Bioorganic & Medicinal Chemistry Letters 21 (2011) 2335–2340

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Discovery of spirocyclic sulfonamides as potent Akt inhibitors with exquisite selectivity against PKA

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ARTICLE INFO

Article history:
Received 21 December 2010
Revised 17 February 2011
Accepted 22 February 2011
Available online 26 February 2011

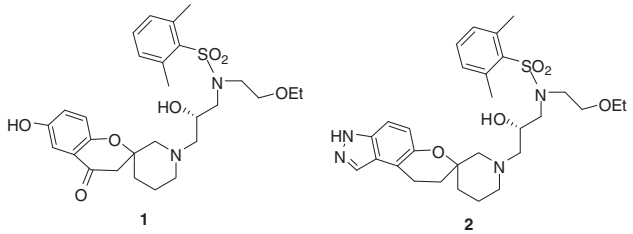
Keywords:
Akt
PKA
Selectivity
Spiro
Kinase

ABSTRACT

We describe the design and synthesis of novel bicyclic spiro sulfonamides as potent Akt inhibitors. Through structure-based rational design, we have successfully improved PKA selectivity of previously disclosed spirochromanes. Representative compounds showed favorable Akt potency while exhibiting up to 1000-fold selectivity against PKA.

Akt, also known as protein kinase B (PKB), is a serine/threonine kinase belonging to the AGC family of kinases. Three isoforms of Akt are known to exist, namely Akt1, Akt2 and Akt3, which exhibit an overall homology of 80%.[1–3] The Akt isoforms share a common domain organization that consists of a pleckstrin homology domain at the N-terminus, followed by a kinase catalytic domain, and a short regulatory region at the C-terminus. Akt plays a central role in the PI3K-Akt-mTOR pathway as a key effector of receptor tyrosine kinase signaling, regulating diverse cellular functions including cell growth, proliferation, apoptosis and metabolism. The upstream receptor tyrosine kinases, PI3K and Akt itself, are commonly mis-regulated or amplified in a variety of human tumors. For example, the tumor suppressor PTEN, a negative regulator of PI3K, is deleted or mutated in many cancers.[4–6] In addition, activating mutations in PIKC3A, one of the class IA PI3K isoforms, are found in a high proportion of breast, endometrial, colon and other cancers.[7] These abnormalities result in activation of the PI3K–Akt pathway which leads to cell proliferation and survival, as well as confers resistance to various types of cancer therapy, such as chemotherapy, radiation, and EGFR inhibition. Accordingly, Akt inhibition has attracted considerable attention as an oncology target.[8–11]

Due to the high degree of homology between the ATP binding sites of protein kinases, the development of selective ATP competitive Akt inhibitors presents a substantial challenge. In a previous report,[12] we reported the discovery of a novel series of Akt inhibitors that contain the spirochromane scaffold resulting from modifications of a HTS hit **1** (Fig. 1). Of particular interest were compounds with a phenol hinge binder that exhibit profound selectivity (>250-fold) against the closely homologous AGC family



1
Akt1 IC_{50}: 3.4 μM
PKA IC_{50} > 50 μM
pPRAS40 IC_{50} >10 μM

2
Akt1 IC_{50}: 9 nM
PKA IC_{50}: 30 nM
pPRAS40 IC_{50}: 44 nM

Figure 1. Spirochromanone Akt inhibitors.[12]

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doi:10.1016/j.bmcl.2011.02.098

