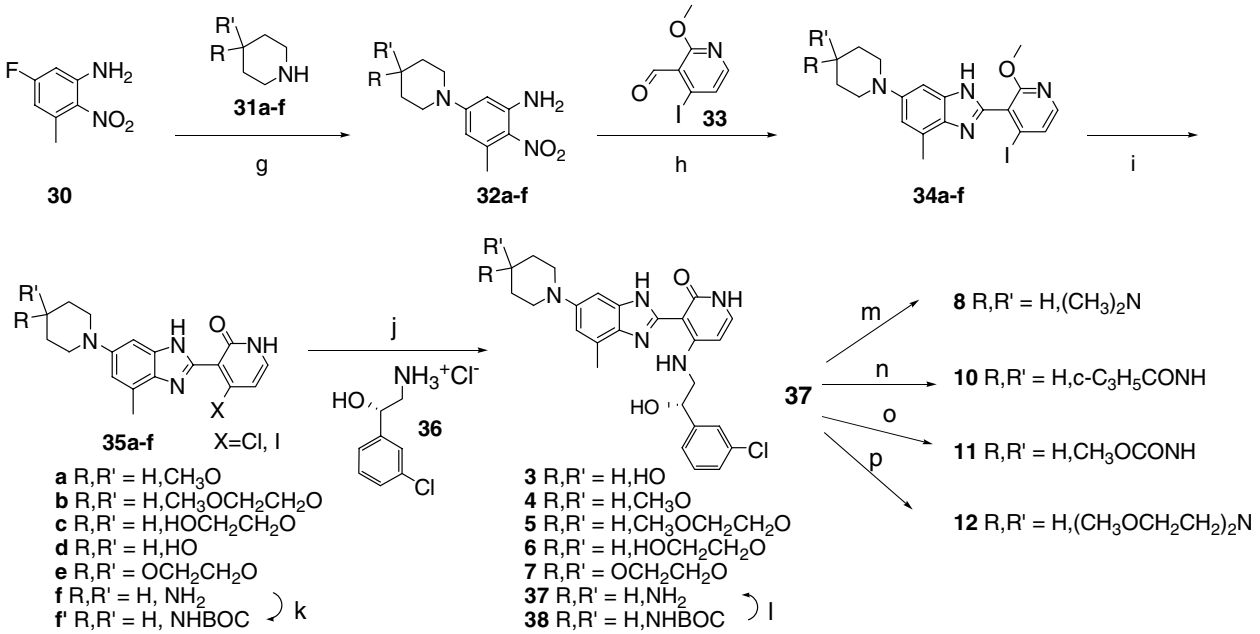
ing conditions yields were generally >80%. This result indicates that this transformation may have broader application than originally realized and may represent a versatile strategy to introducing a methyl group onto electron-rich, neutral, and electron-poor aromatic rings (Scheme 2).

Fluoro-nitro compound **30** reacts with amines **31a**–**f** to give compounds **32**. Following the same synthetic sequence as described in our earlier publication[12] the nitroanilines **32** were hydrogenated (Pd/C, 50 psi) to form the highly air-sensitive *ortho*-diamines, which were immediately condensed with 4-iodo-2-methoxy-pyridine-3-carbaldehyde **33**[22] to give benzimidazoles **34a**–**f** in good yields (Scheme 3).

