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Discovery of dihydrothieno- and dihydrofuropyrimidines as potent pan Akt inhibitors

Josef R. Bencsik [a,*], Dengming Xiao [a], James F. Blake [a], Nicholas C. Kallan [a], Ian S. Mitchell [a], Keith L. Spencer [a], Rui Xu [a], Susan L. Gloor [a], Matthew Martinson [a], Tyler Risom [a], Richard D. Woessner [a], Faith Dizon [a], Wen-I Wu [a], Guy P. A. Vigers [a], Barbara J. Brandhuber [a], Nicholas J. Skelton [b], Wei Wei Prior [b], Lesley J. Murray [b]

[a] Array BioPharma Inc., 3200 Walnut Street, Boulder, CO 80301, USA
[b] Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080-4990, USA

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ABSTRACT

Herein we report the discovery and synthesis of a novel series of dihydrothieno- and dihydrofuropyrimidines (**2** and **3**) as potent pan Akt inhibitors. Utilizing previous SAR and analysis of the amino acid sequences in the binding site we have designed inhibitors displaying increased PKA and general kinase selectivity with improved tolerability compared to the progenitor pyrrolopyrimidine (**1**). A representative dihydrothieno compound (**34**) was advanced into a PC3-NCI prostate mouse tumor model in which it demonstrated a dose-dependent reduction in tumor growth and stasis when dosed orally daily at 200 mg/kg.

There is a growing wealth of evidence implicating the PI3K pathway in the progression of various forms of cancer.[1] A central player within this pathway is the serine/threonine kinase Akt also known as Protein Kinase B (PKB), which is a member of the AGC family of kinases and shares high homology with PKA and PKC. There are three closely related Akt isoforms, Akt1, Akt2 and Akt3, all of which share greater than 80% sequence identity in the kinase domain.[2] Up-regulation of Akt activity has been shown to be an important mechanism in the development, maintenance and growth of various forms of cancer.[3] As Akt has emerged as an attractive anticancer target, several small molecule Akt inhibitors have recently been reported.[4]

In a previous report we described the discovery of a novel class of pyrrolopyrimidine pan Akt inhibitors (**1**, Fig. 1).[5] Although these compounds exhibited excellent potency against Akt, their progression was impaired due to a lack of tolerability in rodents, which was thought to arise from their overall kinase inhibition profile. Of particular concern were the closely related kinases PKA[6] and Rho-associated kinase (ROCK)[7] both of which are implicated in various cardiovascular processes. In order to address the selectivity profile of compounds such as **1**, we chose to target PKA, since selectivity over this closely related kinase would likely improve the overall kinase selectivity. Our earlier efforts identified a trend that led to improved PKA selectivity, namely increased substitution near the gatekeeper residue.[5] Examination of published[8] and internally generated co-crystal structures of PKA indicated that PKA possesses a smaller, more lipophilic pocket in the hinge region, relative to Akt1 (cf. Fig. 2). We hypothesized that selectivity over PKA could be obtained either by increasing the size of the hinge binding core in this region, or by modulating the polarity. Herein we describe the identification and development of a novel series of

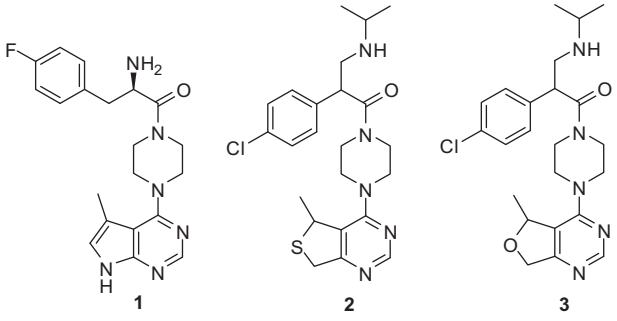

Figure 1. Pan Akt inhibitors featuring the pyrrolo-, dihydrothieno-, and dihydrofuro-pyrimidine cores.

* Corresponding author.
E-mail address: jbencsik@arraybiopharma.com (J.R. Bencsik).