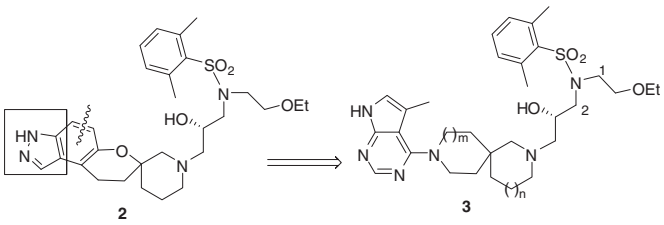
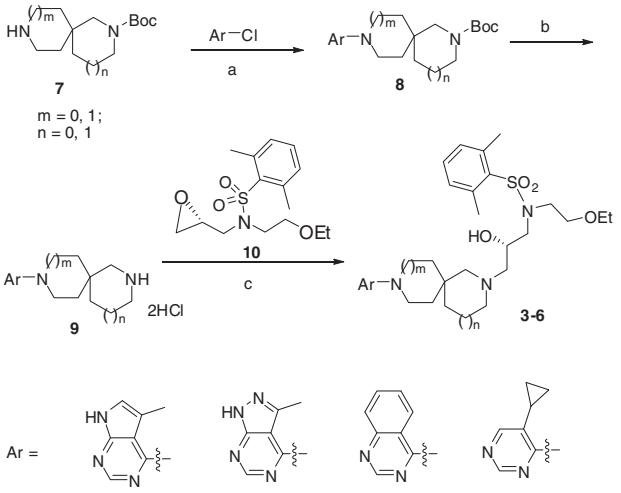
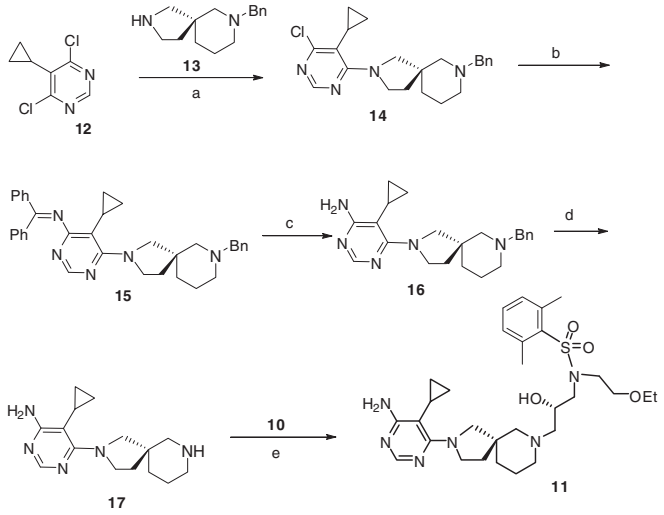


Figure 2. Design of spirobicyclic analogs **3**.

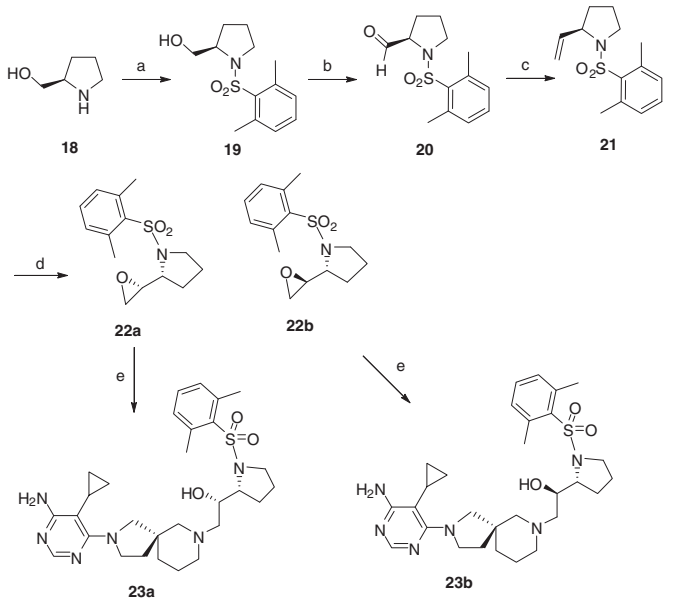


Scheme 1. Reagents and conditions: (a) DIEA, NMP, 70 °C, 16 h, 63–95%; (b) HCl/dioxane, 61–97%; (c) TEA, EtOH, 55 °C, 16 h, 51–87%.

kinase PKA, which we used as a surrogate of general kinase selectivity. Replacement of the phenol ring with a lactam or an indazole resulted in compounds with excellent Akt enzyme and cell potency, but with reduced selectivity over PKA. For example, the



Scheme 2. Reagents and conditions: (a) DIEA, NMP, 80 °C, 1 h, 98%; (b) benzophenone imine, $Pd(OAc)_2$, *rac*-BINAP, $NaOBu^t$, 95 °C, 7 h, 80%; (c) hydroxylamine hydrochloride, NaOAc, MeOH, rt, 16 h, 91%; (d) ammonium formate, 10% Pd/C, MeOH, reflux, 16 h, 78%; (e) TEA, EtOH, 55 °C, 16 h, 53%.

