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First generation 5-vinyl-3-pyridinecarbonitrile PKCθ inhibitors

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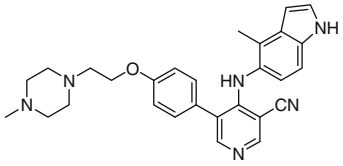
ABSTRACT

A series of 5-vinyl-3-pyridinecarbonitriles were synthesized and evaluated as PKCθ inhibitors. The systematic optimization of 4-[(4-methyl-1*H*-indol-5-yl)amino]-5-[(*E*)-2-phenylvinyl]-3-pyridinecarbonitrile 3 resulted in the identification of compound **23e** as a potent PKCθ inhibitor with good selectivity over PKCδ.

The protein kinase Cs (PKCs) are a family of serine-threonine kinases that vary in their expression and mode of activation.[1] The conventional or classical isoforms (α, β, and γ) require both calcium and diacylglycerol (DAG), the novel isoforms (δ, ε, η, and θ) require only DAG and the atypical isoforms (ξ and λ) require neither calcium or DAG.

PKCθ, a novel isoform, is predominantly expressed on lymphocytes and mast cells and plays a key role in T cell signaling.[2,3] Studies with PKCθ knock out (KO) mice showed that these animals were resistant to the development of T cell mediated diseases including asthma,[4,5] arthritis[6] and multiple sclerosis.[7,8] These findings suggest that small molecule inhibitors of PKCθ may be useful in the treatment of various autoimmune diseases. Among the PKC isoforms, PKCδ has the closest homology to PKCθ.[3] The ATP binding sites of these two kinases differ by only one amino acid. Selectivity for PKCθ is desirable considering reports that PKCδ deficiency in mice led to a hyperproliferation of B cells and overproduction of inflammatory cytokines.[9,10] Therefore PKCδ was used as the primary counter assay in our PKCθ inhibitor program.

A number of small molecules have been reported to be ATP-competitive inhibitors of PKCθ including 3-pyridinecarbonitriles,[11–15] thieno[2,3-b]pyridine-5-carbonitriles,[16–18] and 2,4-diamino-5-nitropyrimidines.[19] Earlier research in our lab identified the 5-phenyl-3-pyridinecarbonitrile **1**[13] which had an IC_{50} value of 7.4 nM for the inhibition of PKCθ and an IC_{50} value of 51 nM for the inhibition of PKCδ. However, compound **1** had metabolic stability issues and its selectivity against PKCδ was only 6.9-fold. To search for more potent and selective PKCθ inhibitors with better physicochemical properties, we expanded SAR studies for the 3-pyridinecarbonitriles by replacement of the phenyl group at C-5 with other groups. Herein we report on the synthesis and biological activities of the first generation of 5-vinyl-3-pyridinecarbonitrile PKCθ inhibitors.



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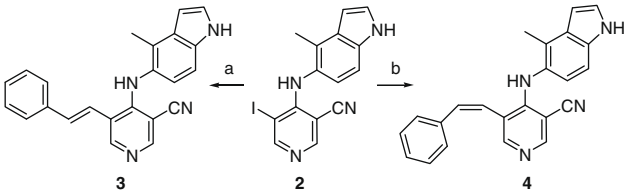
Starting from intermediate **2**[13] the (*E*)-isomer **3** and the (*Z*)-isomer **4** were prepared utilizing Suzuki coupling as shown in Scheme 1. Analog **3** having IC_{50} values of 8.3 nM and 72 nM for the inhibition of PKCθ and PKCδ, respectively, was more potent and selective than **4**, which had IC_{50} values of 79 nM and 350 nM for the inhibition of PKCθ and PKCδ.



3 **2** **4**

Scheme 1. Reagents: (a) *trans*-2-phenylvinylboronic acid, $Pd(PPh_3)_4$, aq $NaHCO_3$, DME; (b) *cis*-2-phenylvinylboronic acid, $Pd(PPh_3)_4$, aq $NaHCO_3$, DME.