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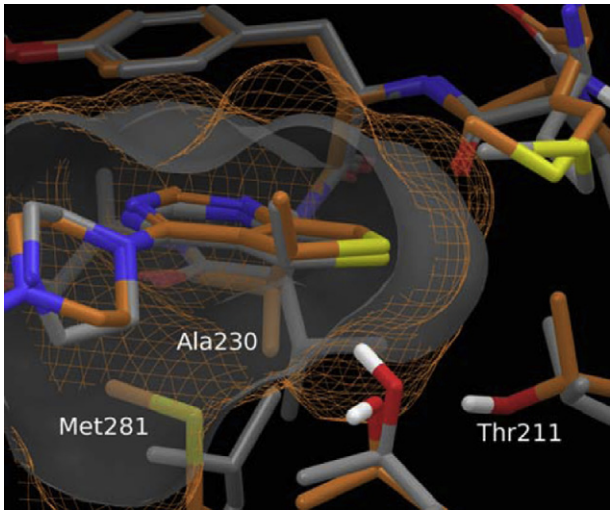


Figure 2. Comparison of the X-ray structures of **26** bound to Akt1 (orange) and PKA (grey). Solvent accessible surfaces depicted, Akt1 numbering used. (PDB code: Akt1—3OW4 and PKA—3OW3)[10]

potent Akt inhibitors with improved selectivity based on the dihydrothieno- (**2**) and dihydrofuropyrimidine scaffolds (**3**).

Synthesis of the requisite pyrimidine cores originated from Michael addition of the corresponding methyl 2-hydroxyacetate or mercaptoacetate **4** with a suitable crotonate ester **5** under mild conditions furnishing bis-ester **6** in near quantitative yield (Scheme 1). Subsequent Dieckmann cyclization to keto-ester **7**, followed by condensation with formamidine in the presence of sodium ethoxide, led to pyrimidinol **8**. Smooth conversion of **8** to chloride **9** was carried out with $POCl_3$ in acetonitrile. Incorporation of the piperazine linker **10** by heating in NMP or *tert*-butyl alcohol, followed by liberation of the protecting group, cleanly afforded **11** as the bis-HCl salt in excellent yield. Enantiomerically pure material was obtained from the racemic mixture via chiral HPLC or SFC separation.

The α- and β-amino acid components reported herein were either derived from commercial sources or synthesized as previously described.[5] Synthesis of the γ-amino acids was achieved as described in Scheme 2. Hydromethylation of the appropriately substituted phenyl acetic esters **12** followed by mesylate activation and elimination afforded acrylates **13** in excellent yields. Introduction of the desired nitroalkane to acrylates **13** in a Michael fashion afforded adducts **14**. Reduction of the nitro group in the presence of excess zinc dust and hydrochloric acid followed by concomitant cyclization and protection to the *tert*-butyl carbamate gave lactams **15**. Hydrolysis of the lactam revealed the desired γ-amino acids **16** in good yield. Subsequent amide coupling of core **11** with the desired amino acid under standard conditions, followed by Boc deprotection under acid conditions afforded the final compounds in excellent yield.

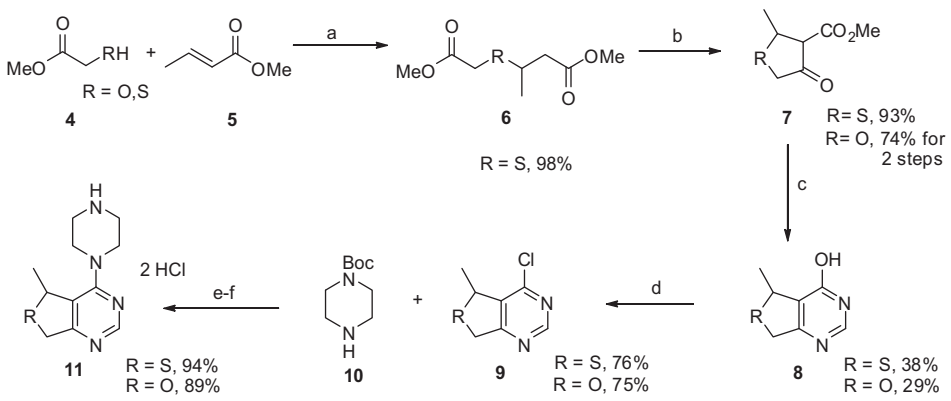
As previously described, compounds were evaluated in several primary in vitro assays: enzyme inhibition of Akt (all three isoforms), PKA (IMAP format), and the cellular inhibition of p-PRAS40 formation in LNCaP cells.[5] Early research focused on the unsubstituted dihydrothieno-pyrimidine **17** containing the 4-Cl phenylalanine amino amide. In accordance with our design hypothesis, **17** showed moderate enzyme and cellular Akt activity and improved PKA selectivity (10-fold) compared to **1** (Table 1). Replacing the sulfur of **17** with a sulfone **18**[9] enhanced the template's selectivity over PKA to 25-fold but lost cellular potency, presumably due to poor cell permeability.