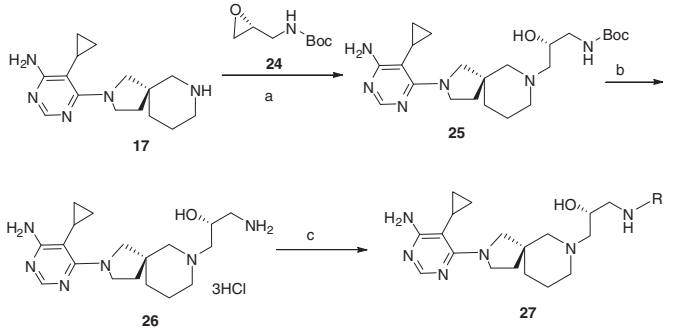


Scheme 3. Reagents and conditions: (a) Et_3N, DCM, 2,6-dimethylbenzene-1-sulfonyl chloride, rt, 2 h, 67%; (b) sulfur trioxide pyridine complex, Et_3N, DMSO, DCM, 0 °C, 1 h; (c) methyltriphenylphosphonium bromide, NaH, DMSO, rt, 16 h, 36% for two steps; (d) m-CPBA, DCM, reflux, 48 h, 64% for **22a**, 19% for **22b**; (e) **17**, TEA, EtOH, 55 °C.

indazole compound **2** was highly potent in a mechanistic cellular assay, with an IC_{50} of 44 nM, but selectivity over PKA dropped to ca. 3-fold.

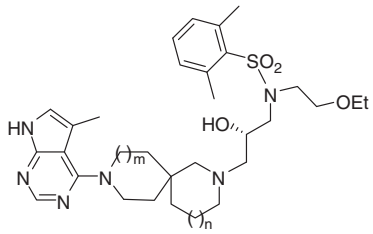
In this Letter, we report our continued efforts to optimize this series with emphasis on improving PKA selectivity while retaining favorable Akt activity. As shown in Figure 2, our SAR studies initiated by breaking the polycyclic indazole spirochromanone scaffold in compound **2** in order to determine whether the chromane ring could be replaced by an azabicyclic spiro system. Initial proof of concept efforts focused on preparation of compounds with the general structure **3**. Based on molecular modeling, compound **3** was postulated to maintain relative arrangement of the key pharmacophore elements.[12] The pyrrolopyrimidine ring in **3** should bind similarly to the hinge as the indozole ring in compound **2**, and the spiro ring-system should maintain the desired conformation to project the 2,6-dimethyl phenyl ring to the P-loop lipophilic pocket observed in crystal structures of the original chromane series.[12]

Preparation of compounds with different hinge binding cores and various azabicyclic spiro linkers are depicted in Scheme 1. S_NAr reaction between readily available mono Boc protected spirobicyclic



Scheme 4. Reagents and conditions: (a) TEA, EtOH, 55 °C 16 h, 91%; (b) HCl, dioxane, 88%; (c) acylation or reductive amination.

Table 1
Azabicyclic spiro linker SAR[a]



Compd	*m*	*n*	Akt1 IC_{50} (μM)	PKA IC_{50} (μM)	PKA/Akt (fold)	pPRAS40 IC_{50} (μM)
3a	1	1	0.041	0.21	5	1.2[b]
3b	0	1	0.002	0.067	28	0.18
3c	0	0	0.017	0.71	42	3.1

[a] Values are means of at least three experiments unless otherwise stated.
[b] Values are means of two experiments.

diamine **7** and aryl chloride gave intermediate **8**. Removal of the Boc group followed by reaction with epoxide **10**[12] afforded compounds **3–6**.

Synthesis of compound **11** with the amino pyrimidine core was carried out as outlined in Scheme 2. S_NAr reaction between 4,6-dichloro-5-cyclopropylpyrimidine (**12**) and (*S*)-7-benzyl-2,7-diazaspiro[4.5]decane (**13**)[13] afforded intermediate **14**. Conversion of **14** to amino pyrimidine intermediate **16** was effected through Buchwald coupling with benzophenone imine followed by deprotection with hydroxylamine. Removal of the benzyl protecting group under transfer hydrogenation conditions gave the amino intermediate **17** in good yield. Subsequent reaction with the epoxide intermediate **10** provided the desired compound **11**. Racemic **11** was prepared following a similar sequence except that racemic 7-Boc-2,7-diazaspiro[4.5]decane was used in the first step.