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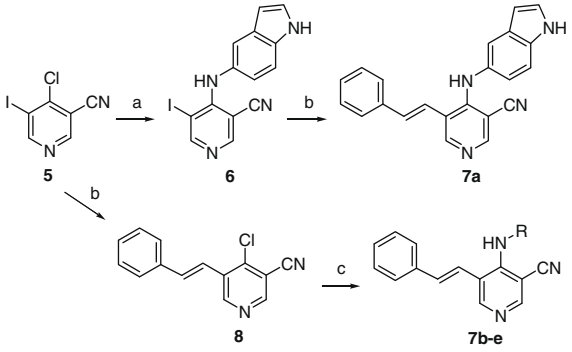
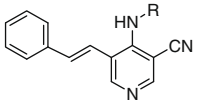
Keeping the C-5 group on the pyridine ring of **3** constant, analogs were prepared varying the indolyl group at C-4 (Scheme 2). Reaction of key intermediate **5**[13] with 5-aminoindole gave **6**. Suzuki coupling of **6** with *trans*-2-phenylvinylboronic acid provided **7a**. Coupling of **5** to *trans*-2-phenylvinylboronic acid gave compound **8**, which was then reacted with 4-aminoindole, 6-aminoindole, 5-amino-1-methylindole, and 5-amino-2-methylindole to provide **7b–e**, respectively. As shown in Table 1, using **3** as the reference compound, the 5-indolyl analog **7a** had threefold reduced potency. The 4-indolyl isomer **7b** was slightly less potent in inhibiting PKCθ than **3**. However, the 6-indolyl analog **7c** with an IC_{50} value of 1400 nM had greatly reduced PKCθ inhibitory activity. Reduced potency was also observed with the 2-Me-5-indolyl analog **7e** which had an IC_{50} value of only 360 nM. The 1-Me-5-indolyl analog **7d** had greatly decreased activity illustrating the importance of the proton at N-1 of the indole. These SAR studies showed the same trend as in our earlier report.[13]

Further variation of the substituents on the indole ring resulted in two new indolyl headpieces as depicted in Scheme 3. 5-Amino-2,4-dimethylindole **11** was obtained by following the reported procedure for the preparation of 5-amino-4-methylindole[20] starting from 2-methyl-5-nitroindole **9**. Conversion of **12** to substituted indole **13** was achieved by using vinyl Grignard reagent.[21] Removal of the acetyl protecting group produced the desired 5-amino-4,7-dimethylindole **14**. Reaction of these indolyl headpieces **11**, **14**, 5-amino-1,4-dimethylindole, 5-amino-6-chloroindole, and 5-amino-7-chloro-4-methylindole with **5** provided **15a–e**, respectively. Heck reaction of **15a** with styrene gave **16a**. Suzuki coupling of

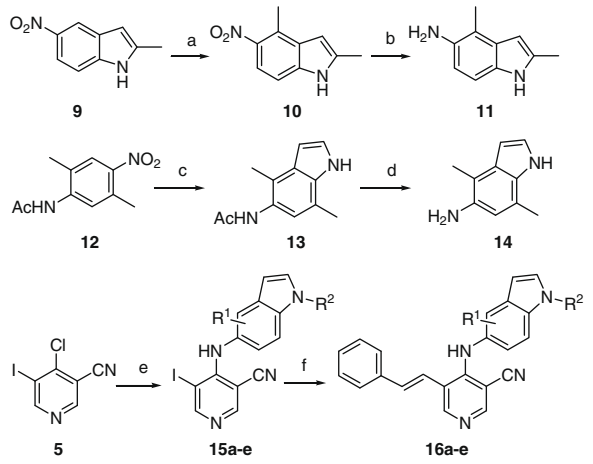


Scheme 2. Reagents: (a) 5-aminoindole, EtOH; (b) *trans*-2-phenylvinylboronic acid, $Pd(PPh_3)_4$, aq $NaHCO_3$, DME; (c) aminoindoles, EtOH.

Table 1
PKCθ and PKCδ inhibitory activity of C-5-vinylphenyl 3-pyridinecarbonitriles with varying indolyl groups at C-4



