Bioorganic & Medicinal Chemistry Letters 21 (2011) 1447–1451

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

3,5-Diarylazoles as novel and selective inhibitors of protein kinase D

Gabriel G. Gamber [a,*], Erik Meredith [a], Qingming Zhu [a], Wanlin Yan [a], Chang Rao [a], Michael Capparelli [a], Robin Burgis [a], Istvan Enyedy [a], Ji-Hu Zhang [a], Nicolas Soldermann [a], Kimberley Beattie [a], Olga Rozhitskaya [a], Keith A. Koch [b], Nikos Pagratis [b], Vinayak Hosagrahara [a], Richard B. Vega [a], Timothy A. McKinsey [b], Lauren Monovich [a]

[a] Novartis Institutes for BioMedical Research, Cambridge, MA 02139, USA
[b] Gilead Colorado, Inc., Boulder, CO 80301, USA

ARTICLE INFO

Article history:
Received 20 May 2010
Revised 5 January 2011
Accepted 6 January 2011
Available online 11 January 2011

Keywords:
Kinase inhibitor
PKD
Protein kinase D
Histone deacetylase
Heart failure
Cardiac hypertrophy

ABSTRACT

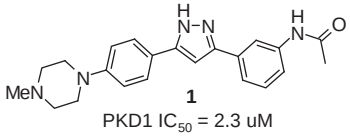
The synthesis and preliminary studies of the SAR of novel 3,5-diarylazole inhibitors of Protein Kinase D (PKD) are reported. Notably, optimized compounds in this class have been found to be active in cellular assays of phosphorylation-dependant HDAC5 nuclear export, orally bioavailable, and highly selective versus a panel of additional putative histone deacetylase (HDAC) kinases. Therefore these compounds could provide attractive tools for the further study of PKD / HDAC5 signaling.

Cardiac hypertrophy is a common response to stress signals in the heart that arise from a variety of cardiovascular disorders, including myocardial infarction and chronic hypertension.[1] Prolonged hypertrophy has been recognized as a major determinant of heart failure,[2] a disease of increasing prevalence and high morbidity and mortality.

Recently, it has been reported that histone deacetylase 5 (HDAC5), acts as a signal responsive repressor of cardiac hypertrophy when it is co-localized with transcription factors, such as MEF2, in the nucleus.[3] In response to stress signals, phosphorylation of HDAC5 by one or more HDAC kinases triggers its export from the nucleus into the cytoplasm and releases the repression of MEF2 responsive genes.[4] This is accompanied by an increase in cardiomyocyte cell size, assembly of sarcomeres, and the activation of a 'fetal' program of gene expression, leading to pathological cardiac hypertrophy. Protein kinase D 1 (PKD1) has been implicated as an HDAC kinase mediating the subcellular localization and signaling of HDAC5 in cardiac tissue.[5,6] Therefore, inhibition of PKD1 would be predicted to block the nuclear export of HDAC5 and blunt the hypertrophic response to stress in cardiac tissue, potentially providing a novel therapy for heart failure.

High throughput screening against recombinant PKD1 identified 3,5-diarylpyrazole **1** as a novel kinase inhibitor scaffold with moderate activity (Figure 1). The synthesis and preliminary SAR studies of benzamide analogs of this chemotype, which resulted in the development of potent, selective, and orally available small molecule inhibitors of PKD, are reported herein.[7]

The synthesis of 3,5-diarylazole PKD inhibitors is shown in Schemes 1–5. The 3,5-diarylpyrazole core[8] of compounds **4a** (Scheme 1), **4b** (Scheme 4), and **4c** (Scheme 5) was constructed via Claisen condensation of a suitably substituted acetophenone (**2a–c**) and dimethyl isophthalate **3**, followed by further condensation of the resultant diketone with hydrazine. Analogously, 3,5-diarylisoxazoles[9] could be formed by reaction of the diketone products of the Claisen condensation with hydroxylamine (not shown). However, this approach generally resulted in mixtures of 3,5-isoxazole regioisomers. Therefore, the 3,5-diarylisoxazole core of compounds **10a** (Scheme 3) and **10b** (Scheme 5) was constructed through the [3+2] cycloaddition of nitrile *N*-oxides (formed in situ from hydroximoyl chlorides **8a–b**) with substituted phenylacetylenes **9a–b**, which provided isoxazoles as single, predictable, isomers.



