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Synthesis and Evaluation of Phosphorus Containing, Specific CDK9/CycT1 Inhibitors

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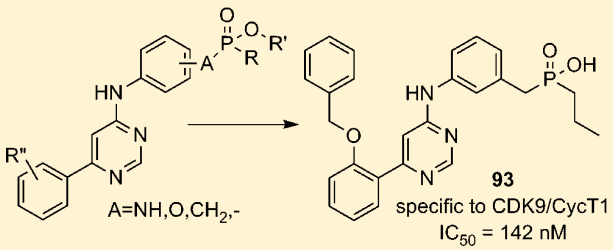
Supporting Information

ABSTRACT: Although there is a significant effort in the design of a selective CDK9/CycT1 inhibitor, no compound has been proven to be a specific inhibitor of this kinase so far. The aim of this research was to develop novel and selective phosphorus containing CDK9/CycT1 inhibitors. Molecules bearing phosphonamidate, phosphonate, and phosphinate moieties were synthesized. Prepared compounds were evaluated in an enzymatic CDK9/CycT1 assay. The most potent molecules were tested in cell-based toxicity and HIV proliferation assays. Selectivity of shortlisted compounds against CDKs and other kinases was tested. The best compound was shown to be a highly specific, ATP-competitive inhibitor of CDK9/CycT1 with antiviral activity.



INTRODUCTION

The development of kinase inhibitors remains an area of significant interest in drug discovery. To date, the FDA has approved 29 small molecule drugs targeting kinases.[1,2] Cyclin dependent kinases (CDKs) are serine/threonine kinases, which belong to a family of 13 protein kinases that share dependence upon the binding of a cyclin subunit for activation.[3] These kinases are valid targets for drug development because their role was revealed in many proliferative disorders (e.g., cancer) and inflammatory diseases.[4] The cell cycle is controlled by the activation and deactivation of CDKs. Consequently, the different CDKs may be drug targets in a range of malignancies. To our knowledge, only a few molecules have been reported as selective inhibitors of CDKs and most of them inhibit at least two of the CDKs by the same order of magnitude. Therefore, there remains a need for more selective, or specific, inhibitors of the members of the CDK family.[5−7]

CDK9 is known to be involved in the molecular pathomechanisms of several diseases; the four most significant maladies are highlighted below.[8,9] The first indication, which is the most important disease for this study is HIV-1 infection.[10] The second area with growing indication is cancer, where the use of selective CDK9 inhibitors may provide an appropriate strategy to drive cancer cells into apoptosis.[11−13] The third area is chronic activation of CDK9 which may cause cardiac hypertrophy and a predisposition to heart failure, therefore the inhibition of CDK9 may constitute a new opportunity for a curative treatment.[14] Finally, CDK9 also acts on several cytokines involved in the regulation of inflammation, thus, CDK9 is considered as a promising target for the treatment of rheumatoid arthritis and chronic inflammatory diseases such as multiple sclerosis or psoriasis.[15]

CDK9 and its cyclin partners (cyclin (Cyc) T1, T2a, b, and K) form dimers upon binding. The CDK9/CycT1 is the most common complex and plays a crucial role in HIV-1 replication.[16]

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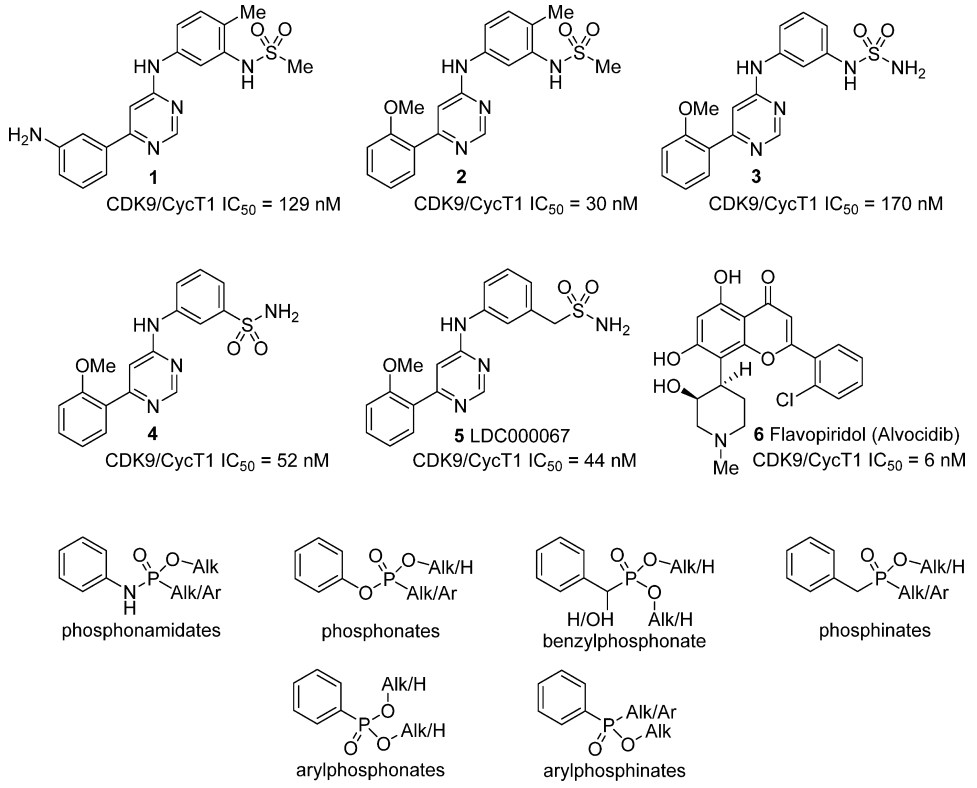

Figure 1. Structure of some representative sulfonamide CDK9 inhibitors (**1**−**5**), the flavopiridol **6**, and general structures of the presented phosphorus moieties. References: **1** and **3**,[5] **2** and **4**,[29] **5**,[21] **6**.[6]

The most important role of CDK9/CycT1 is in the phosphorylation of the C-terminal domain of RNA polymerase II, which leads to the transcription of the viral genome.[10] With the exception of the viral Tat protein, the other associated proteins are members of the transcription machinery of the host cell. The virus hijacks the host cell signaling to turn it to its own benefit. In this context, inhibition of CDK9 could halt or, at least, slow down the HIV propagation.[17]

CDK9 shows high level of sequence conservation compared with other members of the CDK family, thus the design of selective CDK9 inhibitors is highly challenging.[18] The first CDK9 inhibitor involved in clinical trial was flavopiridol, and it was discontinued due to its toxic effects.[6] In our previous work, we described several molecules showing remarkable CDK9 inhibition and high level of selectivity over other CDKs.[5] At that time, they were among the first selective CDK9 inhibitors. Recently, other research groups have published highly potent molecules, however, these compounds have significant effects on other kinases as well.[19,20] During the course of our work, Albert et al. published a highly selective CDK9 inhibitor also based on the 4-aminophenyl-6-phenylpyrimidine scaffold.[21] These facts maintained our interest to synthesize more selective and potent CDK9 inhibitors containing a phosphorus subunit.

Resemblance of phosphorus containing moieties (e.g., phosphonamidates, phosphonates, and phosphinates) to sulfonamides and sulfonyl derivatives is obvious. Their similar shape and electron density make these two types of functionalities to ideal structural mimics of each other.[22,23] Although phosphonamidates, phosphonates, and phosphinates provide higher substituent variability than sulfonyl moieties, they are rarely applied in medicinal chemistry to replace sulfur containing grups. Instead, sulfonamides and sulfonyl derivatives are widely used as mimics of natural phosphate groups.[24,25] Nonetheless, phosphonates and phosphinates were shown to be potent inhibitors of peptidases as stable tetrahedral mimics of the transitional state species of peptides,[26] mimics of phosphorus containing biomolecules involved in signal transduction[27] and other biomolecules.[28]

Using the isosteric relationship between sulfonamides and phosphonamidates, phosphonates, and phosphinates, we anticipated the synthesis of phosphorus containing analogues of previously published sulfonamide CDK9 inhibitors **1**−**5** (Figure 1). Our objective was to synthesize potent kinase inhibitors in which a phosphorus moiety is essential to their inhibitory effect. We aimed to improve selectivity toward the target kinase by using these rarely applied functional groups and planned to demonstrate in vitro efficacy on an HIV infected cell line.

CHEMISTRY

Inspired by the success of our sulfonamide-based CDK9 inhibitors and facing the incomplete selectivity toward the target enzyme, we developed new synthetic approaches of phosphonamidates, phosphonates, and phosphinates targeting CDK9. They were prepared and evaluated against the corresponding known sulfonamides **1**−**5** in biochemical assays. In the enzymatic assays, flavopiridol **6** was used as a reference (Figure 1).

Synthesis of Phosphonamidate Inhibitors (Ar-NH-P(O)ROR′). The aniline core was prepared according to published methodologies, and subsequently the primary amino group of **9** was functionalized with the appropriate phosphonochloridates **8a**−**c**.[5] The phosphonochloridates were prepared by a two-step sequence involving the Arbuzov reaction of ethyl or isopropyl bromide with triethyl or triisopropyl phosphite, respectively, followed by the monochlorination of phosphonates **7a**−**c** with oxalyl chloride (Scheme 1). The reaction of the

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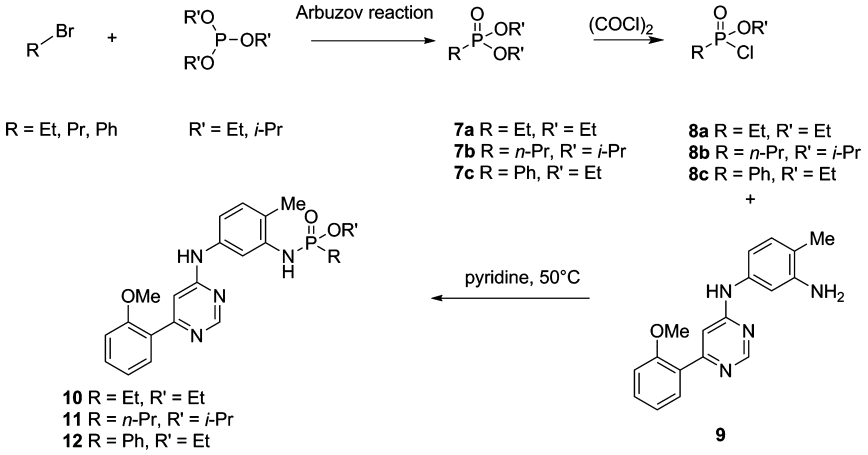
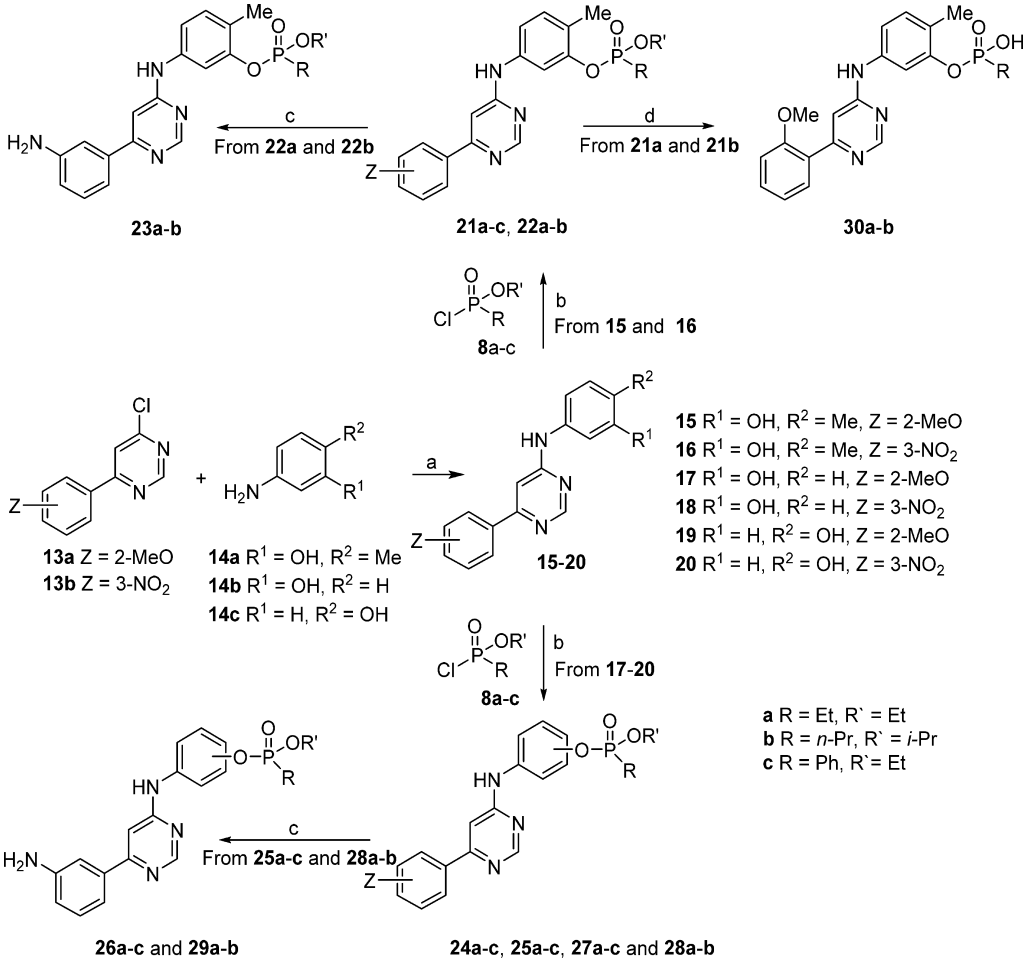
Scheme 1. Synthesis of Phosphonic Acid Chlorides, Preparation of Phosphonamidates 10−12



Scheme 2. Synthesis of Phenol Derivatives, Phosphorylation, and Hydrolysis[a]



[a]Reagents and conditions: (a) IPA, cat. HCl, reflux; (b) *t*-BuOK, THF, RT; (c) $SnCl_2$, EtOH, reflux; (d) Me_3SiCl, KI, acetone, reflux.

primary amino group of **9** with phosphonochloridate **8a−c** in anhydrous pyridine led to the phosphonamidates **10−12** in 9−18% yields. Because of the pH sensitivity of the P−N bond, phosphonamidates were readily hydrolyzed upon workup.[30]

Synthesis of Phosphonate Inhibitors (Ar-O-P(O)ROR′). Phenols **15−20** were readily accessible by the condensation of 4-chloro-6-phenylpyrimidines **13a−b** with aniline derivatives **14a−c** (47−76%) in the presence of potassium *tert*-butoxide. Phosphonates **21−29** were also synthesized by the reaction with phosphonochloridates **8a−c** (9−81%) in better yields compared to phosphonamidates (Scheme 2). The nitro group of phosphonates **22**, **25**, and **28** (Z = NO_2) was consecutively reduced to the corresponding amines **23**, **26**, and **29** by tin(II) chloride in 21−81% yields. Finally, both phosphonic acid analogues **30a** and **30b** were prepared by selective hydrolysis

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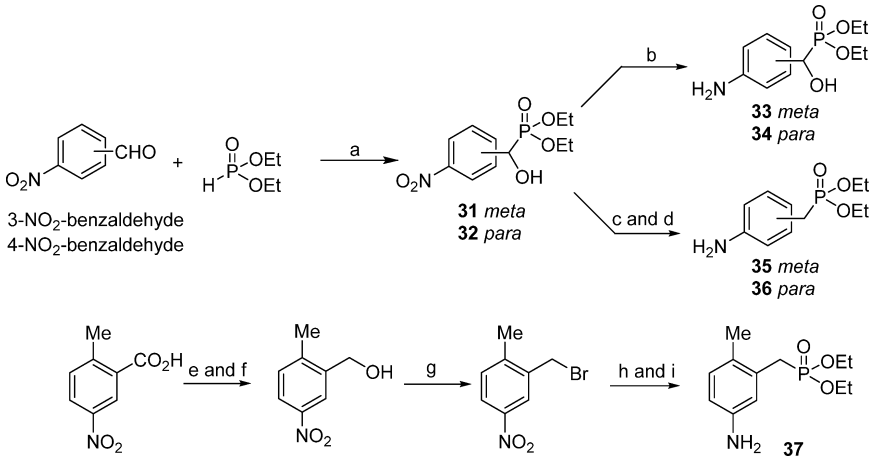
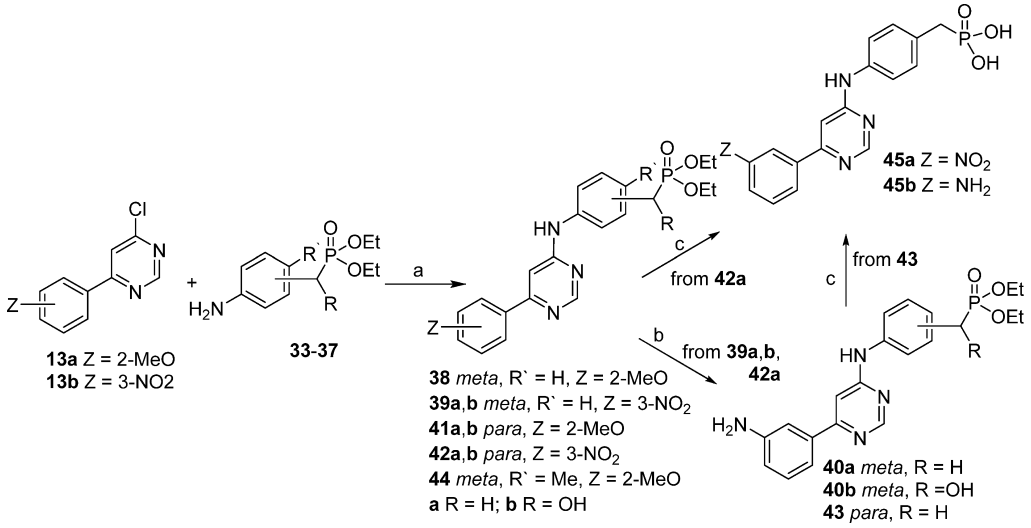
Scheme 3. Synthesis of *meta*- and *para*-Benzylphosphonate Intermediates[a]



[a]Reagents and conditions: (a) TEA, toluene, RT; (b) $HCOOH{\cdot}NH_3$, Pd/C, MeOH, RT; (c) $MeSO_2Cl$, TEA, THF, RT; (d) $NH_2{-}NH_2$, Pd/C, MeOH, RT; (e) cat. H_2SO_4, EtOH, reflux; (f) $LiAlH_4$, THF, RT; (g) PBr_3, CH_2Cl_2, RT; (h) $P(OEt)_3$, neat, 140 °C; (i) $HCOOH{\cdot}NH_3$, Pd/C, MeOH, RT.

Scheme 4. Synthesis of *meta*- and *para*-Benzylphosphonates and Phosphonic Acids[a]



[a]Reagents and conditions: (a) IPA, cat. HCl, reflux; (b) $SnCl_2$, EtOH, reflux; (c) (1) HCl (5 M), reflux, (2) propylene oxide, EtOH, 0 °C.

of the corresponding alkyl phosphonates **21a** and **21b** using TMSCl and KI in 70% and 79% yields, respectively.

Synthesis of Benzylphosphonate Inhibitors (Ar-CH_2-P(O)$(OR)_2$). To obtain hydrolytically stable phosphonates where the nitrogen or the oxygen atoms were replaced by a carbon, benzyl derivatives were synthesized (Scheme 3). The first reaction of the sequence was a Pudovik addition of diethyl phosphite to the 3- or 4-nitro-benzaldehyde with diethyl phosphite in 76% and 60% yields.[31] On one hand, the Pudovik adducts **31** and **32** were reduced to the corresponding amines **33** and **34** by transfer hydrogenation using ammonium formate and Pd/C (y = 72 and 86%). On the other hand, mesylation of **31** and **32** (y = 73 and 52%), followed by reduction with hydrazine and Pd/C, gave the benzylphosphonates **35** and **36** in 78% and 94% yields (Scheme 3). Alternatively, 3-ethylphosphonomethyl-4-methylaniline **37** was prepared from 2-methyl-5-nitrobenzoic acid in five steps due to the limited availability of 2-methyl-5-nitrobenzaldehyde (Scheme 3).

The acid-catalyzed condensation of 4-chloro-6-phenylpyrimidines **13a**–**b** with anilines **33**–**37** was readily accomplished in refluxing 2-propanol, furnishing benzylphosphonates **38**, **39**, **41**, **42**, and **44** in 6% to almost quantitative yields (Scheme 4). Subsequently, the nitro derivatives **39a**–**b** and **42a** were reduced with tin(II) chloride in refluxing ethanol, giving anilines **40a**–**b** and **43** (65–80%), respectively. Hydrolysis of phosphonate esters **42a** and **43** was achieved in refluxing 5 M hydrochloric acid, affording **45a** and **45b** in 66% and 90% yield. The hydrochloride salts were converted into the free bases by treatment with propylene oxide (Scheme 4).

Synthesis of Phosphinates Inhibitors (Ar-CH_2-P(O)-ROR'). Precursor **46** was accessible in three steps from a Michaelis–Becker reaction of 3-nitrobenzyl bromide with phenyl-H-phosphinate (Scheme 5), followed by reduction of the nitro group with tin(II) chloride; overall yield was 35%. During the Michaelis–Becker reaction, the cleavage of the ethyl ester was observed, necessitating an additional re-esterification step with triethylorthoformate. Other precursors were prepared

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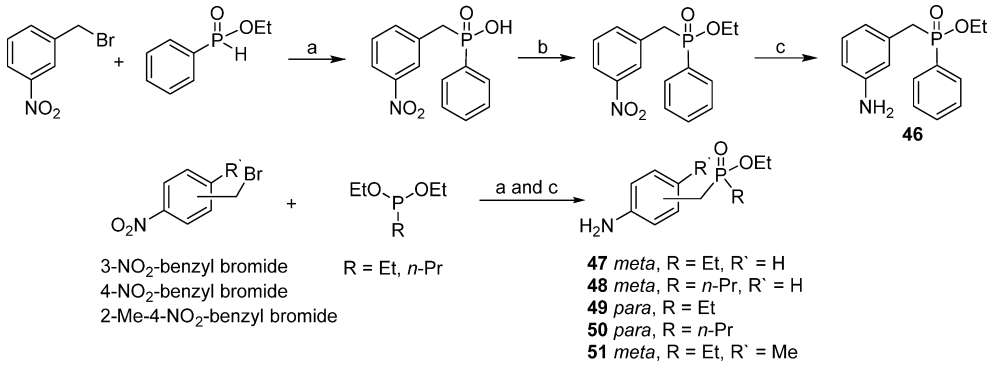
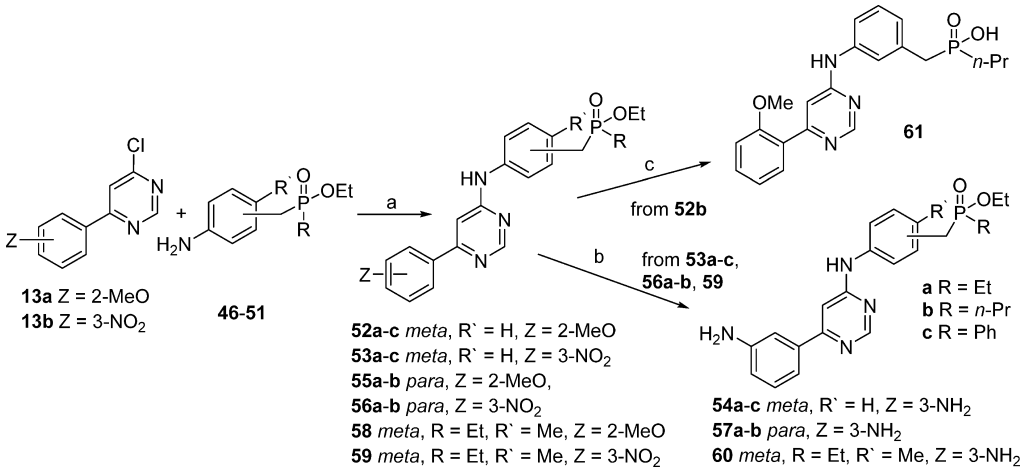
Scheme 5. Synthesis of *meta*- and *para*-Benzylphosphinate Intermediates[a]



[a]Reagents and conditions: (a) neat, 140 °C; (b) $HC(OEt)_3$, RT; (c) $SnCl_2$, EtOH, reflux.

Scheme 6. Synthesis of *meta*- and *para*-Benzylphosphinates and Phosphinic Acids[a]



[a]Reagents and conditions: (a) IPA, cat. HCl, reflux; (b) $SnCl_2$, EtOH, reflux; (c) Me_3SiCl, KI, $CHCl_3$, reflux.

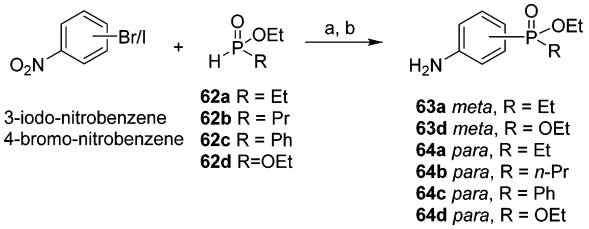
by another pathway starting by the Arbuzov reaction between the corresponding nitrobenzyl bromides and phosphonites,[32] followed by the reduction of the nitro group with tin(II) chloride, furnishing the desired aniline intermediates **47**–**51** in 28–70% overall yield.

Anilines **46**–**51** were reacted with 4-chloro-6-phenylpyrimidines **13a**–**b** under acidic conditions to give a series of benzylphosphinates **52**, **53**, **55**, **56**, **58**, and **59** in yields ranging from 29 to 55%. After reduction of the nitro group with tin(II) chloride, the corresponding anilines **54**, **57**, and **60** were obtained in 77–88% yield. Phosphinic acid **61** was prepared by cleavage of the ester function (**52b**) with trimethylsilyl chloride in the presence of potassium iodide (Scheme 6).