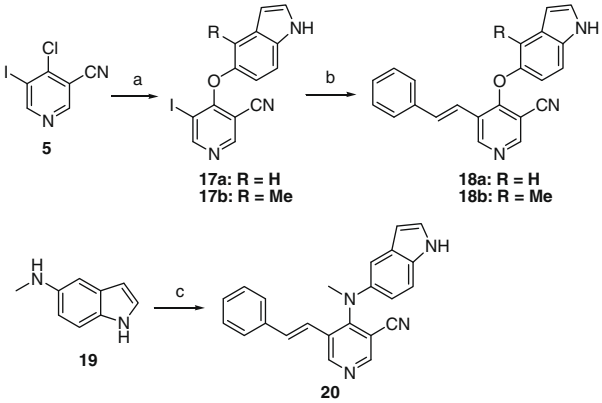
Ex	R	PKCθ IC_{50} nM[23]	PKCδ IC_{50} nM[23]	δ/θ
3	4-Me-5-indolyl	8.3	72	8.7
7a	5-Indolyl	24	240	10
7b	4-Indolyl	13	96	7.4
7c	6-Indolyl	1400	NT[23]	NA[23]
7d	1-Me-5-indolyl	4700	64,000	14
7e	2-Me-5-indolyl	360	800	2.2
16a	2,4-Di-Me-5-indolyl	70	620	8.9
16b	4,7-Di-Me-5-indolyl	34	1400	41
16c	1,4-Di-Me-5-indolyl	190	3500	18
16d	6-Cl-5-indolyl	65	1100	17
16e	7-Cl-4-Me-5-indolyl	77	880	11



Scheme 3. Reagents: (a) MeMgBr, THF; (b) H_2, Pd/C, MeOH; (c) $CH_2CHMgBr$, THF; (d) KOH, EtOH; (e) for **15a**: **11**, EtOH; for **15b**: **14**, EtOH; for **15c**: 5-amino-1,4-dimethylindole, EtOH; for **15d**: 5-amino-6-chloroindole, EtOH; for **15e**: 5-amino-7-chloro-4-methylindole, EtOH; (f) for **16a**: styrene, $Pd(OAc)_2$, $P(o\text{-tolyl})_3$, TEA, DMF; for **16b** and **16c**: *trans*-2-phenylvinylboronic acid, $Pd(PPh_3)_4$, aq $NaHCO_3$, DME; for **16d**: *trans*-2-phenylvinylboronic acid pinacol ester, $Pd(PPh_3)_4$, aq $NaHCO_3$, DME; for **16e**: *trans*-2-phenylvinylboronic acid, $Pd(PPh_3)_2Cl_2$, aq $NaHCO_3$, DME.

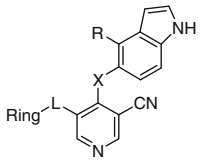
15b–e with *trans*-2-phenylvinylboronic acid or its pinacol ester provided analogs **16b–e**, respectively. Although analogs **16a–e** had 4 to 25-fold reduced PKCθ inhibitory activity compared to **3**, increased selectivity over PKCδ was observed with **16b–e** (Table 1). Among them, the 4,7-dimethyl-5-indolyl analog **16b** was the most potent and selective compound with an IC_{50} value of 34 nM for the inhibition of PKCθ and 41-fold selectivity over PKCδ.

Next, replacement of the NH group at C-4 of **3** with O and NMe was achieved as outlined in Scheme 4. Reaction of 5-hydroxyindole or 5-hydroxy-4-methylindole with **5** gave intermediates **17a** and **17b**, respectively. Suzuki coupling of **17a** and **17b** with *trans*-2-phenylvinylboronic acid afforded analogs **18a** and **18b** with an ether linker at C-4. Both **18a** and **18b** had reduced inhibition of PKCθ activity compared to **3**. Interestingly, addition of a methyl group at C-4 of the indole ring of **18a** to give the 4-methylindole analog **18b** resulted in an almost eightfold increase in activity with good selectivity, compared to **18a**. Treatment of **19** with **8** provided **20** bearing the NMe group at C-4. This analog also had significantly reduced activity for the inhibition of PKCθ with an IC_{50} value of only 440 nM (Table 2). This SAR revealed that the C-4 NH group is critical for PKCθ inhibitory activity and is consistent with what



Scheme 4. Reagents: (a) for **17a**: 5-hydroxyindole, K_2CO_3, MeCN; for **17b**: 5-hydroxy-4-methylindole, K_2CO_3, MeCN; (b) *trans*-2-phenylvinylboronic acid, $Pd(PPh_3)_4$, aq $NaHCO_3$, DME; (c) **8**, EtOH.