Substitution at the R^2-position (Table 1) of the core with either methyl **19** or ethyl **20** increased potency, with little effect on selectivity, consistent with earlier reported SAR trends in this region of the molecule.[5] Interestingly, the 5-position of the saturated dihydrothieno core affords stereospecific access to the lipophilic pocket. The (*S*)-methyl stereoisomer **21**, by virtue of being able to access this lipophilic pocket, was found to be significantly more potent than the (*R*) isomer **22** with no loss of selectivity over PKA.

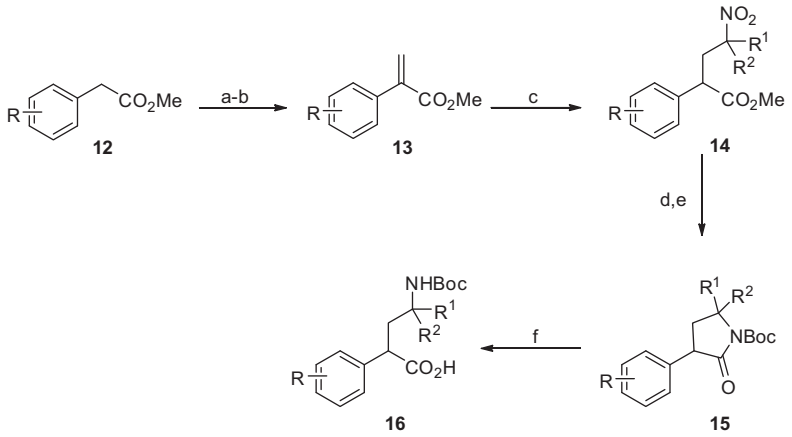
Various phenyl ring substitutions **23**–**25** were investigated at the 3- and 4-positions. As in the pyrrolopyridine series, increased lipophilicity afforded only slight improvements in potency. Despite losing both enzyme and cellular potency, incorporation of an indole **26** demonstrated enhanced PKA selectivity of greater than 35-fold suggesting that the amino amide region also contributes towards selectivity.

In order to address concerns of the possible oxidative liabilities inherent to the dihydrothieno core as well as probe the effects of an oxygen heteroatom on potency and selectivity, several dihydrofuropyrimidine analogs were evaluated. Generally the dihydrofuropyrimidine analogs (**27** vs **21**) were found to be less potent while maintaining PKA selectivity relative to their dihydrothieno counterparts.

X-ray crystallography of the kinase domains of Akt1 and PKA indicates that the dihydrothieno pyrimidine core binds to both enzymes in a similar fashion (Fig. 2). Our strategy for achieving selectivity exploited key differences in the binding pocket between Akt1 and PKA. These subtle changes include a Thr211 (Akt1) to Val (PKA), Met281 (Akt1) to Leu, and Ala230 (Akt1) to Val. These differences produce a narrower cavity in PKA, and should be less forgiving of larger substitutions.[11] Therefore the dihydrothienopyrimidine **17** by virtue of a saturated ring and bulkier sulfur atom near the gatekeeper displays PKA selectivity upwards of 10-fold

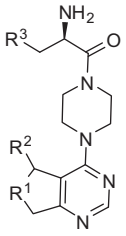


Scheme 1. Reagents and conditions: (a) 1.2 equiv **4**, 0.05 equiv piperidine, neat, rt, 12 h; (b) 1.2 equiv NaOMe, toluene, reflux, 6 h; (c) 1.1 equiv formamidine, 1.0 equiv NaOEt, EtOH, reflux, 12 h; (d) 10 equiv $POCl_3$, CH_3CN, reflux, 2 h; (e) 1.2 equiv **10**, NMP or *tert*-BuOH, 90 °C, 12 h; (f) 5 equiv 4 N HCl in dioxane, DCM, 4 h.



Scheme 2. Reagents and conditions: (a) paraformaldehyde, 10% NaOMe, DMSO, rt, 12 h, 98%; (b) MsCl, 2.5 equiv TEA, DCM, 0 °C to rt, 12 h, 95%; (c) 1.2 equiv $NO_2CHR^1R^2$, 1.2 equiv DBU, CH_3CN, 0 °C to rt, 12 h, 80–95%; (d) 10 equiv Zn dust, 4 equiv concd HCl, EtOH, reflux, 6 h, 80%. (e) 1.1 equiv LHMDS, 1.2 equiv Boc_2O, −78 °C to rt, 3 h, 95%; (f) 3 equiv LiOH–H_2O, THF/MeOH/H_2O (3:1:1), 0 °C to rt, 4 h, 89%.