Synthesis of Arylphosphinate (Ar-P(O)ROR′) and Arylphosphonate (Ar-P(O)(OR)$_2$) Inhibitors. To further explore the SAR of this compound family, it was also planned to directly connect phosphonate and phosphinate moieties to the aromatic ring without NH, O, or methylene spacers. The phosphorus containing group is isosteric with the previously presented scaffolds but closer in proximity to the aromatic ring. Nonetheless, they can provide key information to the structure–activity relationship.

Synthesis of arylphosphonate and phosphinate intermediates was accomplished through a palladium catalyzed coupling reaction between 3-iodo-nitro- or 4-bromo-nitrobenzene and four different phosphinate or phosphonate substrates **62a**–**d** (y = 14–64%).[33] Nitro-phenylphosphonates and phosphinates were reduced by tin(II) chloride to afford anilines in 49–90% yields (Scheme 7).

Scheme 7. Synthesis of Anilinophosphinates and Phosphonates[a]



[a]Reagents and conditions: (a) $Pd(PPh_3)_4$, Et_3N, toluene, reflux; (b) $SnCl_2$, EtOH, reflux.

Next, reactions of anilinophosphonates or phosphinates **63**–**64** with 4-chloro-6-phenylpyrimidines **13a**–**b** led to the *N*-substituted analogues **65**–**74** (20–80% yields, Scheme 8). Reduction of the nitro group by tin(II) chloride provided the corresponding anilines **67**, **70**, and **75** in 59–97% yields. Deprotection of phosphonic acids was accomplished by refluxing in hydrochloric acid followed by neutralization using propylene oxide (y = 22–69%).

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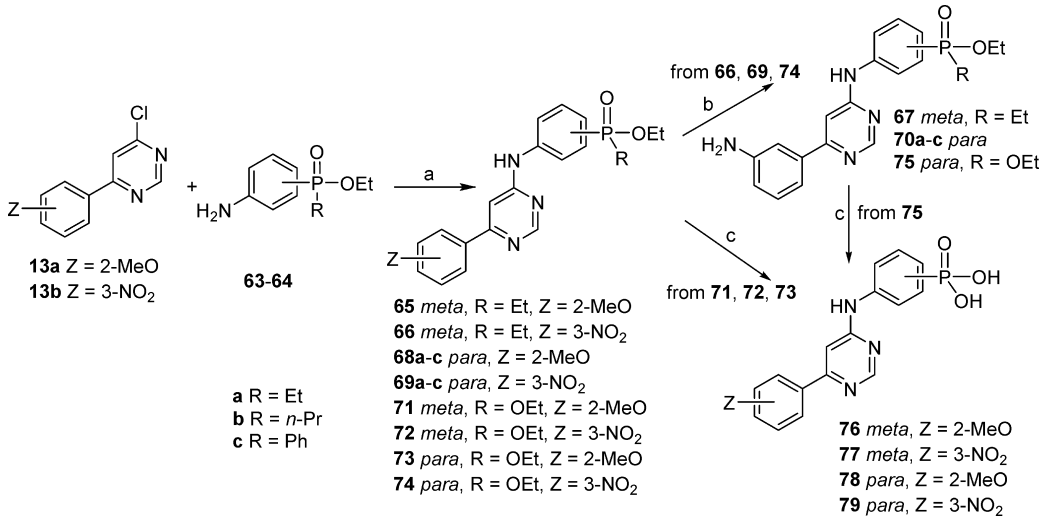
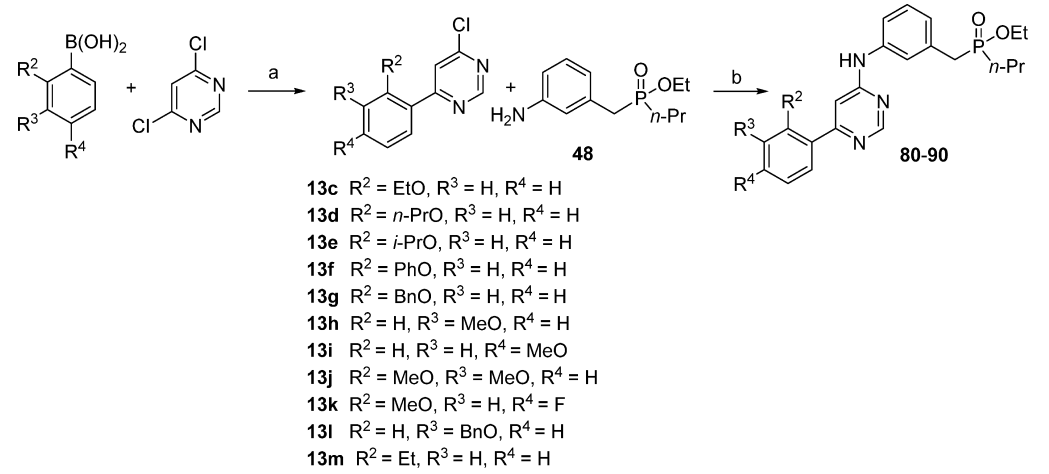
Scheme 8. Synthesis of *meta*- and *para*-Arylphosphinates and Arylphosphinates[a]



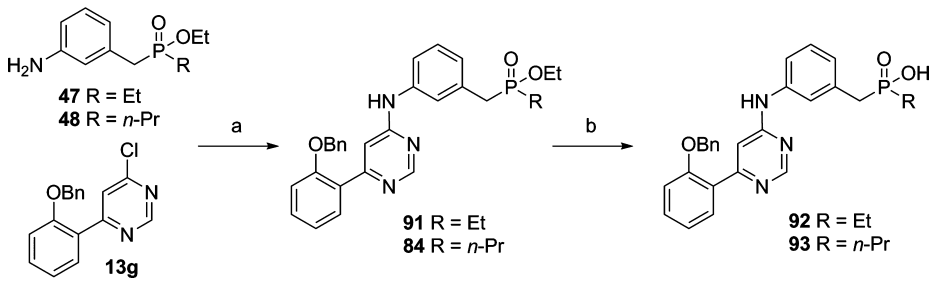
[a]Reagents and conditions: (a) IPA, cat. HCl, reflux; (b) $SnCl_2$, EtOH, reflux; (c) (1) HCl (5 M), reflux, (2) propylene oxide, EtOH, 0 °C.

Scheme 9. Synthesis of 6-Phenyl Analogues[a]



[a]Reagents and conditions: (a) $Pd(PPh_3)_4$, Na_2CO_3, DME, H_2O, RT, reflux; (b) IPA, cat. HCl, reflux.

Scheme 10. Synthesis of the Compounds with the Optimal Substituent Combination[a]



[a]Reagents and conditions: (a) IPA, cat. HCl, reflux; (b) Me_3SiCl, KI, $CHCl_3$, reflux.

Modifications on the 6-Phenyl Ring. Until now, no variation was made on the phenyl ring apart from the methoxy, nitro, and amino substituents. With this in mind, the effect of a wider range of substituents on biological activity was investigated. Targeted compounds **80**–**90** were prepared in two steps from previously synthesized precursors (Scheme 9). First of all, 4-chloro-6-phenylpyrimidines **13c**–**m** were prepared by the Suzuki coupling of the appropriate boronic acids and 4,6-dichloropyrimidine in yields ranging from 20 to 80%.[34] Synthesized intermediates **13c**–**m** were then reacted with anilinophosphinate **48**, affording aminopyrimidines **80**–**90** in 10–67% yields. This aniline was preferred because its preparation was more convenient than the ethyl counterpart **47**.

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Benzyloxyphenyl-chloropyrimidine **13g** was coupled with the aniline **47** ($y = 32\%$). Then the phosphonic esters **84** and **91** were hydrolyzed to acids **92** and **93** in moderate yield ($y = 32$ and 19%, respectively), Scheme 10.

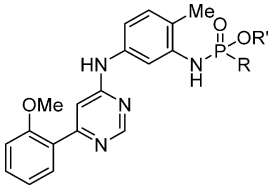
Preparation of phosphorus containing compounds is usually more difficult than the corresponding sulfonamide analogues, which led sometimes to low yields. Although, there were some analogies between the different reactions applied in this work, the yields were strongly affected by the different substitutions. The conditions for the condensation reaction of 4-chloro-6-phenyl-pyrimidines with anilines were developed as a general method. However, conversions and yields of this reaction highly depended on the nucleophilicity of the aniline, moreover, minor modifications on the phosphorus groups showed a strong influence on the reactivity of anilines.

RESULTS AND DISCUSSION

For a comparison of phosphorus-based inhibitors with sulfonamide derivatives, an in vitro test was conducted in first intention. The kinase inhibitory profiles of the most potent derivatives were determined, and then the efficiency of this small set of compounds was validated on HIV infected cells. Finally, kinetics of kinase inhibition was studied.

In vitro enzymatic assays showed that phosphonamidates **10**–**12** (Table 1) were significantly weaker inhibitors of CDK9 than

Table 1. In Vitro Activity of Phosphonamidates



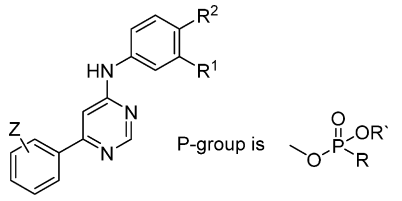
	R	R′	CDK9/CycT1 IC_{50} (nM)
10	Et	H	1450
11	*n*-Pr	Me	3170
12	Ph	H	5240

the corresponding sulphonamides (compounds **1**–**5**, Figure 1). Their low stability toward hydrolysis prompted us to focus our attention on the synthesis of phosphonate derivatives.

Potency of phosphonates **21a**–**30b** showed to be deeply dependent on the substituents of aromatic rings and on the phosphorus atom (Table 2). Not surprisingly, all the nitro-derivatives **22a**–**b**, **25a**–**c**, and **28a**–**b** were not active at all. 2-Methoxy-derivatives (**21a**–**c**, **24a**–**c**, and **27a**–**b**) were shown to be more active than the corresponding 3-aminophenyl analogues (**23a**–**b**, **26a**–**b**, and **29a**–**b**). The position of the phosphonate group did not considerably influence the inhibitory effect, meanwhile the size of phosphorus substituents on CDK9 inhibition followed the order: ethyl > propyl > phenyl. Free phosphonic acids have a negative charge at physiologic pH; the comparison between the alkyl ester **21a** and the acid **30a** showed that the charged species is less active than the neutral one. Comparison of ester **21b** and acid **30b** showed increasing potency. Overall, three phosphonate inhibitors **24a**, **27a**, and **27b** achieved an IC_{50} close to 400 nM.

Methylene spacer between the phenyl ring and the phosphonate group improved biological activity. Methoxy- (**38**, **41a**–**b**) and aminophenyl (**40a**–**b**, **43**) compounds were the most potent ones. Nitrophenyl derivatives **39a**–**b** and **42a** were

Table 2. In Vitro Activity Phosphonates and Phosphonic Acids



	R^1	R^2	R	R′	Z	CDK9/CycT1 IC_{50} (nM)
21a	P-group	Me	Et	Et	2-MeO	813
21b	P-group	Me	*n*-Pr	*i*-Pr	2-MeO	3057
21c	P-group	Me	Ph	Et	2-MeO	4137
22a	P-group	Me	Et	Et	3-NO_2	>10000
22b	P-group	Me	*n*-Pr	*i*-Pr	3-NO_2	>10000
23a	P-group	Me	Et	Et	3-NH_2	870
23b	P-group	Me	*n*-Pr	*i*-Pr	3-NH_2	5385
24a	P-group	H	Et	Et	2-MeO	400
24b	P-group	H	*n*-Pr	*i*-Pr	2-MeO	1180
24c	P-group	H	Ph	Et	2-MeO	3100
25a	P-group	H	Et	Et	3-NO_2	>10000
25b	P-group	H	*n*-Pr	*i*-Pr	3-NO_2	>10000
25c	P-group	H	Ph	Et	3-NO_2	>10000
26a	P-group	H	Et	Et	3-NH_2	1800
26b	P-group	H	*n*-Pr	*i*-Pr	3-NH_2	6430
26c	P-group	H	Ph	Et	3-NH_2	5330
27a	H	P-group	Et	Et	2-MeO	360
27b	H	P-group	*n*-Pr	*i*-Pr	2-MeO	407
27c	H	P-group	Ph	Et	2-MeO	2840
28a	H	P-group	Et	Et	3-NO_2	>10000
28b	H	P-group	*n*-Pr	*i*-Pr	3-NO_2	>10000
29a	H	P-group	Et	Et	3-NH_2	3840
29b	H	P-group	*n*-Pr	*i*-Pr	3-NH_2	6060
30a	P-group	Me	Et	H	2-MeO	1490
30b	P-group	Me	*n*-Pr	H	2-MeO	1457

inactive, but a moderate activity was found with **42b** and **45a** (Table 3). Substitution on the methylene spacer was not beneficial. The phosphorus pattern attached to the *meta*-position gave a better biological response than their *para*-counterparts. Benzylphosphonate **44** with methyl substituent in the *para*-position (IC_{50} = 5220 nM) was only a weak inhibitor of CDK9. In this series, biological activity of phosphonic acid derivatives **45a** and **45b** increased in comparison to their ethyl ester counterpart molecule **42a** and **43**. The most potent benzyl-phosphonates **38** and **40a** (IC_{50} = 333 and 332 nM, respectively) were better than their phosphonate counterparts **24a** and **26a** (IC_{50} = 400 and 1800 nM, Table 2), respectively.

Replacement of the phosphonate by a phosphinate group resulted in a significant increase in potency (Table 4). The 3-nitro-phenyl derivatives **53**, **56**, and **59** were found to be weak inhibitors, in accordance with previous results reported in both phosphonate series (Table 2–3). Once again, compounds of the 2-methoxy series possessed the best bioactivities among the 2-methoxy, 3-nitro, and 3-amino derivatives. Ethyl and propyl substitution on the phosphinate did not make a significant difference, whereas the bigger phenyl group conferred lower activity. *meta*-Phosphinates were shown to be more potent than their *para*-equivalents. Hydrolysis of the ester **52b** to **61** acid slightly decreased the potency. For instance, compound **52a** exhibited an IC_{50} lower than 200 nM, whereas its phosphonate

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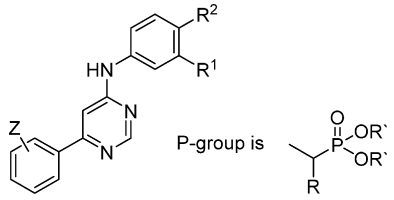
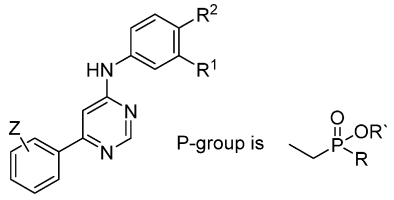
Table 3. In Vitro Activity of Benzylphosphonates and Benzylphosphonic Acids



	R^1	R^2	R	R′	Z	CDK9/CycT1 IC_{50} (nM)
38	P-group	H	H	Et	2-MeO	333
39a	P-group	H	H	Et	3-NO_2	9870
39b	P-group	H	OH	Et	3-NO_2	>10000
40a	P-group	H	H	Et	3-NH_2	332
40b	P-group	H	OH	Et	3-NH_2	1401
41a	H	P-group	H	Et	2-MeO	490
41b	H	P-group	OH	Et	2-MeO	510
42a	H	P-group	H	Et	3-NO_2	>10000
42b	H	P-group	OH	Et	3-NO_2	4577
43	H	P-group	H	Et	3-NH_2	3110
44	P-group	Me	H	Et	2-MeO	5220
45a	H	P-group	H	H	3-NO_2	2100
45b	H	P-group	H	H	3-NH_2	1130

Table 4. In Vitro Activity of Benzylphosphinates and Benzylphosphinic Acid

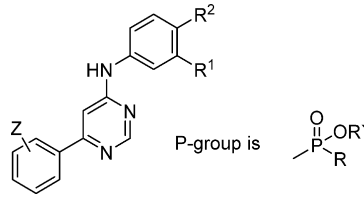


	R^1	R^2	R	R′	Z	CDK9/CycT1 IC_{50} (nM)
52a	P-group	H	Et	Et	2-MeO	197
52b	P-group	H	*n*-Pr	Et	2-MeO	296
52c	P-group	H	Ph	Et	2-MeO	517
53a	P-group	H	Et	Et	3-NO_2	6432
53b	P-group	H	*n*-Pr	Et	3-NO_2	8056
53c	P-group	H	Ph	Et	3-NO_2	>10000
54a	P-group	H	Et	Et	3-NH_2	327
54b	P-group	H	*n*-Pr	Et	3-NH_2	682
54c	P-group	H	Ph	Et	3-NH_2	1019
55a	H	P-group	Et	Et	2-MeO	743
55b	H	P-group	*n*-Pr	Et	2-MeO	652
56a	H	P-group	Et	Et	3-NO_2	7774
56b	H	P-group	*n*-Pr	Et	3-NO_2	5525
57a	H	P-group	Et	Et	3-NH_2	7533
57b	H	P-group	*n*-Pr	Et	3-NH_2	7474
58	P-group	Me	Et	Et	2-MeO	366
59	P-group	Me	Et	Et	3-NO_2	7022
60	P-group	Me	Et	Et	3-NH_2	346
61	P-group	H	*n*-Pr	H	2-MeO	261

counterpart **24a** was 2-fold higher (400 nM). Similarly, the methyl substituted analogue **58** (IC_{50} = 366 nM) was 4-fold more potent than the phosphonamidate **10** (IC_{50} = 1 450 nM) and 2-fold more potent than the phosphonate **21a** (IC_{50} = 813 nM). Finally, three molecules **52a**, **52b**, and **61**, showed IC_{50} lower than 300 nM, and all of them contained the phosphorus substituent in the *meta*-position.

When the phosphorus atom was directly bounded to the aniline ring, no improved biological activity was observed both in arylphosphinate and arylphosphonate series (Table 5). The 2-

Table 5. In Vitro Activity of Arylphosphinates and Phosphonates



	R^1	R^2	R	R′	Z	CDK9/CycT1 IC_{50} (nM)
65	P-group	H	Et	Et	2-MeO	842
66	P-group	H	Et	Et	3-NO_2	>10000
67	P-group	H	Et	Et	3-NH_2	9802
68a	H	P-group	Et	Et	2-MeO	418
68b	H	P-group	*n*-Pr	Et	2-MeO	1149
68c	H	P-group	Ph	Et	2-MeO	523
69a	H	P-group	Et	Et	3-NO_2	>10000
69b	H	P-group	*n*-Pr	Et	3-NO_2	>10000
69c	H	P-group	Ph	Et	3-NO_2	>10000
70a	H	P-group	Et	Et	3-NH_2	>10000
70b	H	P-group	*n*-Pr	Et	3-NH_2	>10000
70c	H	P-group	Ph	Et	3-NH_2	6501
71	P-group	H	EtO	Et	2-MeO	1040
72	P-group	H	EtO	Et	3-NO_2	>10000
73	H	P-group	EtO	Et	2-MeO	1020
74	H	P-group	EtO	Et	3-NO_2	>10000
75	H	P-group	EtO	Et	3-NH_2	>10000
76	P-group	H	OH	H	2-MeO	429
77	P-group	H	OH	H	3-NO_2	4100
78	H	P-group	OH	H	2-MeO	580
79	H	P-group	OH	H	3-NH_2	3320

methoxy substituted derivatives were found to be the best inhibitors regardless of the substituent R or the phosphorus position. Compounds bearing a nitro group were once again weak inhibitors, apart from phosphonic acid **77**, which had a moderate activity (IC_{50} = 4 100 nM). Surprisingly, none of the 3-amino analogues exhibited a considerable inhibitory effect on CDK9 activity. In this series, phosphonic acids (**76**–**79**) had significantly lower IC_{50}s than their ester counterparts (**71**–**73**, **75**). Again, the ethylphosphinate derivative (**68a**, IC_{50} = 418 nM) was shown to be the most potent inhibitor of this series.

Substituent variations on the 6-phenyl ring provided a clear structure–activity relationship. In general, substitutions in position 2 were preferred (Table 6). Kinase inhibition was optimum with inhibitors containing 2-alkoxy substituents and weakly dependent on the nature of the alkyl substituent. Meanwhile, any substituents in other positions caused a significant decrease of biological activity. If these alkoxy groups were replaced by an alkyl substituent (**90**) or were moved to another position (**85**, **86**, **89**), the activity significantly decreased. This clearly showed that an alkoxy group is essential in the position 2.

On the basis of the results obtained from this structure–activity study, a fragment-based approach was applied involving

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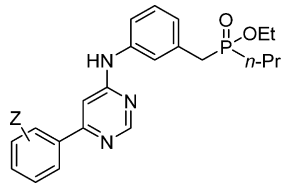
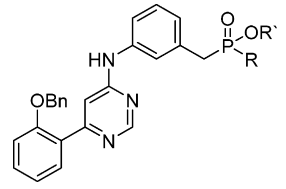
Table 6. In Vitro Activity of Phosphinates with 6-Phenyl Variations



	Z	CDK9/CycT1 IC_{50} (nM)
80	2-EtO	254
81	2-*n*-PrO	248
82	2-*i*-PrO	210
83	2-PhO	601
84	2-BnO	143
85	3-MeO	6937
86	4-MeO	5414
87	2,3-diMeO	2387
88	2-MeO-4-F	186
89	3-BnO	>10000
90	2-Et	>10000

identified groups which gave high inhibitory activity.[35] On the 4-aminophenyl ring, the optimal substituent was the ethylphosphinate derivative in the *meta*-position (compound **52a**, IC_{50} = 197 nM). On the terminal 6-phenyl ring, the best biological result was observed with an *ortho*-benzyloxy substituent (compound **84**, IC_{50} = 143 nM). Combination of these functionalities (compound **91**) had a slightly weaker activity (IC_{50} = 212 nM) compared to its methoxyphenyl counterpart **52a**. Moreover, it was less active than the propylphosphinate derivative **84**. After hydrolysis of ester **91**, its activity increased considerably (compound **92**; IC_{50} = 163 nM). Interestingly, no change in activity was observed after the hydrolysis of ester **84** to the phosphinic acid **93** (IC_{50} = 143 and 142 nM, respectively; Table 7).

Table 7. In Vitro Activity of the Phosphinates with the Best Substituent Combinations



	R	R′	CDK9/CycT1 IC_{50} (nM)
91	Et	Et	212
84	*n*-Pr	Et	143
92	Et	H	163
93	*n*-Pr	H	142

The development of a new drug candidate through the fragment-based approach is an iterative process, and some general structure−activity relationships stand out from these results. First, the ethyl substituted phosphonamidate, phosphonates, and phosphinates were the best inhibitors. Second, the smaller the substituent on the phosphorus atom, the higher the biological effect observed. Phosphinates with methylene spacer in the *meta* position were shown to be the most potent inhibitors. Examination of substituent variations on the 6-phenyl ring indicated that 2-alkoxy substitutions were the most beneficial. The 3-amino moiety was slightly weaker in activity than the 2-alkoxy, while the 3-nitro and 2-alkyl moieties were inactive. Among the 2-alkoxy moieties, the trend was the bigger the substituent, the lower the IC_{50}.

One of the aims of this project was to construct a potent kinase inhibitor whose phosphorus moiety was crucial to its inhibitory effect, and this goal was achieved. The examination of the chemical stability of the phosphorus moiety provided the evidence that in the case of the phosphonamidates, it is probable that the P−N bond was cleaved at non-neutral pH. In this case, a low IC_{50} of aniline would have been expected,[5] however, it was not the case. In the case of phosphonates, hydrolysis of the P−O bond may occur, however, good kinase inhibitory effects of phenols were not observed.[5] In the case of benzyl and arylphosphinates and phosphonates, the possibility of hydrolysis may be excluded.

Selectivity of Inhibitors. We aimed to synthesize selective CDK9 inhibitors. For this purpose, inhibitory activity of the best compounds was measured in an in vitro activity assay against the CDK2/CycE and the CDK4/CycD1, which are two of the most important regulators of the cell cycle among the CDKs. CDK9 selectivity was improved from phosphonates to phosphinates (Table 8), and two compounds (**52a**, **52b**) showed almost complete CDK9 inhibition with moderate effects on CDK2 and CDK4.

Table 8. CDK Selectivity Profile of Selected Compounds[a]

	CDK2/CycE inhibition (%)	CDK4/CycD1 inhibition (%)	CDK9/CycT1 inhibition (%)
6	99	84	100
11	32	2	83
12	19	18	71
21a	1	13	100
21b	6	21	83
21c	8	19	75
30b	34	46	88
41a	77	51	98
41b	94	68	97
43	14	30	80
52a	36*	24*	98*
52b	23*	14*	95*
54a	18*	22*	96*
73	69	22	106
75	18	35	43
76	56	40	91
79	98	67	100

[a]Compound concentration was 10 μM, except * 1 μM.

As a consequence, lead compounds **52a** and **52b** were further investigated on a panel of 30 kinases in in vitro activity assays. Results of this screen suggested outstanding selectivity: only **52a** shows moderate inhibition on cKit and Ret kinases, 28 and 34% inhibition at 1 μM, respectively (Table 9).

The most potent CDK9 inhibitor, compound **93**, was subjected to a wider selectivity profiling against 451 kinases in binding assays. A similar kinase profiling experiment has already been published with flavopiridol **6** on 442 kinases.[36] We used these results as a basis for comparison. Compound **93** showed noticeable affinity toward only IRAK3 (18% of the control at 1 μM concentration), which means that its selectivity score is S(% Ctrl <35) = 0.003 for nonmutant kinases (Figure 2). Interestingly, this compound does not bind to the inactive

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Table 9. Kinase Selectivity Profile of Selected Compounds[a]

	ABL	AKT1	AXL	bRAF	CDK2/CycE	CDK4/CycD1	CDK9/CycT1	CHK1	cKIT	cMET	CSK
52a	20	11	21	0	36	24	98	12	28	22	24
52b	9	−1	7	5	23	14	95	14	16	6	14

	DDR1	ERBB2	FGFR3	FLT3	IKKβ	INSR	IRAK4	JAK3	JNK1	mTOR	PAK1
52a	13	11	8	12	15	12	16	9	19	3	20
52b	7	5	1	6	7	2	9	0	8	9	10

	PAK4	PDGFRb	PIM1	PKCa	RET	ROCK2	SRC	SYK	TIE2	TrkA	VEGFR2
52a	25	18	8	8	34	14	18	8	10	8	11
52b	19	2	−2	9	16	7	4	−1	5	−1	6

[a]Inhibition (%) at 1 μM compound concentration.

