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Purine analogs as phosphatidylinositol 4-kinase IIIβ inhibitors

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ABSTRACT

We report on an extensive structure–activity relationship study of novel PI4K IIIβ inhibitors. The purine derivative of the potent screening hit T-00127-HEV1 has served as a suitable starting point for a thorough investigation of positions 8 and 2. While position 8 of the purine scaffold can only bear a small substituent to maintain the inhibitory activity, position 2 is opened for extensive modification and can accommodate even substituted phenyl rings without the loss of PI4K IIIβ inhibitory activity. These empirical observations nicely correlate with the results of our docking study, which suggests that position 2 directs towards solution and can provide the necessary space for the interaction with remote residues of the enzyme, whereas the cavity around position 8 is strictly limited. The obtained compounds have also been subjected to antiviral screening against a panel of (+)ssRNA viruses.

Phosphatidylinositol 4-kinases (PI4Ks) catalyze the transfer of phosphate from ATP to position 4 of phosphatidylinositol, resulting in the formation of phosphatidylinositol 4-phosphate (PI4P). This important phosphoinositide is involved in numerous cellular processes such as vesicular budding and membrane dynamics. Apart from these signaling roles, PI4P also serves as a crucial intermediate in the synthesis of other phosphoinositides, including phosphatidylinositol 4,5-bisphosphate (PI(4,5)P2) and phosphatidylinositol 3,4,5-trisphosphate (PI(3,4,5)P3). Mammalian cells contain four different PI4K isoforms catalogued into class II (PI4K IIα and PI4K IIβ) and class III (PI4K IIIα and PI4K IIIβ).[1–3] Both members of class III have been proven to be implicated in the replication of various ss(+)RNA viruses. Specific virus-encoded proteins are able to recruit these PI4Ks and misuse them to produce highly phosphorylated membrane compartments, which serve as a base for the replication complex. In particular, PI4K IIIβ is known to be indispensable in the replication of a number of viruses from the *Picornaviridae* family, including the most common human viral pathogens, Rhinoviruses and Enteroviruses.[4–7] Furthermore, this enzyme is implicated in the replication of *Coronaviruses*, represented by SARS-CoV.[8] In addition, both isoforms from class III PI4K family, PI4K IIIβ and PI4K IIIα, have been shown to be necessary host factors involved in the life cycle of the hepatitis C virus.[9–11] Recently, several groups have identified new inhibitors of class II PI4Ks[12–15] and selective inhibitors of PI4K IIIα[16–18] and PI4K IIIβ.[11,18–21] Furthermore, the crystal structures of PI4K IIα,[22] PI4K IIβ[23] and PI4K IIIβ,[24,25] were solved during the last year, thus allowing further optimization of inhibitor efficiency and selectivity.[26]

Generally, two distinct types of selective PI4K IIIβ inhibitors have been introduced (Fig. 1). Firstly, some compounds can be regarded as derivatives of PIK93 possessing a five-membered central core connected to an aromatic side chain. In contrast, the second type of PI4K IIIβ inhibitors with the archetypal example being T-00127-HEV1 is characterized by a bicyclic central core and a similar aromatic sidechain.[3] Within this study, we have used purine derivatives and several other structurally related bicycles as potential analogs of the latter group. Our major goals were to complete the structure–activity relationship study and to understand the role of methyl substituents on the central purine core. Although our initial results indicated that the purine analog is approximately six times less active than the parent compound T-00127-HEV1,[6] we decided to use this structural pattern to explore mainly the potential substitution at positions 8 and 2 because of easy access to a vast variety of these derivatives.

Our exploration of the SAR started with the preparation of 7-deaza derivative **6**. The 6-chloro-7-deazapurine **2** served as the starting material to be treated with 3,4-dimethoxyphenylboronic

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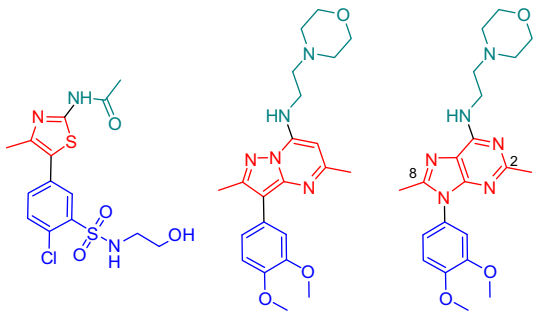


Figure 1. Examples of PI4K IIIβ inhibitors.