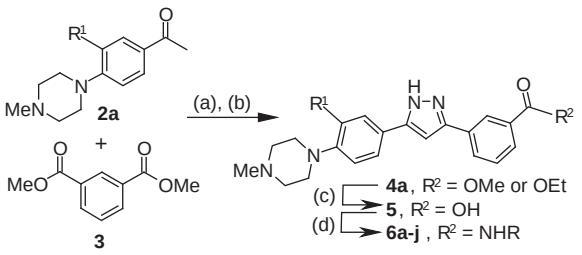
1

PKD1 IC_{50} = 2.3 uM

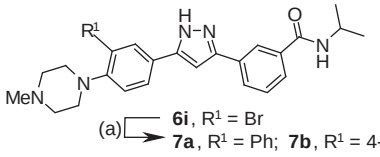
Figure 1. Initial 3,5-diarylazole hit.

* Corresponding author.
E-mail address: gabriel.gamber@novartis.com (G.G. Gamber).

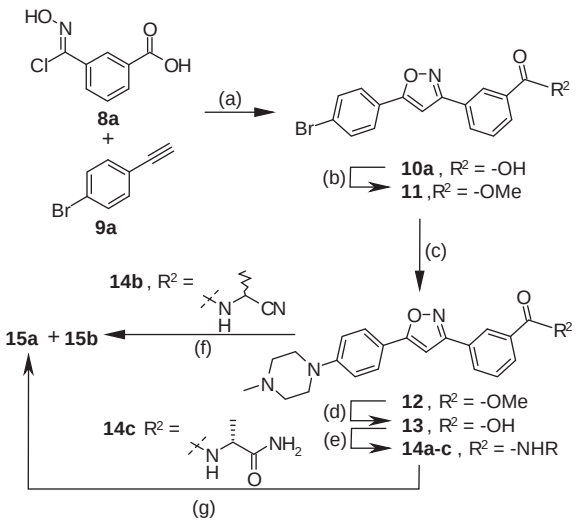
0960-894X/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2011.01.014



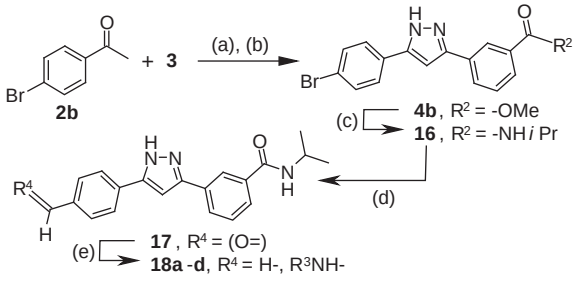
Scheme 1. R and R^1 are defined in Table 1. Reagents: (a) NaH, THF or NaOEt, EtOH; (b) hydrazine, EtOH; (c) LiOH, THF:H_2O; (d) HATU, R-NH_2, DiPEA, DMF.



Scheme 2. Reagents and conditions: (a) Aryl$B(OH)_2$, Pd(dppf)Cl_2, K_2CO_3 (aq), 1:10 EtOH in PhMe, 110 °C.



Scheme 3. Unless otherwise indicated, R is defined in Table 1. Reagents and conditions: (a) DiPEA, CH_2Cl_2; (b) TMSCl, MeOH; (c) Pd$(OAc)_2$, BINAP, $Cs(CO_3)_2$, PhMe, reflux; (d) LiOH, THF:H_2O; (e) HATU, R-NH_2, DiPEA, DMF; (f) Chiral HPLC, Chiralpak IA column, 0.2% TEA:1% EtOH; ACN; (g) TFAA, Et_3N.