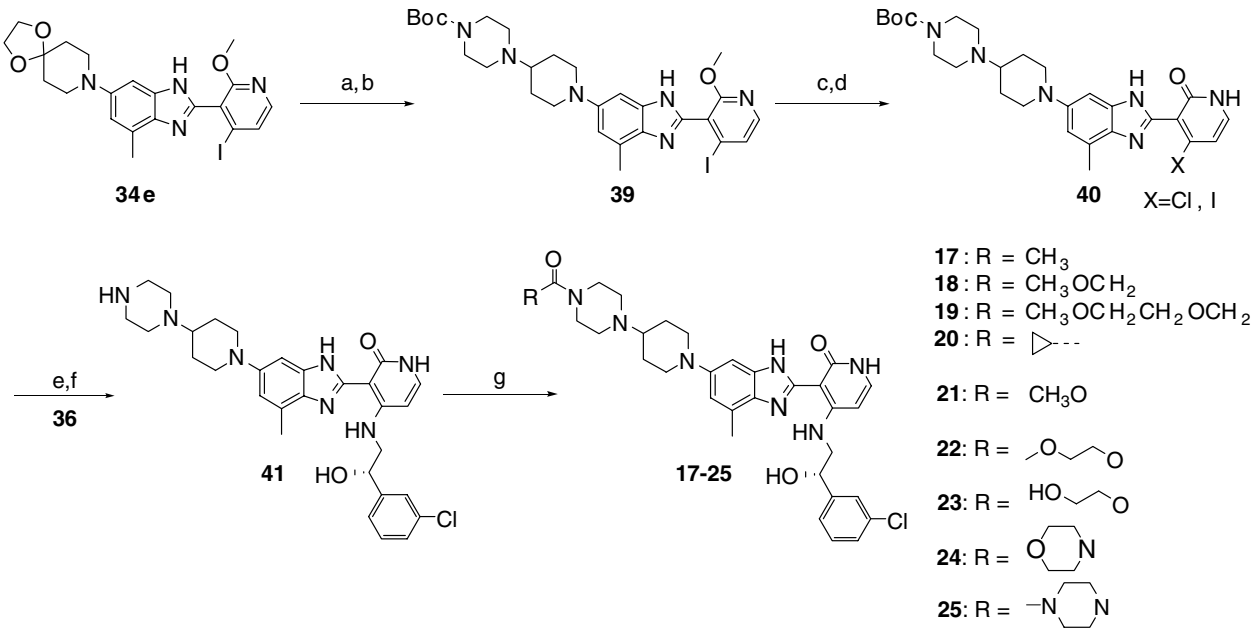
Treatment of benzimidazoles **34a–f** with aq HCl in dioxane results in hydrolysis of the methoxy-pyridine to the corresponding iodo-pyridone **35a–f**, with partial exchange of I with Cl (and cleavage of the BOC-protecting group in case of **35f**). It is noteworthy that the spiroketal functionality in **35e** is not cleaved by these conditions.[23] Addition/elimination reaction with an excess of amino alcohol **36**[12] gives products **3**, **4**, **5**, **6**, and **7**. The primary amine **37** can be made directly from **35f**, but is contaminated with self-condensation product. We got better results by BOC-protecting **35f** to **35f'**, then performing the S_NAr reaction and cleaving BOC again afterward. Reductive amination of amine **37** with formaldehyde or 2-methoxy-acetaldehyde[24] forms **8** and **12**. Acylation of amine **37** with cyclopro-



Scheme 3. Reagents and conditions: (a) acetone, aq HCl, 18 h reflux; (b) amine, $ZnCl_2$, $NaCNBH_3$, MeOH, 20 °C, ~70%.



Scheme 2. Reagents and conditions: (g) Huenig's base, DMSO, 80 °C, 15 h, 80%; (h) H_2/Pd/C, 50 psi, 16 h; then **33**; air, 20 °C, 63%; (i) aq HCl, dioxane, 3 h, 70 °C; (j) **36**, Huenig's base, CH_3CN, 80 °C 16 h, 50–80%; (k) BOC_2O, Huenig's base, CH_2Cl_2, 20 °C; (l) CF_3COOH, CH_2Cl_2, 20 °C; (m) aq H_2CO, $NaCNBH_3$, $HC(OCH_3)_3$, HOAc, 20 °C; (n) *c*-C_3H_5COCl, Huenig's base, MeOH, 0–20 °C; (o) CH_3OCOCl, Huenig's base, MeOH, 20 °C; (p) aq HCl, acetone, 1,1,2-trimethoxyethane, 5 min 80 °C; then **37**, $NaCNBH_3$, $HC(OCH_3)_3$, NaOAc, 20 °C.



Scheme 4. Reagents and conditions: (a) acetone, aq HCl, 18 h reflux; (b) *N*-BOC-piperazine, $ZnCl_2$, $NaCNBH_3$, 20 °C, 80%; (c) aq HCl, dioxane, 1 h, 85 °C; (d) BOC_2O, Huenig's base, CH_2Cl_2, 20 °C; (e) **36**, Huenig's base, CH_3CN, 80 °C 16 h, 50%, three steps; (f) CF_3COOH, CH_2Cl_2, 20 °C; (g) RCOCl or $(RCO)_2O$, Huenig's base, MeOH, 0–20 °C, ~80%.

pane carbonyl chloride or methyl chloroformate results in formation of **10** and **11**. This order of steps was advantageous to introduce diversity late in the synthesis. For selective syntheses of any one of these compounds we got better results by reversing the order of steps, performing the acylation or reductive amination first, followed by the addition/elimination reaction.