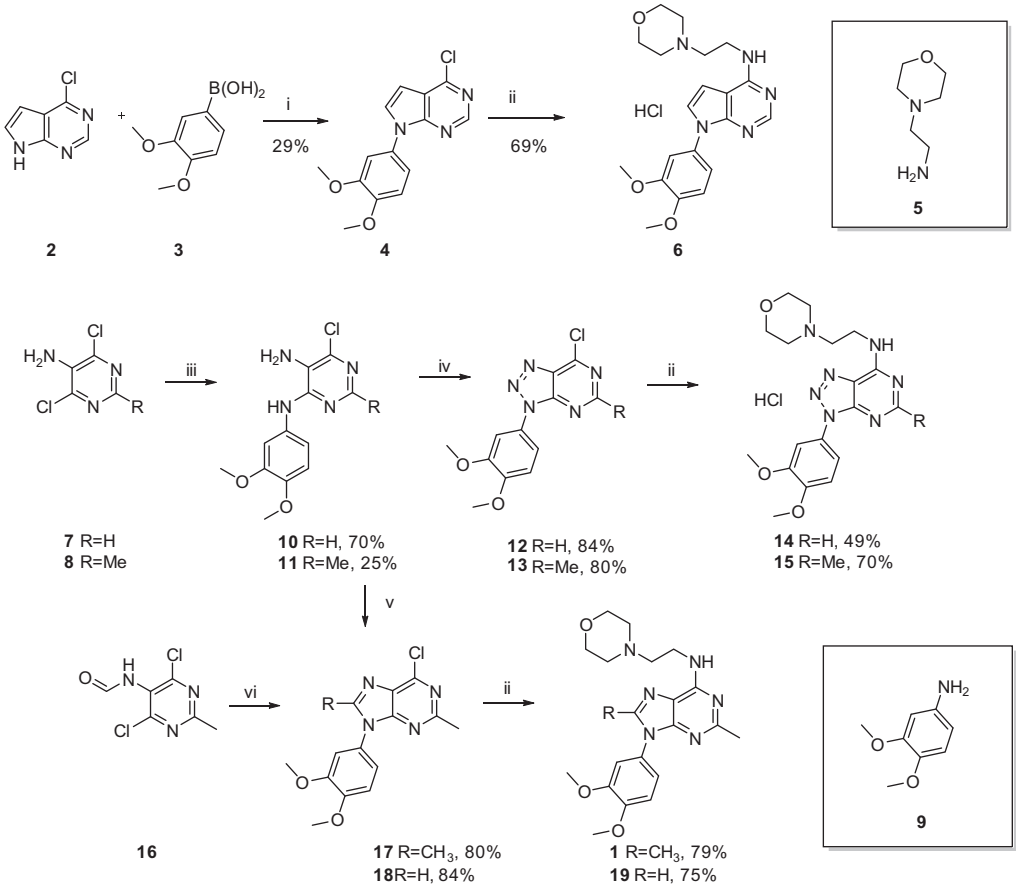
acid **3** under Chan–Lam cross-coupling conditions, which afforded compound **4** (Scheme 1).

Nucleophilic substitution followed by hydrochloride formation gave the desired analog **6**, as depicted in Scheme 1. The synthesis of 6-aminoalkyl-substituted 9-aryl-8-azapurine derivatives **14** and **15** started from commercially available 4,6-dichloro-5-aminopyrimidine **7** and 4,6-dichloro-2-methyl-5-aminopyrimidine **8**, respectively. Nucleophilic displacement with 3,4-dimethoxyaniline followed by the formation of the 8-azapurine moiety furnished the key intermediates **12** and **13**. The treatment of these compounds with 4-(2-aminoethyl)morpholine and conversion into hydrochloride salts (ethereal HCl in CH_2Cl_2 at 0 °C) afforded the desired compounds **14** and **15** (Scheme 1).