Table 1
α-Amino amide series SAR



Compound	R^1	R^2	R^3	Akt1 Enz IC_{50}[a] (nM)	PKA Enz IC_{50}[a] (nM)	Akt cell IC_{50} LNCaP[b] (nM)
1	—	—	—	3.0 ± 2	6 ± 2	160 ± 2
17	S	H	4-Cl-Ph	22 ± 6	223 ± 41	3846 ± 100
18	SO_2	H	4-Cl-Ph	52 ± 19	1300 ± 499	21,010 ± 1100
19	S	Me	4-Cl-Ph	4 ± 1	31 ± 5	310 ± 20
20	S	Et	4-Cl-Ph	7 ± 2	52 ± 8	1201 ± 150
21	S	(*S*)-Me	4-Cl-Ph	1 ± 0	13 ± 1	184 ± 89
22	S	(*R*)-Me	4-Cl-Ph	260 ± 61	1710 ± 93	18,469 ± 1198
23	S	(*S*)-Me	3-F, 4-Cl-Ph	2 ± 0	8 ± 2	176 ± 15
24	S	(*S*)-Me	4-F-Ph	11 ± 4	104 ± 25	1592 ± 22
25	S	(*S*)-Me	3,4-DiF-Ph	4 ± 0	30 ± 4	602 ± 35
26	S	(*S*)-Me	3-Indole	22 ± 3	742 ± 69	3629 ± 248
27	O	(*S*)-Me	4-Cl-Ph	7 ± 3	61 ± 6	615 ± 119

Akt2 potency was generally 5–10-fold less than Akt1, while Akt3 potency was generally 3–6-fold less than Akt1 (data not shown).
[a] Values are means of three or more experiments, standard deviation is given.
[b] Values are means of two or more experiments, standard deviation is given.

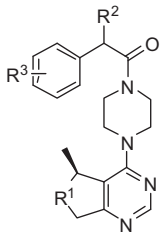
over Akt1 compared to 3-fold for pyrrolopyrimidine (**1**). Oxidation of the sulfide to the sulfone **18** would place an oxygen atom of the sulfone near the hydroxyl side chain of Thr211 in Akt1. By contrast the Val of PKA at this position would place the sulfone oxygen in an unfavorable lipophilic environment, resulting in both a loss of PKA potency and enhanced selectivity to 25-fold. In order to capitalize on the amino amide contribution towards selectivity, several substituted β-amino amides were prepared (Table 2). In contrast to the cyclopropyl primary amine **28**, the secondary **29** and tertiary **30** amines demonstrated excellent enzyme and cellular potency, with greater than 25-fold PKA selectivity.

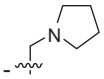
Only modest changes in potency were observed through different phenyl substituent with the 4-methyl **31** and 4-Cl **29** found to be nearly equipotent. The 3-F, 4-Cl **32** substituent exhibited a slight improvement in the cellular potency at the expense of selectivity, the less lipophilic 3,4-diF **33** lost potency, while retaining selectivity. Similar to our earlier report[5] the (*S*)-β amino stereochemistry of **34** was found to be significantly more potent than the (*R*) isomer **35**.[12]

Further carbon extension of the β-amino amides to provide the γ-amino amide analogs were also investigated. The most potent analogs were found to contain substitution alpha to the primary amine such as the cyclopropyl **36** or the gem dimethyl (**37** and **38**). However, the best γ-amino amide analogs were found to be generally 2–3-fold less potent on Akt1 and less selective than the corresponding β-amino amides. Several dihydrofuropyrimidine analogs covering both the β- (**39** vs **31**, **40** vs **32**, **41** vs **34**) and γ-amino amides (**42** vs **38**) were synthesized and similar to that observed in the α-amino amide series, were found to be less potent and PKA selective relative to their dihydrothieno counterparts.