Table 2
PKCθ and PKCδ inhibitory activity of 3-pyridinecarbonitriles with various groups at C-4 and C-5



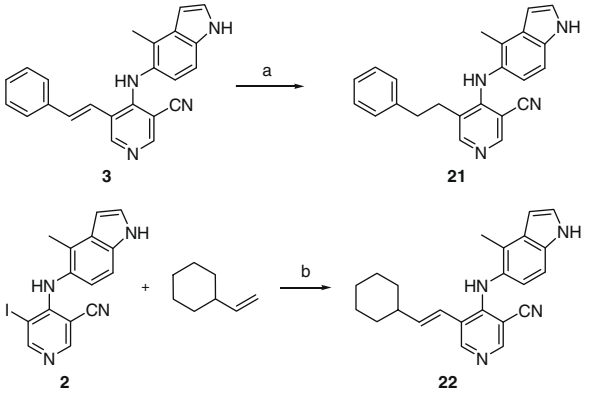
Ex	R	Ring	L	X	PKCθ IC_{50} nM[23]	PKCδ IC_{50} nM[23]	θ/δ
3	Me	Phenyl	Vinyl	NH	8.3	72	8.7
18a	H	Phenyl	Vinyl	O	690	NT[23]	NA[23]
18b	Me	Phenyl	Vinyl	O	90	1600	18
20	H	Phenyl	Vinyl	NMe	440	10,000	23
21	Me	Phenyl	Ethyl	NH	34	670	20
22	Me	Cyclohexyl	Vinyl	NH	26	420	16

was seen in the 4-(indol-5-ylamino)thieno[2,3-b]pyridine-5-carbonitriles and other series of 3-pyridinecarbonitriles.[13,16]

Saturation of the C-5 vinyl bridge of **3** by hydrogenation gave the C-5 ethyl analog **21** (Scheme 5). Replacement of the phenyl ring of **3** with cyclohexane produced analog **22**. As shown in Table 2, while **21** and **22** were weaker PKCθ inhibitors than **3**, modestly enhanced selectivity over PKCδ was observed.

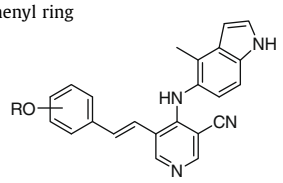
The above SAR studies demonstrated the critical role of the 5-amino-4-methylindole group at C-4 and of the C-5 vinylphenyl group to achieve good potency for the inhibition of PKCθ. The earlier report on the series of 5-phenyl-3-pyridinecarbonitriles revealed that incorporating a water solubilizing group on the phenyl ring to provide analogs such as **1**, improved the PKCθ inhibitory activity and physicochemical properties.[13] Therefore further SAR studies focused on the modification of the C-5 vinylphenyl group. The analogs in Table 3 were prepared as shown in Scheme 6. Heck reaction of **2** with 2-methoxystyrene afforded **23a**. Suzuki coupling of **2** to 3- or 4-methoxyphenylvinyl boronic acids gave **23b** and **23c**. Treatment of **2** with tributyl(vinyl)tin gave **24**, which was reacted with 2-, 3- or 4-bromophenyl 2-chloroethyl ether followed by reaction with amines, providing compounds **23d–h** bearing water solubilizing groups on the phenyl ring. Heck coupling of **24** with 1-[2-(4-bromophenoxy)ethyl]pyrrolidine provided **23i**.

The 2-OMe analog **23a** had an IC_{50} value of 8.2 nM for the inhibition of PKCθ and was 13-fold selective over PKCδ. The 3-OMe analog **23b** retained the potency and selectivity of **3**. The 4-OMe analog **23c** had an IC_{50} value of 13 nM for the inhibition of PKCθ with slightly enhanced selectivity over PKCδ. Analogs **23d–i** bearing water solubilizing groups had IC_{50} values ranging from 3.6 to 13 nM for the inhibition of PKCθ. Minimal variation in selectivity

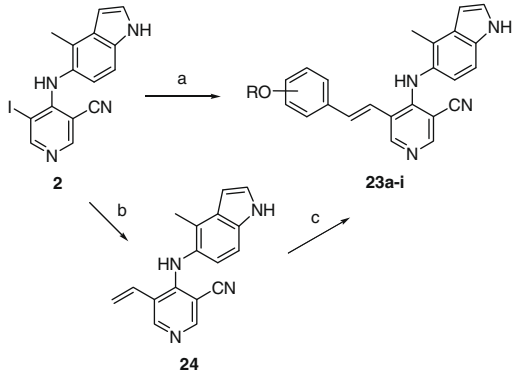


Scheme 5. Reagents: (a) H_2, Pd/C, MeOH; (b) $Pd(OAc)_2$, P(*o*-tolyl)$_3$, TEA, DMF.