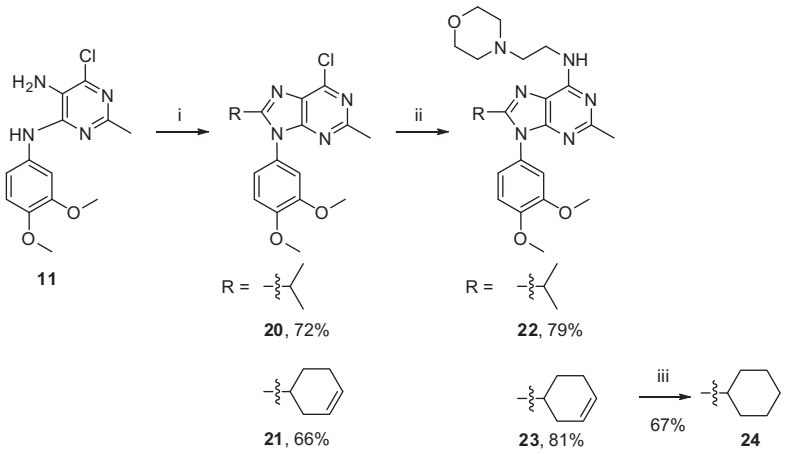
Subsequently, the SAR of purine derivatives began with the variation of the substituents at position 8 (H, CH_3, isopropyl, cyclohexenyl, cyclohexanyl, etc.). We used a built-up strategy similar to procedures previously reported by us and others,[27–29] starting from 3,4-dimethoxyaniline. Compound **1** was prepared in three steps, including the reaction of 3,4-dimethoxyaniline with 2-methyl-4,6-dichloro-5-aminopyrimidine **8**, giving derivative **11**, an imidazole ring-closure reaction (both under microwave irradiation), yielding compound **17**, and the nucleophilic replacement of the chlorine atom with 4-(2-aminoethyl)morpholine **5**. A similar reaction sequence was used for the preparation of compound **19**—analog bearing hydrogen at position 8. In this case, we directly prepared purine derivative **18** in one step by the reaction of the 3,4-dimethoxyaniline **9** with 2-methyl-4,6-dichloro-5-formylaminopyrimidine **16** under microwave irradiation. The chlorine atom was then again replaced by amine **5** to afford analog **19**.

Compound **11** was also utilized in the subsequent preparation of derivatives **22** and **23**, which were obtained in two steps—iron (III) chloride/silica gel-mediated imidazole ring formation and the subsequent nucleophilic displacement of the chlorine at position 6 of the purine skeleton (Scheme 2). Compound **23** was also easily converted to analog **24** by palladium-catalyzed hydrogenation.

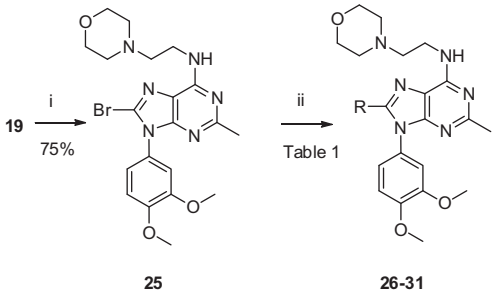
Aryl members of the 8-substituted series were prepared from 8-bromo derivative **25**, which had been obtained by lithiation with LDA at −78 °C, followed by quenching the resulting lithiated species with 1,2-dibromotetrachloroethane. With this important precursor in hand, a small set of 8-aryl and 8-heteroaryl-substituted derivatives has been prepared (Scheme 3 and Table 1). Moreover,



Scheme 1. The reagents and conditions: (i), $Cu(OAc)_2{\cdot}H_2O$, NEt_3, CH_2Cl_2, rt, overnight; (ii) (a) **5**, DIPEA, *i*-PrOH, 120 °C, MW; (b) HCl/Et_2O, CH_2Cl_2, 0 °C; (iii) **9**, HCl cat., *n*-BuOH, 150 °C, MW, 30 min; (iv) $NaNO_2$, 50% aq AcOH, CH_2Cl_2, rt, 30 min; (v) $CH_3CH(OEt)_3$, Ac_2O, MW, 120 °C, 75 min; (vi) **9**, DIPEA, *n*-BuOH, 140 °C.



Scheme 2. The reagents and conditions: (i) R-CHO, $FeCl_3/SiO_2$, dioxane, rt (1 h)–100 °C (16 h); (ii) **5**, DIPEA, *i*-PrOH, 120 °C, MW; (iii) H_2, $Pd(OH)_2$, MeOH, rt, 12 h.