Scheme 4. Substituent R^3 is defined in Table 2. Reagents and conditions: (a) NaH, THF; (b) hydrazine, DiPEA; (c) $AlMe_2$, $NH_2(iPr)$; (d) i) BuLi, −78 °C; (ii) DMF, −78 °C; (e) NH_2-R^3, $Na(OAc)_3BH$.

Further elaboration of pyrazole ester **4a** to compounds **6a–j** was achieved through saponification to carboxylate **5**, followed by HATU mediated amide bond formation (Scheme 1).[10] Compounds **7a–b** were synthesized by a further Suzuki–Miyaura coupling of the bromide of **6i** with the respective aryl boronic acid (Scheme 2).[11]

Synthesis of the piperazine-containing isoxazole compounds **14a–c** (Scheme 3) required protection of bromo-acid **10a** as a methyl ester (**11**) before installation of the piperazine ring using Buchwald–Hartwig amination[12] conditions to provide intermediate **12**. By analogy to the route illustrated in Scheme 1, isoxazole ester **12** was saponified to provide carboxylic acid **13**, which could be coupled with amines to provide amides **14a–c**. Chiral, non-racemic compounds **15a–b** were resolved from the racemate **14b** by standard HPLC techniques on a chiral stationary phase. Alternatively, dehydration of chiral, non-racemic D-alanine amide **14c** proceeded with complete retention of enantiopurity to provide **15a**.[13] In addition to providing convenient access to enantiomerically pure (>98% ee) materials from a chiral pool source, this orthogonal strategy also allowed the assignment of the absolute stereochemistry of the aminonitrile enantiomers.

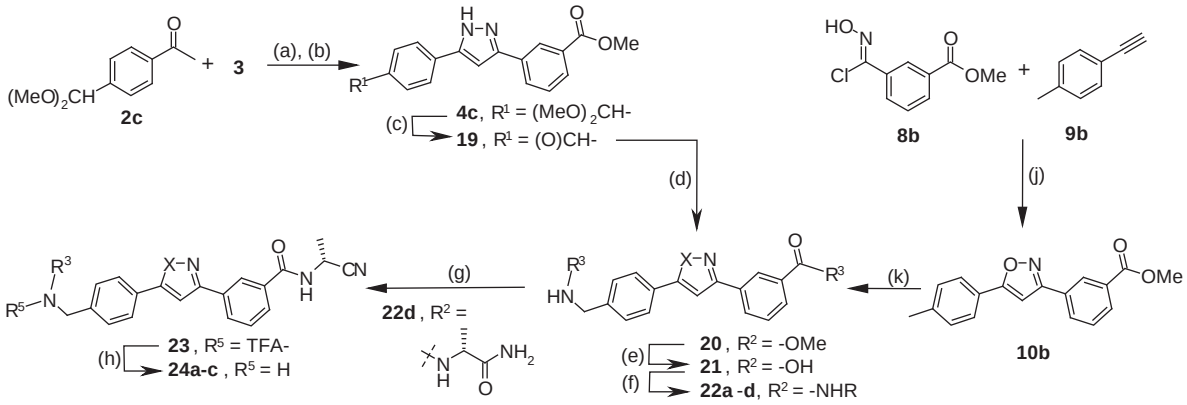
Pyrazole compounds **18a–d**, in which the piperazine ring has been replaced with a benzylic amine, were synthesized from bromo ester **4b** (Scheme 4). Amidation of the methyl ester was mediated by trimethylaluminum[14] to afford bromo-amide **16**. Lithium–halogen exchange followed by quenching with DMF provided aldehyde **17**, which was converted to benzylic amines **18a–d** by reductive amination. The benzylic amine of pyrazole **20** (Scheme 5, X = NH) was installed through an alternate sequence starting from dimethyl acetal **4c**. Hydrolysis of the acetal with aqueous acid provided aldehyde **19**, which was converted to a benzylic amine by reductive amination. Benzylamine-substituted isoxazole **20** (Scheme 5, X = O), was synthesized from compound **10b** by radical bromination of the tolyl group with NBS, followed by trapping of the benzyl bromide intermediate with amines.