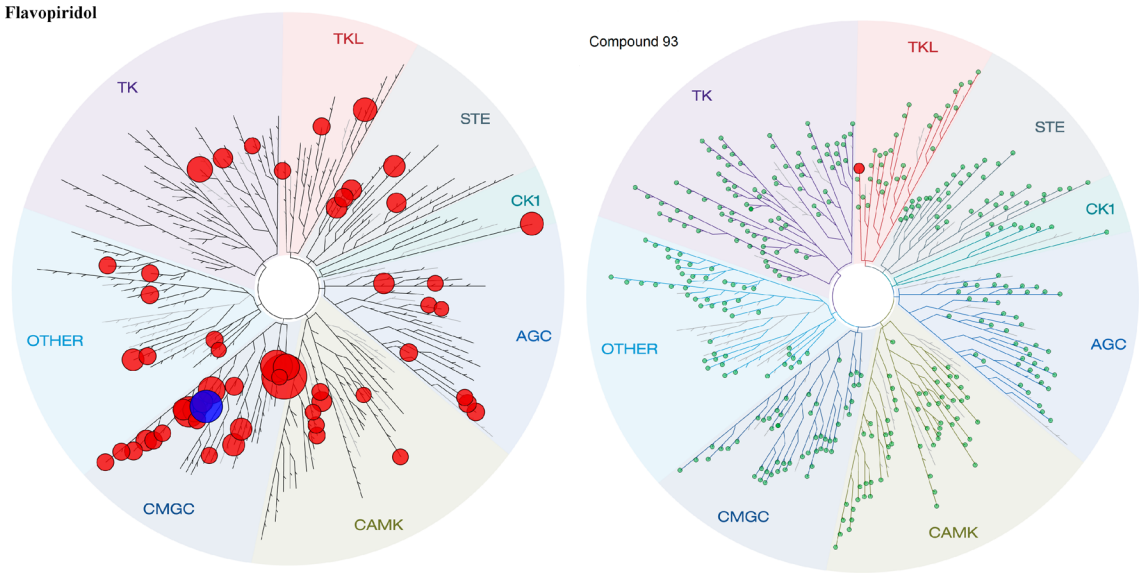

Figure 2. Kinase selectivity profiles of flavopiridol ($K_d \leq 1$ μM; CDK9 is highlighted with blue)[38] and compound **93**.

form of CDK9,[37] which was used in this assay. It does, however, inhibit the activity of CDK9/CycT1 in the nanomolar range.

According to these results the phosphonic acid **93** is a highly specific inhibitor of the CDK9/CycT1 complex. Generally, known CDK9 inhibitors inhibit other CDKs in the nanomolar range. The most selective CDK9 inhibitor published so far is LDC000067, which does not inhibit other CDKs, however, its off-targets are GSK3A and HGK/MAP4K4.[21] Although the structural similarities between our compounds and LDC000067 are obvious (compound **5**, Figure 1), specificity of compound **93** toward CDK9/CycT1 is higher.

Cell-Based Assays. Cytotoxic effect of selected compounds was tested in vitro on MT4 human T lymphocyte cell line by MTT cell proliferation assay. MT4 cells are ideal model for HIV-1 infection experiments.[39] After 7 days incubation with different compound concentrations (2500 and 1250 nM), we identified the proliferative activity of remaining cells. Viability was determined as relative value to the untreated cells (100%). Most of the compounds did not affect cell viability at 1250 nM; moreover compound **93** seemed to be triggering cell proliferation. The tested phosphonamidate **10**, phosphonate **23a**, and phosphonic acid **30a** showed some toxic effect at 2500 nM concentration (Table 10). According to these results, 1250 nM concentration was chosen for the HIV-1 proliferation assay.

Given the fact that CDK9/CycT1 is a validated target in HIV-1 infection, the most potent compounds were tested in an HIV-1 proliferation assay. This experiment is a cell proliferation assay

Table 10. Cell Viability on MT4 Cells after 7 Days Incubation

	viability (% of the ctrl)	
	2500 nM	1250 nM
10	29 ± 26	96 ± 22
21a	108 ± 62	78 ± 16
23a	76 ± 22	72 ± 20
30a	74 ± 14	78 ± 14
38	100 ± 20	91 ± 11
52a	94 ± 24	94 ± 18
52b	81 ± 9	66 ± 9
76	90 ± 15	90 ± 7
84	93 ± 13	86 ± 23
91	94 ± 27	98 ± 30
92	104 ± 18	110 ± 20
93	141 ± 11	158 ± 11

(MTT) on HIV-1 infected MT4 cells. Proliferation of virus infected cells decreased compared to noninfected ones. If the tested compound inhibited virus proliferation, higher proliferative activity would be observed compared to the untreated, infected control.[40] The HIV-1 infected untreated cells were considered to be 100%. The best CDK9 inhibitors from each group were tested. The treatment concentration was 1250 nM; AZT (azidothymidine) was used as the positive control[41] at 25 nM. Phosphonamidate **10**, phosphonates **21a**, **23a**, and **40a**, and phosphonic acid **30a** did not show any inhibition of HIV-1 proliferation. However, phosphinates (**52a**, **52b**, **84**, **91**−**93**) did

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protect MT4 cells against viral infection similarly to the positive control AZT. Higher viability correlated with lower CDK9 IC_{50}. Compound **76** did not fit to this trend. It was hypothesized that this molecule, as a phosphonic acid, may bind and inhibit some proteins other than CDK9 which are beneficial for HIV-1 proliferation inhibition (Table 11). This hypothesis is supported by the lower selectivity of phosphonic and phosphinic acids (**30b**, **76**, **79** in Table 8).

Table 11. HIV-1 Proliferation Assay in MT4 Cells

	viability (rel % to infected, untreated cells)	CDK9/CycT1 IC_{50} (nM)
10	102 ± 18	1453
21a	95 ± 15	813
23a	99 ± 23	870
30a	96 ± 20	1490
AZT	158 ± 24	
40a	96 ± 36	332
52a	105 ± 23	197
52b	131 ± 21	296
76	130 ± 31	429
AZT	132 ± 29	
84	148 ± 12	143
91	135 ± 16	212
92	124 ± 21	163
93	141 ± 25	142
AZT	135 ± 22	

Kinetics. For further development, it was beneficial to determine the mechanism of kinase inhibition. We hypothesized that these compounds were ATP-competitive inhibitors. To prove this theory, the kinase inhibition was measured at different ATP concentrations.[42] The inhibitor concentration was kept at a constant 260 nM in each experiment. Five ATP concentrations were applied: the K_{mATP} (for this enzyme it was 12 mM), two lower (4 and 1.33 mM) and two higher (36 and 108 mM) concentrations. If these compounds were ATP-competitive inhibitors, the value of the K_i would be half of the measured IC_{50} according to the Cheng–Prusoff equation,[43] and the ratio of IC_{50}/K_i would be increased at higher ATP concentration. According to the results (Figure 3), our compounds were shown to be ATP-competitive inhibitors.

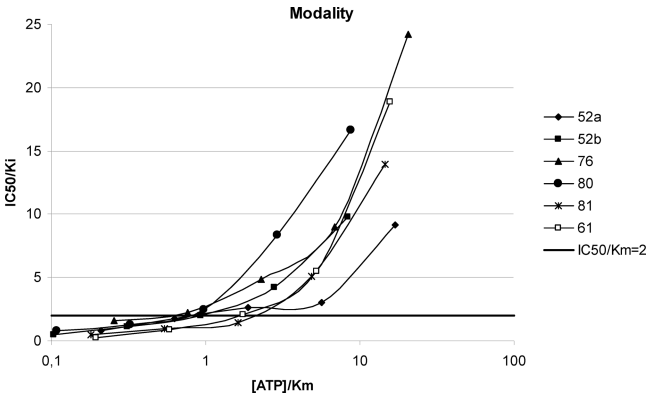

Figure 3. Determination of ATP competition of six inhibitors at 260 nM inhibitor concentration.

CONCLUSION

Different phosphinates, phosphonates, and phosphonamides were prepared in a few steps from readily available starting materials through affordable and general methods. They were considered as bioisosteres of sulfonamide-based CDK9 inhibitors. In these series, the most potent inhibitor was the phosphinic acid **93**, which was proved to be highly specific to CDK9/CycT1 and acts in an ATP-competitive manner. Although its inhibitory activity is slightly lower than the best CDK9 inhibitors in the literature, its high specificity for CKD9/CycT1 is exceptional. These results suggested that **93** would have the potential to control HIV-1 replication in vivo while having a lower risk of inhibiting other kinases and consequently causing undesired toxicity.

In general, these results demonstrate the bioisosteric utility of the phosphonamidate, phosphonate, and phosphinate moieties in the design of novel kinase inhibitors.

EXPERIMENTAL SECTION

Reagents and solvents were purchased from Sigma-Aldrich Co., AlfaAesar Ltd., or Apollo Ltd. and were used without further purification or drying. Melting points were measured on a Buchi B-540 apparatus, and measured data are uncorrected. For column chromatography, Merck silica gel 60 (35–70 μm) was used or Silica gel 60 F254 1 mm preparative thin layer plates were applied from Merck GmbH. NMR spectra were recorded on different apparatus as it is indicated in the assignation:

A Bruker AC 300 for ^{1}H-300 MHz, ^{31}P-121 MHz, ^{13}C-75 MHz measurements.

A Bruker AC 400 for ^{1}H-400 MHz, ^{31}P-162 MHz, ^{13}C-101 MHz measurements.

A Bruker AC 250 for ^{1}H-250 MHz, ^{31}P-101 MHz, ^{13}C-63 MHz measurements.

A Varian Unity Inova 600 for ^{1}H-600 MHz, ^{31}P-242 MHz measurements.

Chemical shifts are given in parts per million (δ) referenced to TMS (δ = 0.00 ppm ^{1}H-, ^{13}C NMR) or 85% H_3PO_4 (δ = 0.00 ppm ^{31}P NMR). Coupling constants are given in hertz. Electrospray ionization mass spectra were recorded on Waters 2795 HPLC, equipped with Waters 996 photodiode array detector and Micromass ZMD 2000 LC-MS system, which were also used to determine the purity of certain materials. Retention times concern to a Supelco Discovery C18, 5 cm × 4.6 mm, 5 μm column. Eluents were water/0.05% HCOOH and MeCN/0.05% HCOOH in gradient. Flow rate was 2 mL/min. Injected quantity of each sample was 3 μg. MW-reactor: for 0,2–20 mL, a Personal Chemistry, Emrys Creator; for 30–1000 mL, a Milestone Inc., Ethos MicroSYNTH Labstation reactor was used. Purity of prepared compounds was determined by LC-MS, ^{1}H and ^{31}P NMR. All compounds tested in biological assay were >95%. Purity of intermediates was >90%, unless otherwise stated.

Chemistry. *Ethyl Ethylphosphonochloridate (**8a**).* Ethyl diethylphosphonate (0.84 mL, 5 mmol) and one drop of dry DMF were dissolved in dry CH_2Cl_2 (5 mL). The mixture was cooled to 0 °C, and oxalyl chloride (1.27 mL, 15 mmol) was added slowly. The mixture was stirred at ambient temperature for 5–6 h then the volatiles were evaporated and additional CH_2Cl_2 (10 mL) was evaporated two more times to obtain 0.704 g (90%) as a brown oil. Product was used without further purification. ^{31}P NMR ($CDCl_3$, 162 MHz): δ 46.7 ppm. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.10–4.30 (m, 2H), 2.00–2.15 (m, 2H), 1.28–1.38 (m, 3H), 1.13–1.27 (m, 3H).

*Isopropyl Propylphosphonochloridate (**8b**).* Triisopropyl-phosphite (12.3 mL, 50 mmol) and 1-bromopropane (18.2 mL, 200 mmol) were reacted in Arbuzov reaction at 150 °C for 4 h in a microwave reactor. The product (**7b**) was purified by vacuum distillation, and a colorless oil was obtained (6.551 g, 63%); bp = 72–76 °C (3.35 mbar). ^{31}P NMR ($CDCl_3$,162 MHz): δ 30.3 ppm. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 4.60–4.70 (m, 2H), 1.55–1.70 (m, 4H), 1.20–

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1.30 (m, 12H), 0.92−1.00 (m, 3H). The acid chloride was prepared with the method described for the preparation of **8a**; 0.830 g (90%) of a brown oil was obtained. ^{31}P NMR ($CDCl_3$, 162 MHz): δ 43.2 ppm. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 4.80−4.95 (m, 1H), 1.95−2.13 (m, 2H), 1.55−1.80 (m, 2H), 1.20−1.40 (m, 6H), 0.90−1.05 (m, 3H).

*Ethyl Phenylphosphonochloridoate (**8c**).* Compound **8c** was prepared according to the method used for **8a**, but the mixture was refluxed for 24 h, giving a brown oil (0.920 g, 90%). Product **8c** was used without further purification. ^{31}P NMR ($CDCl_3$, 162 MHz): δ 29.3 ppm. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.75−7.95 (m, 2H), 7.50−7.6 (m, 1H), 7.35−7.5 (m, 2H), 4.25−4.45 (m, 2H), 1.43 (t, $^3J_{HH}$ = 7.1 Hz, 3H).

*N^1-[6-(2-Methoxyphenyl)pyrimidin-4-yl]-4-methylbenzene-1,3-diamine (**9**).* 2-Methyl-5-nito aniline (1.52 g, 10 mmol) was dissolved in dry pyridine (50 mL). Isobutyl chloroformate (1.42 mL, 11 mmol) was added in one portion. The reaction mixture was stirred at RT overnight then evaporated to dryness. The crude product was suspended in 1 M HCl and the precipitate was filtered off and the resulting solid was dried in a desiccator over P_2O_5, giving a yellow powder (1.915 g, 76%). If necessary, it can be recrystallized from 2-propanol; mp = 118 °C (IPA). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.74 (s, 1H), 7.8 (dd, $^3J_{HH}$ = 8.3 Hz, $^4J_{HH}$ = 2.3 Hz, 1H), 7.23 (d, $^3J_{HH}$ = 8.6 Hz, 1H), 6.45 (s, 1H), 3.94 (d, $^3J_{HH}$ = 6.8 Hz, 2H), 2.29 (s, 3H), 1.95 (m, 1H), 0.92 (d, $^3J_{HH}$ = 6.8 Hz, 6H). The (2-methyl-5-nitro-phenyl)-carbamic acid isobutyl ester was dissolved in MeOH (5 mmol in 100 mL), and 10% Pd/C (10% w/w) was added to the solution. The mixture was stirred under atmospheric pressure of H_2. When the consumption of H_2 was finished, the catalyst was filtered off through a pad of celite and washed with MeOH. The filtrate was evaporated to give (5-amino-2-methyl-phenyl)-carbamic acid isobutyl ester as a pink or brown powder (∼80%); mp = 100−101 °C (MeOH). ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.34 (s, 1H), 6.94 (d, $^3J_{HH}$ = 8.0 Hz, 1H), 6.38 (dd, $^3J_{HH}$ = 8.0 Hz, $^4J_{HH}$ = 2.3 Hz, 2H), 3.97 (d, $^3J_{HH}$ = 6.8 Hz, 2H), 3.05 (br, 2H), 2.17 (s, 3H), 2.00 (m, 1H), 0.99 (d, $^3J_{HH}$ = 6.8 Hz, 6H). (5-Amino-2-methyl-phenyl)-carbamic acid isobutyl ester (0.222 g, 1 mmol) and 4-chloro-6-(2-methoxy-phenyl)-pyrimidine **13a** (0.22 g, 1 mmol) were dissolved in 2-propanol (10 mL) then a solution of HCl saturated 2-propanol (2 mL) was added to the mixture. The reaction mixture was refluxed for 3−4 h then it was concentrated under vacuum. The residue was suspended in satd $NaHCO_3$ and extracted with EtOAc:THF (2:1, 3 × 50 mL). The combined organics were washed with brine and dried with Na_2SO_4. After evaporation of solvents under reduced pressure, the crude product was recrystallized from MeCN to give the {5-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-2-methyl-phenyl}-carbamic acid isobutyl ester as a pale-yellow powder (0.304 g, 75%); mp = 155 °C (MeCN). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.58 (s, 1H), 8.84 (s, 1H), 8.66 (d, $^4J_{HH}$ = 1.2 Hz, 1H), 7.95 (dd, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 1.8 Hz, 1H), 7.68 (d, $^4J_{HH}$ = 2.3 Hz, 1H), 7.47 (m, 2H), 7.43 (d, $^4J_{HH}$ = 1.2 Hz, 1H), 7.18 (d, $^3J_{HH}$ = 7.6 Hz, 1H), 7.14 (d, $^3J_{HH}$ = 8.8 Hz, 1H), 7.07 (td, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.0 Hz, 1H), 3.9 (s, 3H), 3.86 (d, $^3J_{HH}$ = 6.8 Hz, 2H), 2.17 (s, 3H), 1.92 (m, 1H), 0.94 (d, $^3J_{HH}$ = 6.8 Hz, 6H). MS[ES$^+$, Q-TOF]: M + H$^+$ = 407.25 *m*/*z*, 2M + H$^+$ = 813.41 *m*/*z*. The {5-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-2-methyl-phenyl}-carbamic acid isobutyl ester and 5 mol equiv of KOH were refluxed overnight in EtOH:water (4:1, 1 mmol in 50 mL). The reaction mixture was concentrated under vacuum, and the residue was suspended in water and 0.5 mL of EtOAc. This mixture was stirred for 15 min, and then it was filtered off. The white powder was washed with Et_2O (80%). If necessary, it can be recrystallized from MeCN; mp = 168 °C (MeCN). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.19 (s, 1H), 8.54 (s, 1H), 7.85 (dd, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.8 Hz, 1H), 7.37 (dd, $^3J_{HH}$ = 8.4 Hz, $^4J_{HH}$ = 1,8 Hz, 1H), 7.31 (d, $^4J_{HH}$ = 1.3 Hz, 1H), 7.08 (d, $^3J_{HH}$ = 7.6 Hz, 1H), 6.99 (dd, $^3J_{HH}$ = 7.6 Hz, 1H), 6.86 (s, 1H), 6.79 (d, $^3J_{HH}$ = 8.1 Hz, 1H), 6.66 (d, $^3J_{HH}$ = 7.8 Hz, 1H), 4.79 (br, 2H), 3.81 (s, 3H), 1.95 (s, 3H). MS[ES$^+$, Q-TOF]: M + H$^+$ = 307,18 *m*/*z*.

General Procedure for the Preparation of Phosphonamidates. The aniline **9** (0.061 g, 0.2 mmol) was dissolved in dry pyridine (5 mL) and the appropriate phosphonic acid **8a−c** (0.4 mmol) was added and the mixture was stirred at 50 °C for 24 h under N_2 atmosphere. The volatiles were evaporated then the residue was suspended in satd NH_4Cl aqueous solution (10 mL). The product was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with 1 M aqueous NaOH (2 × 10 mL), with brine (30 mL), and dried with Na_2SO_4. After concentration under vacuum, the crude product was further purified by preparative TLC with 100% EtOAc as eluent. For the required purity, two−three elutions were necessary. The desired product was washed with MeOH from silica. If the product contained some traces of phosphonic acid (coming from its hydrolysis on silica), it was dissolved in CH_2Cl_2 (20 mL) washed with 1 M aqueous NaOH (20 mL), dried with Na_2SO_4, and evaporated. The product was recrystallized from MeCN.

*Ethyl P-Ethyl-N-(5-{[6-(2-methoxyphenyl)pyrimidin-4-yl]amino}-2-methylphenyl)phosphonamidate (**10**).* Prepared by the reaction of aniline **9** and phosphonochloridate **8a**. Cream-colored powder (0.014 g, 17%); mp = ∼RT, amorphous. ^{31}P NMR (DMSO-d_6, 162 MHz): δ 32.1 ppm. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.58 (s, 1H), 8.62 (d, $^4J_{HH}$ = 1.1 Hz, 1H), 7.91 (dd, $^3J_{HH}$ = 7.7 Hz, $^4J_{HH}$ = 1.8 Hz, 1H), 7.56 (d, $^4J_{HH}$ = 2.0 Hz, 1H), 7.42−7.48 (m, 1H), 7.41 (d, $^4J_{HH}$ = 1.1 Hz, 1H), 7.31 (dd, $^3J_{HH}$ = 8.3 Hz, $^4J_{HH}$ = 2.0 Hz, 1H), 7.17 (d, $^3J_{HH}$ = 7.7 Hz, 1H), 7.04−7.10 (m, 2H), 6.48 (d, $^2J_{PH}J_{PH}$ = 7.3 Hz, 1H), 3.95−4.01 (m, 2H), 3.88 (s, 3H), 2.19 (s, 3H), 1.75−1.90 (m, 2H), 1.25 (t, $^3J_{HH}$ = 6.8 Hz, 3H), 1.05 (dt, $^3J_{PH}$ = 19.7 Hz, $^3J_{HH}$ = 7.6 Hz, 3H). MS[ES$^+$, Q-TOF]: M + H$^+$ = 427.23 *m*/*z*; 2M + H$^+$ = 853.35 *m*/*z*.

*Isopropyl N-(5-{[6-(2-Methoxyphenyl)pyrimidin-4-yl]amino}-2-methylphenyl)-P-propylphosphonamidate (**11**).* Prepared by the reaction of aniline **9** and phosphonochloridate **8b**. Creamy colored powder (0.008 g, 9%); mp = 151 °C (MeCN). ^{31}P NMR (DMSO-d_6, 162 MHz): δ 29.3 ppm. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.52 (s, 1H), 8.62 (s, 1H), 7.92 (d, $^3J_{HH}$ = 6.1 Hz, 1H), 7.6 (s, 1H), 7.42−7.48 (m, 1H), 7.41 (s, 1H), 7.27 (d, $^3J_{HH}$ = 6.1 Hz, 1H), 7.17 (d, $^3J_{HH}$ = 8.6 Hz, 1H), 7.04−7.10 (m, 2H), 6.38 (d, $^3J_{HH}$ = 7.1 Hz; 1H), 4.57−4.67 (m, 1H), 3.89 (s, 3H), 2.19 (s, 3H), 1.70−1.90 (m, 2H), 1.48−1.60 (m, 2H), 1.24 (dd, $^4J_{PH}$ = 25.2 Hz, $^3J_{HH}$ = 6.1 Hz, 6H), 1.0 (dt, $^4J_{PH}$ = 40.6 Hz, $^3J_{HH}$ = 7.2 Hz, 3H). MS[ES$^+$, Q-TOF]: M + H$^+$ = 455.27 *m*/*z*.

*Ethyl N-(5-{[6-(2-Methoxyphenyl)pyrimidin-4-yl]amino}-2-methylphenyl)-P-phenylphosphonamidate (**12**).* Prepared by the reaction of aniline **9** and phosphonochloridate **8c**. Creamy colored powder (0.017 g, 18%); mp = 172 °C (MeCN). ^{31}P NMR (DMSO-d_6, 162 MHz): δ 17.2 ppm. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.46 (s, 1H), 8.58 (s, 1H), 7.91 (d, $^3J_{HH}$ = 9.2 Hz, 1H), 7.82 (dd, $^3J_{PH}$ = 12.8 Hz, $^3J_{HH}$ = 7.2 Hz, 2H), 7.53−7.59 (m, 2H), 7.46−7.53 (m, 2H), 7.45 (t, $^3J_{HH}$ = 8.4 Hz, 1H), 7.36 (s, 1H), 7.26 (d, $^3J_{HH}$ = 7.7 Hz, 1H), 7.17 (d, $^3J_{HH}$ = 8.5 Hz, 1H), 7.08 (t, $^3J_{HH}$ = 7.4 Hz, 1H), 6.99−7.05 (m, 2H), 4.10 (dq, $^3J_{PH}$ ≈ $^3J_{HH}$ ≈ 7.2 Hz, 2H), 3.88 (s, 3H), 2.19 (s, 3H), 1.29 (t, $^3J_{HH}$ = 7.2 Hz, 3H). MS[ES$^+$, Q-TOF]: M + H$^+$ = 475.21 *m*/*z*; 2 M + H$^+$ = 949.39 *m*/*z*.

*4-Chloro-6-(2-methoxyphenyl)pyrimidine (**13a**) and 4-Chloro-6-(3-nitrophenyl)pyrimidine (**13b**).* These compounds were prepared according to ref 5.

*5-{[6-(2-Methoxyphenyl)pyrimidin-4-yl]amino}-2-methylphenol (**15**).* 5-Amino-2-methyl-phenol **14a** (0.682 g, 5.5 mmol) and 4-chloro-6-(2-methoxy-phenyl)-pyrimidine **13a** (1.10 g, 5.0 mmol) were dissolved in 2-propanol (25 mL) then HCl saturated 2-propanol (5 mL) was added to the mixture. The reaction mixture was refluxed for 1 h then it was evaporated. The residue was suspended in satd $NaHCO_3$ and extracted with EtOAc (3 × 50 mL). The combined organics were washed with brine and dried with Na_2SO_4. After evaporation under reduced pressure, the crude product was recrystallized from MeCN to give a pale-yellow, cream-colored powder (0.924 g, 60%); mp = 220−223 °C (MeCN). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.42 (s, 1H, exch with D_2O), 9.32 (s, 1H, exch with D_2O), 8.65 (d, $^4J_{HH}$ = 1.2 Hz, 1H), 7.93 (dd, $^3J_{HH}$ = 7.7 Hz, $^4J_{HH}$ = 1.8 Hz, 1H), 7.45 (td, $^3J_{HH}$ = 7.5 Hz, $^4J_{HH}$ = 1.8 Hz, 1H), 7.40 (d, $^4J_{HH}$ = 1.1 Hz, 1H), 7.27 (s, 1H), 7.17 (d, $^3J_{HH}$ = 7.8 Hz, 1H), 7.08 (td, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 1.0 Hz, 1H), 6.98 (m, 2H), 3.89 (s, 3H), 2.08 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 160.4 (1C), 159.2 (1C), 157.8 (1C), 157.5 (1C), 155.3 (1C), 138.4 (1C), 131.0 (1C), 130.3 (1C), 130.1 (1C), 125.9 (1C), 120.5 (1C), 118.0 (1C), 112.0 (2C), 110.6 (1C), 106.7 (1C), 55.7 (1C), 15.5 (1C). MS[ES+, Q-TOF]: M + H$^+$ = 308.13 *m*/*z*.