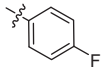
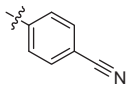
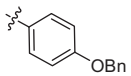
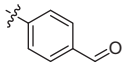
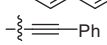
Scheme 3. The reagents and conditions: (i) (a) LDA, THF, −78 °C, 30 min; (b) CCl_2BrCCl_2Br, THF, 2 h; (ii) method (A) R-$B(OH)_2$, $PdCl_2(dppf)$, Na_2CO_3, dioxane/H_2O, 95 °C, 16 h; method (B) phenylacetylene, $PdCl_2(PPh_3)_2$, CuI, NEt_3, THF, 60 °C, 28 h (see Table 1).

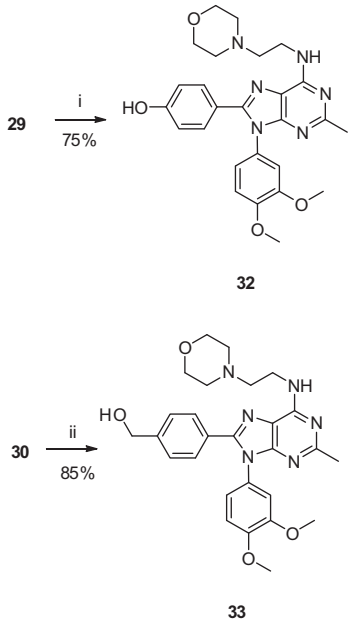
compound **25** was treated with phenylacetylene under classic Sonogashira conditions, affording compound **31**. Furthermore, the compounds **29** and **30** were subjected to catalytic hydrogenation and reduction, respectively, which provided derivatives **32** and **33** in good yields (depicted in Scheme 4).

The lithiation strategy was also used for the preparation of 8-iodo derivative **34**. In this case, an excess of LDA enables direct preparation of this derivative, which can be subsequently easily transformed into 8-methoxy analog **35** by nucleophilic substitution using sodium methoxide in methanol (Scheme 5). In contrast, a one-pot lithiation of compound **18** followed by the addition of DMF and reduction of the resulting aldehyde led to hydroxymethyl derivative **36**, which was converted to the desired final compound **37** by the nucleophilic displacement of the chlorine atom at position 6. The 8-substituted series was finalized by the preparation of 8-trifluoroderivative, which was performed by the treatment of diamine **11** with trifluoroacetic anhydride, followed by heating with the pyridine dioxane mixture, which led to the 6-oxo derivative **38**. This compound was converted into the target compound **39** by (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP)-catalyzed amination reaction.

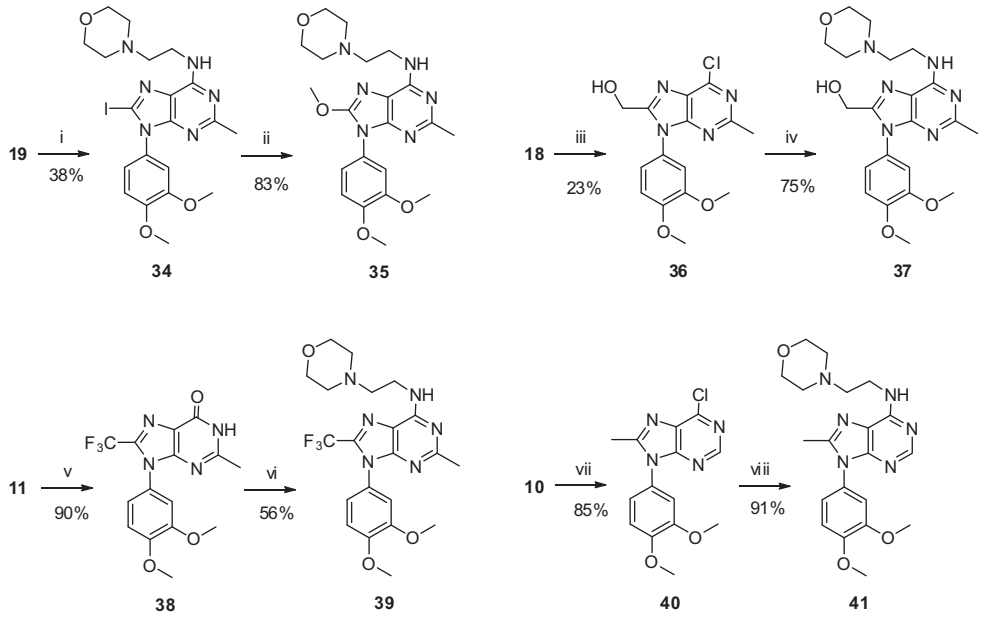
The second part of our work focused on the synthesis of a series of compounds modified at position 2. Firstly, a simplified derivative with hydrogen atom at position 2 was prepared. The synthesis of this compound was accomplished starting from compound **10** with the procedure being similar to that used for compound **1**, consisting of imidazole-ring construction followed by amino sidechain installation. The desired product **41** was obtained in very good overall yield. The whole series of 2-substituted derivatives was prepared via the crucial intermediate **45**, which was prepared starting from diaminopyrimidine derivative **42** and 3,4-dimethoxyaniline.