Having identified several potent compounds with modest selectivity over PKA, representatives from the dihydrothieno- **29**[13] and dihydrofuropyrimidine **41** series were screened against a panel of 40 related protein kinases at 1 μM. Both compounds exhibited an improvement in overall kinase selectivity, inhibiting only three enzymes at greater than 50% (PKA, p70S6K and PKCη), and compared to earlier analogs bearing the pyrrolopyrimidine core (**1**)

Table 2
β- and α-Amino amide series SAR



Compound	R^1	R^2	R^3	Akt1 Enz IC_{50}[a] (nM)	PKA Enz IC_{50}[a] (nM)	Akt Cell IC_{50} LNCaP[b] (nM)
28	S		4-Cl	42 ± 5	308 ± 89	2468 ± 111
29	S	$-CH_2NH$isopropyl	4-Cl	3 ± 1	80 ± 24	159 ± 30
30	S		4-Cl	3 ± 0	75 ± 16	178 ± 11
31	S	$-CH_2NH$isopropyl	4-Me	3 ± 0	101 ± 11	216 ± 69
32	S	$-CH_2NH$isopropyl	3-F,4-Cl	2 ± 0	30 ± 3	92 ± 22
33	S	$-CH_2NH$isopropyl	3,4-diF	10 ± 1	285 ± 9	759 ± 67
34	S	(*S*)-CH_2NHisopropyl	4-Cl	1 ± 0	35 ± 3	137 ± 9
35	S	(*R*)-CH_2NHisopropyl	4-Cl	127 ± 34	5620 ± 635	ND
36	S		3-F,4-Cl	3 ± 1	30 ± 8	250 ± 17
37	S	$-CH_2C(CH_3)_2NH_2$	4-Cl	6 ± 2	73 ± 10	438 ± 55
38	S	$-CH_2C(CH_3)_2NH_2$	3-F,4-Cl	7 ± 3	63 ± 12	587 ± 100
39	O	$-CH_2NH$isopropyl	4-Me	16 ± 0	315 ± 61	995 ± 248
40	O	$-CH_2NH$isopropyl	3-F,4-Cl	6 ± 1	88 ± 10	315 ± 11
41	O	(*S*)-CH_2NHisopropyl	4-Cl	3 ± 1	52 ± 9	125 ± 6
42	O	$-CH_2C(CH_3)_2NH_2$	3-F,4-Cl	18 ± 10	91 ± 9	592 ± 141

[a] Values are means of three or more experiments, standard deviation is given.
[b] Values are means of two or more experiments, standard deviation is given.

which showed greater than 50% inhibition in 23 of the 40 kinases tested at a similar 1 μM concentration.

Representative dihydrothieno- **34** and dihydrofuropyrimidine **41** analogs were evaluated in various in vitro ADME assays. Both **34** and **41** gave similar predicted clearance across species in hepatocytes[14] and liver microsomes. Metabolism studies identified that amine de-alkylation, and not sulfur oxidation, as the major metabolic reaction. Next, **34** was evaluated in rat PK and although the clearance of **34** was high (Cl = 94 mL/min/kg) at 5 mg/kg iv, a surprisingly high bioavailability (*F* >100%) with reasonable plasma levels (56.2 μg h/mL) was achieved when dosed at 50 mg/kg. Based upon its selectivity, overall physiochemical properties, in vivo PK profile and low plasma protein binding (compounds typically range between 70% and 80% bound) we elected to advance **34** into a dose escalation PK/PD study in nude mice bearing subcutaneous U87 human glioblastoma xenografts (Fig. 3).

At the 1 and 4 h time points the plasma levels of **34** increased in a linear fashion as the dose was increased from 50 to 100 mg/kg, with little increase in exposure at the 200 mg/kg dose (possibly as a result of solubility limited exposure). The corresponding p-PRAS40 knockdown at 1 h was observed to be 85–90% starting at the 50 mg/kg dose. At the 4 h time point p-PRAS40 knockdown ranging from 60% (50 mg/kg) to 83% (200 mg/kg) was achieved. At 12 h only the 200 mg/kg dose group demonstrated significant (65%) p-PRAS40 knockdown. Based upon these results compound

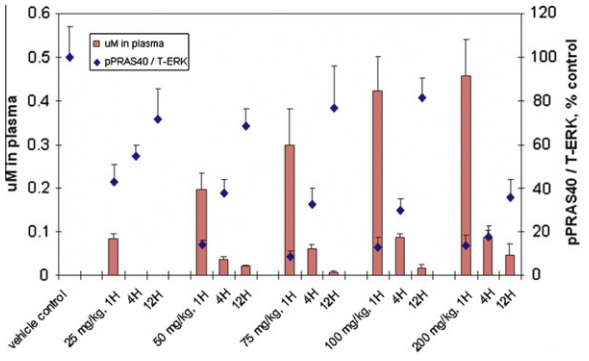


Figure 3. Oral dose PK/PD of **34** in nude mice bearing U87 tumor xenografts. Four mice per group. Compound dosed as a 10 mL/kg solution in water up to 100 mg/kg and as a suspension at 200 mg/kg.