Table 3
PKCθ and PKCδ inhibitory activities of C-5-vinylphenyl 3-pyridinecarbonitriles with alkoxy groups on the phenyl ring



Ex	OR	PKCθ IC_{50} nM[23]	PKCδ IC_{50} nM[23]	δ/θ	$T_{1/2}$ (min) RLM[23]
23a	2-OMe	8.2	110	13	
23b	3-OMe	7.0	62	8.9	
23c	4-OMe	13	150	12	
23d	2-OCH_2CH_2-N-Me-piperazine	7.6	34	4.5	5
23e	3-OCH_2CH_2-N-Me-piperazine	4.7	53	11	21
23f	4-OCH_2CH_2-N-Me-piperazine	3.6	41	11	5
23g	2-OCH_2CH_2-pyrrolidine	13	140	11	10
23h	3-OCH_2CH_2-pyrrolidine	4.7	25	5.3	11
23i	4-OCH_2CH_2-pyrrolidine	9.1	81	8.9	21



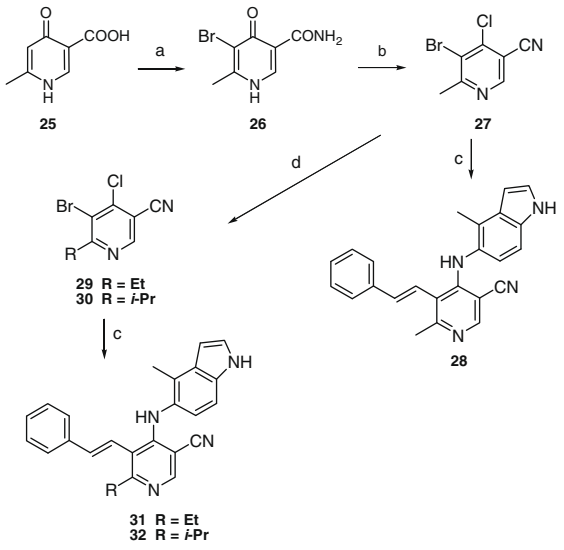
Scheme 6. Reagents: (a) for **23a**: 2-methoxystyrene, $Pd(OAc)_2$, P(*o*-tolyl)$_3$, TEA, DMF; for **23b**: 3-methoxyphenylvinyl boronic acid pinacol ester, $Pd(PPh_3)_4$, satd $NaHCO_3$, DME; for **23c**: 4-methoxyphenylvinyl boronic acid, $Pd(PPh_3)_4$, satd $NaHCO_3$, DME; (b) tributyl(vinyl)tin, $Pd(PPh_3)_4$, toluene, DMF; (c) for **23d–h**: (1) 2-, 3-, or 4-bromophenyl 2-chloroethyl ether, $Pd(OAc)_2$, P(*o*-tolyl)$_3$, TEA, DMF; (2) amines, NaI, DME; for **23i**: 1-[2-(4-bromophenoxy)ethyl]pyrrolidine, $Pd(OAc)_2$, P(*o*-tolyl)$_3$, TEA, DMF.

for PKCθ over PKCδ was seen, with **23d–i** being 4.5–11-fold selective. Of these, **23d** had an IC_{50} value of 7.6 nM for the inhibition of PKCθ, but was only 4.5-fold selective over PKCδ. Switching the solubilizing group from the *ortho*- to *para*-position on the phenyl ring increased the potency and selectivity with **23f** having IC_{50} values of 3.6 nM and 41 nM for the inhibition of PKCθ and PKCδ, respectively. Analog **23f** was also more potent and selective than the previously reported inhibitor **1**. Good potency and selectivity was seen with the *meta*-substituted analog **23e**, which had an IC_{50} value of 4.7 nM for the inhibition of PKCθ with 11-fold selectivity over PKCδ. Great improvement in rat liver microsome metabolic stability was also observed with **23e** which had a half-life of 21 min compared to **23d** (5 min) and **23f** (5 min). Analog **23g** had an IC_{50} value of 13 nM for the inhibition of PKCθ and was 11-fold selective over PKCδ. The isomer **23h** increased the PKCθ inhibitory potency (4.7 nM), but was only 5.3-fold selective over PKCδ. Analog **23i** had IC_{50} values of 9.1 nM and 81 nM for the inhibition of PKCθ and PKCδ, respectively. It also had improved metabolic stability in rat liver microsomes with a half-life of 21 min compared to **23g** (10 min) and **23h** (11 min).