Table 1
The preparation of the derivatives **26**–**31** via Scheme 1

Compd	R	Method	Yield (%)
26		A	46
27		A	94
28		A	89
29		A	96
30		A	75
31		B	57



Scheme 4. The reagents and conditions: (i) H_2, $Pd(OH)_2/C$, THF/EtOH, rt, 16 h; (ii) $NaBH_4$, CH_2Cl_2/MeOH, 0 °C to rt, 16 h.

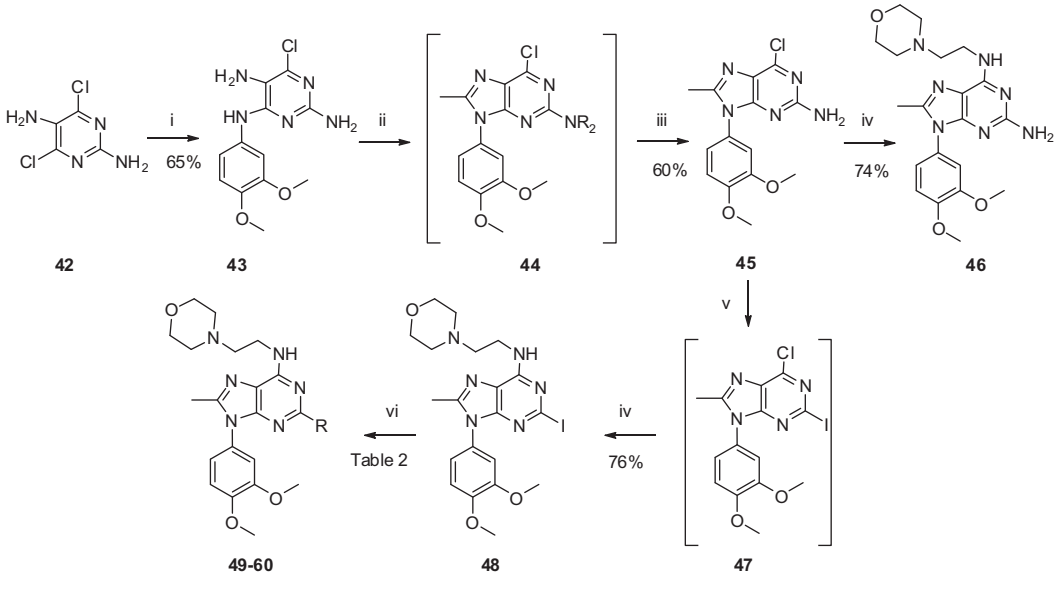


Scheme 5. The reagents and conditions: (i) (a) LDA, THF, −78 °C, 30 min; (b) I_2, THF, −78 °C; (ii) MeONa, MeOH, reflux, 72 h; (iii) (a) LDA, THF, −78 °C, 30 min; (b) DMF, THF, −78 °C; (c) $NaBH_4$, THF–H_2O; (iv) **5**, DIPEA, MW, CH_3CN, 150 °C, 45 min; (v) (a) $(CF_3CO)_2O$, DCM, pyridine; (b) pyridine, dioxane, 100 °C; (vi) **5**, BOP reagent, DBU, CH_3CN; (vii) $CH_3CH(OEt)_3$, Ac_2O, MW, 120 °C, 75 min; (viii) **5**, DIPEA, EtOH, 75 °C.