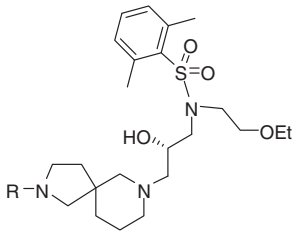
We further extended our SAR to encompass conformationally constrained pyrrolidine analogues as described in Scheme 3. Commercially available (*R*)-prolinol (**18**) was reacted with 2,6-dimethylbenzenesulfonyl chloride to give sulfonamide **19**. Oxidation to the aldehyde **20** was carried out with sulfur trioxide pyridine complex in DMSO at 0 °C. Aldehyde **20** was converted to olefin **21** by Wittig reaction with methyltriphenylphosphonium bromide in good yield. Epoxidation of **21** with mCPBA produced oxiranes **22a** (*erythro*) and **22b** (*threo*) in a combined 83% total yield with an *erythro*/*threo* ratio of 3:1. The mixture of **22a** and **22b** was readily separated by silica gel column chromatography. Subsequent reaction of both intermediates with **17** gave compounds **23a** and **23b**.

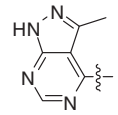
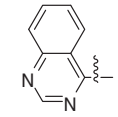
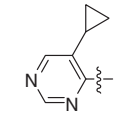
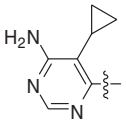
Scheme 4 summarizes the synthesis of compounds of general structure **27**. Reaction of amine **17** and epoxide **24**[14] gave alcohol **25** in good yield. Subsequent deprotection of the Boc group with HCl gave intermediate **26**, which was then converted to **27** by acylation or reductive amination.

As described previously,[15,16] the resulting compounds were evaluated for their ability to inhibit Akt1 activity in an enzyme assay (IMAP format) and phosphorylation of PRAS40 in LNCaP cells (PRAS40 is a direct substrate of Akt). Selectivity was assessed by their ability to inhibit PKA activity in a biochemical assay (IMAP format). We initially prepared compounds **3a–c** with various azabicyclic spiro linkers while keeping the pyrrolopyrimidine core and the sulfonamide moiety constant. The enzyme and cellular activities are summarized in Table 1. To our delight, all three compounds had good potency (<100 nM) in the Akt1 enzyme assay. Compound **3b** with the 2,7-diazaspiro[4.5]decane linker showed the best potency, with an IC_{50} of 2 nM in the Akt1 enzyme assay, and an IC_{50} of 0.18 μM in the pPRAS40 assay. However, all three compounds only exhibited moderate selectivity against PKA (PKA/Akt1 = 5–42). Despite this, we remained encouraged by these early results, since the pyrrolopyrimidine core had relatively low PKA selectivity.[15,17]

We then turned our attention to evaluating a series of heterocyclic ring hinge binders (Table 2). The pyrazolopyrimidine **4** was found to be moderately selective against PKA (27-fold). However, PKA selectivity was greatly improved in compounds **5**, **6** and (±)-**11** with the quinazoline and pyrimidine cores. The vastly different levels of PKA selectivity for these cores could be explained by our observations from other series of inhibitors that PKA selectivity can be modulated by modifying the hinge interactions and increasing the size of substituents near Met227, the gatekeeper residue in Akt1.[12,15,16] Improved hinge interactions tend to greatly benefit

Table 2
Core SAR[a]



	R	Akt1 IC_{50} (μM)	PKA IC_{50} (μM)	PKA/Akt (fold)	pPRAS40 IC_{50} (μM)
4		0.021	0.56	27	0.31
5		0.038	4.7	120	2.4
6		0.012	3.4	280	0.74
(±)-**11**		0.012	2.2	180	0.47

[a] Values are means of at least three experiments.