*2-Methyl-5-{[6-(3-nitrophenyl)pyrimidin-4-yl]amino}phenol (**16**).* **16** was prepared according to the procedure used for compound **15** starting from 5-amino-2-methyl-phenol **14a** (0.677 g, 5.5 mmol) and 4-

chloro-6-(3-nitrophenyl)-pyrimidine **13b** (1.178 g, 5.0 mmol). **16** was recrystallized from MeCN to give a yellow powder (0.757 g, 47%); mp = 240−245 °C (MeCN). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.58 (s, 1H), 9.34 (s, 1H), 8.81 (s, 1H), 8.73 (s, 1H), 8.43 (s, 1H), 8.36 (s, 1H), 7.83 (s, 1H), 7.34 (s, 1H), 7.26 (s, 1H), 7.00 (s, 2H), 2.09 (s, 3H). Each peak is a broad singlet. LC-MS: R_t = 3.44 min. (ESI): m/z = 323 $[M + H]^+$.

*3-{[6-(2-Methoxyphenyl)pyrimidin-4-yl]amino}phenol (**17**).* **17** was prepared according to the procedure used for compound **15** starting from 3-amino-phenol **14b** (0.600 g, 5.5 mmol) and 4-chloro-6-(2-methoxyphenyl)-pyrimidine **13a** (1.100 g, 5.0 mmol). **17** was recrystallized from MeCN to give a yellow powder (0.923 g, 63%); mp = 217 °C (MeCN). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.5 (s, 1H), 9.38 (s, 1H), 8.68 (s, 1H), 7.95 (dd, $^3J_{HH}$ = 7.7 Hz, $^4J_{HH}$ = 1.7 Hz, 1H), 7.40−7.50 (m, 1H), 7.46 (s, 1H), 7.28 (s, 1H), 7.17 (d, $^3J_{HH}$ = 8.2 Hz, 1H), 7.05−7.15 (m, 3H), 6.43 (d, $^3J_{HH}$ = 7.4 Hz, 1H), 3.90 (s, 3H). LC-MS: R_t = 0.47 min; 1.98 min; 2.25 min. (ESI): m/z = 294 $[M + H]^+$.

*3-{[6-(3-Nitrophenyl)pyrimidin-4-yl]amino}phenol (**18**).* **18** was prepared according to the procedure used for compound **15** starting from 3-amino-phenol **14b** (0.600 g, 5.5 mmol) and 4-chloro-6-(3-nitrophenyl)-pyrimidine **13b** (1.178 g, 5.0 mmol). **18** was recrystallized from MeCN to give a yellow powder (1.17 g, 76%); mp = 250−252 °C (MeCN). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 10.31 (br, 1H), 9.5 (br, 1H), 8.82 (s, 1H), 8.78 (s, 1H), 8.43 (d, $^3J_{HH}$ = 7.8 Hz, 1H), 8.38 (d, $^3J_{HH}$ = 7.8 Hz, 1H), 7.86 (t, $^3J_{HH}$ = 7.9 Hz, 1H), 7.58 (s, 1H), 7.33 (s, 1H), 7.08−7.33 (m, 2H), 6.5 (d, $^3J_{HH}$ = 7.8 Hz, 1H). LC-MS: R_t = 3.20 min. (ESI): m/z = 309 $[M + H]^+$.

*4-{[6-(2-Methoxyphenyl)pyrimidin-4-yl]amino}phenol (**19**).* It was prepared according to the procedure used for compound **15** starting from 4-amino-phenol **14c** (0.600 g, 5.5 mmol) and 4-chloro-6-(2-methoxyphenyl)-pyrimidine **13a** (1.100 g, 5.0 mmol). **19** was recrystallized from MeCN to give a brown powder (0.835 g, 57%); mp = 249 °C (MeCN). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.29 (s, 1H), 9.2 (s, 1H), 8.58 (s, 1H), 7.91 (d, $^3J_{HH}$ = 6.6 Hz, 1H), 7.38−7.5 (m, 3H), 7.29 (s, 1H), 7.15 (d, $^3J_{HH}$ = 8.3 Hz, 1H), 7.06 (t, $^3J_{HH}$ = 7.5 Hz, 1H), 6.75 (d, $J_{AABB}J_{AABB}$ = 8.7 Hz, 2H), 3.86 (s, 3H). LC-MS: R_tR_t = 0.45 min; 1.85 min; 2.27 min. (ESI): m/z = 294 $[M + H]^+$.

*4-{[6-(3-Nitrophenyl)pyrimidin-4-yl]amino}phenol (**20**).* It was prepared according to the procedure used for compound **15** starting from 4-amino-phenol **14c** (0.600 g, 5.5 mmol) and 4-chloro-6-(3-nitrophenyl)-pyrimidine **13b** (1.178 g, 5.0 mmol). **20** was filtered from Et_2O to give a yellow powder (1.263 g, 82%); mp = 242−243 °C (Et_2O). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.49 (br, 2H), 8.79 (s, 1H), 8.66 (s, 1H), 8.41 (d, $^3J_{HH}$ = 6.3 Hz, 1H), 8.34 (d, $^3J_{HH}$ = 7.4 Hz, 1H), 7.82 (t, $^3J_{HH}$ = 7.5 Hz, 1H), 7.41 (d, J_{AABB} = 7.0 Hz, 2H), 7.22 (s, 1H), 6.77 (d, J_{AABB} = 7.5 Hz, 2H). LC-MS: R_t = 2.85 min. (ESI): m/z = 309 $[M + H]^+$.

General Procedure for the Preparation of Phosphonates (Ar-O-P(O)ROR′). The appropriate phenol (**15**−**20**) (0.5 mmol) was dissolved in anhydrous THF (25 mL) then KOtBu (0.067 g, 0.6 mmol) was added in one portion. The mixture was stirred for 30 min at RT, and then the corresponding phosphonochloridate **8a**−**c** (0.75 mmol) was added. The reaction mixture was stirred overnight at RT and concentrated under vacuum. The residue was suspended in 2 M aqueous NaOH (30 mL), and it was extracted with EtOAc (3 × 70 mL). The combined organic phases were washed with brine, dried with $MgSO_4$, and evaporated. For further purification and characterization see the individual compounds.

*Ethyl 5-{[6-(2-Methoxyphenyl)pyrimidin-4-yl]amino}-2-methylphenyl Ethylphosphonate (**21a**).* **21a** was prepared by the reaction of phenol **15** and phosphonochloridate **8a**. It was purified by column chromatography: 100% EtOAc to EtOAc:MeOH (1:1) in gradient. **21a** was crystallized from MeCN to give a white powder (0.062 g, 29%); mp = 134−135 °C (MeCN). ^{31}P NMR (162 MHz): DMSO-d_6, δ 30.9 ppm. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.76 (s, 1H), 8.68 (s, 1H), 7.95 (dd, $^3J_{HH}$ = 7.7 Hz, $^4J_{HH}$ = 1.7 Hz, 1H), 7.75 (s, 1H), 7.43−7.51 (m, 3H), 7.21 (d, $^3J_{HH}$ = 8.0 Hz, 1H), 7.19 (d, $^3J_{HH}$ = 8.0 Hz), 7.08 (t, $^3J_{HH}$ = 7.9 Hz, 1H), 4.07−4.20 (m, 2H), 3.9 (s, 3H), 2.2 (s, 3H), 1.97 (dq, $^2J_{PH}$ = 17.8 Hz, $^3J_{HH}$ = 7.6 Hz, 2H), 1.25 (t, $^3J_{HH}$ = 7.0 Hz, 3H), 1.16 (dt, $^3J_{PH}$ = 20.6 Hz, $^3J_{HH}$ = 7.6 Hz, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 160.2 (1C), 159.4 (1C), 157.7 (1C), 157.5 (1C), 148.5 (d, $^2J_{PC}$ = 9.5 Hz, 1C), 138.8 (d, $^4J_{PC}$ = 1.5 Hz, 1C), 131.2 (1C), 131.0 (1C), 130.1 (1C), 125.7 (1C), 122.3 (d, $^3J_{PC}$ = 4.4 Hz, 1C), 120.6 (1C), 115.7 (1C), 112.1 (1C), 111.4 (d, $^3J_{PC}$ = 2.9 Hz, 1C), 107.2 (1C), 62.1 (d, $^2J_{PC}J_{PC}$ = 6.6 Hz, 1C), 55.7 (1C), 18.4 (d, $^1J_{PC}$ = 140.5 Hz, 1C), 16.2 (d, $^3J_{PC}$ = 5.1 Hz, 1C), 15.5 (1C), 6.5 (1C). MS[ES$^+$, Q-TOF]: M + H$^+$ = 428.12 m/z; 2 M + H$^+$ = 855.27 m/z.

*Isopropyl 5-{[6-(2-Methoxyphenyl)pyrimidin-4-yl]amino}-2-methylphenyl propylphosphonate (**21b**).* **21b** was prepared by the reaction of phenol **15** and phosphonochloridate **8b**. It was purified by column chromatography in 100% EtOAc. **21b** was crystallized from diisopropylether to give a white powder (0.118 g, 52%). ^{31}P NMR (DMSO-d_6, 162 MHz): δ 28.5 ppm. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.71 (s, 1H), 8.67 (d, $^5J_{HH}$ = 1.0 Hz, 1H), 7.95 (dd, $^3J_{HH}$ = 7.7 Hz, $^4J_{HH}$ = 1.8 Hz, 1H), 7.77 (s, 1H), 7.44−7.48 (m, 2H), 7.45 (d, $^5J_{HH}$ = 1.2 Hz, 1H), 7.21 (d, $^3J_{HH}$ = 7.8 Hz, 1H), 7.18 (d, $^3J_{HH}$ = 7.6 Hz, 1H), 7.09 (t, $^3J_{HH}$ = 6.7 Hz, 1H), 4.65−4.75 (m, 1H), 3.91 (s, 3H), 2.19 (s, 3H), 1.88−1.99 (m, 2H), 1.56−1.71 (m, 2H), 1.28 (d, $^3J_{HH}$ = 6.1 Hz, 3H), 1.18 (d, $^3J_{HH}$ = 6.1 Hz, 3H), 1.02 (dt, $^3J_{HH}$ = 7.4 Hz, $^4J_{PH}$ = 1.4 Hz, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 160.2 (1C), 159.4 (1C), 157.6 (1C), 157.5 (1C), 148.6 (d, $^2J_{PC}$ = 8.6 Hz, 1C), 138.8 (d, $^4J_{PC}$ = 1.2 Hz, 1C), 131.2 (1C), 131.0 (1C), 130.1 (1C), 125.7 (1C), 122.3 (d, $^3J_{PC}$ = 5.5 Hz, 1C), 120.6 (1C), 115.6 (1C), 112.1 (1C), 111.6 (1C), 107.1 (1C), 70.5 (d, $^2J_{PC}$ = 6.7 Hz, 1C), 55.7 (1C), 27.8 (d, $^1J_{PC}$ = 139.7 Hz, 1C), 23.7 (d, $^3J_{PC}$ = 4.3 Hz, 1C), 23.5 (d, $^3J_{PC}$ = 4.3 Hz, 1C), 15.9 (d, $^2J_{PC}$ = 5.5 Hz, 1C), 15.6 (1C), 14.9 (d, $^3J_{PC}$ = 17.2 Hz, 1C). MS[ES$^+$, Q-TOF]: M + H$^+$ = 456.17 m/z; 2 M + H$^+$ = 911.36 m/z.

*Ethyl 5-{[6-(2-Methoxyphenyl)pyrimidin-4-yl]amino}-2-methylphenyl Phenylphosphonate (**21c**).* **21c** was prepared by the reaction of phenol **15** and phosphonochloridate **8c**. It was purified by column chromatography in EtOAc:hexane (9:1). **21c** was crystallized from MeCN to give a white powder (0.021 g, 9%); mp = 146 °C (MeCN). ^{31}P NMR (DMSO-d_6, 162 MHz): δ 14.7 ppm. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.69 (s, 1H), 8.62 (s, 1H), 7.95 (dd, $^3J_{HH}$ = 7.5 Hz, $^4J_{HH}$ = 1.7 Hz, 1H), 7.83−7.89 (m, 2H), 7.76 (s, 1H), 7.67−7.73 (m, 1H), 7.58−7.63 (m, 2H), 7.44−7.48 (m, 1H), 7.42 (s, 1H), 7.40−7.42 (m, 1H), 7.18 (d, $^3J_{HH}$ = 8.6 Hz, 2H), 7.09 (t, $^3J_{HH}$ = 7.3 Hz, 1H), 4.21 (m, 2H), 3.90 (s, 3H), 2.15 (s, 3H), 1.29 (t, $^3J_{HH}$ = 7.0 Hz, 3H). MS[ES$^+$, Q-TOF]: M + H$^+$ = 476.1 m/z; 2 M + H$^+$ = 951.25 m/z.

*Ethyl 2-Methyl-5-{[6-(3-nitrophenyl)pyrimidin-4-yl]amino}phenyl Ethylphosphonate (**22a**).* **22a** was prepared by the reaction of phenol **16** and phosphonochloridate **8a**. **22a** was recrystallized from MeCN to give a pale-yellow powder (0.177 g, 79%); mp = 194−195 °C (MeCN). ^{31}P NMR (DMSO-d_6, 243 MHz): δ 29.8 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.9 (s, 1H), 8.83 (s, 1H), 8.76 (s, 1H), 8.46 (d, $^3J_{HH}$ = 7.6 Hz, 1H), 8.36 (d, $^3J_{HH}$ = 7.9 Hz, 1H), 7.84 (t, $^3J_{HH}$ = 7.9 Hz, 1H), 7.74 (s, 1H), 7.46 (d, $^3J_{HH}$ = 7.9 Hz, 1H), 7.32 (s, 1H), 7.23 (d, $^3J_{HH}$ = 8.1 Hz, 1H), 4.07−4.19 (m, 2H), 2.21 (s, 3H), 1.91−2.07 (m, 2H), 1.25 (t, $^3J_{HH}$ = 7.0 Hz, 3H), 1.13 (dt, $^3J_{PH}$ = 20.5 Hz, $^3J_{HH}$ = 7.6 Hz, 3H). LC-MS: R_t = 4.05 min. (ESI): m/z = 443 $[M + H]^+$.

*Isopropyl 2-Methyl-5-{[6-(3-nitrophenyl)pyrimidin-4-yl]amino}-phenyl Propylphosphonate (**22b**).* **22b** was prepared by the reaction of phenol **16** and phosphonochloridate **8b**. **22b** was recrystallized from MeCN to give a pale-yellow powder (0.111 g, 47%); mp = 164−166 °C (MeCN). ^{31}P NMR (DMSO-d_6, 243 MHz): δ 27.6 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.85 (s, 1H), 8.82 (s, 1H), 8.74 (s, 1H), 8.45 (d, $^3J_{HH}$ = 7.8 Hz, 1H), 8.35 (dd, $^3J_{HH}$ = 7.4 Hz, $^4J_{HH}$ = 1.4 Hz, 1H), 7.83 (t, $^3J_{HH}$ = 8.0 Hz, 1H), 7.74 (s, 1H), 7.44 (d, $^3J_{HH}$ = 8.1 Hz, 1H), 7.36 (s, 1H), 7.21 (d, $^3J_{HH}$ = 8.3 Hz, 1H), 4.65−4.72 (m, 1H), 2.19 (s, 3H), 1.86−1.98 (m, 2H), 1.58−1.66 (m, 2H), 1.27 (d, $^3J_{HH}$ = 6.1 Hz, 3H), 1.17 (d, $^3J_{HH}$ = 6.1 Hz, 3H), 1.01 (t, $^3J_{HH}$ = 7.1 Hz, 3H). LC-MS: R_t = 4.55 min. (ESI): m/z = 271 $[M + H]^+$.

*5-{[6-(3-Aminophenyl)pyrimidin-4-yl]amino}-2-methylphenyl Ethyl Ethylphosphonate (**23a**).* The nitro-compound **22a** (0.049 g, 0.11 mmol) was dissolved in the mixture of MeOH:CH_2Cl_2 (20 mL:10 mL). Ammonium formate (0.069 g, 1.1 mmol) and 10% Pd/C (0.005 g, 10% w/w) were added. Reaction mixture was stirred under inert atmosphere overnight at RT. After the reduction was completed, catalyst was filtered off on a celite pad and washed with MeOH (10 mL). Filtrate was concentrated under vacuum. The residue was suspended in satd aqueous Na_2CO_3 (30 mL) and extracted with EtOAc (3 × 70 mL). The combined organic phases were washed with brine and dried with $MgSO_4$. After evaporation, the product **23a** was crystallized from the

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mixture of 2-propanol and hexane to obtain an off-white powder (0.031 g, 67%); mp = 148−150 °C (*i*-PrOH, hexane). ^{31}P NMR (DMSO-d_6, 243 MHz): δ 29.9 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.66 (s, 1H), 8.63 (s, 1H), 7.70 (s, 1H), 7.42 (d, $^3J_{HH}$ = 7.6 Hz, 1H), 7.28 (s, 1H), 7.19 (d, $^3J_{HH}$ = 8.4 Hz, 1H), 7.00−7.20 (m, 3H), 6.60−6.70 (m, 1H), 5.24 (br, 2H), 4.11 (q, $^3J_{HH}$ = 6.7 Hz, 2H), 2.18 (s, 3H), 1.89−2.19 (m, 2H), 1.23 (t, $^3J_{HH}$ = 6.7 Hz, 3H), 1.14 (dt, $^3J_{PH}$ = 20.4 Hz, $^3J_{HH}$ = 7.4 Hz, 3H). LC-MS: R_t = 2.69 min. (ESI): m/z = 413 $[M + H]^+$.

*5-{[6-(3-Aminophenyl)pyrimidin-4-yl]amino}-2-methylphenyl Isopropyl Propylphosphonate (**23b**).* The nitro-compound **22b** (0.094 g, 0.2 mmol) was reduced with the method used for **23a**. After evaporation of organic phases, the product was dissolved in dry EtOAc (5 mL) and the HCl salt was prepared with 0.5 mL of EtOAc satd with HCl. The precipitate was filtered and washed with Et_2O, affording a yellow powder (0.060 g, 63%); mp = 165 °C dec (EtOAc). ^{31}P NMR (DMSO-d_6, 243 MHz): δ 27.7 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 11.00 (s, 1H), 8.82 (s, 1H), 7.73 (br, 2H), 7.20−7.60 (m, 7H), 6.00 (br, 2H), 4.65−4.70 (m, 1H), 2.22 (s, 3H), 1.89−2.21 (m, 2H), 1.60−1.65 (m, 2H), 1.27 (d, $^3J_{HH}$ = 5.6 Hz, 3H), 1.18 (d, $^3J_{HH}$ = 5.6 Hz, 3H) 1.14 (t, $^3J_{HH}$ = 6.8 Hz, 3H). LC-MS: R_t = 3.08 min. (ESI): m/z = 441 $[M + H]^+$.

*Ethyl 3-{[6-(2-Methoxyphenyl)pyrimidin-4-yl]amino}phenyl Ethylphosphonate (**24a**).* **24a** was prepared by the general method used for phosphonates by the reaction of phenol **17** (0.060 g; 0.2 mmol) and the phosphonochloridate **8a** (0.047 g; 0.3 mmol). The product was purified by preparative TLC in 100% EtOAc, giving a light-brown viscous oil (0.049 g, 59%). ^{31}P NMR (DMSO-d_6, 243 MHz): δ 33.0 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.77 (s, 1H), 8.72 (s, 1H), 7.96 (dd, $^3J_{HH}$ = 7.7 Hz, $^4J_{HH}$ = 1.7 Hz, 1H), 7.73 (s, 1H), 7.53 (d, $^3J_{HH}$ = 8.3 Hz, 1H), 7.48 (s, 1H), 7.47 (dt, $^3J_{HH}$ = 8.4 Hz, $^4J_{HH}$ = 1.8 Hz, 1H), 7.32 (t, $^3J_{HH}$ = 8.3 Hz, 1H), 7.19 (d, $^3J_{HH}$ = 8.3 Hz, 1H), 7.08 (t, $^3J_{HH}$ = 7.4 Hz, 1H), 6.83 (d, $^3J_{HH}$ = 8.1 Hz, 1H), 4.09−4.20 (m, 2H), 3.91 (s, 3H), 1.86−2.00 (m, 2H), 1.26 (t, $^3J_{HH}$ = 7.0 Hz, 3H), 1.13 (dt, $^3J_{PH}$ = 20.4 Hz, $^3J_{HH}$ = 7.6 Hz, 3H). LC-MS: R_t = 2.77 min. (ESI): m/z = 414 $[M + H]^+$.

*Isopropyl 3-{[6-(2-Methoxyphenyl)pyrimidin-4-yl]amino}phenyl Propylphosphonate (**24b**).* **24b** was prepared by the general method used for phosphonates by the reaction of phenol **17** (0.060 g; 0.2 mmol) and the phosphonochloridate **8b** (0.055 g; 0.3 mmol). The product was purified by preparative TLC in 100% EtOAc, affording a light-brown viscous oil (0.058 g, 66%). ^{31}P NMR (DMSO-d_6, 243 MHz): δ 30.3 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.76 (s, 1H), 8.71 (s, 1H), 7.96 (dd, $^3J_{HH}$ = 7.7 Hz, $^4J_{HH}$ = 1.6 Hz, 1H), 7.73 (s, 1H), 7.43−7.54 (m, 2H), 7.48 (s, 1H), 7.32 (t, $^3J_{HH}$ = 8.2 Hz, 1H), 7.19 (d, $^3J_{HH}$ = 8.3 Hz, 1H), 7.08 (t, $^3J_{HH}$ = 7.4 Hz, 1H), 6.83 (d, $^3J_{HH}$ = 8.0 Hz, 1H), 4.65−4.77 (m, 1H), 3.91 (s, 3H), 1.83−1.93 (m, 2H), 1.54−1.67 (m, 2H), 1.28 (d, $^3J_{HH}$ = 6.2 Hz, 3H), 1.22 (d, $^3J_{HH}$ = 6.2 Hz, 3H), 1.00 (t, $^3J_{HH}$ = 7.2 Hz, $^4J_{PH}$ = 1.0 Hz, 3H). LC-MS: R_t = 3.16 min. (ESI): m/z = 442 $[M + H]^+$.

*Ethyl 3-{[6-(2-Methoxyphenyl)pyrimidin-4-yl]amino}phenyl Phenylphosphonate (**24c**).* **24c** was prepared by the general method used for phosphonates by the reaction of phenol **17** (0.060 g; 0.2 mmol) and the phosphonochloridate **8c** (0.061 g; 0.3 mmol). The product was purified by preparative TLC in EtOAc:hexane = 1:1, giving a light-brown viscous oil (0.037 g, 40%). ^{31}P NMR (DMSO-d_6, 243 MHz): δ 17.1 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.75 (s, 1H), 8.68 (s, 1H), 7.95 (dd, $^3J_{HH}$ = 7.5 Hz, $^4J_{HH}$ = 1.3 Hz, 1H), 7.84 (dd, $^3J_{PH}$ = 13.5 Hz, $^3J_{HH}$ = 7.2 Hz; 2H), 7.75 (s, 1H) ; 7.65−7.71 (m, 1H), 7.55−7.62 (m, 2H), 7.4−7.5 (m, 2H), 7.45 (s, 1H), 7.28 (t, $^3J_{HH}$ = 8.1 Hz, 1H), 7.18 (d, $^3J_{HH}$ = 8.1 Hz, 1H), 7.08 (t, $^3J_{HH}$ = 7.3 Hz, 1H), 6.79 (d, $^3J_{HH}$ = 8.1 Hz, 1H), 4.15−4.25 (m, 2H), 3.90 (s, 3H), 1.29 (t, $^3J_{HH}$ = 7.2 Hz, 3H). LC-MS: R_t = 3.14 min. (ESI): m/z = 462 $[M + H]^+$.

*Ethyl 3-{[6-(3-Nitrophenyl)pyrimidin-4-yl]amino}phenyl Ethylphosphonate (**25a**).* **25a** was prepared by the general method used for phosphonates by the reaction of phenol **18** (0.090 g; 0.29 mmol) and the phosphonochloridate **8a** (0.068 g; 0.44 mmol). The product was recrystallized from MeCN to give a yellow powder (0.075 g, 60%); mp = 142−144 °C (MeCN). ^{31}P NMR (DMSO-d_6, 243 MHz): δ 33.0 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.96 (s, 1H), 8.83 (s, 1H), 8.80 (s, 1H), 8.47 (d, $^3J_{HH}$ = 7.7 Hz, 1H), 8.37 (d, $^3J_{HH}$ = 8.0 Hz, 1H), 7.85 (t, $^3J_{HH}$ = 8.0 Hz, 1H), 7.75 (s, 1H), 7.53 (d, $^3J_{HH}$ = 7.7. Hz, 1H), 7.41 (s, 1H), 7.35 (t, $^3J_{HH}$ = 8.1 Hz, 1H), 6.87 (d, $^3J_{HH}$ = 7.7 Hz, 1H), 4.08−4.2 (m, 2H), 1.87−2.01 (m, 2H), 1.26 (t, $^3J_{HH}$ = 7.0 Hz, 3H), 1.13 (dt, $^3J_{PH}$ = 20.5 Hz, $^3J_{HH}$ = 7.6 Hz, 3H). LC-MS: R_t = 3.79 min. (ESI): m/z = 429 $[M + H]^+$.