In this case, conventional heating provided better yields of coupling product **43** than the microwave-assisted built-up procedure. The subsequent closure of the imidazole ring under microwave conditions afforded a complex mixture of compounds with a partially or fully acetylated amino group in position 2 (**44**). Therefore, the crude mixture was heated under acidic conditions, which led to the desired intermediate **45** in 60% yield. The final 2-aminoderivative **46** was then obtained by the nucleophilic substitution in similar fashion as in the previous cases in 65% yield. Compound **45** served as a suitable starting material also for the preparation of iodo derivative **48**, which was acquired in two successive steps—iodine introduction via the Sandmeyer reaction and the subsequent nucleophilic displacement of the chlorine at position 6.

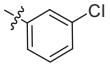
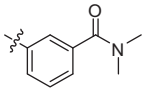
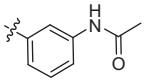
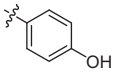
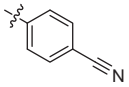
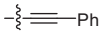
Compound **48** served as a starting material for the preparation of a small library of compounds with variously modified position 2 (Scheme 6 and Table 2).

The aromatic and heteroaromatic substituents were installed by Suzuki coupling reactions, the alkynes were introduced by Sonogashira cross-coupling and the cyano derivative was obtained by a palladium-catalyzed reaction with Bu_3SnCN. The OMe derivative **60** was prepared by the nucleophilic displacement of the iodine with sodium methoxide. Finally, a homo-derivative of the parent



Scheme 6. The reagents and conditions: (i) **9**, DIPEA, *n*-BuOH, 3 d; (ii) $CH_3CH(OEt)_3$, Ac_2O, MW, 120 °C, 75 min; (iii) HCl, THF–H_2O, reflux, 1 h; (iv) **5**, DIPEA, EtOH, 75 °C; (v) CuI, isoamylnitrite, CH_2I_2, THF, (vi) method (A) R-$B(OH)_2$, $PdCl_2$(dppf), Na_2CO_3, dioxane/H_2O, 95 °C, 16 h; method (B) (1) TMS–acetylene, $PdCl_2(PPh_3)_2$, CuI, Et_3N, DMF, 60 °C, o/n, (2) K_2CO_3, THF–MeOH (1:4), rt, 1.5 h; method (C) phenylacetylene, $PdCl_2(PPh_3)_2$, CuI, Et_3N, DMF, 65 °C; (D) Bu_3SnCN, $Pd(PPh_3)_4$, DMF, 17 h, 120 °C; (E) MeONa, MeOH, reflux, 72 h; (see Table 2).

Table 2
The preparation of the derivatives **49**–**60** via Scheme 6

Compd	R	Method	Yield (%)
49		A	64
50		A	60
51		A	68
52		A	62
53		A[a]	54[b]
54		A	60
55		A	58
56		A	66
57		B	55[b]
58		C	79
59	CN	D	92
60	OCH_3	E	60

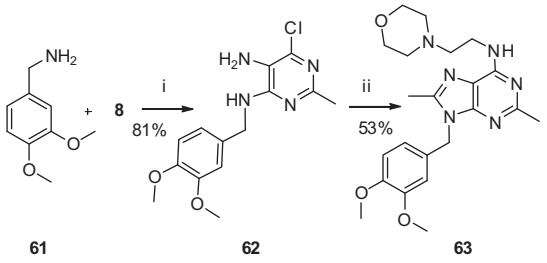
[a] Derivative **53** was prepared from its benzylated precursor similarly to derivative **32**. (Step 2: H_2, $Pd(OH)_2/C$, THF/EtOH, rt, 16 h, yield over two steps.)
[b] Yield over two steps.

compound **1** was prepared. This compound with a 3,4-dimethoxybenzyl substituent was easily prepared by a build-up procedure in three steps (Scheme 7).

The effect of the compounds on PI4K IIIβ and PI4K IIIα was measured using the PI4K ADP-Glo assay.[30] Most of the compounds exerted no or minimal effect on PI4K IIIα, whereas the inhibitory activity against PI4K IIIβ was strongly dependent on the substitution at both investigated positions. We initially measured inhibition at 10 μM and subsequently IC_{50} values if the residual activity was lower than 25% of control.

Our data clearly show two trends (Table 3). Firstly, any substitution at position 8 led to a decrease of inhibitory activity in comparison with the parent methyl derivative. The position is only opened for a small substituent, and, besides the methyl derivative only the 8-bromo derivative **25** exerted mediocre inhibitory activity. All the other bigger substituents resulted in a complete loss of inhibitory activity.