Saponification of the methyl ester of **20** (Scheme 5, X = N or O) to carboxylate **21**, followed by amide bond formation provided compounds **22a–d**. Further transformation of the D-alanine amide of **22d** by dehydration with trifluoroacetic anhydride provided aminonitrile **23**, in which the benzylic amine was simultaneously protected by trifluoroacetic anhydride. The resulting trifluoroacetamide could be removed cleanly and chemoselectively by treatment with sodium borohydride in methanol[15] to provide compounds **24a–c** in excellent enantiopurity (>98% ee). Compound **24d**, the enantiomer of compound **24c**, was synthesized by the same methods and in similar enantiopurity by substituting L-alanine amide in the amide bond formation step from acid **21**.

Preliminary structure–activity relationship (SAR) data is provided in Tables 1 and 2. In general, equivalently substituted pyrazole- and isoxazole-derived compounds show similar potency as PKD1 inhibitors (cf. Table 1, **6c**, **14a**; Table 2, **24a**, **24b**).

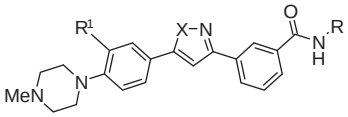
In order to improve the moderate PKD1 inhibitory potency observed with **1** (Figure 1), a series of varied benzamide derivatives were synthesized (Table 1, **6a–i**). Alkyl amides (**6a–b**) show potency against PKD1 similar to **1**. However, an α-aminonitrile amide (**6c**) provides a significant (~18-fold) improvement in potency. While the nature of the interaction of the nitrile with the PKD1 binding site is unknown, the effect of this substituent appears to be quite specific, as amide substituents bearing other polar and/or hydrogen bond-accepting functionality (**6e–h**), or even an additional methylene spacer (β-aminonitrile **6d**), uniformly fail to provide increases in potency similar to the α-aminonitrile, and are, in some cases, even detrimental to PKD1 inhibitory activity compared to a simple alkyl amide (**6a–b**). The beneficial effect of the α-aminonitrile is also observed with the 3,5-diarylisoxazole core (**14a**, also cf. **22a**, **22b**).

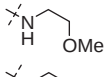
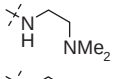
Notably, a modest but consistent increase in potency is observed with addition of α-branching on the aminonitrile substitu-



Scheme 5. Unless otherwise indicated, substituents R, R^3, and X are defined in Table 2. Reagents and conditions: (a) NaH, THF; (b) hydrazine, DiPEA; (c) TFA, H_2O:DCM; (d) NH_2-R^3, $Na(OAc)_3BH$, DCM; (e) LiOH, H_2O:THF; (f) NH_2-R, HATU, DiPEA, DMF; (g) TFAA, TEA, THF; (h) $NaBH_4$, MeOH; (j) DiPEA, DCM; (k) (i) NBS, AIBN, CCl_4, reflux; (ii) NH_2-R^3.

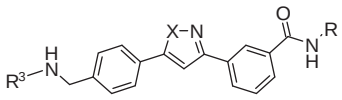
Table 1
PKD1 inhibitory activity, microsomal stability, and solubility of 3,5-diarylazoles[a]

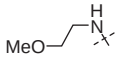
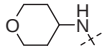
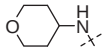
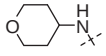
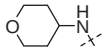
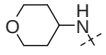


Compd	-NHR	R^1-	-X-	PKD1 IC_{50} (μM)	RLM $t_{1/2}$ (min)	Sol (μM)
6a		-H	–NH–	2.5	4	330
6b		-H	–NH–	1.0	3	270
6i		-Br	–NH–	0.28	5	40
7a		-Ph	–NH–	0.98	22	<10
7b		-4-Py	–NH–	0.20	51	<10
6c		-H-	–NH–	0.14	3	50
6j		-Br	–NH–	0.087	9	<10
6d		-H	–NH–	0.75	4	650
6e		-H	–NH–	6.9	4	760
6f		-H	–NH–	1.6	11	170
6g		-H	–NH–	2.0	11	>960
6h		-H	–NH–	1.1	2	170
14a		-H	–O–	0.20	<2	<10
15a		-H	–O–	0.060	<2	<10
15b		-H	–O–	0.43	<2	<10

[a] All in vitro assay results reported as mean of $n \geqslant 2$ experiments.