*Isopropyl 3-{[6-(3-Nitrophenyl)pyrimidin-4-yl]amino}phenyl Propylphosphonate (**25b**).* **25b** was prepared by the general method used for phosphonates by the reaction of phenol **18** (0.090 g; 0.29 mmol) and the phosphonic acid chloride **8b** (0.057 g; 0.44 mmol). The product was recrystallized from MeCN to give a yellow powder (0.057 g, 60%); mp = 163−164 °C (MeCN). ^{31}P NMR (DMSO-d_6, 243 MHz): δ 27.4 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 10.04 (s, 1H), 8.84 (s, 1H), 8.79 (s, 1H), 8.47 (d, $^3J_{HH}$ = 7.5 Hz, 1H), 8.37 (d, $^3J_{HH}$ = 8.1 Hz, 1H), 7.85 (t, $^3J_{HH}$ = 8.0 Hz, 1H), 7.76 (s, 1H), 7.53 (d, $^3J_{HH}$ = 8.1 Hz, 1H),7.44 (s, 1H), 7.34 (t, $^3J_{HH}$ = 8.1 Hz, 1H), 6.86 (d, $^3J_{HH}$ = 7.8 Hz, 1H), 4.68−4.75 (m, 1H), 1.84−1.96 (m, 2H), 1.57−1.65 (m, 2H), 1.28 (d, $^3J_{HH}$ = 6.0 Hz, 3H), 1.22 (d, $^3J_{HH}$ = 6.0 Hz, 3H), 1.00 (t, $^3J_{HH}$ = 7.1 Hz, 3H). LC-MS: R_t = 4.28 min. (ESI): m/z = 457 $[M + H]^+$.

*Ethyl 3-{[6-(3-Nitrophenyl)pyrimidin-4-yl]amino}phenyl Phenylphosphonate (**25c**).* **25c** was prepared by the general method used for phosphonates by the reaction of phenol **18** (0.102 g; 0.33 mmol) and the phosphonochloridate **8c** (0.102 g; 0.54 mmol). The product was recrystallized from MeCN to give a cream-colored powder (0.083 g, 53%); mp = 162−164 °C (MeCN). ^{31}P NMR (DMSO-d_6, 243 MHz): δ 17.2 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.94 (s, 1H), 8.83 (s, 1H), 8.77 (s, 1H), 8.42 (dd, $^3J_{PH}$ = 27.2 Hz, $^3J_{HH}$ = 7.1 Hz, 2H), 7.80−7.90 (m, 3H), 7.76 (s, 1H), 7.65−7.7 (m, 1H), 7.55−7.65 (m, 2H), 7.47 (d, $^3J_{HH}$ = 7.2 Hz, 1H), 7.38 (s, 1H), 7.31 (t, $^3J_{HH}$ = 7.5 Hz, 1H), 6.82 (d, $^3J_{HH}$ = 7.4 Hz, 1H), 4.18−4.24 (m, 2H), 1.29 (t, $^3J_{HH}$ = 6.2 Hz, 3H). LC-MS: R_t = 4.28 min. (ESI): m/z = 457 $[M + H]^+$.

*3-{[6-(3-Aminophenyl)pyrimidin-4-yl]amino}phenyl Ethyl Ethylphosphonate (**26a**).* The nitro compound **25a** (0.055 g, 0.13 mmol) and $SnCl_2$ (0.099 g; 0.52 mmol) were dissolved in EtOH (10 mL), and the mixture was refluxed for 4 h. After the reaction was completed, volatiles were evaporated then the residue was suspended in 2 M aqueous NaOH (10 mL). The precipitate was filtered and washed with EtOAc. The filtrate was extracted with EtOAc (3 × 20 mL), and the organic phases were washed with brine and dried with $MgSO_4$. After evaporation, the pure product was dissolved in the minimal quantity of EtOH, and the HCl salt was prepared by adding 4 M HCl in dioxane. Volatiles were evaporated, and dry toluene (30 mL) was added and distilled from the residue. The hydrochloride salt of the **26a** was suspended in Et_2O, filtered, and dried to obtain a yellow powder (0.042 g, 74%); mp = 205−206 °C (EtOH, Et_2O). ^{31}P NMR (DMSO-d_6, 243 MHz): δ 33.1 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 10.94 (s, 1H), 8.85 (s, 1H), 7.77 (s, 1H), 7.73 (br, 2H), 7.55−7.62 (m, 2H), 7.36−7.42 (m, 2H), 7.39 (s, 1H), 6.96 (d, $^3J_{HH}$ = 8.1 Hz, 1H), 5.50 (br, 2H), 4.05−4.21 (m, 2H), 1.90−1.99 (m, 2H), 1.26 (t, $^3J_{HH}$ = 7.0 Hz, 3H), 1.13 (dt, $^3J_{PH}$ = 20.5 Hz, $^3J_{HH}$ = 7.7 Hz, 3H). LC-MS: R_t = 0.43 min; 2.48 min; 2.57 min. (ESI): m/z = 399 $[M + H]^+$.

*3-{[6-(3-Aminophenyl)pyrimidin-4-yl]amino}phenyl Isopropyl Propylphosphonate (**26b**).* Compound **25b** (0.133 g, 0.29 mmol) was reduced according to the preparation of **26a**, giving a green−yellow powder (0.109 g, 81%); mp = 148−150 °C (EtOH, Et_2O). ^{31}P NMR (DMSO-d_6, 243 MHz): δ 30.4 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 10.35 (s, 1H), 8.72 (s, 1H), 7.70 (s, 1H), 7.30−7.60 (m, 3H), 7.20−7.30 (m, 3H), 7.06 (br, 1H), 6.84 (br, 1H), 4.67 (br, 1H), 3.70 (br, $2H_2$), 1.75−1.90 (m, 2H), 1.50−1.60 (m, 2H), 1.24 (s, 3H), 1.19 (s, 3H), 0.96 (br, 3H). LC-MS: R_t = 3.00 min. (ESI): m/z = 427 $[M + H]^+$.

*3-{[6-(3-Aminophenyl)pyrimidin-4-yl]amino}phenyl Ethyl Phenylphosphonate (**26c**).* Compound **25c** (0.065 g, 0.14 mmol) was reduced according to the preparation of **26a**, giving a yellow powder (0.051 g, 76%); mp = 214−215 °C (EtOH, Et_2O). ^{31}P NMR (DMSO-d_6, 243 MHz): δ 17.3 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 10.89 (s, 1H), 8.82 (s, 1H), 7.50−7.90 (m, 10H), 7.30−7.50 (m, 3H), 6.91 (d, $^3J_{HH}$ = 7.8 Hz, 1H), 5.40 (br, 2H), 4.15−4.26 (m, 2H), 1.29 (t, $^3J_{HH}$ = 6.9 Hz, 3H). LC-MS: R_t = 2.96 min. (ESI): m/z = 447 $[M + H]^+$.

*Ethyl 4-{[6-(2-Methoxyphenyl)pyrimidin-4-yl]amino}phenyl Ethylphosphonate (**27a**).* **27a** was prepared by the general method used for phosphonates by the reaction of phenol **19** (0.033 g; 0.11 mmol) and the phosphonochloridate **8a** (0.060 g; 0.17 mmol). The product was purified by preparative TLC in 100% EtOAc, providing a light-brown viscous oil (0.022 g 48%). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.64 (s,

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1H), 8.67 (s, 1H), 7. 95 (dd, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.5 Hz, 1H), 7.69 (d, J_{AABB} = 8.8 Hz, 2H), 7.45 (dt, $^3J_{HH}$ = 8.6 Hz, $^4J_{HH}$ = 1.5 Hz, 1H), 7.42 (s, 1H), 7.18 (d, J_{AABB} = 8.3 Hz, 2H), 7.17 (d, $^3J_{HH}$ = 7.8 Hz, 1H), 7.08 (t, $^3J_{HH}$ = 7.5 Hz, 1H), 4.04−4.16 (m, 2H), 3.90 (s, 3H), 1.83−1.98 (m, 2H), 1.24 (t, $^3J_{HH}$ = 7.0 Hz, 3H), 1.11 (dt, $^3J_{PH}$ = 20.3 Hz, $^3J_{HH}$ = 7.6 Hz, 3H). LC-MS: R_t = 2.70 min. (ESI): m/z = 414 $[M + H]^+$.

*Isopropyl 4-{[6-(2-Methoxyphenyl)pyrimidin-4-yl]amino}phenyl Isopropylphosphonate (**27b**).* **27b** was prepared by the general method used for phosphonates by the reaction of phenol **19** (0.100 g; 0.34 mmol) and the phosphonochloridate **8b** (0.094 g; 0.51 mmol). The product was purified by preparative TLC in 100% EtOAc, yielding a yellow powder (0.020 g, 13%); mp = 119−121 °C (CH_2Cl_2). ^{31}P NMR (DMSO-d_6, 243 MHz): δ 30.6 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.63 (s, 1H), 8.67 (s, 1H), 7.95 (d, $^3J_{HH}$ = 6.8 Hz, 1H), 7.69 (J_{AABB} = 7.4 Hz, 2H), 7.35−7.50 (m, 2H), 7.15−7.18 (m, 3H), 7.05−7.13 (m, 1H), 4.60−4.70 (m, 1H), 3.9 (s, 3H), 1.81−1.90 (m, 2H), 1.49−1.70 (m, 2H), 1.27 (d, $^3J_{HH}$ = 5.1 Hz, 3H), 1.20 (d, $^3J_{HH}$ = 5.1 Hz, 3H), 0.99 (t, $^3J_{HH}$ = 6.6 Hz, 3H). LC-MS: R_t = 3.07 min. (ESI): m/z = 442 $[M + H]^+$.

*Ethyl 4-{[6-(2-Methoxyphenyl)pyrimidin-4-yl]amino}phenyl Phenylphosphonate (**27c**).* **27c** was prepared by the general method used for phosphonates by the reaction of phenol **19** (0.033 g; 0.11 mmol) and the phosphonochloridate **8c** (0.035 g; 0.17 mmol). The product was purified by preparative TLC in EtOAc:hexane = 1:1, affording a light-brown viscous oil (0.041 g, 81%). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.63 (s, 1H), 8.66 (s, 1H), 7.94 (dd, $^3J_{HH}$ = 7.7 Hz, $^4J_{HH}$ = 1.2 Hz, 1H), 7.82 (dd, $^3J_{PH}$ = 13.3 Hz, $^3J_{HH}$ = 7.1 Hz, 2H), 7.60−7.75 (m, 3H), 7.50−7.60 (m, 2H), 7.45 (t, $^3J_{HH}$ = 7.8 Hz, 1H), 7.40 (s, 1H), 7.17 (d, $^3J_{HH}$ = 8.3 Hz, 1H), 7.13 (d, J_{AABB} = 8.5 Hz, 2H), 7.07 (t, $^3J_{HH}$ = 7.6 Hz, 1H), 4.13−4.22 (m, 2H), 3.88 (s, 3H), 1.27 (t, $^3J_{HH}$ = 7.0 Hz, 3H). LC-MS: R_t = 3.06 min. (ESI): m/z = 462 $[M + H]^+$.

*Ethyl 4-{[6-(3-Nitrophenyl)pyrimidin-4-yl]amino}phenyl Ethylphosphonate (**28a**).* **28a** was prepared by the general method used for phosphonates by the reaction of phenol **20** (0.150 g; 0.49 mmol) and the phosphonochloridate **8a** (0.115 g; 0.74 mmol). After recrystallization from MeCN, a yellow powder was obtained (0.085 g, 41%); mp = 187 °C (MeCN). ^{31}P NMR (DMSO-d_6, 243 MHz): δ 33.2 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.81 (s, 1H), 8.86 (s, 1H), 8.75 (s, 1H), 8.45 (d, $^3J_{HH}$ = 7.8 Hz, 1H), 8.36 (d, $^3J_{HH}$ = 8.1 Hz, 1H), 7.84 (t, $^3J_{HH}$ = 8.0 Hz, 1H), 7.71 (d, J_{AABB} = 8.8 Hz, 2H), 7.34 (s, 1H), 7.19 (d, J_{AABB} = 8.5 Hz, 2H), 4.04−4.19 (m, 2H), 1.90 (dq, $^3J_{PH}$ = 7.6 Hz, $^3J_{HH}$ = 7.6 Hz, 2H), 1.25 (t, $^3J_{HH}$ = 7.0 Hz, 3H), 1.12 (dt, $^3J_{PH}$ = 20.4 Hz, $^3J_{HH}$ = 7.6 Hz, 3H). LC-MS: R_t = 3.63 min. (ESI): m/z = 429 $[M + H]^+$.

*Isopropyl 4-{[6-(3-Nitrophenyl)pyrimidin-4-yl]amino}phenyl Propylphosphonate (**28b**).* **28b** was prepared by the general method used for phosphonates by the reaction of phenol **20** (0.154 g; 0.50 mmol) and the phosphonochloridate **8b** (0.138 g; 0.75 mmol). After recrystallization from MeCN, a cream-colored powder was obtained (0.012 g, 12%); mp = 187 °C (MeCN). ^{31}P NMR (DMSO-d_6, 243 MHz): δ 27.6 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.86 (s, 1H), 8.82 (s, 1H), 8.75 (s, 1H), 8.45 (d, $^3J_{HH}$ = 7.3 Hz, 1H), 8.36 (d, $^3J_{HH}$ = 7.6 Hz, 1H), 7.84 (t, $^3J_{HH}$ = 8.0 Hz, 1H), 7.71 (d, J_{AABB} = 8.1 Hz, 2H), 7.36 (s, 1H), 7.18 (d, J_{AABB} = 8.1 Hz, 2H), 4.60−4.70 (m, 1H), 1.81−1.93 (m, 2H), 1.55−1.63 (m, 2H), 1.27 (d, $^3J_{HH}$ = 5.8 Hz, 3H), 1.20 (d, $^3J_{HH}$ = 5.7 Hz, 3H), 1.00 (t, $^3J_{HH}$ = 6.6 Hz, 3H). LC-MS: R_t = 4.20 min. (ESI): m/z = 457 $[M + H]^+$.

*4-{[6-(3-Aminophenyl)pyrimidin-4-yl]amino}phenyl Ethyl Ethylphosphonate (**29a**).* Compound **28a** (0.067 g, 0.16 mmol) was reduced according to the preparation of **26a**, giving a yellow powder (0.043 g, 62%); mp = 207−209 °C (EtOH, Et_2O). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.63 (s, 1H), 8.64 (s, 1H), 7.68 (d, J_{AABB} = 8.7 Hz, 2H), 7.28 (s, 1H), 7.09−7.19 (m, 5H), 6.68 (d, $^3J_{HH}$ = 6.4 Hz, 1H), 5.26 (br, 2H), 4.40−4.17 (m, 2H), 1.83−1.98 (m, 2H), 1.24 (t, $^3J_{HH}$ = 7.05 Hz, 3H), 1.11 (dt, $^3J_{PH}$ = 12.7 Hz, $^3J_{HH}$ = 7.6 Hz, 3H). LC-MS: R_t = 0.43 min 2.28 min; 2.47 min. (ESI): m/z = 399 $[M + H]^+$.

*4-{[6-(3-Aminophenyl)pyrimidin-4-yl]amino}phenyl Isopropyl Propylphosphonate (**29b**).* Compound **28b** (0.076 g, 0.17 mmol) was reduced according to the preparation of **26a**, affording a yellow powder (0.016 g, 21%); mp = 150−160 °C (EtOH, Et_2O). ^{31}P NMR (DMSO-d_6, 243 MHz): δ 27.6 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.62 (s, 1H), 8.64 (s, 1H), 7.68 (d, J_{AABB} = 8.9 Hz, 2H), 7.28 (s, 1H), 7.12−7.23 (m, 4H), 7.09 (s, 1H, H12), 6.68 (d, $^3J_{HH}$ = 5.6 Hz, 1H), 5.26 (br, 2H), 4.64−4.71 (m, 1H), 1.81−1.9 (m, 2H), 1.58−1.63 (m, 2H), 1.27 (d, $^3J_{HH}$ = 6.2 Hz, 3H), 1.20 (d, $^3J_{HH}$ = 6.2 Hz, 3H), 1.00 (t, $^3J_{HH}$ = 6.3 Hz, 3H). LC-MS: R_t = 2.78 min. (ESI): m/z = 427 $[M + H]^+$.

*4-{[6-(2-Methoxyphenyl)pyrimidin-4-yl]amino}phenyl Hydrogen Ethylphosphonate (**30a**).* Chlorotrimethylsilane (0.21 mL, 1.65 mmol) and potassium iodide (0.274 g; 1.65 mmol) were dissolved in anhydrous acetone (20 mL). The mixture was stirred for 30 min at RT then the solution of phosphonate **21a** (0.235 g, 0.55 mmol in 30 mL anhydrous acetone) was added. The reaction mixture was refluxed for 20 h, and then it was concentrated under vacuum. The crude product was suspended in satd NH_4Cl solution and 0.5 mL of EtOAc. The suspension was stirred for 1 h at RT then it was filtered off and washed with Et_2O, giving **30a** as a yellow powder was prepared (0.154 g, 70%); mp = 240−242 °C (water). ^{31}P NMR (DMSO-d_6, 243 MHz): δ 26.9 ppm. ^{1}H NMR (DMSO-d_6, at 110 °C, 300 MHz): δ 10.02 (br, 1H), 8.71 (s, 1H), 7.85 (d, $^3J_{HH}$ = 7.8 Hz, 1H), 7.61 (s, 1H), 7.40−7.55 (m, 3H), 7.41 (s, 1H), 7.2 (d, $^3J_{HH}$ = 7.4 Hz, 1H), 7.11 (t, $^3J_{HH}$ = 7.4 Hz, 1H), 4.89 (br, 1H), 3.91 (s, 3H), 2.24 (s, 3H), 1.77−1.92 (m, 2H), 1.17 (dt, $^3J_{PH}$ = 19.9 Hz, $^3J_{HH}$ = 7.6 Hz, 3H). LC-MS: R_t = 2.43 min; (ESI): m/z = 400 $[M + H]^+$. MS[ES$^+$, Q-TOF]: M + H$^+$ = 400.11 m/z; 2 M + H$^+$ = 799.18 m/z.

*4-{[6-(2-Methoxyphenyl)pyrimidin-4-yl]amino}phenyl Hydrogen Propylphosphonate (**30b**).* Deprotection of phosphonate **21b** (0.050 g; 0.11 mmol) was performed according to the preparation of **30a**, affording **30b** as a brown powder (0.036 g, 79%); mp = 170 °C (water). ^{31}P NMR (DMSO-d_6, 162 MHz): δ 26.6 ppm. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 10.48 (br, 1H), 8.81 (s, 1H), 7.78 (d, $^3J_{HH}$ = 7.4 Hz, 1H), 7.57 (s, 1H), 7.56 (t, $^3J_{HH}$ = 7.5 Hz, 1H), 7.49 (d, $^3J_{HH}$ = 8.2 Hz, 1H), 7.32 (s, 1H), 7.25 (d, $^3J_{HH}$ = 8.4 Hz, 1H), 7.24 (d, $^3J_{HH}$ = 8.6 Hz, 1H), 7.14 (t, $^3J_{HH}$ = 7.5 Hz, 1H), 3.50 (s, 1H), 3.90 (s, 3H), 2.21 (s, 3H), 1.77−1.86 (m, 2H), 1.58−1.67 (m, 2H), 1.01 (t, $^3J_{HH}$ = 7.1 Hz, 3H). LC-MS: R_t = 2.53 min. (ESI): m/z = 414 $[M + H]^+$. MS[ES$^+$, Q-TOF]: M + H$^+$ = 414.12 m/z; 2 M + H$^+$ = 827.22 m/z.

*Diethyl [Hydroxy(3-nitrophenyl)methyl]phosphonate (**31**).* 3-Nitrobenzaldehyde (7.55 g, 50 mmol) was dissolved in toluene (50 mL) then diethyl phosphite (7.59 g, 55 mmol) and triethylamine (5.56 g, 55 mmol) were added and stirred at RT overnight. Water (50 mL) was added to the reaction mixture then the organic phase was washed with 1 M aqueous HCl solution (50 mL). Combined aqueous phases were extracted with toluene (30 mL). The organic phases were washed with brine and dried with $MgSO_4$. After concentration, **31** was recrystallized from toluene to give a pale-yellow powder (11.04 g, 76%); mp = 92 °C (toluene). ^{31}P NMR (DMSO-d_6, 242 MHz): δ 19.8 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.28 (d, $^4J_{HH}$ = 1.6 Hz, 1H), 8.14 (d, $^3J_{HH}$ = 8.0 Hz, 1H), 7.86 (d, $^3J_{HH}$ = 7.5 Hz, 1H), 7.65 (t, $^3J_{HH}$ = 7.9 Hz, 1H), 6.52 (dd, $^3J_{PH}$ = 14.5 Hz, $^3J_{HH}$ = 5.9 Hz, 1H), 5.2 (dd, $^2J_{PH}$ = 14.1 Hz, $^3J_{HH}$ = 5.9 Hz, 1H), 3.90−4.04 (m, 4H), 1.16 (t, $^3J_{HH}$ = 7.0 Hz, 6H). LC-MS: R_t = 2.83 min. (ESI): m/z = 290 $[M + H]^+$.

*Diethyl [Hydroxy(4-nitrophenyl)methyl]phosphonate (**32**).* **32** was prepared similarly to compound **31** from 4-nitrobenzaldehyde (7.550 g, 50 mmol). **32** was prepared as a pale-yellow powder (8.67 g, 60%); mp = 88−90 °C (toluene). ^{31}P NMR (DMSO-d_6, 242 MHz): δ 19.4 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.21 (d, J_{AABB} = 8.6 Hz, 2H), 7.68 (dd, J_{AABB} = 8.9 Hz, J = 2.2 Hz 2H), 6.50 (dd, $^4J_{PH}$ = 14.6 Hz, $^3J_{HH}$ = 5.7 Hz, 1H), 5.18 (dd, $^2J_{PH}$ = 15.4 Hz, $^3J_{HH}$ = 5.7 Hz), 3.90−4.05 (m, 4H), 1.16 (dt, $^3J_{HH}$ = 7.0 Hz, J = 3.0 Hz, 6H). LC-MS: R_t = 2.84 min. (ESI): m/z = 290 $[M + H]^+$.

*Diethyl [(3-Aminophenyl)(hydroxy)methyl]phosphonate (**33**).* Diethyl [hydroxy(3-nitrophenyl)methyl]phosphonate **31** (1.455 g; 5.0 mmol) and ammonium formate (3.150 g, 50.0 mmol) were dissolved in MeOH (100 mL) under un inert atmosphere. Then 10 m/m % Pd/C (0.145 g, 10 w/w%) was added to the mixture and stirred for 24 h at RT. Catalyst was filtered off on a Celite pad and washed with MeOH (20 mL). After concentration of the filtrate, the residue was suspended in satd aqueous Na_2CO_3 (50 mL) and it was extracted with EtOAc (3 × 50 mL). The combined organics were washed with brine and dried with $MgSO_4$. After evaporation of volatiles under reduced pressure, **33** was obtained as a yellow oil (0.936 g; 72%). ^{31}P NMR (DMSO-d_6, 242 MHz): δ 21.1 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 6.93 (t, $^3J_{HH}$ =

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7.7 Hz, 1H), 6.65 (d, $^4J_{HH}$ = 1.5 Hz, 1H), 6.54 (d, $^3J_{HH}$ = 7.3 Hz, 1H), 6.44 (d, $^3J_{HH}$ = 7.8 Hz, 1H), 5.92 (dd, $^3J_{PH}$ = 16.7 Hz, $^3J_{HH}$ = 5.5 Hz, 1H), 5.00 (br, 2H), 4.7 (dd, $^2J_{PH}$ = 13.1 Hz, $^3J_{HH}$ = 5.5 Hz, 1H), 3.82−3.99 (m, 4H), 1.15 (dt, $^3J_{HH}$ = 7.0 Hz, $^4J_{PH}$ = 10.6 Hz, 6H). LC-MS: R_t = 0.48 min; 1.49 min; 2.18 min. (ESI): m/z = 260 $[M+H]^+$.

*Diethyl [(4-Aminophenyl)(hydroxy)methyl]phosphonate (**34**).* **34** was synthesized according to the preparation of compound **33** from diethyl [hydroxy(4-nitrophenyl)methyl]phosphonate **32** (1.50 g, 5.19 mmol). **34** was filtered from Et_2O to give a yellow powder (1.16 g, 86%); mp = 157−158 °C (Et_2O). ^{31}P NMR (DMSO-d_6, 242 MHz): δ 21.8 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.07 (dd, J_{AABB} = 8.3 Hz, J = 1.7 Hz 2H), 6.50 (d, J_{AABB} = 8.3 Hz, 2H), 5.80 (br, 1H), 5.03 (br, 2H), 4.66 (d, $^2J_{PH}$ = 11.7 Hz), 3.90−4.01 (m, $^3J_{HH}$ = 7.2 Hz, 2H), 3.70−3.90 (m, $^3J_{HH}$ = 7.2 Hz, 2H), 1.18 (t, $^3J_{HH}$ = 7.0 Hz, 3H), 1.11 (t, $^3J_{HH}$ = 7.0 Hz, 3H). LC-MS: decomposition, R_t = 0.45 min. (ESI): m/z = 242 $[M - H_2O + H]^+$.