Secondly, we observed an interesting structure–activity relationship regarding position 2. Once again, small substituents, e.g.,



Scheme 7. The reagents and conditions: (i) DIPEA, *n*-BuOH, 150 °C, MW, 2 h; (ii) (a) $CH_3CH(OEt)_3$, CH_3SO_3H, 80 °C; (b) **5**, CH_3CN/DIPEA, 150 °C, MW, 1 h.

Table 3
Inhibitory activity against PI4K IIIβ and results of antiviral screening against Coxsackievirus B3 (CVB3), human rhinovirus (HRVM) and hepatitis C virus (HCV)

Compd	PI4K IIIβ % control at 10 μM[a]	IC_{50} (μM)	CVB3 EC_{50} (μM)	HRVM EC_{50} (μM)	HCV 1B EC_{50} (μM)	Hela CC_{50} (μM)
1	14 ± 0	0.91	8	40	>44	>50
6	74 ± 7	–	>50	–	22	>50
14	41 ± 14	–	>50	–	32	>50
15	31 ± 10	–	26	–	33	>50
19	26 ± 3	–	34	–	11.5	>50
22	65 ± 23	–	>50	–	>44	>50
23	75 ± 34	–	>50	>50	>44	>50
24	79 ± 25	–	>50	>50	>44	>50
25	17 ± 3	5.20	11	25	6.7	>50
26	94 ± 27	–	>50	>50	>44	>50
27	78 ± 21	–	>50	>50	>44	>50
28	97 ± 33	–	>50	>50	>44	>50
29	112 ± 17	–	ND	9.6	>44	26
30	138 ± 8	–	>50	>50	>44	>50
31	96 ± 31	–	>50	>50	30	>50
32	125 ± 17	–	>50	>50	>44	>50
33	103 ± 23	–	>50	>50	>44	>50
34	38 ± 7	–	40	>50	20	>50
35	86 ± 21	–	>50	>50	>44	>50
37	62 ± 21	–	>50	–	>44	>50
39	99 ± 10	–	>50	>50	>44	>50
41	13 ± 0	1.61	5	28	19	>50
46	25 ± 5	1.44	19	49	40	>50
48	33 ± 7	–	9	16	10	>50
49	46 ± 2	–	–	>50	23	>50
50	67 ± 12	–	>50	9	5	>50
51	16 ± 2	1.09	1.1	3.3	3.8	>50
52	14 ± 4	2.14	1.6	9.3	5.9	>50
53	18 ± 4	2.37	1.8	3.0	1.3	>50
54	97 ± 28	–	9.9	3.0	3.9	>50
55	36 ± 7	–	14	3.3	15	>50
56	66 ± 23	–	27	3.4	4.4	>50
57	18 ± 4	1.91	>50	26	13	>50
58	58 ± 7	–	5	8	6	48
59	24 ± 5	2.07	>50	31	14	>50
60	15 ± 3	2.99	>50	16	6	>50
63	126 ± 27	–	>50	>50	43	>50

[a] All data are mean values ± standard deviation for at least three independent experiments.

the amino, nitrile or acetylene group, are tolerated while with the growth of the substituent the activity generally drops. Interestingly, derivatives with hydrogen-bond acceptor groups as a *meta*- or *para*-substituent on phenyl rings, such as compounds **51** and **52**, regain the inhibitory activity. This suggests the formation of a novel interaction between the ligand and the enzyme.

We and others were able to crystalize PI4K IIIβ in complex with inhibitors and ATP during the preparation of this Letter, which allows deeper understanding of the observed structure–activity relationship. We performed a series of docking studies based on these recently published structural data in order to elucidate these phenomena. The removal of the nitrogen atom at position 7 is accompanied by significant drop of activity (compound **6**), which can be easily explained by missing hydrogen bond between the core of the inhibitor and amide moiety of Val613 and steric hindrance of additional hydrogen atom, which causes additional distortion of the amino sidechain and loss of another hydrogen contact with carbonyl moiety of Val613 (Supporting Fig. 1B). The docking results nicely explain also the observed lack of activity of 8-substituted derivatives caused by a limited space of the binding cavity, which is appropriate for the accommodation of a methyl group (Supporting Figs. 1 and 2). The partial loss of activity of compounds **14** and **15** with the additional nitrogen at position 8 could be explained by repulsion of electron pair of this nitrogen atom, which occupy this small cavity, and carbonyl group of Glu611(Supporting Fig. 1C and D).