Table 2
PKD1 inhibitory activity, microsomal stability, and solubility of 3,5-diarylazoles[a]



Compd	-NHR	(R^3)NH-	-X-	PKD1 IC_{50} (μM)	RLM $t_{1/2}$ (min)	Sol (μM)
18a			–NH–	0.10	107	>970
18b			–NH–	0.43	67	910
18c			–NH–	0.39	16	220
18d			–NH–	6.0	21	<10
24a			–NH–	0.0037	>198	>990
24b			–O–	0.009	54	>870
22a			–O–	0.22	41	140
22b			–O–	0.019	>176	170
22c			–O–	0.049	40	70
24c			–O–	0.0055	144	240
24d			–O–	0.095	58	110

[a] All in vitro assay results reported as mean of $n \geqslant 2$ experiments.

ent (cf. Table 1, **14a**, **15a**; Table 2, **22b**, **24c**). This effect is stereospecific, with the *R*-nitrileamide inhibiting PKD1 more potently than the *S*-enantiomer (cf. Table 1, **15a**, **15b**; Table 2, **24c**, **24d**). Consistent with this observation, α,α′-dimethylation provides observed potency intermediate to the two mono-methyl enantiomers (cf. Table 2, **22c**, **24c** and **24d**).

With compounds bearing a methylpiperazine moiety (Table 1) poor metabolic stability in liver microsomes was generally observed,[16] presumably due to oxidation of the piperazine ring. This metabolism can be moderated by the introduction of sterically bulky R^1 groups on the aromatic core *ortho*- to the piperazine ring, and, in some cases, these modifications also provide an increase in PKD1 inhibitory potency (cf. **6b**, **6i**, **7a**–**b**; **6c**, **6j**). However, this solution is less than ideal, as increasing the size of R^1 also results in reduced solubility,[17] to undetectable levels in some cases.

Modification of the linker between the basic amine moiety and the aromatic core proved to be a more effective solution to balancing potency, metabolic stability, and solubility. Notably, when the piperazine (Table 1) is replaced with a benzylic amine (Table 2) a significant improvement in all three of these parameters is observed (cf. **6b**, **18a**; **14a**, **22b**; **15a**, **24b** and **24c**). These effects might be partially due to the increased basicity of the benzylic amine versus the aryl piperazine, as, consistent with this interpretation, substituents that would reduce the pK_a of the benzylic amine, such as cyclopropyl (**18c**), methoxyethyl (**18b**), or trifluoroethyl (**18d**), generally result in attenuated inhibition of PKD1, reduced metabolic stability, and reduced solubility.

Table 3
PKD inhibitor **24c** is highly selective against a panel of additional putative *h*HDAC kinases

Kinase	% inhibition at 1 μM[a]	IC_{50}[b] (μM)
*h*PKD1	94	0.0055
*h*PKD2	85	0.048
*h*PKD3		0.017
*h*CaMKIδ	0	
*r*CaMKIIα	−2	
*h*CaMKIIβ	22	
*h*CaMKIIδ	37	>7.9[c]
*h*CaMKIV	26	
*h*MARK1	29	
*h*SIK1	15	
*h*GRK5	−4	
*h*PKCδ	−9	
*h*PKCε	−2	

[a] Mean of $n = 2$ measurements, inhibition assays conducted by Milllipore (http://www.millipore.com/drugdiscovery/dd3/KinaseProfiler).
[b] Mean of $n \geqslant 2$ experiments.
[c] Values of 5.7 μM, >10 μM were obtained.