*Diethyl (3-Aminobenzyl)phosphonate (**35**).* Diethyl [hydroxy(3-nitrophenyl)methyl]phosphonate **31** (1.455 g; 5.0 mmol) and triethylamine (0.83 mL, 6.0 mmol) were dissolved in dry THF (25 mL) and cooled to 0 °C. Methanesulfonic acid chloride (0.43 mL, 5.5 mmol) was added dropwise, and the resulting mixture was stirred for 2 h at RT. After concentration, the residue was partitioned between water and EtOAc (50−50 mL). Aqueous phase was extracted with EtOAc (2 × 50 mL). The combined organic phases were washed with 1 M aqueous HCl (50 mL), with satd aqueous $NaHCO_3$ (50 mL) and with brine and dried with $MgSO_4$. After concentration, the methanesulfonate intermediate was filtered from Et_2O to give a white powder (1.343 g, 73%); mp = 81−82 °C (Et_2O). ^{31}P NMR (DMSO-d_6, 242 MHz): δ 13.2 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.33 (s, 1H), 8.25 (d, $^3J_{HH}$ = 8.0 Hz, 1H), 7.93 (d, $^3J_{HH}$ = 7.4 Hz, 1H), 7.75 (t, $^3J_{HH}$ = 8.0 Hz, 1H), 6.35 (d, $^2J_{PH}$ = 15.9 Hz), 3.96−4.14 (m, 4H), 3.22 (s, 3H), 1.18 (dt, $^3J_{HH}$ = 7.0 Hz, $^4J_{PH}$ = 10.0 Hz, 6H). LC-MS: R_t = 3.33 min; (ESI): m/z = 368 $[M + H]^+$. (Diethoxyphosphoryl)(3-nitrophenyl)methyl methanesulfonate (0.367 g, 1.0 mmol) was dissolved in MeOH (20 mL) under an inert atmosphere. Then 10 m/m % Pd/C (0.037 g, 10 w/w %) and 70% aqueous solution of hydrazine (2 mL) were added carefully under stirring. After 24 h vigorous stirring at RT, the catalyst was filtered off on a celite pad and washed with MeOH (20 mL) then the filtrate was concentrated under vacuum. The residue was suspended in sat aqueous $NaHCO_3$ (20 mL), and it was extracted with EtOAc (3 × 20 mL). The organic phases were washed with brine and dried with $MgSO_4$. After concentration under vacuum, the title compound **35** was obtained as a yellow oil (0.190 g, 78%). ^{31}P NMR (DMSO-d_6, 242 MHz): δ 25.5 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.20 (br, 2H), 7.17 (t, $^3J_{HH}$ = 7.7 Hz, 1H), 6.81−6.88 (m, 3H), 3.93 (dq, $^3J_{PH}\approx{}^3J_{HH}$ = 7.1 Hz, 4H), 3.14 (d, $^2J_{PH}$ = 21.6 Hz, 2H), 1.16 (t, $^3J_{HH}$ = 7.0 Hz, 6H). LC-MS: R_t = 0.46 min; 1.89 min. (ESI): m/z = 244 $[M + H]^+$.

*Diethyl (4-Aminobenzyl)phosphonate (**36**).* Diethyl [hydroxy(4-nitrophenyl)methyl]phosphonate **32** (1.445 g; 5.0 mmol) was mesylated similarly to the synthesis of **35**. The methanesulfonate intermediate was isolated as pale-yellow powder (0.954 g, 52%); mp = 79−80 °C (Et_2O). ^{31}P NMR (DMSO-d_6, 242 MHz): δ 12.9 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.28 (d, J_{AABB} = 8.7 Hz, 2H), 7.74 (dd, J_{AABB} = 8.8 Hz, J = 2.0 Hz, 2H), 6.33 (d, $^2J_{PH}$ = 16.7 Hz, 1H), 3.96−4.12 (m, 4H), 3.23 (s, 3H, H8), 1.18 (dt, $^3J_{HH}$ = 7.0 Hz, J = 4.2 Hz, 6H). LC-MS: R_t = 3.34 min. (ESI): m/z = 368 $[M + H]^+$. (Diethoxyphosphoryl)-(4-nitrophenyl)methyl methanesulfonate (0.734 g; 2.0 mmol) was hydrogenated according to the preparation of compound **35**. The title compound **36** was obtained as a white powder (0.456 g, 94%); mp = 90−91 °C (EtOAc). ^{31}P NMR (DMSO-d_6, 242 MHz): δ 26.7 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 6.90 (dd, J_{AABB} = 8.3 Hz, J = 2.2 Hz 2H), 6.49 (d, J_{AABB} = 8.3 Hz, 2H), 4.92 (br, 2H), 3.90 (dq, $^3J_{PH}$ = 7.3 Hz, $^3J_{HH}$ = 7.2 Hz, 4H), 2.97 (d, $^2J_{PH}$ = 20.6 Hz, 2H), 1.16 (t, $^3J_{HH}$ = 7.0 Hz, 6H). LC-MS: R_t = 0.45 min; 1.69 min. (ESI): m/z = 244 $[M + H]^+$.

*Diethyl (5-Amino-2-methylbenzyl)phosphonate (**37**).* 2-Methyl-5-nitro benzoic acid (5.00 g; 27.6 mmol) was dissolved in abs EtOH (200 mL), and 96% H_2SO_4 (2 mL) was added to the solution then it was refluxed for 24 h. The reaction mixture was concentrated under vacuum, and the residue was dissolved in EtOAc (200 mL). The organic phase was washed with 1 M NaOH (2 × 50 mL) with brine and dried with $MgSO_4$. After concentration, the ethyl benzoate was obtained as a pale-yellow liquid which crystallizes to yellow crystals upon standing (4.978 g, 92%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.75 (d, $^4J_{HH}$ = 2.5 Hz, 1H), 8.23 (dd, $^3J_{HH}$ = 8.3 Hz, $^4J_{HH}$ = 2.5 Hz, 1H), 7.43 (d, $^3J_{HH}$ = 8.4 Hz, 1H), 4.42 (q, $^3J_{HH}$ = 7.4 Hz, 2H), 2.72 (s, 3H), 1.44 (t, $^3J_{HH}$ = 7.1 Hz, 3H). LC-MS: R_t = 4.11 min. (ESI): m/z = no molecular ion was observed. The ethyl 2-methyl-5-nitrobenzoate (4.967 g; 23.8 mmol) was dissolved in dry THF (100 mL) and cooled to 0 °C. $LiAlH_4$ (3.612 g, 95.1 mmol) was added in small portions. After the addition, the reaction mixture was stirred for 2.5 h at RT. Then 2-propanol was added drop by drop until the release of hydrogen stopped. After the addition of 2 M aqueous NaOH was added (50 mL), the precipitated white gel was filtered on celite and washed with EtOAc. The filtrate was separated, and the aqueous layer was extracted with EtOAc (3 × 75 mL). The combined organic phases were washed with brine, dried with $MgSO_4$, and concentrated. The benzyl alcohol intermediate was titurated and filtered from Et_2O to give an orange powder (1.97 g, 50%); mp = 159−162 °C (Et_2O). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.87 (s, 1H), 7.71 (dd, $^3J_{HH}$ = 8.1 Hz, $^4J_{HH}$ = 2.3 Hz, 1H), 7.25 (d, $^3J_{HH}$ = 8.1 Hz, 1H), 4.73 (s, 2H), 2.36 (s, 3H), 1.52 (br, 1H). LC-MS: R_t = 3.43 min. (ESI): m/z = no molecular ion was observed. The (2-methyl-5-nitro-phenyl)-methanol (0.20 g; 1.2 mmol) was dissolved in dry THF (20 mL) and cooled to −10 °C. PBr_3 (0.056 mL, 0.6 mmol) was added in one portion. After 1.5 h stirring at RT, the reaction mixture was concentrated to dryness. The residue was dissolved in EtOAc:THF (2:1, 80 mL), and it was washed with water (2 × 30 mL) and with brine. The organic layer was dried with Na_2SO_4 than it was concentrated. The crude benzyl bromide was titurated and filtered from Et_2O to give a yellow to brown powder (0.233 g, 85%); mp = 195−198 °C (Et_2O). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.81 (d, $^4J_{HH}$ = 2.1 Hz, 1H), 7.72 (dd, $^3J_{HH}$ = 7.9 Hz, $^4J_{HH}$ = 2.1 Hz, 1H), 7.25 (d, $^3J_{HH}$ = 8.2 Hz, 1H), 4.52 (s, 2H), 2.43 (s, 3H). LCMS: compound was decomposed on LC. 2-(Bromomethyl)-1-methyl-4-nitrobenzene (0.23 g, 1.0 mmol) was suspended in triethyl-phosphite (4 mL, 23.0 mmol) and was stirred in a closed flask in a microwave reactor at 100 °C for 10 min. The mixture was cooled to 0 °C, and 36% aqueous HCl solution (1 mL) was added. After 30 min stirring, the product was extracted with EtOAc:THF (2:1, 3 × 20 mL). The combined organics were washed with satd aqueous $NaHCO_3$ (20 mL) and with brine and dried with $MgSO_4$. After evaporation, the benzyl-phosphonate was crystallized from Et_2O to give an orange powder (0.11 g, 38%); mp = 117−119 °C (Et_2O). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.77 (s, 1H), 7.67 (d, $^3J_{HH}$ = 8.0 Hz, 1H), 7.39 (d, $^3J_{HH}$ = 8.0 Hz, 1H), 3.90−4.03 (m, 4H), 3.40 (d, $^2J_{PH}$ = ∼22.0 Hz, 2H), 2.43 (s, 3H), 1.18 (t, $^3J_{HH}$ = 7.0 Hz, 6H). LC-MS: R_t = 4.18 min. (ESI): m/z = no molecular ion was observed. Diethyl (2-methyl-5-nitrobenzyl)phosphonate (0.100 g, 0.36 mmol) was dissolved in MeOH (20 mL), and ammonium formate (0.227 g, 3.60 mmol) was added to the mixture under inert atmosphere followed by the addition of 10 m/m % Pd/C (0.010 g, 10 w/w%). The reaction mixture was stirred at RT for 20 h, and the catalyst was filtered off on a celite pad and washed with MeOH (20 mL) then the filtrate was evaporated to dry. The residue was dissolved in EtOAc (50 mL) and was washed with satd aqueous $NaHCO_3$ (20 mL) with brine and dried with $MgSO_4$. After evaporation of the volatiles under reduced pressure the title compound **37** was obtained as a yellow oil (0.071 g, 77%), which was used without further purification. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 6.78 (d, $^3J_{HH}$ = 8.0 Hz, 1H), 6.45 (t, $^4J_{HH}$ = 2.5 Hz, 1H), 6.35 (dt, $^3J_{HH}$ = 8.0 Hz, $^4J_{HH}$ = 2.3 Hz, 1H), 4.77 (br, 2H), 3.85−3.98 (m, 4H), 2.98 (d, $^2J_{PH}$ = 21.6 Hz, 2H), 2.13 (s, 3H), 1.17 (t, $^3J_{HH}$ = 7.0 Hz, 6H). LC-MS: R_t = 0.45 min; 2.16 min. (ESI): m/z = 258 $[M + H]^+$.

*General Procedure for the Coupling Reaction of 4-Chloro-6-phenyl-pyrimidines (**13**) and Phosphorus Containing Anilines.* The appropriate aniline was dissolved in the necessary volume of EtOH and a few drops of 4 M HCl in dioxane were added (approximately 0.1 mL). The volatiles were evaporated then dry toluene (30 mL) was distilled from the residue. The 4-chloro-6-phenyl-pyrimidine **13** was added to the residue then it was refluxed for 3−24 h in anhydrous 2-propanol (35 mL). Reactions were followed by TLC with toluene:MeOH (4:1) as eluent. After the reaction was complete, volatiles were evaporated then the residue was suspended in satd aqueous $NaHCO_3$ (30 mL). The product was extracted with EtOAc (3 × 70 mL). The combined organic

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phases were washed with brine and dried with $MgSO_4$, and then solvents were evaporated under reduced pressure. For the exact quantity of reagents, for further purifications, yields, and analytical data see the examples.

*Diethyl (3-{[6-(2-Methoxyphenyl)pyrimidin-4-yl]amino}benzyl)-phosphonate (**38**).* According to the general coupling procedure 4-chloro-6-(2-methoxyphenyl)-pyrimidine **13a** (0.165 g, 0.75 mmol) and diethyl (3-aminobenzyl)phosphonate·HCl **35** (0.252 g, 0.9 mmol) were reacted. The crude product was purified by preparative TLC in EtOAc:EtOH (9:1). The product was extracted from the silica with MeOH. After evaporation, the residue was dissolved in EtOAc (100 mL), washed with 1 M aqueous HCl (100 mL) with satd aqueous $NaHCO_3$ (100 mL) with brine and then dried with $MgSO_4$. After concentration, a yellow powder was obtained (0.041 g, 13%); mp = 217−218 °C (EtOAc). ^{31}P NMR ($CDCl_3$, 121 MHz): δ 29.4 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.62 (s, 1H), 8.68 (s, 1H), 7.94 (dd, $^3J_{HH}$ = 7.7 Hz, $^4J_{HH}$ = 1.5 Hz, 1H), 7.55−7.66 (m, 2H), 7.45 (s, 2H), 7.27 (t, $^3J_{HH}$ = 7.7 Hz, 0.1H), 7.18 (d, $^3J_{HH}$ = 8.3 Hz, 1H), 7.08 (t, $^3J_{HH}$ = 7.5 Hz, 1H), 6.93 (d, $^3J_{HH}$ = 7.6 Hz, 1H), 3.80−4.00 (m, 4H), 3.90 (s, 3H), 3.20 (d, $^2J_{PH}$ = 22.1 Hz, 2H), 1.18 (t, $^3J_{HH}$ = 7.0 Hz, 6H). LC-MS: R_t = 2.58 min; 2.73 min. (ESI): m/z = 428 $[M + H]^+$.

*Diethyl (3-{[6-(3-Nitrophenyl)pyrimidin-4-yl]amino}benzyl)-phosphonate (**39a**).* According to the general coupling procedure, 4-chloro-6-(3-nitrophenyl)-pyrimidine **13b** (0.230 g, 0.98 mmol) and diethyl (3-aminobenzyl)phosphonate·HCl **35** (0.408 g, 1.46 mmol) were reacted. The crude product was recrystallized from MeCN and washed with Et_2O to give a yellow powder (0.228 g, 53%); mp = 188−190 °C (MeCN). ^{31}P NMR (DMSO-d_6, 242 MHz): δ 25.6 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.83 (s, 1H), 8.83 (s, 1H), 8.76 (s, 1H), 8.47 (d, $^3J_{HH}$ = 7.6 Hz, 1H), 8.36 (d, $^3J_{HH}$ = 7.9 Hz, 1H), 7.83 (t, $^3J_{HH}$ = 7.9 Hz, 1H), 7.59−7.70 (m, 2H), 7.40 (s, 1H), 7.29 (t, $^3J_{HH}$ = 7.5 Hz, 1H), 6.97 (d, $^3J_{HH}$ = 6.9 Hz, 1H), 3.92−4.03 (m, 4H), 3.24 (d, $^2J_{PH}$ = 21.5 Hz, 2H), 1.19 (t, $^3J_{HH}$ = 6.9 Hz, 6H). LC-MS: R_t = 3.66 min. (ESI): m/z = 443 $[M + H]^+$.

*Diethyl [Hydroxy(3-{[6-(3-nitrophenyl)pyrimidin-4-yl]amino}-phenyl)methyl]phosphonate (**39b**).* According to the general coupling procedure, 4-chloro-6-(3-nitrophenyl)-pyrimidine **13b** (0.230 g, 0.98 mmol) and diethyl [(3-aminophenyl)(hydroxy)methyl]phosphonate·HCl **33** (0.433 g, 1.46 mmol) were reacted. The crude product was recrystallized from MeCN and washed with Et_2O to give a yellow powder (0.329 g, 73%); mp = 191 °C (MeCN). ^{31}P NMR (DMSO-d_6, 242 MHz): δ 20.8 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.85 (s, 1H), 8.84 (s, 1H), 8.77 (s, 1H), 8.48 (d, $^3J_{HH}$ = 7.8 Hz, 1H), 8.36 (dd, $^3J_{HH}$ = 8.1 Hz, $^4J_{HH}$ = 1.5 Hz, 1H), 7.84 (t, $^3J_{HH}$ = 8.0 Hz, 1H), 7.69−7.78 (m, 2H), 7.41 (s, 1H), 7.33 (t, $^3J_{HH}$ = 8.1 Hz, 1H), 7.12 (d, $^3J_{HH}$ = 7.4 Hz, 1H), 6.21 (dd, $^3J_{PH}$ = 16.2 Hz, $^3J_{HH}$ = 5.5 Hz, 1H), 4.95 (dd, $^2J_{PH}$ = 13.4 Hz, $^3J_{HH}$ = 5.5 Hz, 1H), 3.88−4.06 (m, 4H), 1.18 (t, $^3J_{HH}$ = 6.9 Hz, 6H). LC-MS: R_t = 3.26 min. (ESI): m/z = 459 $[M + H]^+$.

*Diethyl (3-{[6-(3-Aminophenyl)pyrimidin-4-yl]amino}benzyl)-phosphonate (**40a**).* According to the nitro group reduction described for compound **26a**: reduction of compound **39a** (0.100 g, 0.23 mmol) gave a yellow powder (0.075 g, 73%); mp = 186 °C (Et_2O). ^{31}P NMR (DMSO-d_6, 242 MHz): δ 28.5 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 11.02 (s, 1H), 8.84 (s, 1H), 7.45−7.70 (m, 5H), 7.30−7.40 (m, 3H), 7.05−7.15 (m, 1H), 3.95−4.00 (m, 4H), 3.26 (d, $^2J_{PH}$ = 21.0 Hz, 2H), 1.19 (s, 6H). LC-MS: R_t = 2.38 min; 2.48 min. (ESI): m/z = 413 $[M + H]^+$.

*Diethyl [(3-{[6-(3-Aminophenyl)pyrimidin-4-yl]amino}phenyl)-(hydroxy)methyl]phosphonate (**40b**).* According to the nitro group reduction described for compound **26a**: reduction of compound **39b** (0.100 g, 0.22 mmol) afforded a yellow powder (0.082 g, 80%); mp = 265−267 °C (Et_2O). ^{31}P NMR (DMSO-d_6, 242 MHz): δ 23.6 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 11.14 (s, 1H), 8.86 (s, 1H), 7.10−7.80 (m, 9H), 6.00 (br, 3H), 4.98 (d, $^2J_{PH}$ = 13.2 Hz, 1H), 3.95−4.00 (m, 4H), 1.17 (s, 6H). LC-MS: R_t = 2.01 min; 2.23 min. (ESI): m/z = 429 $[M + H]^+$.

*Diethyl (4-{[6-(2-Methoxyphenyl)pyrimidin-4-yl]amino}benzyl)-phosphonate (**41a**).* According to the general coupling procedure, 4-chloro-6-(2-methoxyphenyl)-pyrimidine **13a** (0.221 g, 1.0 mmol) and diethyl (4-aminobenzyl)phosphonate·HCl **36** (0.419 g, 1.5 mmol) were reacted. The crude product was recrystallized from MeCN to give a yellow powder (0.212 g, 50%); mp = 151 °C (MeCN). ^{31}P NMR (DMSO-d_6, 242 MHz): δ 25.9 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.57 (s, 1H; 8.66 (s, 1H), 7.93 (d, $^3J_{HH}$ = 7.5 Hz, 1H), 7.62 (d, J_{AABB} = 8.2 Hz, 2H), 7.43 (t, $^3J_{HH}$ = 8.4 Hz, 1H), 7.42 (s, 1H), 7.22 (dd, J_{AABB} = 8.4 Hz, $^4J_{PH}$ = 1.8 Hz, 2H), 7.16 (d, $^3J_{HH}$ = 8.3 Hz, 1H), 7.06 (t, $^3J_{HH}$ = 7.5 Hz, 1H), 3.90−3.99 (m, 4H), 3.88 (s, 3H, H20), 3.15 (d, $^2J_{PH}$ = 21.2 Hz, 2H), 1.17 (t, $^3J_{HH}$ = 7.0 Hz, 6H). LC-MS: R_t = 2.41 min; 2.56 min. (ESI): m/z = 428 $[M + H]^+$.

*Diethyl [Hydroxy(4-{[6-(2-methoxyphenyl)pyrimidin-4-yl]amino}-phenyl)methyl]phosphonate (**41b**).* According to the general coupling procedure, 4-chloro-6-(2-methoxyphenyl)-pyrimidine **13a** (0.221 g, 1.0 mmol) and diethyl [(4-aminophenyl)(hydroxy)methyl]phosphonate·HCl **34** (0.44 g, 1.5 mmol) were reacted. The crude product was recrystallized first from hexane/CH_2Cl_2 then from MeCN to give a yellow powder (0.140 g, 32%); mp = 195−196 °C (MeCN). ^{31}P NMR (DMSO-d_6, 242 MHz): δ 21.0 ppm (82%) and 7.4 ppm (18%). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.62 (s, 1H), 8.69 (s, 1H), 7.95 (d, $^3J_{HH}$ = 5.2 Hz, 1H), 7.55−7.7 (m, 2H), 7.3−7.5 (m, 4H), 7.18 (d, $^3J_{HH}$ = 6.4 Hz, 1H), 7.08 (s, 1H), 6.09 (d, $^3J_{PH}$ = 12.4 Hz, 1H), 4.88 (d, $^2J_{PH}$ = 11.1 Hz, 1H), 3.9−4.05 (m, 7H), 1.17 (s, 6H). Peaks are broads, some of them split in 3 to 1 ratio on heating. We hypothesize that α-hydroxy protons can form intramolecular H-bonds with the oxygen of phosphorus, and these asymmetric ring formation causes odd spectra. Derivatives without α-hydroxy group never show this phenomenon. LC-MS: R_t = 0.46 min; 2.14 min; 2.32 min. (ESI): m/z = 444 $[M + H]^+$.

*Diethyl (4-{[6-(3-Nitrophenyl)pyrimidin-4-yl]amino}benzyl)-phosphonate (**42a**).* According to the general coupling procedure, 4-chloro-6-(3-nitrophenyl)-pyrimidine **13b** (0.236 g, 1.0 mmol) and diethyl (4-aminobenzyl)phosphonate·HCl **36** (0.419 g, 1.5 mmol) were reacted. Purification was different from the general procedure: after the suspension of the crude product in satd $NaHCO_3$, EtOAc (0.5 mL) was added and the mixture was stirred at 0 °C for 30 min. The precipitate was filtered and washed with Et_2O. The desired compound was isolated as a yellow powder (0.44 g, 99%); mp = 204 °C (water, EtOAc). ^{31}P NMR (DMSO-d_6, 242 MHz): δ 25.8 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.81 (s, 1H), 8.81 (s, 1H), 8.75 (s, 1H), 8.43 (d, $^3J_{HH}$ = 7.7 Hz, 1H), 8.35 (d, $^3J_{HH}$ = 8.1 Hz, 1H), 7.83 (t, $^3J_{HH}$ = 7.9 Hz, 1H), 7.65 (d, J_{AABB} = 8.1 Hz, 2H), 7.36 (s, 1H), 7.25 (dd, J_{AABB} = 8.7 Hz, J = 2.1 Hz, 2H), 3.89−4.00 (m, 4H), 3.18 (d, $^2J_{PH}$ = 21.2 Hz, 2H), 1.17 (t, $^3J_{HH}$ = 7.0 Hz, 6H). LC-MS: R_t = 3.62 min. (ESI): m/z = 443 $[M + H]^+$.

*Diethyl [Hydroxy(4-{[6-(3-nitrophenyl)pyrimidin-4-yl]amino}-phenyl)methyl]phosphonate (**42b**).* According to the general coupling procedure, 4-chloro-6-(3-nitrophenyl)-pyrimidine **13b** (0.220 g, 0.93 mmol) and diethyl [(4-aminophenyl)(hydroxy)methyl]phosphonate·HCl **34** (0.363 g, 1.4 mmol) were reacted. The crude product was purified by column chromatography in 100% EtOAc. Fractions containing the desired compound were combined and concentrated. The product was isolated after recrystallization from MeCN as a pale-yellow powder (0.024 g, 6%); mp = 205 °C, dec (MeCN). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.81 (s, 1H), 8.82 (s, 1H), 8.78 (s, 1H), 8.45 (s, 1H), 8.37 (s, 1H), 7.84 (s, 1H), 7.69 (s, 2H), 7.4 (br, 3H), 6.11 (d, $^3J_{PH}$ = 14.7 Hz, 1H), 4.90 (d, $^2J_{PH}$ = 9.8 Hz, 1H), 3.98 (br, 4H), 1.18 (br, 6H). The spectrum has the similar phenomena as those of compound **41b**. LC-MS: R_t = 3.22 min. (ESI): m/z = 459 $[M + H]^+$.

*Diethyl (4-{[6-(3-Aminophenyl)pyrimidin-4-yl]amino}benzyl)-phosphonate (**43**).* According to the nitro group reduction described for compound **26a**: reduction of compound **42a** (0.300 g, 0.68 mmol) afforded a yellow powder (0.182 g, 65%); mp = 62−65 °C (EtOAc), amorph. ^{31}P NMR (DMSO-d_6, 242 MHz): δ 25.8 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.57 (s, 1H), 8.64 (s, 1H), 7.62 (d, J_{AABB} = 8.2 Hz, 2H), 7.21−7.27 (m, 3H), 7.09−7.16 (m, 3H), 6.67 (d, $^3J_{HH}$ = 6.8 Hz, 1H), 5.26 (br, 2H), 3.88−3.99 (m, 4H), 3.15 (d, $^2J_{PH}$ = 21.2 Hz, 2H), 1.17 (t, $^3J_{HH}$ = 7.0 Hz, 6H). LC-MS: R_t = 0.46 min; 2.22 min; 2.44 min. (ESI): m/z = 413 $[M + H]^+$.

*Diethyl (5-{[6-(2-Methoxyphenyl)pyrimidin-4-yl]amino}-2-methylbenzyl)phosphonate (**44**).* According to the general coupling procedure, 4-chloro-6-(2-methoxyphenyl)-pyrimidine **13a** (0.165 g, 0.75 mmol) and diethyl (5-amino-2-methylbenzyl)phosphonate·HCl **37** (0.072 g, 0.25 mmol) were reacted. The crude product was purified

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by preparative TLC with EtOAc:hexane (8:1). The pure product was extracted from the silica with MeOH. After evaporation of solvents under vacuum, a yellow powder was obtained (0.04 g, 53%); mp = 134−137 °C (MeOH). ^{31}P NMR (DMSO-d_6, 242 MHz): δ 28.9 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.56 (s, 1H), 8.56 (s, 1H), 7.93 (dd, $^{3}J_{HH}$ = 7.7 Hz, $^{4}J_{HH}$ = 1.5 Hz, 1H), 7.41−7.56 (m, 3H), 7.42 (s, 1H), 7.17 (d, $^{3}J_{HH}$ = 8.3 Hz, 1H; 7.13 (d, $^{3}J_{HH}$ = 8.1 Hz, 1H), 7.07 (t, $^{3}J_{HH}$ = 7.4 Hz, 1H), 3.89−4.00 (m, 4H), 3.89 (s, 3H), 3.17 (d, $^{2}J_{PH}$ = 21.6 Hz, 2H), 2.29 (s, 3H), 1.18 (t, $^{3}J_{HH}$ = 7.0 Hz, 6H). LC-MS: R_t = 2.92 min. (ESI): m/z = 442 $[M + H]^+$.