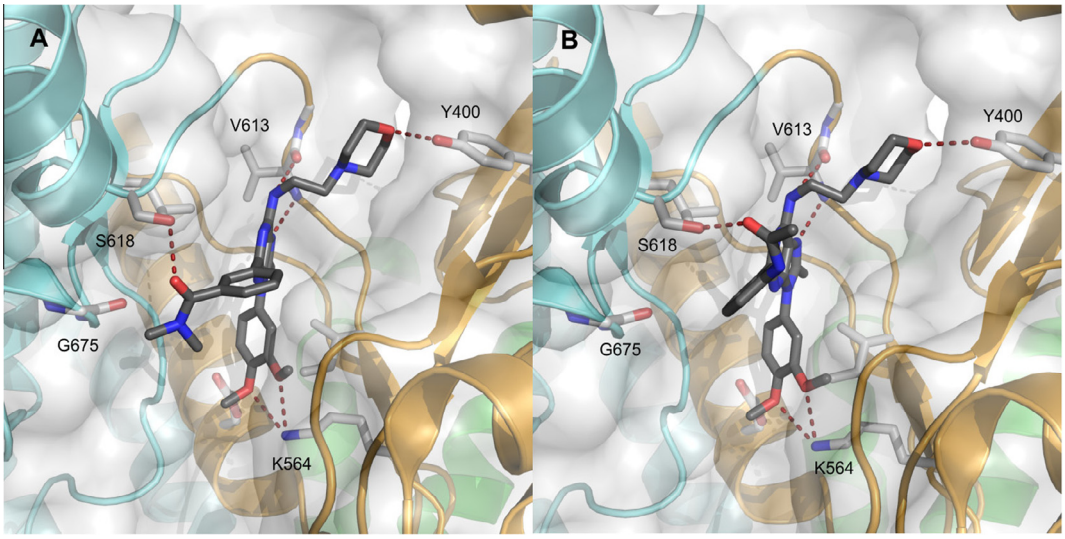


Figure 2. The docking study of (A) derivative **51** and (B) derivative **52.**[31]

Our data also indicate that the carbonyl oxygen of the amide group attached to the phenyl substituent at position 2 of derivative **51** can easily form a hydrogen bond with Ser618 and enhance the inhibitory effect of the inhibitor (Fig. 2). Similarly, compound **52** can easily accommodate the position with the carbonyl moiety in close proximity to the Ser618, although an alternative binding mode with an amide hydrogen interacting with the carbonyl group of Gly675 might also be possible according to our docking results (Supporting Fig. 3).

Apart from the enzymatic studies, we also evaluated the antiviral activity of the compounds against a panel of (+)ssRNA viruses containing Coxsackievirus B3 (CVB3), human rhinovirus (HRVM) and hepatitis C virus (HCV). In the 8-substituted series, the antiviral activity largely correlated with the observed inhibitory activity against PI4K IIIβ, and thus only the methyl derivative **1** and the 8-bromo analog **25** exerted significant activities in the antiviral screening. In the 2-substituted series, the derivatives with small substituents exerted generally lower antiviral activities than the compounds from the 2-phenyl series. The highest antiviral activity of the whole series was observed for the *meta*- and *para*-substituted 2-phenyl derivatives **51**, **52** and **53**. To our surprise, however, we observed antiviral effects against all tested viruses, not only for the compounds that inhibited PI4K IIIβ but also for the other 2-phenyl derivatives, e.g., **54**–**56**. This might be attributed to some off-target effect or cytotoxicity.

In conclusion, we have prepared a series of novel purine derivatives in order to study the effects of substituents at positions 8 and 2 on inhibitory activity against PI4K IIIβ. Our study clearly proves that position 8 is not suitable for any extensive modification with the methyl group being the optimum. On the other hand, the opposite side of the purine scaffold (position 2) can be decorated by various substituents. Although we have observed a significant drop of inhibitory activity for derivatives with simple aromatic rings, the analogs bearing appropriately substituted phenyls have exerted restored inhibitory activities against the title enzyme and have also proved to be the most potent in antiviral screening against various (+)ssRNA viruses.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2016.04.002.

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