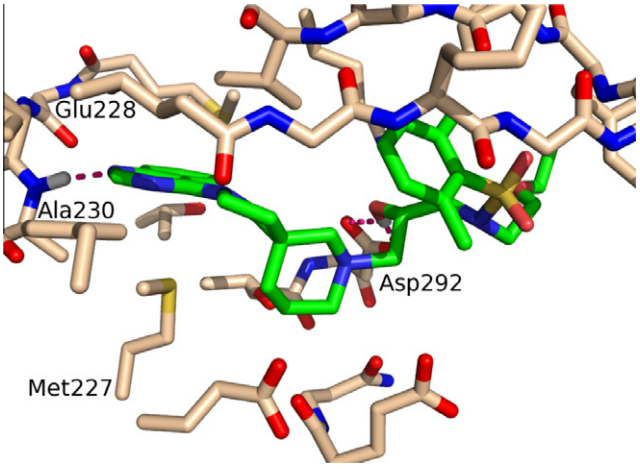


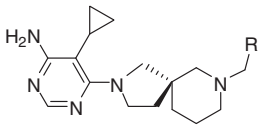
Figure 3. X-ray structure of **5** bound to Akt1 (PDB code: 3QKM).[18]

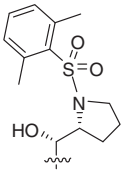
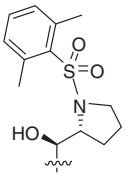
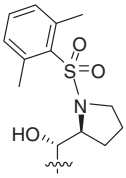
PKA inhibition while having modest effects on Akt potency.[12] For example, both **3b** and **4** are capable of forming a pair of hydrogen bonds with the backbone structure of Ala230 and Glu228 (Akt1), while the quinazoline and pyrimidine cores in **5** and **6** can only act as hydrogen bond acceptors. Clearly, loss of the H-bond donor interaction from the core affects potency at PKA more than Akt1. In addition, as we noted in previous studies,[15,16] there are several key differences between the active site residues of Akt1 and PKA that could be exploited to influence the selectivity of various inhibitors. In particular, the substitutions of Akt1-Ala230 to PKA-Val, Akt1-Thr211 to PKA-Val, Akt1-Met281 to PKA-Leu gives rise to a narrower cavity in PKA. The narrower cavity of PKA, relative to Akt1 was found to be less forgiving of larger substituents, leading to increased selectivity. This seems to be borne out in the pyrimidine series, where the larger cyclopropyl substitution of compound **6** leads to 280-fold selectivity relative to PKA. Interestingly, although the amino pyrimidine compound (±)-**11** can also interact with the hinge via a pair of hydrogen bonds, it retained 180-fold selectivity against PKA, again illustrating the effects of increasing size as a means of improving the selectivity profile. It is worthwhile to note that selectivity against p70S6K, another closely related protein kinase in the AGC family, generally parallels the PKA selectivity. For example, compounds **3a**, **3b**, **3c**, **4** and **5** were about 3-, 25-, 43-, 4- and 230-fold selective against p70S6K, respectively.

The X-ray structure of **5** in complex with Akt1 has been determined (Fig. 3) and revealed that the (*R*)-enantiomer of the 2,7-diazaspiro[4.5]decane linker binds preferentially.[18] The crystal structure also confirmed that the quinazoline nitrogen acts as a hydrogen bond acceptor in binding to the backbone NH of Ala230 (*N*–*N* distance 2.82 Å). The piperidine nitrogen and the hydroxyl group form bifurcated interaction with Asp292, while the 2,6-dimethyl phenyl ring occupies a lipophilic pocket underneath the glycine-rich loop.

Encouraged by the selectivity and potency of (±)-**11**, we prepared the active (*R*)-enantiomer. Consistent with the SAR in the spirochromane series,[12] (*R*)-**11** was about 2-fold more potent than the racemate (Akt1 IC_{50} = 6 nM and pPRAS40 IC_{50} = 0.38 μM). This compound also exhibited good selectivity against PKA, with a PKA/Akt1 ratio of 180-fold. Although compound (*R*)-**11** exhibited acceptable potency, we were concerned about the impact of high molecular weight (ca. 587), high *C* log *P* (4.2) and large number of rotatable bonds (14 total) on ADME. In order to improve the drug-like properties of compound (*R*)-**11**, conformationally restricted analogs **23a–c** were prepared (Table 3). These were designed to restrain the rotation of sp^3–sp^3 bonds by connecting the propyl linker and ethoxy ethyl side chain of **3** via a pyrrolidine ring.[19] Among the three compounds examined, **23a** had the best potency, comparable to **11**. The corresponding (*R*)-alcohol **23b** was found to be 28-fold less potent than **23a**. A modest difference in potency was observed between the two stereoisomers of the pyrrolidine ring, with the (*R*)-isomer slightly preferred (**23a** vs **23c**).