Analog **23e** was profiled against additional PKC family members. While **23e** had IC_{50} values of 330 nM and 7 nM for the inhibition of the novel isoforms PKCη and PKCε, respectively, it was a weak inhibitor of PKCβ (IC_{50} = 1.3 μM), a classical isoform. No inhibition of PKCζ, an atypical isoform, was observed (IC_{50} >100 μM). Additional kinase profiling of **23e** provided IC_{50} values of 520 nM for both Lyn and Lck and greater than 8 μM for MK2, p38, PDGFR, and ROCK1.

The cellular activity of **23e** was evaluated in an assay using T cells stimulated with anti-CD3 and anti-CD28 to induce IL-2 expression.[11] Analog **23e** blocked the production of IL-2 with an IC_{50} value of 110 nM in the T cells isolated from wild-type (WT) mice. As was expected based on the rather selective inhibition of PKCθ, the compound had a greatly reduced activity with T cells from PKCθ KO mice (IC_{50} >3300 nM). It should be noted that some of the activity in these cell assays may be due to off target activities by **23e**. In pharmaceutical profiling assays, **23e** had good permeability of 3.28×10^{-6} cm/s in a PAMPA format, but poor solubility at pH 7.4 (5 μg/mL). It also exhibited acceptable metabolic stability in mouse and human liver microsomes with half-lives of 16 min and 20 min, respectively.

Lastly, modification of the C-6 position of **3** by addition of an alkyl group is shown in Scheme 7. Bromination of 6-methylpyridone **25**[22] followed by treatment with 1,1′-carbonyldiimidazole and ammonium hydroxide gave pyridone **26**. Subsequently, dehydration and concomitant chlorination of **26** with phosphorus oxychloride afforded the key intermediate **27**. Reaction of **27** with 5-amino-4-methylindole followed by Suzuki coupling with *trans*-2-phenylvinylboronic acid produced C-6 methyl substituted analog **28**. Treatment of **27** with lithium bis(trimethylsilyl)amide followed by the addition of iodomethane gave intermediates **29** and **30**. The desired analog **31** with an ethyl group at C-6 and **32** with an isopropyl group at the C-6 position were prepared by the same procedure used for the preparation of **28**. The methyl substituted analog **28** retained potency as compared to **3**, with an IC_{50} value of 9 nM for the inhibition of PKCθ. This was accompanied by enhanced selectivity for PKCδ (IC_{50} = 250 nM). However, extending the methyl group at the C-6 position to an ethyl group, as in **31** significantly reduced the PKCθ inhibitory activity (IC_{50} = 1.4 μM). The isopropyl analog **32** had further reduced activity with an IC_{50} value of greater than 19 μM for the inhibition of PKCθ.



Scheme 7. Reagents: (a) (1) Br_2, HOAc, pyridine; (2) 1.CDI, DMF; 2. aq NH_4OH; (b) $POCl_3$; (c) (1) 4-Me-5-NH_2-indole, EtOH; (2) *trans*-2-phenylvinylboronic acid, $Pd(PPh_3)_4$, aq $NaHCO_3$, DME; (d) LiHMDS, MeI, THF.

In summary, we have described the synthesis and biological evaluation of the first generation of 5-vinyl-3-pyridinecarbonitriles as PKCθ inhibitors. This report identified compound **23e** as a potent PKCθ inhibitor with good selectivity over PKCδ. With this foundation, we are continuing to develop the SAR of this series. Ongoing efforts to further enhance the potency of this series against PKCθ, selectivity over PKCδ, and optimize the physicochemical properties of the series will be reported in due course.

Acknowledgments

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23. For assay protocols see Ref. 11. The IC_{50} values are the mean of at least two separate determinations with typical variation of less than 30% between replicate values. NT: compound was not tested. NA: selectivity ratio is not available. RLM: rat liver microsome.