Combination of the *R*-α-aminopropionitrile amide substituent with benzylic basic amine substituents identified through our SAR studies resulted in compounds with low nanomolar potencies against PKD1, good in vitro metabolic stability, and moderate to excellent solubility (**24a**–**c**).

Isoxazole compound **24c** was further profiled against a panel of kinases that have been implicated in the regulation of HDAC sub-

Table 4
PKD1 inhibitors block HDAC5 nuclear export (EC_{50} >1 μM observed with other compounds in Tables 1 and 2)[a]

Compd	EC_{50} (μM)
6j	0.68
15a	0.57
24a	0.53
24b	0.46
24c	0.24

[a] Mean of $n \geqslant 2$ experiments.

Table 5
Pharmacokinetic parameters for compound **24c**[a]

$AUC_{0\text{-}8h}$ (nM h)	840 ± 80
CL (mL/min/kg)	93 ± 9
Vd_{ss} (L/kg)	6.0 ± 1.4
$t_{1/2}$ (h)	1.2 ± 0.1
F (%)	38

[a] Sprague–Dawley rat PK. Animals were dosed either iv (2 mg/kg, $n = 2$) or po (5 mg/kg, $n = 3$) with compound in 10% NMP, 10% Cremophor, 80% pH 4.63 buffer vehicle. PK parameters derived from iv dosing, and are reported as mean ± SD.

cellular localization and signaling (Table 3).[6,18] This compound was found to inhibit all PKD family members with nanomolar IC_{50}s, although with 9-fold and 3-fold selectivity for PKD1 versus PKD2 and PKD3, respectively. Notably, compound **24c** appears to be >1000-fold selective versus other members of the panel. Further, in a wider panel of 230 kinases, compound **24c** inhibited only 4 with >50% efficacy at 1 μM. Therefore, the observed sub-micromolar inhibition of the phosphorylation-dependant nuclear export of GFP-HDAC5 over-expressed in neonatal rat ventricular myocytes (NRVMs)[5a,7a,b] is consistent with inhibition of PKD family members in the cellular environment by this compound, and, by extension, other compounds of this series (Table 4).

Pharmacokinetic studies in rats (Table 5) indicate that compound **24c** is orally available (38% F) with a relatively short plasma $t_{1/2}$ (Table 5). The large volume of distribution observed with this compound suggests distribution to peripheral tissues, potentially driven by the basicity of the benzylic amine ($pK_a = 7.7$).

In summary, a novel 3,5-diarylazole PKD inhibitor chemotype has been identified. SAR studies have allowed the development of compounds with low nanomolar potency against the isolated enzyme, sub-micromolar activity in a cellular assay of PKD signaling, and impressive selectivity against a panel of additional kinases (including putative HDAC kinases). As such, these compounds could provide excellent tools for the further study of PKD signaling.

Acknowledgments

We thank Patrick Cronan for high resolution mass spectrometry data, the NIBR Analytical Sciences group for LC–MS and NMR support, and the NIBR Metabolism and Pharmacokinetics group for in vitro solubility and liver microsome stability data, as well as in vivo and bioanalytical support for pharmacokinetic studies.

Supplementary data

Supplementary data (experimental details for the PKD1 and HDAC export assays and characterization data for compounds **6a–j**, **7a–b**, **14a–b**, **15a–b**, **18a–d**, **22a–c**, and **24a–d**) associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2011.01.014.