Hydrolysis of the ketal **6** to the corresponding ketone can be achieved using HCl/acetone. This ketone exists as a mixture with its hydrate or—when isolated from MeOH—methyl-hemiketal. Reductive amination with methylamine or cyclic secondary amines yields products **7**, **9**, and **13**-**16**.

Selective hydrolysis of the spiroketal functionality of **34e** (via transketalization) is accomplished using HCl/acetone. Reductive amination of this ketone with mono-N-BOC-protected piperazine leads to **39**. Treatment with aq HCl/dioxane hydrolyzes the methoxypyridine, followed by BOC re-protection to give **40**. Addition of amino alcohol **36**,[12] followed by deprotection gives **41**. Final acylation with acid chlorides, anhydrides or chloroformates gives access to products **17**–**25**. To generate hydroxyethyl-carbamate **23** we treated commercially available mono-THP-protected ethylene glycol with phosgene and pyridine and used the resulting solution to acylate **41**. The THP group was then cleaved using HCl/MeOH. This order of synthetic transformations allowed us to introduce diversity at the last step. For selective syntheses of any one of these compounds **17**–**25** a modified synthetic sequence, deprotection of **39**, followed by acylation, then S_NAr reaction (steps c then g then e in Scheme 4) is two steps shorter.

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References and notes

1. (a) Foulstone, E.; Prince, S.; Zaccheo, O.; Burns, J. L.; Harper, J.; Jacobs, C.; Church, D.; Hassan, A. B. *J. Pathol.* **2005**, *205*, 145. and the references cited therein; (b) Larsson, O.; Girnita, A.; Girnita, L. *Br. J. Cancer* **2005**, *92*, 2097. and the references cited therein; (c) Yee, D. *Br. J. Cancer* **2006**, *94*, 465. and the references cited therein.
2. (a) Garcia-Echeverria, C. Small-molecule Receptor Tyrosine Kinase Inhibitors in Targeted Cancer Therapy. In *Oncogenomics Handbook*; Humana Press Inc.: Totowa, NJ, USA, 2005; p 531 (and the references cited therein); (b) Mitsiades, C. S.; Mitsiades, N. *Expert Rev. Anticancer Ther.* **2005**, *5*, 487. and the references cited therein.
3. Haluska, P.; Carboni, J. M.; Loegering, D. A.; Lee, F. Y.; Wittman, M.; Saulnier, M. G.; Frennesson, D. B.; Kalli, D. A.; Conover, C. A.; Attar, R. M.; Kaufmann, S. H.; Gottardis, M.; Erlichman, C. *Cancer Res.* **2006**, *66*, 362. and the references cited therein.
4. Ma, J.; Pollak, M. N.; Giovannucci, E.; Chan, J. M.; Tao, Y.; Hennekens, C. H.; Stampfer, M. J. J. *Natl. Cancer Inst.* **1999**, *91*, 620.
5. (a) Hankinson, S. E.; Willett, W. C.; Colditz, G. A.; Hunter, D. J.; Michaud, D. S.; Deroo, B.; Rosner, B.; Speizer, F. E.; Pollak, M. *Lancet* **1998**, *351*, 1393; (b) Martin, J. L. In *Insulin-Like Growth Factors*; LeRoith, D., Zumkeller, W., Baxter, R. C., Eds.; Landes Bioscience: Georgetown, TX, 2003; p 367.
6. Chan, J. M.; Stampfer, M. J.; Giovannucci, E.; Gann, P. H.; Ma, J.; Wilkinson, P.; Hennekens, C. H.; Pollak, M. *Science* **1998**, *279*, 563.
7. Wolk, A.; Mantzoros, C. S.; Andersson, S. O.; Bergstrom, R.; Signorello, L. B.; Lagiou, P.; Adami, H. O.; Trichopoulos, D. J. *Natl. Cancer Inst.* **1998**, *90*, 911.
8. Yu, H.; Spitz, M. R.; Mistry, J.; Gu, J.; Hong, W. K.; Wu, X. J. *Natl. Cancer Inst.* **1999**, *91*, 151.
9. (a) Mitsiades, C. S.; Mitsiades, N. S.; McMullan, C. J.; Poulaki, V.; Shringarpure, R.; Akiyama, M.; Hideshima, T.; Chauhan, D.; Joseph, M.; Libermann, T. A.; Garcia-Echeverria, C.; Pearson, M. A.; Hofmann, F.; Anderson, K. C.; Kung, A. L. *Cancer Cell* **2004**, *5*, 221; (b) Garcia-Echeverria, C.; Pearson, M. A.; Marti, A.; Meyer, T.; Mestan, J.; Zimmermann, J.; Gao, J.; Brueggen, J.; Capraro, H. G.; Cozens, R.; Evans, D. B.; Fabbro, D.; Furet, P.; Porta, D. G.; Liebetanz, J.; Martiny-Baron, G.; Ruetz, S.; Hofmann, F. *Cancer Cell* **2004**, *5*, 231.
10. Blum, G.; Gazit, A.; Levitzki, A. *J. Biol. Chem.* **2003**, *278*, 40442.
11. Girnita, A.; Girnita, L.; del Prete, F.; Bartolazzi, A.; Larsson, O.; Axelson, M. *Cancer Res.* **2004**, *64*, 236.
12. Wittman, M.; Carboni, J.; Attar, F.; Balasubramanian, B.; Balimane, P.; Brassil, P.; Beaulieu, F.; Chang, C.; Clarke, W.; Dell, J.; Eummer, J.; Frennesson, D.; Gottardis, M.; Greer, A.; Hansel, S.; Hurlburt, W.; Jacobson, B.; Krishnananthan, S.; Lee, F. Y.; Li, A.; Liu, P.; Ouellet, C.; Sang, X.; Saulnier, M.; Stoffan, K.; Sun, Y.; Velaparthi, U.; Vyas, D.; Wong, H.; Yang, Z.; Zimmermann, K.; Zoeckler, M. *J. Med. Chem.* **2005**, *48*, 5639.
13. (a) Wittman, M. D.; Balasubramanian, N.; Velaparthi, U.; Zimmermann, K.; Saulnier, M. G.; Liu, P.; Sang, X.; Frennesson, D. B.; Stoffan, K. M.; Tarrant, J. G.; WO 2002/079192 A1.; (b) Wittman M. D.; Balasubramanian N.; Velaparthi U.; Zimmermann K.; Saulnier M. G.; Liu P.; Sang X.; Frennesson D. B.; Stoffan K. M.; Tarrant J. G.; Marinier A.; Roy S.; WO 2004/031401 A2.
14. Velaparthi, U.; Liu, P.; Balasubramanian, B.; Carboni, J.; Attar, R.; Gottardis, M.; Li, A.; Greer, A.; Zoeckler, M.; Wittman, M. D.; Vyas, D. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3072.
15. Velaparthi, U.; Wittman, M.; Liu, P.; Stoffan, K.; Zimmermann, K.; Sang, X.; Carboni, J.; Li, A.; Attar, R.; Gottardis, M.; Greer, A.; Chang, C. Y.; Jacobsen, B. L.; Sack, J. S.; Sun, Y.; Langley, D. R.; Balasubramanian, B.; Vyas, D. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2317.