*(4-{[6-(3-Nitrophenyl)pyrimidin-4-yl]amino}benzyl)phosphonic Acid (**45a**).* Diethyl (4-{[6-(3-nitrophenyl)pyrimidin-4-yl]amino}-benzyl)phosphonate **42a** (0.100 g, 0.23 mmol) was refluxed in 5 M aqueous HCl solution (30 mL) for 24 h. Volatiles were evaporated then the residue was dissolved in water (25 mL) and it was washed with DEE (3 × 100 mL). Water was evaporated then dry toluene (20 mL) was distilled from the residue. The dry residue was dissolved in abs EtOH (5 mL) and cooled to −9 °C then propylene-oxide (0.5 mL) was added to the mixture. After 15 min stirring, the precipitate was filtered and washed with Et_2O. Compound **45a** was isolated as a yellow powder (0.059g, 66%); mp = 265−270 °C, dec (EtOH). ^{31}P NMR (DMSO-d_6, 242 MHz): δ 20.1 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 10.48 (s, 1H), 8.79 (s, 1H), 8.77 (s, 1H), 8.39 (dd, $^{3}J_{HH}$ = $^{3}J_{HH}$ = 7.8 Hz, 2H), 7.85 (t, $^{3}J_{HH}$ = 8.0 Hz, 1H), 7.63 (d, J_{AABB} = 7.8 Hz, 2H), 7.15 (s, 1H), 7.24 (d, J_{AABB} = 7.5 Hz, 2H), 5.2 (br, 2H), 2.93 (d, $^{2}J_{PH}$ = 21.4 Hz, 2H). LC-MS: R_t = 2.40 min. (ESI): m/z = 387 $[M + H]^+$.

*(4-{[6-(3-Aminophenyl)pyrimidin-4-yl]amino}benzyl)phosphonic Acid (**45b**).* Compound **45b** was prepared with the method described for compound **45a** starting from diethyl phosphonate **43** (0.128 g, 0.31 mmol), yielding a yellow powder (0.11 g, 99%); mp> 300 °C (EtOH). ^{31}P NMR (DMSO-d_6, 242 MHz): δ 20.4 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 11.08 (s, 1H), 8.73 (s, 1H), 7.52 (d, J_{AABB} = 8.1 Hz, 2H), 7.38−7.48 (m, 3H), 7.24 (d, J_{AABB} = 8.1 Hz, 2H), 7.12−7.20 (m, 1H), 7.14 (s, 1H), 6.30 (br, 4H), 2.98 (d, $^{2}J_{PH}$ = 21.4 Hz, 2H). LC-MS: R_t = 0.46 min; 1.64 min. (ESI): m/z = 357 $[M + H]^+$.

*Ethyl (3-Aminobenzyl)phenylphosphinate (**46**).* Ethyl phenylphosphinate (1.02 g, 6.0 mmol) was dissolved in anhydrous THF (20 mL) then triethylamine (0.97 mL; 7.0 mmol) and trimethylsilyl chloride (0.89 mL; 7.0 mmol) were added to the solution, respectively. The mixture was stirred for 1 h at RT then the precipitate was filtered off. Filtrate was evaporated under reduced pressure then anhydrous toluene (30 mL) was evaporated from the residue. To the obtained yellow oil, 3-nitrobenzyl bromide (1.08 g; 5.0 mmol) was added and the mixture was heated to 140 °C under argon flow for 4.5 h. When the reaction mixture was cooled to 50−60 °C and diluted with $CHCl_3$ (5 mL) then it was cooled further to 0 °C and 5 M aqueous HCl solution (2 mL) was added. After 15 min of stirring, the mixture was diluted with water (10 mL) and was extracted with $CHCl_3$ (3 × 50 mL). Combined organic phases were washed with 2 M aqueous NaOH solution (2 × 50 mL) and with brine then it was dried with Mg SO_4. After evaporation of the solvent, the phosphinic acid was obtained as a yellow powder (0.645 g, 47%); mp = 127−128 °C ($CHCl_3$). ^{31}P NMR (DMSO-d_6, 242 MHz): δ 54.9 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.03 (d, $^{3}J_{HH}$ = 5.4 Hz, 1H), 7.98 (s, 1H), 7.45−7.75 (m, 7H), 3.43 (d, $^{2}J_{PH}$ = 17.3 Hz, 2H). LC-MS: R_t = 2.62 min. (ESI): m/z = 278 $[M + H]^+$. (3-Nitrobenzyl)phenylphosphinic acid (0.880 g; 3.18 mmol) was dissolved in DMF (10 mL) then triethyl orthoformate (5.28 mL; 31.80 mmol) and one drop trifluoroacetic acid was added. The reaction mixture was stirred for 1 week at 80 °C, and then it was evaporated. The residue was suspended in 2 M aqueous NaOH solution (50 mL), and it was extracted with EtOAc (3 × 75 mL). The combined organic layers were washed with brine and dried with $MgSO_4$. After evaporation, the phosphonic ester was obtained as a yellow oil (0.729 g, 75%). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.03 (d, $^{3}J_{HH}$ = 5.1 Hz, 1H), 8.00 (s, 1H), 7.60−7.75 (m, 2H), 7.45−7.60 (m, 5H), 3.80−3.97 and 3.60−3.75 (2xm, 2 × 1H), 3.66 (d, $^{2}J_{PH}$ = 17.3 Hz, 2H), 1.18 (t, $^{3}J_{HH}$ = 6.9 Hz, 3H). LC-MS: R_t = 3.45 min. (ESI): m/z = 306 $[M + H]^+$. Reduction of ethyl (3-nitrobenzyl)phenylphosphinate (0.72 g, 2.36 mmol) to compound **46** was carried out according to the nitro group reduction described for compound **26a** giving a yellow oil (0.586 g, 90%). ^{31}P NMR (242 MHz): DMSO-d_6, δ 41.5 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.9 (br, 2H), 7.63−7.77 (m, 2H), 7.57 (d, $^{3}J_{HH}$ = 5.9 Hz, 1H), 7.40−7.60 (m, 2H), 7.15 (t, $^{3}J_{HH}$ = 7.0 Hz, 1H), 6.80−7.00 (m, 2H), 6.83 (d, $^{3}J_{HH}$ = 4.8 Hz, 1H), 3.75−3.85 and 3.85−3.95 (2 × m, 2 × 1H), 3.42 (d, $^{2}J_{PH}$ = 17.2 Hz, 2H), 1.16 (t, $^{3}J_{HH}$ = 6.7 Hz, 3H). LC-MS: R_t = 0.45 and 2.28 min; (ESI): m/z = 276 $[M + H]^+$.

*Ethyl (3-Aminobenzyl)ethylphosphinate (**47**).* Diethyl ethylphosphonite was prepared from triethyl-phosphite (16.6 g, 100 mmol) and ethyl bromide (16.35 g, 150 mmol) according to the method described by Petnehazy et al.[32] The ethylphosphonite was isolated as a colorless oil (11.25 g, 50%). ^{31}P NMR ($CDCl_3$, 121 MHz): δ 185.6 ppm. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.72−3.97 (m, J_{PH} = 12.1 Hz, 4H), 1.86 (dt, J_{HH} = 6.4 Hz, J_{PH} = 12.8 Hz, 2H), 1.26 (t, J_{HH} = 7.1 Hz, 6H), 1.05 (dt, J_{HH} = 6.5 Hz, J_{PH} = 14.3 Hz, 3H). 3-Nitro-benzylbromide (1.08 g; 5.0 mmol) and diethyl ethylphosphonite (1.125 g; 7.5 mmol) were heated to 140 °C under argon flow for 1 h. When the reaction mixture was cooled to 50−60 °C and diluted with $CHCl_3$ (5 mL) then it was cooled further to 0 °C and 5 M aqueous HCl solution (2 mL) was added. After 15 min of stirring, the mixture was diluted with water (10 mL) and was extracted with $CHCl_3$ (3 × 50 mL). Combined organic phases were washed with 2 M aqueous NaOH solution (2 × 50 mL) and with brine then it was dried with Mg SO_4. After evaporation of the volatiles under reduced pressure, the residue was suspended in MeOH (100 mL) and it was discolored by charcoal. After filtration on a celite pad and concentration, the phosphinate was obtained as a yellow oil (0.846 g, 66%). It was used in the next step without further purification. ^{31}P NMR (DMSO-d_6, 242 MHz): δ 54.9 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.18 (s, 1H), 8.10 (d, $^{3}J_{HH}$ = 7.0 Hz, 1H), 7.73 (d, $^{3}J_{HH}$ = 7.2 Hz, 1H), 7.62 (t, $^{3}J_{HH}$ = 7.5 Hz, 1H), 3.80−4.00 (m, 2H), 3.40 (d, $^{2}J_{PH}$ = 16.4 Hz, 2H), 1.60−1.70 (m, 2H), 1.16 (s, 3H), 1.00 (dt, $^{3}J_{PH}$ = 18.1 Hz, $^{3}J_{HH}$ = 7.4 Hz, 3H). LC-MS: R_t = 2.91 min. (ESI): m/z = 258 $[M + H]^+$. Reduction of ethyl ethyl [(3-nitrobenzyl)phosphinate (0.837 g, 3.26 mmol) to compound **47** was carried out according to the nitro group reduction described for compound **26a**, giving a yellow oil (0.69 g, 93%). ^{31}P NMR (DMSO-d_6, 242 MHz): δ 56.1 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 6.92 (s, 1H), 6.47 (s, 1H), 6.41 (s, 2H), 5.07 (br, 2H), 3.80−3.90 (m, 2H), 2.97 (d, $^{2}J_{PH}$ = 16.5 Hz, 2H), 1.50−1.60 (m, 2H), 1.18 (s, 3H), 0.97 (dt, $^{3}J_{PH}$ = 17.6 Hz, $^{3}J_{HH}$ ~ 8.7 Hz, 3H). LC-MS: R_t = 0.45 and 1.73 min. (ESI): m/z = 228 $[M + H]^+$.

*Ethyl (3-Aminobenzyl)propylphosphinate (**48**).* The diethyl propylphosphonite was prepared from (18.45 g; 150 mmol) propyl bromide and (16.6 g; 100 mmol) triethyl-phosphite according to the method described by Petnehazy et al.[32] The propylphosphonite was isolated as a colorless oil (17.71 g, 72%). ^{31}P NMR ($CDCl_3$, 121 MHz): δ 184.9 ppm. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.70−3.91 (m, 4H), 1.85 (dt, J_{HH} = 6.6 Hz, J_{PH} = 12.0 Hz, 2H), 1.42−1.51 (m, 2H), 1.24 (t, J_{HH} = 7.0 Hz, 6H), 0.99 (t, J_{HH} = 6.6 Hz, 3H). Diethyl propylphosphonite (2.61 g, 17.4 mmol) was reacted with 3-nitrobenzyl bromide (2.51 g, 11.6 mmol) as it is described for compound **47**. The propylphosphinate was isolated as a brown oil (2.88 g; 92%) and was used without further purification. ^{31}P NMR ($CDCl_3$, 121 MHz): δ 50.8 ppm. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.17 (d, $^{4}J_{HH}$ = 1.2 Hz, 1H), 8.11 (d, $^{3}J_{HH}$ = 6.9 Hz, 1H), 7.70 (d, $^{3}J_{HH}$ = 7.5 Hz, 1H), 7.54 (t, $^{3}J_{HH}$ = 7.2 Hz, 1H), 3.94−4.16 (m, 2H), 3.27 (d, $^{2}J_{PH}$ = 15.6 Hz, 2H), 1.56−1.80 (m, 4H), 1.27 (t, $^{3}J_{HH}$ = 6.9 Hz, 3H), 1.02 (t, $^{3}J_{HH}$ = 7.2 Hz, 3H). Reduction of ethyl (3-nitrobenzyl)propylphosphinate (0.88 g, 10.6 mmol) to compound **48** was carried out according to the nitro group reduction described for compound **26a**, yielding a yellow oil (2.148 g, 84%). ^{31}P NMR ($CDCl_3$, 121 MHz): δ 53.1 ppm. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.07 (t, $^{3}J_{HH}$ = 7.8 Hz, 1H), 6.68 (d, $^{4}J_{HH}$ = 1.5 Hz, 1H), 6.63 (d, $^{3}J_{HH}$ = 8.4 Hz, 1H), 6.60 (d, $^{3}J_{HH}$ = 8.4 Hz, 1H), 3.95−4.05 (m, 2H), 3.03 (d, $^{2}J_{PH}$ = 16.8 Hz, 2H), 1.50−1.70 (m, 4H), 1.26 (t, $^{3}J_{HH=}$ 7.2 Hz, 3H), 0.96 (t, $^{3}J_{HH}$ = 6.9 Hz, 3H).

*Ethyl (4-Aminobenzyl)ethylphosphinate (**49**).* The 4-nitrobenzyl bromide (1.296 g 6.0 mmol) and 1.35 g diethyl ethylphosphonite (9.0 mmol) were reacted according to the preparation of **47**, giving a yellow oil (0.847 g, 55%). ^{31}P NMR (DMSO-d_6, 242 MHz): δ 54.7 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.18 (d, J_{AABB} = 7.6 Hz, 2H), 7.55 (d, J_{AABB} = 6.6 Hz, 2H), 3.90−3.93 (m, 2H), 3.39 (d, $^{2}J_{PH}$ = 16.8 Hz, 2H), 1.60−1.68 (m, 2H), 1.16 (t, $^{3}J_{HH}$ = 6.8 Hz, 3H), 1.00 (dt, $^{3}J_{PH}$ = 18.1 Hz, $^{3}J_{HH}$ = 7.4 Hz, 3H). LC-MS: R_t = 2.88 min. (ESI): m/z = 258 $[M + H]^+$.

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Reduction of ethyl ethyl (4-nitrobenzyl)phosphinate (0.843 g, 3.28 mmol) was carried out according to the nitro group reduction described for compound **26a**, providing a brown oil (0.375 g, 50%). LC-MS: R_t = 0.44 min. (ESI): m/z = 228 $[M + H]^+$. Compound **49** was used without further purification and characterization.

*Ethyl (4-Aminobenzyl)propylphosphinate (**50**).* The 4-nitro-benzyl bromide (1.296 g, 6.0 mmol) and diethyl propylphosphonite (1.476 g; 9.0 mmol) were reacted according to the preparation of **47**, yielding a brown oil (1.426 g; 88%). ^{31}P NMR (DMSO-d_6, 242 MHz): δ 53.1 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.18 (d, J_{AABB} = 7.6 Hz, 2H), 7.55 (d, J_{AABB} = 7.5 Hz, 2H), 3.90−3.95 (m, 2H), 3.39 (d, $^2J_{PH}$ = 17.0 Hz, 2H), 1.55−1.65 (m, 2H), 1.40−1.50 (m, 2H), 1.13−1.22 (m, 3H), 0.93 (br, 3H). LC-MS: R_t = 3.16 min. (ESI): m/z = 272 $[M + H]^+$. Reduction of ethyl (4-nitrobenzyl)propylphosphinate (1.42 g, 5.24 mmol) was carried out according to the nitro group reduction described for compound **26a**, giving a brown oil (1.005 g; 80%). LC-MS: R_t = 0.44 and 1.89 min. (ESI): m/z = 242 $[M - H]^+$. Compound **50** was used without further purification and characterization.

*Ethyl (5-Amino-2-methylbenzyl)ethylphosphinate (**51**).* The 2-(bromomethyl)-1-methyl-4-nitrobenzene (1.150 g, 5.0 mmol, issued from the synthesis of **37**) and diethyl ethylphosphonite (1.294 g; 7.5 mmol) were reacted according to the reaction described for compound **47**, affording a brown oil (0.918 g, 68%). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.78 (s, 1H), 7.66 (d, $^3J_{HH}$ = 6.9 Hz, 1H), 7.38 (d, $^3J_{HH}$ = 7.2 Hz, 1H), 3.80−4.10 (m, 2H), 3.30 (2H, overlaps with DMSO's water), 2.44 (s, 3H), 1.65−1.70 (m, 2H), 1.13 (t, $^3J_{HH}$ = 6.9 Hz, 3H), 1.04 (dt, $^3J_{PH}$ = 17.7 Hz, $^3J_{HH}$ = 8.1 Hz, 3H). Reduction of ethyl ethyl (2-methyl-5-nitrobenzyl)phosphinate (0.90 g, 3.32 mmol) was carried out according to the nitro group reduction described for compound **26a**, giving a brown oil (0.411 g, 51%). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 6.78 (d, $^3J_{HH}$ = 7.1 Hz, 1H), 6.45 (s, 1H), 6.34 (d, $^3J_{HH}$ = 5.8 Hz, 1H), 4.70 (br, 2H), 3.80−4.00 (m, 2H), 2.97 (d, $^2J_{PH}$ = 16.7 Hz, 2H), 1.91 (s, 3H), 1.55−1.75 (m, 2H), 1.16 (br, 3H), 1.00 (t, $^3J_{HH}$ = 7.5 Hz, 3H). According to the ^{1}H NMR spectra purity of compound **51** was about 50%. It was used without further purification in the next step. LC-MS: R_t = 0.44 min. (ESI): m/z = 242 $[M + H]^+$.

*Ethyl Ethyl (3-{[6-(2-Methoxyphenyl)pyrimidin-4-yl]amino}-benzyl)phosphinate (**52a**).* According to the general coupling procedure, 4-chloro-6-(2-methoxyphenyl)-pyrimidine **13a** (0.075 g, 0.34 mmol) and ethyl (3-aminobenzyl)ethylphosphinate·HCl **47** (0.108 g, 0.41 mmol) were reacted. The crude product was purified by preparative TLC using EtOAc:hexane (8:1) and 1 v/v% AcOH as eluent. The product was extracted from the silica with MeOH. After concentration, **52a** was dissolved in EtOAc (100 mL) and it was washed with 0.1 M aqueous AcOH solution (3 × 30 mL), with satd aqueous $NaHCO_3$ solution (100 mL), and with brine (100 mL). The organic phase was dried with $MgSO_4$ and evaporated under vacuum. **52a** was obtained as yellow powder (0.045 g, 32%); mp = 30 °C. ^{31}P NMR (DMSO-d_6, 242 MHz): δ 55.6 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.62 (s, 1H), 8.67 (s, 1H), 7.94 (d, $^3J_{HH}$ = 6.2 Hz, 1H), 7.55−7.68 (m, 2H), 7.45 (s, 2H), 7.27 (t, $^3J_{HH}$ = 7.7 Hz, 1H), 7.17 (d, $^3J_{HH}$ = 7.5 Hz, 1H), 7.08 (t, $^3J_{HH}$ = 7.5 Hz, 1H), 6.93 (d, $^3J_{HH}$ = 7.6 Hz, 1H), 3.80−4.00 (m, 2H), 3.90 (s, 3H), 3.17 (d, $^2J_{PH}$ = 16.5 Hz, 2H), 1.50−1.70 (m, 2H), 1.18 (t, $^3J_{HH}$ = 7.0 Hz, 3H), 1.00 (dt, $^3J_{PH}$ = 17.6 Hz, $^3J_{HH}$ = 7.2 Hz, 3H). LC-MS: R_t = 2.56 min. (ESI): m/z = 412 $[M + H]^+$.

*Ethyl (3-{[6-(2-Methoxyphenyl)pyrimidin-4-yl]amino}benzyl)-propylphosphinate (**52b**).* According to the general coupling procedure, 4-chloro-6-(2-methoxyphenyl)-pyrimidine **13a** (0.17 g; 0.77 mmol) and ethyl (3-aminobenzyl)propylphosphinate·HCl **48** (0.229 g; 0.83 mmol) were reacted. The crude product was purified by column chromatography with 100% EtOAc to EtOAc:EtOH (1:1). After concentration, **52b** was obtained as a yellow oil (0.16 g, 50%). ^{31}P NMR ($CDCl_3$, 121 MHz): δ 52.5 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.67 (s, 1H), 8.68 (s, 1H), 7.94 (d, $^3J_{HH}$ = 6.2 Hz, 1H), 7.55−7.68 (m, 2H), 7.45 (s, 2H), 7.28 (t, $^3J_{HH}$ = 7.1 Hz, 1H), 7.17 (d, $^3J_{HH}$ = 8.0 Hz, 1H), 7.09 (t, $^3J_{HH}$ = 6.8 Hz, 1H), 6.93 (d, $^3J_{HH}$ = 5.8 Hz, 1H), 3.89 (s, 5H), 3.16 (d, $^2J_{PH}$ = 16.5 Hz, 2H), 1.35−1.70 (m, 4H), 1.18 (t, $^3J_{HH}$ = 6.8 Hz, 3H), 0.92 (br, 3H). LC-MS: R_t = 2.75 min. (ESI): m/z = 426 $[M + H]^+$.

*Ethyl (3-{[6-(2-Methoxyphenyl)pyrimidin-4-yl]amino}benzyl)-phenylphosphinate (**52c**).* According to the general coupling procedure, 4-chloro-6-(2-methoxyphenyl)-pyrimidine **13a** (0.157 g, 0.71 mmol) and ethyl (3-aminobenzyl)phenylphosphinate·HCl **46** (0.332 g, 1.07 mmol) were reacted. The crude product was purified by preparative TLC with EtOAc:hexane (8:1) and 1 v/v% AcOH as eluent. The product was extracted with MeOH from the silica. After evaporation, the residue was dissolved in EtOAc (100 mL) and washed with 0.1 M aqueous AcOH solution (3 × 30 mL), with satd aqueous $NaHCO_3$ solution (100 mL), and with brine (100 mL). The organic phase was dried with $MgSO_4$ and evaporated under reduced pressure. **52c** was obtained as yellow powder (0.094 g, 29%); mp = 103−104 °C (EtOAc). ^{31}P NMR (DMSO-d_6, 242 MHz): δ 41.5 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.56 (s, 1H), 8.64 (s, 1H), 7.93 (d, $^3J_{HH}$ = 6.2 Hz, 1H), 7.30−7.75 (m, 8H), 7.00−7.20 (m, 4H), 6.73 (d, $^3J_{HH}$ = 3.9 Hz, 1H), 3.90−4.00 (m, 1H), 3.90 (s, 3H), 3.80−3.88 (m, 1H), 3.42 (d, $^2J_{PH}$ = 17.3 Hz, 2H), 1.18 (t, $^3J_{HH}$ = 6.0 Hz, 3H). LC-MS: R_t = 2.92 min. (ESI): m/z = 460 $[M + H]^+$.

*Ethyl Ethyl (3-{[6-(3-Nitrophenyl)pyrimidin-4-yl]amino}benzyl)-phosphinate (**53a**).* According to the general coupling procedure, 4-chloro-6-(3-nitrophenyl)-pyrimidine **13b** (0.118 g, 0.5 mmol) and ethyl (3-aminobenzyl)ethylphosphinate·HCl **47** (0.158 g, 0.6 mmol) were reacted. The crude product was recrystallized from MeCN to give a yellow powder (0.118 g, 55%); mp = 189−190 °C (MeCN). ^{31}P NMR (DMSO-d_6, 242 MHz): δ 55.8 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.81 (s, 1H), 8.84 (s, 1H), 8.76 (s, 1H), 8.48 (d, $^3J_{HH}$ = 6.9 Hz, 1H), 8.36 (d, $^3J_{HH}$ = 7.5 Hz, 1H), 7.84 (t, $^3J_{HH}$ = 7.7 Hz, 1H), 7.55−7.65 (m, 2H), 7.41 (s, 1H), 7.30 (t, $^3J_{HH}$ = 7.2 Hz, 1H), 6.99 (d, $^3J_{HH}$ = 4.8 Hz, 1H), 3.90−4.00 (m, 2H), 3.19 (d, $^2J_{PH}$ = 16.5 Hz, 2H), 1.60−1.70 (m, 2H), 1.19 (t, $^3J_{HH}$ = 6.3 Hz, 3H), 1.01 (dt, $^3J_{PH}$ = 17.7 Hz, $^3J_{HH}$ = 8.8 Hz, 3H). LC-MS: R_t = 3.41 min. (ESI): m/z = 427 $[M + H]^+$.

*Ethyl (3-{[6-(3-Nitrophenyl)pyrimidin-4-yl]amino}benzyl)-propylphosphinate (**53b**).* According to the general coupling procedure, 4-chloro-6-(3-nitrophenyl)-pyrimidine **13b** (0.22 g, 0.92 mmol) and ethyl (3-aminobenzyl)propylphosphinate·HCl **48** (0.25 g, 1.04 mmol) were reacted. After the reaction the crude product was filtered from the $NaHCO_3$ suspension. The resulting solid was recrystallized from MeCN to give a yellow powder (0.12 g, 29%); mp = 173−176 °C (MeCN). ^{31}P NMR (DMSO-d_6, 242 MHz): δ 54.3 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.82 (s, 1H), 8.84 (s, 1H), 8.76 (s, 1H), 8.48 (d, $^3J_{HH}$ = 6.8 Hz, 1H), 8.36 (d, $^3J_{HH}$ = 6.2 Hz, 1H), 7.83 (t, $^3J_{HH}$ = 7.7 Hz, 1H), 7.55−7.65 (m, 2H), 7.42 (s, 1H), 7.30 (s, 1H), 6.99 (s, 1H), 3.90−4.00 (m, 2H), 3.18 (d, $^2J_{PH}$ = 16.7 Hz, 2H), 1.50−1.70 (m, 4H), 1.19 (s, 3H), 0.93 (s, 1H). LC-MS: R_t = 3.63 min. (ESI): m/z = 441 $[M + H]^+$.