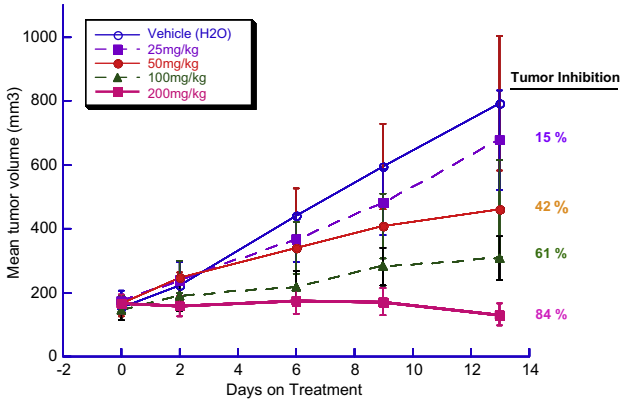


Figure 4. Evaluation of **34** dosed QD at 25, 50, 100, and 200 mg/kg PO for 14 days in PC3-NCI prostate tumor bearing mice. Ten mice per group. Compound dosed as a 10 mL/kg solution in water up to 50 mg/kg and as a suspension at 100 and 200 mg/kg.

34 was progressed into a proof-of-concept tumor growth inhibition (TGI) study. Female nude mice were subcutaneously implanted with PC3-NCI prostate tumor cells and once established to a tumor size of 150–200 mm^3, **34** was dosed daily at 25, 50, 100 and 200 mg/kg PO for 14 days (Fig. 4). Compound **34** was found to be well tolerated for the duration of the study and demonstrated a dose-dependent reduction in tumor growth ($P = 0.008$ comparing 200 mg/kg dose with vehicle-dosed controls on day 14) with stasis observed at the highest dose. The observed TGI correlated well with the 14 day end of study 1 h and 4 h post dose PD knockdown (data not shown).

In summary, we have described a novel class of oral pan Akt inhibitors based upon the dihydrothieno- and dihydrofuropyrimidine scaffolds. Integration of these cores with various amino acids, led to the identification of several analogs displaying enhanced PKA selectivity which was used as a surrogate for general kinase selectivity. Compound **34** was found to be well tolerated in a 14 day PC3-NCI prostate cancer xenograft model, demonstrating a dose-dependent tumor reduction with stasis observed at 200 mg/kg oral daily dosing. Further refinements to improve potency, kinase selectivity and overall ADME properties are currently underway, the results of which will be reported in future communications.

Acknowledgements

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9. Oxidation of the dihydrothienopyrimidine **17** to the sulfone **18** was carried out using 5 equiv of m-CPBA in 86% yield.
10. Atomic coordinates for structure **26** bound to Akt1 and PKA were deposited with the RCSB Protien Data Bank (PDB) under the accession codes 3OW4 for Akt1 and 3OW3 for the PKA.
11. A similar observation and strategy was recently published by researchers in their efforts to obtain Akt selectivity over ROCK1. Lin, H.; Yamashita, D. S.; Zeng, J.; Xie, R.; Wang, W.; Nidarmarthy, S.; Luengo, J. I.; Rhodes, N.; Knick, V. B.; Choudhry, A. E.; Lai, Z.; Minithorn, E. A.; Strum, S. L.; Wood, E. R.; Elkins, P. A.; Concha, N. O.; Heerding, D. A. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 673.
12. This stereochemical assignment is consistent with maintaining the same overall amine and phenyl orientation as observed in the (*R*) α-amino amide series.
13. Historically the selectivity profiles obtained for both the racemic and enantiopure analogs were found to be essentially identical within this series and therefore the enantiopure data was not deemed critical in our decision to progress **34**.
14. The measured in vitro clearance of **34** in hepatocytes was found to be; mice Cl = 23 mL/min/kg, rat Cl = 25 mL/min/kg and human Cl = 14 mL/min/kg. The measured in vitro clearance of **41** in hepatocytes was found to be; mice Cl = 22.8 mL/min/kg and human Cl = 13.8 mL/min/kg.