References and notes

1. (a) McKinsey, T. A.; Kass, D. A. *Nat. Rev. Drug Disc.* **2007**, *6*, 617; (b) Mann, D. L.; Bristow, M. R. *Circulation* **2005**, *111*, 2837; (c) MacLellan, W. R.; Schneider, M. D. *Ann. Rev. Physiol.* **2000**, *62*, 289.
2. (a) Gosse, P. *J. Hypertens.* **2005**, *23*, S27; (b) Frey, N.; Katus, H. A.; Olson, E. N.; Hill, J. A. *Circulation* **2004**, *109*, 1580; (c) Gardin, J. M.; Lauer, M. S. *JAMA* **2004**, *292*, 2343; (d) Frey, N.; Olson, E. N. *Ann. Rev. Physiol.* **2003**, *65*, 45.
3. (a) Zhang, C. L.; McKinsey, T. A.; Chang, S.; Antos, C. L.; Hill, J. A.; Olson, E. N. *Cell* **2002**, *110*, 479; (b) Chang, S.; McKinsey, T. A.; Zhang, C. L.; Richardson, J. A.; Hill, J. A.; Olson, E. N. *Mol. Cell. Biol.* **2004**, *24*, 8467.
4. Grozinger, C. M.; Scheiber, S. L. *Proc. Nat. Acad. Sci.* **2000**, *97*, 7835.
5. (a) Monovich, L.; Vega, R. B.; Meredith, E.; Miranda, K.; Rao, C.; Capparelli, M.; Lemon, D. D.; Phan, D.; Koch, K. A.; Chapo, J. A.; Hood, D. B.; McKinsey, T. A. *FEBS Lett.* **2010**, *584*, 631; (b) Vega, R. B.; Harrison, B. C.; Meadows, E.; Roberts, C. R.; Papst, P. J.; Olson, E. N.; McKinsey, T. A. *Mol. Cell. Biol.* **2004**, *24*, 8374; (c) Rykx, A.; De Kempe, L.; Mikhalap, S.; Vantus, T.; Seufferlein, T.; Vandenheede, J. R.; Van Lint, J. *FEBS Lett.* **2003**, *546*, 81.
6. McKinsey, T. A. *Cardiovasc. Res.* **2007**, 667.
7. For other small molecule inhibitors of PKD, see: (a) Meredith, E. L.; Ardayfio, O.; Beattie, K.; Dobler, M.; Enyedy, I.; Gaul, C.; Hosagrahara, V.; Jewell, C.; Koch, K.; Lee, W.; Lehmann, H.; McKinsey, T. A.; Miranda, K.; Pagratis, N.; Pancost, M.; Patnaik, A.; Phan, D.; Plato, C.; Qian, M.; Rajaramna, V.; Rao, C.; Rozhitskaya, O.; Ruppen, T.; Shi, J.; Siska, S. J.; Springer, C.; van Eis, M.; Vega, R. B.; von Matt, A.; Yang, L.; Yoon, T.; Zhang, J.-H.; Zhu, N.; Monovich, L. G. *J. Med. Chem.* **2010**, *53*, 5422; (b) Meredith, E. L.; Beattie, K.; Burgis, R.; Capparelli, M.; Chapo, J.; DiPietro, L.; Gamber, G.; Enyedy, I.; Hood, D. B.; Hosagrahara, V.; Jewell, C.; Koch, K. A.; Lee, W.; Lemon, D. D.; McKinsey, T. A.; Miranda, K.; Pagratis, N.; Phan, D.; Plato, C.; Rao, C.; Rozhitskaya, O.; Soldermann, N.; Springer, C.; van Eis, M.; Vega, R. B.; Yan, W.; Zhu, Q.; Monovich, L. G. *J. Med. Chem.* **2010**, *53*, 5400; (c) Sharlow, E. R.; Giridhar, K. V.; LaValle, C. R.; Chen, J.; Leimgruber, S.; Barrett, R.; Bravo-Altamirano, K.; Wipf, P.; Lazo, J. S.; Wang, Q. J. *J. Biol. Chem.* **2008**, *283*, 33516; (d) Gschwendt, M.; Kittstein, W.; Johannes, F.-J. *FEBS Lett.* **1998**, *421*, 165; (e) Gschwendt, M.; Dietrich, S.; Rennecke, J.; Kittstein, W.; Mueller, H.-J.; Johannes, F.-J. *FEBS Lett.* **1996**, *392*, 77; (f) Singh, R.; Li, H.; Zhao, H.; Payan, D. G.; Kolluri, R.; Tso, K.; Ramphal, J.; Gu, S. WO 2009012421.; (g) Yokoyama, S. WO 2008088006.; (h) Raynham, T. M.; Hammonds, T. R.; Charles, M. D.; Pave, G. A.; Foxton, C. H.; Blackaby, W. P.; Stevens, A. P.; Ekwuru, C. T. WO 2008074997.; (i) Raynham, T. M.; Hammonds, T. R.; Gilliat, J. H.; Charles, M. D.; Pave, G. A.; Foxton, C. H.; Carr, J. L.; Mistry, N. S. WO 2007125331.