16. Wittman, M. D.; Balasubramanian, B.; Stoffan, K.; Velaparthi, U.; Liu, P.; Krishnanathan, S.; Carboni, J.; Li, A.; Greer, A.; Attar, R.; Gottardis, M.; Chang, C.; Jacobson, B.; Sun, Y.; Hansel, S.; Zoeckler, M.; Vyas, D. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 974.
17. Compounds **3** and **5** have high rates of metabolism in mouse liver microsomes (>0.20 nmol/min/mg). Compounds **1**, **2**, **4**, **6**, **10**, **11**, and **13** have moderate rates (0.10–0.20 nmol/min/mg), Compounds **7**, **8**, **9**, and **14**–**25** have low rates (<0.10 nmol/min/mg). We do not have data for **12**.
18. For example: pK_a for ethylamine = 10.81, 2-methoxyethylamine = 9.89 *Data from CRC Handbook of Chemistry and Physics*; Weast, R. C., Astle, M. J., Beyer, W. H., Eds., 66th ed.; CRC Press: Boca Raton, FL, 1986.
19. IGF-IR kinase and IR kinase have an overall 84% sequence identity, but 100% identity of the amino acids lining the ATP-binding cleft: Fevelyukis, S.; Till, J. H.; Hubbard, S. R.; Miller, W. T. *Nat. Struct. Biol.* **2001**, *8*, 1058.
20. Incomplete conversion even with high catalyst loads, difficult purifications.
21. Toussaint, O.; Capdevielle, P.; Maumy, M. *Tetrahedron* **1984**, *40*, 3229.
22. Fang, F. G.; Xie, S.; Lowery, M. W. *J. Org. Chem.* **1994**, *59*, 6142.
23. It is possible that the spiroketal re-forms upon evaporation of volatiles out of the acidic crude reaction mixture.
24. From 1,1,2-trimethoxyethane by heating to 80 °C in aq HCl for 5 min.