Table 3
Constrained analogs[a]



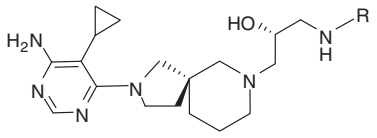
	R	Akt1 IC_{50} (μM)	PKA IC_{50} (μM)	PKA/Akt (fold)	pPRAS40 IC_{50} (μM)
23a		0.009	3.9	430	0.69
23b		0.25	>10	>40	13[b]
23c		0.019	4.7	250	2.4

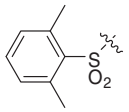
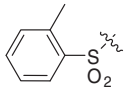
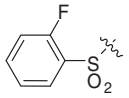
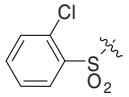
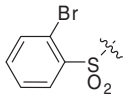
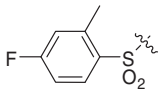
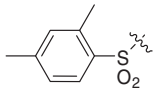
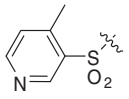
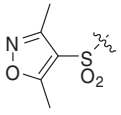
[a] Values are means of at least three experiments unless otherwise stated.
[b] Values are means of two experiments.

Further SAR of the sulfonamide region attempted to replace the sulfonamide group with an amide, carbamate, urea or benzyl amine. All modifications led to substantial losses in potency (data not shown). Interestingly, removal of the ethoxy ethyl side chain in (*R*)-**11** retained Akt1 activity (Table 4, compound **27a**, Akt1 IC_{50} = 4 nM and pPRAS40 IC_{50} = 0.90 μM), and maintained excellent selectivity against PKA (850-fold). To better understand the hydrophobic interactions of the benzene ring with the lipophilic pocket under the nucleotide binding loop, we prepared a series of sulfonamide analogs (**27b–i**). The 2-methyl compound **27b** had comparable potency to **27a**, while the 2-F compound **27c** was about 20-fold less potent. Increasing the size of the *ortho*-substituent recovered Akt1 activity (**27d** and **27e**). Fluorine substitution at the *para* position (**27f**) was tolerated, while substitution with a larger methyl group resulted in 40-fold drop in activity (**27g**). Potency also decreased sharply by replacing the 2-methyl benzene group with a 4-methyl-3-pyridyl moiety (**27h**), which is consistent with the highly lipophilic nature of the binding pocket. We also evaluated replacement of the phenyl group with five-membered heterocycles. The isoxazole analog **27i** was found to be the most potent compound in this group, with an Akt1 enzyme IC_{50} of 3 nM, cell potency of 0.49 μM, and greater than 600-fold selectivity against PKA.

In summary, we have described the syntheses and biological activities of several novel and potent bicyclic spiro sulfonamide Akt inhibitors. We have successfully improved the selectivity against PKA of previously published spirochromanes.[12] Future studies will probe other aspects of these compounds to evaluate

Table 4
Sulfonamide SAR[a]



	R	Akt1 IC_{50} (μM)	PKA IC_{50} (μM)	PKA/Akt (fold)	pPRAS40 IC_{50} (μM)
27a		0.004	3.4	850	0.90
27b		0.009	5.0	560	1.2
27c		0.081	>10	>120	14
27d		0.009	8.3	920	1.9
27e		0.017	9.4	550	2.0
27f		0.008	7.8	970	2.2
27g		0.16	>10	>63	18[b]
27h		1.1	>10	>9	ND
27i		0.003	1.9	630	0.49

ND = not determined.
[a] Values are means of at least three experiments unless otherwise stated.
[b] Values are means of two experiments.

their suitability for continued development as potential drug candidates.

Acknowledgments

We would like to thank James Graham and Dr. Francis Sullivan for helpful discussions and careful proofreading in the preparation of this manuscript. The authors also thank Dr. Lingyang Zhu for NMR support.

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silica gel column separation of the two diastereomers, 63% yield for two steps; (3) Boc deprotection with 4N HCl in dioxane; (4) reductive amination of the resulting amine with benzaldehyde, $NaBH(OAc)_3$, THF, HOAc, rt, 16 h, 91% yield for two steps; (5) amide hydrolysis with 9N HCl, dioxane, reflux, 36 h, 73%.

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18. Atomic co-ordinates of the structure **5** bound to Akt1 were deposited with the RCSB Protein Data Bank (PDB) under the accession code 3QKM.
19. Such a linkage was compatible with the conformation of compound **5** observed in the co-crystal structure with Akt1 (Fig. 3).