8. For reviews of pyrazoles, see: (a) Yet, L. In *Comprehensive Heterocyclic Chemistry III*; Joule, J. A., Ed.; Elsevier: Oxford, 2008; Vol. 4, p 1; (b) Makino, K.; Kim, H. S.; Yoshihisa, K. *J. Heterocycl. Chem.* **1999**, *36*, 321; (c) Elguero, J. In *Comprehensive Heterocyclic Chemistry II*; Shinkai, I., Ed.; Elsevier: Oxford, 1996; Vol. 3, p 1; (d) Kost, A. N.; Grandberg, I. I. *Adv. Heterocycl. Chem.* **1966**, *6*, 347.
9. For reviews of isoxazoles, see: (a) Giomi, D.; Cordero, F. M.; Machetti, F. In *Comprehensive Heterocyclic Chemistry III*; Joule, J. A., Ed.; Elsevier: Oxford, 2008; Vol. 4, p 365; (b) Pinho e Mehlo, T. M. V. D. *Curr. Org. Chem.* **2005**, *9*, 925; (c) Sutharchandevi, M.; Murugan, R. In *Comprehensive Heterocyclic Chemistry II*; Shinkai, I., Ed.; Elsevier: Oxford, 1996; Vol. 3, p 221; (d) Wakefield, B. J.; Wright, D. J. *Adv. Heterocycl. Chem.* **1979**, *25*, 147; (e) Kochetkov, N. K.; Sokolov, S. D. *Adv. Heterocycl. Chem.* **1963**, *2*, 365.
10. Speicher, A.; Klaus, T.; Eicher, T. *J. Prakt. Chem.* **1998**, *340*, 581.
11. (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457; (b) Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, 2419; (c) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461.
12. (a) Tasler, S.; Mies, J.; Lang, M. *Adv. Synth. Catal.* **2007**, *349*, 2286; (b) Hartwig, J. F. *Synlett* **2006**, 1283; (c) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131.
13. (a) Campagna, F.; Carotti, A.; Casini, G. *Tetrahedron Lett.* **1977**, *21*, 1813; (b) Altmann, E.; Betschart, C.; Buhl, T.; Green, J.; Lattmann, R.; Missbach, M. *Bioorg. Med. Chem. Lett.* **2006**, 2549.
14. Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, *18*, 4171.
15. Weygland, F.; Frauendorfer, E. *Chem. Ber.* **1970**, *103*, 2437.
16. Lau, Y. Y.; Krishna, G.; Yumibe, N. P.; Grotz, D. E.; Sapidou, E.; Norton, L.; Chu, I.; Chen, C.; Soares, A. D.; Lin, C. C. *Pharm. Res.* **2002**, *19*, 1606. Compounds were incubated at 1 μM in 96-well assay plates with rat liver microsomes and selected cofactors. Half-life is determined by the measurement of test compound concentration at four time points.
17. Zhou, L.; Yang, L.; Tilton, S.; Wang, J. *J. Pharm. Sci.* **2007**, *96*, 3052.
18. (a) Berdeaux, X.; Goebel, N.; Banaszynski, L.; Takemori, H.; Wandless, T.; Shelton, G. D.; Montminy, M. *Nat. Med.* **2007**, *13*, 597; (b) Martini, J. S.; Raake, P.; Vinge, L. E.; DeGeorge, B. R., Jr.; Chuprun, J. K.; Harris, D. M.; Gao, E.; Eckhart, A. D.; Pitcher, J. A.; Koch, W. J. *Proc. Natl. Acad. Sci.* **2008**, *105*, 12457.