*Ethyl (3-{[6-(3-Nitrophenyl)pyrimidin-4-yl]amino}benzyl)-phenylphosphinate (**53c**).* According to the general coupling procedure, 4-chloro-6-(3-nitrophenyl)-pyrimidine **13b** (0.118 g, 0.5 mmol) and ethyl (3-aminobenzyl)phenylphosphinate·HCl **46** (0.187 g, 0.6 mmol) were reacted. The crude product was recrystallized from MeCN to give a yellow powder (0.101 g, 43%); mp = 188−190 °C (MeCN). ^{31}P NMR (DMSO-d_6, 242 MHz): δ 41.7 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.76 (s, 1H), 8.84 (s, 1H), 8.73 (s, 1H), 8.48 (d, $^3J_{HH}$ = 6.3 Hz, 1H), 8.36 (d, $^3J_{HH}$ = 7.1 Hz, 1H), 7.84 (t, $^3J_{HH}$ = 6.6 Hz, 1H), 7.65−7.75 (m, 2H), 7.40−7.60 (m, 5H), 7.39 (s, 1H), 7.18 (t, $^3J_{HH}$ = 6.9 Hz, 1H), 6.79 (d, $^3J_{HH}$ = 5.1 Hz, 1H), 3.90−3.95 (m, 1H), 3.80−3.85 (m, 1H), 3.45 (d, $^2J_{PH}$ = 17.3 Hz, 2H), 1.18 (s, 3H). LC-MS: R_t = 3.83 min. (ESI): m/z = 475 $[M + H]^+$.

*Ethyl (3-{[6-(3-Aminophenyl)pyrimidin-4-yl]amino}benzyl)-ethylphosphinate (**54a**).* Reduction of nitro compound **53a** (0.099 g, 0.23 mmol) was carried out according to the nitro group reduction described for compound **26a**, yielding a yellow powder (0.079 g, 79%); mp = 208−211 °C (EtOH, Et_2O). ^{31}P NMR (DMSO-d_6, 242 MHz): δ 55.6 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 11.09 (s, 1H), 8.84 (s, 1H), 7.50−7.80 (m, 5H), 7.30−7.45 (m, 3H), 7.09 (d, $^3J_{HH}$ = 5.4 Hz, 1H), 5.30 (br, 2H), 3.80−3.95 (m, 2H), 3.22 (d, $^2J_{PH}$ = 16.2 Hz, 2H), 1.60−1.67 (m, 2H), 1.18 (t, $^3J_{HH}$ = 6.7 Hz, 3H), 1.00 (dt, $^3J_{PH}$ = 17.6 Hz, $^3J_{HH}$ = 7.2 Hz, 3H). LC-MS: R_t = 0.45 and 2.06 and 2.35 min. (ESI): m/z = 397 $[M + H]^+$.

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*Ethyl (3-{[6-(3-Aminophenyl)pyrimidin-4-yl]amino}benzyl)-propylphosphinate (**54b**).* Reduction of nitro compound **53b** (0.10 g, 0.23 mmol) was carried out according to the nitro group reduction described for compound **26a**, affording a yellow powder (0.079 g, 77%); mp = 206−208 °C (EtOH, Et_2O). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 11.02 (s, 1H), 8.83 (s, 1H), 7.65−7.75 (m, 2H), 7.50−7.65 (m, 3H), 7.30−7.45 (m, 3H), 7.05−7.15 (m, 1H). 5.47 (br, 2H), 3.85−4.00 (m, 2H), 3.21 (d, $^2J_{PH}$ = 15.9 Hz, 2H), 1.60−1.70 (m, 2H), 1.45−1.55 (m, 2H), 1.17 (t, $^3J_{HH}$ = 6.9 Hz, 3H), 0.93 (t, $^3J_{HH}$ = 6.3 Hz, 3H). LC-MS: R_t = 0.43 and 2.37 and 2.55 min. (ESI): m/z = 411 $[M + H]^+$.

*Ethyl (3-{[6-(3-Aminophenyl)pyrimidin-4-yl]amino}benzyl)-phenylphosphinate (**54c**).* Reduction of nitro compound **53c** (0.08 g, 0.17 mmol) was carried out according to the nitro group reduction described for compound **26a**, giving a yellow powder (0.068 g, 84%); mp = 208−209 °C (EtOH, Et_2O). ^{31}P NMR (DMSO-d_6, 242 MHz): δ 41.7 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 10.82 (s, 1H), 8.80 (s, 1H), 7.45−7.75 (m, 10H), 7.20−7.45 (m, 3H), 6.89 (d, $^3J_{HH}$ = 6.0 Hz, 1H). 4.25 (br, 2H), 3.90−3.95 (m, 1H), 3.80−3.85 (m, 1H), 3.48 (d, $^2J_{PH}$ = 17.3 Hz, 2H), 1.18 (t, $^3J_{HH}$ = 5.4 Hz, 3H). LC-MS: R_t = 2.73 min. (ESI): m/z = 445 $[M + H]^+$.

*Ethyl Ethyl (4-{[6-(2-Methoxyphenyl)pyrimidin-4-yl]amino}-benzyl)phosphinate (**55a**).* According to the general coupling procedure, 4-chloro-6-(2-methoxyphenyl)-pyrimidine **13a** (0.11 g, 0.5 mmol) and ethyl (4-aminobenzyl)ethylphosphinate·HCl **49** (0.158 g, 0.6 mmol) were reacted. The crude product was purified by preparative TLC, for the first elution 100% EtOAc, for the second one EtOAc:hexane (8:1), were used as eluents. The pure product was extracted with MeOH from the silica. After evaporation, an amorphous solid was obtained (0.028 g, 14%); mp = 30 °C (MeOH), ^{31}P NMR (DMSO-d_6, 242 MHz): δ 55.6 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.61 (s, 1H), 8.67 (s, 1H), 7.94 (d, $^3J_{HH}$ = 7.1 Hz, 1H), 7.63 (d, J_{AABB} = 7.3 Hz, 2H), 7.40−7.50 (m, 2H), 7.23 (d, J_{AABB} = 6.6 Hz, 2H), 7.19 (t, $^3J_{HH}$ = 8.1 Hz, 1H), 7.07 (d, $^3J_{HH}$ = 6.6 Hz, 1H), 3.85−4.00 (m, 5H), 3.13 (d, $^2J_{PH}$ = 16.6 Hz, 2H), 1.50−1.65 (m, 2H), 1.18 (t, $^3J_{HH}$ = 6.6 Hz, 3H), 0.98 (dt, $^3J_{PH}$ = 17.4 Hz, $^3J_{HH}$ = 8.4 Hz, 3H). LC-MS: R_t = 2.5 min. (ESI): m/z = 412 $[M + H]^+$.

*Ethyl (4-{[6-(2-Methoxyphenyl)pyrimidin-4-yl]amino}benzyl)-propylphosphinate (**55b**).* According to the general coupling procedure, 4-chloro-6-(2-methoxyphenyl)-pyrimidine **13a** (0.11 g, 0.5 mmol) and ethyl (4-aminobenzyl)propylphosphinate·HCl **50** (0.167 g; 0.6 mmol) were reacted. The crude product was purified by preparative TLC, for the first elution 100% EtOAc, for the second one EtOAc:hexane (8:1), were used as eluents. The pure product was extracted with MeOH from the silica. After evaporation amorphous solid was obtained (0.026 g, 12%); mp = 30 °C (MeOH). ^{31}P NMR (DMSO-d_6, 242 MHz): δ 54.1 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.61 (s, 1H), 8.67 (s, 1H), 7.94 (d, $^3J_{HH}$ = 6.2 Hz, 1H), 7.63 (d, J_{AABB} = 7.2 Hz, 2H), 7.40−7.50 (m, 2H), 7.22 (d, J_{AABB} = 6.8 Hz, 2H), 7.15−7.20 (m, 1H), 7.07 (t, $^3J_{HH}$ = 6.6 Hz, 1H), 3.85−4.00 (m, 5H), 3.12 (d, $^2J_{PH}$ = 16.3 Hz, 2H), 1.35−1.70 (m, 4H), 1.18 (t, $^3J_{HH}$ = 6.6 Hz, 3H), 0.92 (br, 3H). LC-MS: R_t = 2.48 and 2.68 min. (ESI): m/z = 426 $[M + H]^+$.

*Ethyl Ethyl (4-{[6-(3-Nitrophenyl)prymidin-4-yl]amino}benzyl)-phosphinate (**56a**).* According to the general coupling procedure, 4-chloro-6-(3-nitrophenyl)-pyrimidine **13b** (0.118 g; 0.5 mmol) and ethyl (4-aminobenzyl)ethylphosphinate·HCl **49** (0.158 g; 0.6 mmol) were reacted. The crude product was recrystallized from MeCN to give a yellow powder (0.104 g, 49%); mp = 226 °C (MeCN). ^{31}P NMR (DMSO-d_6, 242 MHz): δ 55.6 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.8 (s, 1H), 8.82 (s, 1H), 8.76 (s, 1H), 8.44 (d, $^3J_{HH}$ = 6.8 Hz, 1H), 8.36 (d, $^3J_{HH}$ = 6.3 Hz, 1H), 7.84 (t, $^3J_{HH}$ = 6.3 Hz, 1H), 7.65 (d, J_{AABB} = 6.2 Hz, 2H), 7.35 (s, 1H), 7.25 (d, J_{AABB} = 5.4 Hz, 2H), 3.90−3.95 (m, 2H), 3.14 (d, $^2J_{PH}$ = 16.4 Hz, 2H), 1.50−1.70 (m, 2H), 1.18 (br, 3H), 0.99 (dt, $^3J_{PH}$ = 17.4 Hz, $^3J_{HH}$ = 8.7 Hz, 3H). LC-MS: R_t = 3.33 min. (ESI): m/z = 427 $[M + H]^+$.

*Ethyl (4-{[6-(3-Nitrophenyl)pyrimidin-4-yl]amino}benzyl)-propylphosphinate (**56b**).* According to the general coupling procedure, 4-chloro-6-(3-nitrophenyl)-pyrimidine **13b** (0.118 g, 0.5 mmol) and ethyl (4-aminobenzyl)propylphosphinate·HCl **50** (0.167 g, 0.6 mmol) were reacted. The crude product was recrystallized from MeCN to give a yellow powder (0.085 g, 39%); mp = 219−220 °C (MeCN). ^{31}P NMR (DMSO-d_6, 242 MHz): δ 54.3 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.80 (s, 1H), 8.82 (s, 1H), 8.76 (s, 1H), 8.44 (d, $^3J_{HH}$ = 6.4 Hz, 1H), 8.36 (d, $^3J_{HH}$ = 6.8 Hz, 1H), 7.84 (t, $^3J_{HH}$ = 7.1 Hz, 1H), 7.66 (d, J_{AABB} = 7.0 Hz, 2H), 7.35 (s, 1H), 7.25 (d, J_{AABB} = 5.7 Hz, 2H), 3.90−3.95 (m, 2H), 3.13 (d, $^2J_{PH}$ = 16.2 Hz, 2H), 1.45−1.63 (m, 4H), 1.18 (br, 3H), 0.99 (br, 3H). LC-MS: R_t = 3.58 min. (ESI): m/z = 441 $[M + H]^+$.

*Ethyl (4-{[6-(3-Aminophenyl)pyrimidin-4-yl]amino}benzyl)-ethylphosphinate (**57a**).* Reduction of nitro compound **56a** (0.081 g; 0.19 mmol) was carried out according to the nitro group reduction described for compound **26a**, giving a yellow powder (0.062 g, 75%); mp = 152−155 °C (EtOH, Et_2O). ^{31}P NMR (DMSO-d_6, 242 MHz): δ 55.3 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 11.09 (s, 1H), 8.82 (s, 1H), 7.50−7.70 (m, 5H), 7.25−7.50 (m, 4H), 4.50 (br, 2H), 3.90−3.95 (m, 2H), 3.17 (d, $^2J_{PH}$ = 15.6 Hz, 2H), 1.55−1.65 (m, 2H), 1.18 (t, $^3J_{HH}$ = 7.0 Hz, 3H), 0.99 (dt, $^3J_{PH}$ = 17.4 Hz, $^3J_{HH}$ = 8.7 Hz, 3H). LC-MS: R_t = 0.44 min, 2.09 and 2.29 min. (ESI): m/z = 397 $[M + H]^+$.

*Ethyl (4-{[6-(3-Aminophenyl)pyrimidin-4-yl]amino}benzyl)-propylphosphinate (**57b**).* Reduction of nitro compound **56b** (0.063 g, 0.14 mmol) was carried out according to the nitro group reduction described for compound **26a**, affording a brown powder (0.053 g, 85%); mp = 200 °C (EtOH, Et_2O). ^{31}P NMR (DMSO-d_6, 242 MHz): δ 54.0 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 11.20 (s, 1H), 8.85 (s, 1H), 7.50−7.70 (m, 5H), 7.25−7.50 (m, 4H), 4.50 (br, 2H), 3.80−4.10 (m, 2H), 3.17 (d, $^2J_{PH}$ = 16.2 Hz, 2H), 1.55−1.60 (m, 2H), 1.40−1.50 (m, 2H), 1.18 (t, $^3J_{HH}$ = 7.0 Hz, 3H), 0.92 (t, $^3J_{HH}$ = 7.0 Hz, 3H). LC-MS: R_t = 0.42 min, 2.36 and 2.51 min. (ESI): m/z = 411 $[M + H]^+$.

*Ethyl Ethyl (5-{[6-(2-Methoxyphenyl)pyrimidin-4-yl]amino}-2-methylbenzyl)phosphinate (**58**).* According to the general coupling procedure, 4-chloro-6-(2-methoxyphenyl)-pyrimidine **13a** (0.117 g, 0.5 mmol) and ethyl (5-amino-2-methylbenzyl)ethylphosphinate·HCl **51** (0.296 g, 1.07 mmol) were reacted. The crude product was purified by preparative TLC with EtOAc:hexane (8:1) as eluent. The pure product was extracted from the silica with MeOH. After evaporation, a yellow powder was obtained (0.053 g, 24%); mp = 94 °C, (MeOH). ^{31}P NMR (DMSO-d_6, 242 MHz): δ 55.6 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.53 (s, 1H), 8.64 (s, 1H), 7.92 (d, $^3J_{HH}$ = 6.8 Hz, 1H), 7.40−7.60 (m, 4H), 7.00−7.20 (m, 3H), 3.85−3.90 (m, 5H), 3.13 (d, $^2J_{PH}$ = 16.3 Hz, 2H), 2.30 (s, 3H), 1.60−1.80 (m, 2H), 1.15 (t, $^3J_{HH}$ = 6.3 Hz, 3H), 1.03 (dt, $^3J_{PH}$ = 17.0 Hz, $^3J_{HH}$ = 8.5 Hz, 3H). LC-MS: R_t = 2.78 min. (ESI): m/z = 426 $[M + H]^+$.

*Ethyl Ethyl (2-Methyl-5-{[6-(3-nitrophenyl)pyrimidin-4-yl]amino}-benzyl)phosphinate (**59**).* According to the general coupling procedure, 4-chloro-6-(3-nitrophenyl)-pyrimidine **13b** (0.118 g, 0.5 mmol) and ethyl (5-amino-2-methylbenzyl)ethylphosphinate·HCl **51** (0.208 g, 0.75 mmol) were reacted. The crude product was recrystallized from MeCN to give a yellow powder (0.033 g, 15%); mp = 200−203 °C (MeCN). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.72 (s, 1H), 8.84 (s, 1H), 8.72 (s, 1H), 8.49 (d, $^3J_{HH}$ = 6.8 Hz, 1H), 8.35 (d, $^3J_{HH}$ = 6.7 Hz, 1H), 7.83 (t, $^3J_{HH}$ = 8.1 Hz, 1H), 7.52 (s, 1H), 7.47 (d, $^3J_{HH}$ = 6.9 Hz, 1H), 7.38 (s, 1H), 7.15 (d, $^3J_{HH}$ = 6.9 Hz, 1H), 3.80−4.00 (m, 2H), 3.17 (d, $^2J_{PH}$ = 15.7 Hz, 2H), 2.31 (s, 3H), 1.60−1.80 (m, 2H), 1.15 (t, $^3J_{HH}$ = 6.3 Hz, 3H), 1.05 (dt, $^3J_{PH}$ = 17.9 Hz, $^3J_{HH}$ = 8.9 Hz, 3H). LC-MS: R_t = 3.04 min. (ESI): m/z = 441 $[M + H]^+$.

*Ethyl (5-{[6-(3-Aminophenyl)pyrimidin-4-yl]amino}-2-methylbenzyl)ethylphosphynate (**60**).* Reduction of nitro compound **59** (0.023 g, 0.05 mmol) was carried out according to the nitro group reduction described for compound **26a**. The free base was prepared as a yellow powder (0.018 g, 81%); mp = 180−181 °C (EtOH). ^{31}P NMR (DMSO-d_6, 242 MHz): δ 55.7 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 10.93 (s, 1H), 8.81 (s, 1H), 7.40−7.70 (m, 5H), 7.10−7.40 (m, 3H), 4.20 (br, 2H), 3.80−4.00 (m, 2H), 3.19 (d, $^2J_{PH}$ = 14.7 Hz, 2H), 2.34 (s, 3H), 1.60−1.80 (m, 2H), 1.15 (t, $^3J_{HH}$ = 6.3 Hz, 3H), 1.04 (dt, $^3J_{PH}$ = 17.7 Hz, $^3J_{HH}$ = 9.0 Hz, 3H). LC-MS: R_t = 0.53 and 1.18 min. (ESI): m/z = 411 $[M + H]^+$.

*(3-{[6-(2-Methoxyphenyl)pyrimidin-4-yl]amino}benzyl)-propylphosphinic Acid (**61**).* Chloro (trimethyl)silane (0.076 mL; 0.6 mmol) and potassium iodide (0.02 g; 0.12 mmol) were dissolved in chloroform (20 mL). The mixture was stirred for 30 min at RT then the

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solution of phosphinate **52b** (0.05 g, 0.12 mmol in 3 mL $CHCl_3$) was added. The reaction mixture was refluxed for 30 h, and then additional chloro (trimethyl)silane (0.076 mL, 0.6 mmol) and potassium iodide (0.04 g; 0.24 mmol) were added. The reaction mixture was refluxed for further 24 h then satd NH_4Cl (10 mL) was added. After 5 min stirring, volatiles were evaporated under reduced pressure. The crude product was suspended in water (20 mL) and was extracted with $CHCl_3$ (3 × 30 mL). The combined organic phases were washed with brine and dried with $MgSO_4$. After evaporation, the product was further purified by preparative TLC with 100% EtOH as eluent. The pure product was extracted from the silica with MeOH. After evaporation under vacuum, a white powder was obtained (0.017 g, 36%); mp = 122−125 °C (MeOH). ^{31}P NMR (DMSO-d_6, 121 MHz): δ 36.5 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.99 (s, 1H), 8.63 (s, 1H), 7.90−7.93 (m, 1H), 7.70−7.74 (m, 1H), 7.7−7.5 (m, 3H), 7.0−7.2 (m, 3H), 6.83−6.88 (m, 1H), 3.87 (s, 3H), 2.72 (d, $^2J_{PH}$ = 14.4 Hz, 2H), 1.35−1.50 (m, 2H), 1.15−1.3 (m, 2H), 1.04 (t, $^3J_{HH}$ = 8.4 Hz, 3H). LC-MS: R_t = 0.44 and 2.41 min. (ESI): m/z = 397 $[M + H]^+$.

General Method for the Pd-Catalyzed Coupling of H-Phosphinates and Aromatic Halogens. The appropriate halogeno-nitrobenzene (1 equiv) was dissolved in dry toluene (5 mL/mmol) then the H-phosphinate (1.1 equiv), triethylamine (4 equiv), and tetrakis (triphenylphosphine)palladium (0) (0.02 equiv) were added under inert atmosphere. The reaction mixture was refluxed for 20 h under inert atmosphere. The mixture was cooled to RT then the precipitate was filtered off. The filtrate was evaporated to dryness then the residue was dissolved in EtOAc (25 mL/mmol). This organic layer was washed with 1 M HCl (15 mL/mmol), 2 M NaOH (15 mL/mmol), and with brine (15 mL/mmol), respectively. Organic phase was dried with $MgSO_4$, and volatiles were evaporated under reduced pressure. The crude product was purified by chromatography in hexane:EtOAc (1:1) to 100% EtOAc. For the exact quantity of reagents, for further purifications, yields, and analytical data see the exact examples.

*Ethyl (3-Aminophenyl)ethylphosphinate (**63a**).* According to the general Pd-catalyzed coupling procedure, 3-iodo-nitrobenzene (0.996 g, 4.0 mmol) and ethyl ethylphosphinate **62a** (0.537 g, 4.4 mmol) were reacted, giving a yellow oil (0.14 g, 14%). ^{31}P NMR (DMSO-d_6, 242 MHz): δ 45.8 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.40−8.50 (m, 2H), 8.14 (t, $^3J_{PH} \sim {}^3J_{HH}$ = 7.7 Hz, 1H), 7.86 (t, $^3J_{HH}$ = 8.5 Hz, 1H), 3.95−4.00 (m, 1H), 3.80−3.90 (m, 1H), 1.95−2.25 (m, 2H), 1.22 (s, 3H), 0.96 (dt, $^3J_{PH}$ = 19.1 Hz, $^3J_{HH}$ = 9.0 Hz, 3H). LC-MS: R_t = 2.83 min. (ESI): m/z = 244 $[M + H]^+$. Reduction of ethyl ethyl (3-nitrophenyl)phosphinate (0.105 g, 0.43 mmol) was carried out according to the nitro group reduction described for compound **26a**. The free base was prepared as a yellow oil (0.078 g, 85%). ^{31}P NMR (DMSO-d_6, 242 MHz): δ 48.3 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.10−7.20 (m, 1H), 6.93 (d, $^3J_{PH}$ = 12.9 Hz, 1H), 6.70−6.88 (m, 2H), 5.34 (br, 2H), 3.85−3.95 (m, 1H), 3.70−3.80 (m, 1H), 1.75−1.85 (m, 2H), 1.19 (t, $^3J_{HH}$ = 6.9 Hz, 3H), 0.94 (dt, $^3J_{PH}$ = 18.5 Hz, $^3J_{HH}$ = 7.4 Hz, 3H). LC-MS: R_t = 2.03 min. (ESI): m/z = 214 $[M + H]^+$.

*Diethyl (3-Aminophenyl)phosphonate (**63d**).* According to the general Pd-catalyzed coupling procedure, 3-iodo-nitrobenzene (2.49 g, 10.0 mmol) and diethylphosphite **62d** (1.518 g, 11.0 mmol) were reacted, giving a yellow oil (0.951 g, 37%). ^{31}P NMR (DMSO-d_6, 242 MHz): δ 13.5 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.47 (d, $^3J_{HH}$ = 8.6 Hz, 1H), 8.40 (d, $^3J_{PH}$ = 14.2 Hz, 1H), 8.14 (dd, $^3J_{PH}$ = 12.3 Hz, $^3J_{HH}$ = 7.5 Hz, 1H), 7.86 (dt, $^3J_{HH}$ = 8.5 Hz, $^4J_{PH}$ = 4.1 Hz, 1H), 4.00−4.15 (m, 4H), 1.26 (t, $^3J_{HH}$ = 7.0 Hz, 6H). LC-MS: R_t = 3.20 min. (ESI): m/z = 260 $[M + H]^+$. Reduction of diethyl (3-nitrophenyl)phosphonate (0.804 g, 3.1 mmol) was carried out according to the nitro group reduction described for compound **26a**. The free base was prepared as a yellow oil (0.638 g, 90%). ^{31}P NMR (DMSO-d_6, 242 MHz): δ 16.4 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.25−7.50 (m, 4H), 5.80 (br, 2H), 3.95−4.05 (m, 4H), 1.24 (t, $^3J_{HH}$ = 7.1 Hz, 6H). LC-MS: R_t = 2.34 min. (ESI): m/z = 230 $[M + H]^+$.

*Ethyl (4-Aminophenyl)ethylphosphinate (**64a**).* According to the general Pd-catalyzed coupling procedure, 4-bromo-nitrobenzene (2.02 g, 10.0 mmol) and ethyl ethylphosphinate **62a** (1.342 g, 11.0 mmol) were reacted, yielding a yellow oil (1.312 g, 54%), which upon standing crystallized. ^{31}P NMR (DMSO-d_6, 242 MHz): δ 45.7 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.36 (d, J_{AABB} = 6.7 Hz, 2H), 8.02 (dd, $^3J_{PH} \sim J_{AABB}$ = 9.0 Hz, 2H), 3.92−4.0 (m, 1H), 3.8−3.9 (m, 1H), 1.93−2.05 (m, 2H), 1.21 (t, $^3J_{HH}$ = 6.8 Hz, 3H), 0.95 (dt, $^3J_{PH}$ = 19.2 Hz, $^3J_{HH}$ = 8.0 Hz, 3H). LC-MS: R_t = 2.86 min. (ESI): m/z = 244 $[M - H]^+$. Reduction of ethyl ethyl (4-nitrophenyl)phosphinate (1.302 g, 5.36 mmol) was carried out according to the nitro group reduction described for compound **26a**. The free base was prepared as a yellow oil (0.654 g, 49%). ^{31}P NMR (DMSO-d_6, 242 MHz): δ 48.8 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.32 (dd, $^3J_{PH} \sim J_{AABB}$ = 8.4 Hz, 2H), 6.61 (d, J_{AABB} = 5.7 Hz, 2H), 5.73 (br, 2H), 3.75−3.85 (m, 1H), 3.65−3.75 (m, 1H), 1.72−1.75 (m, 2H), 1.16 (br, 3H), 0.91 (dt, $^3J_{PH}$ = 18.3 Hz, $^3J_{HH}$ = 8.4 Hz, 3H). LC-MS: R_t = 2.16 min. (ESI): m/z = 214 $[M + H]^+$.

*Ethyl (4-Aminophenyl)propylphosphinate (**64b**).* According to the general Pd-catalyzed coupling procedure, 4-bromo-nitrobenzene (2.02 g, 10.0 mmol) and ethyl propylphosphinate **62b** (1.496 g, 11.0 mmol) were reacted, giving a yellow oil (1.305 g, 54%). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.35 (d, J_{AABB} = 6.8 Hz, 2H), 8.02 (dd, $^3J_{PH} \sim J_{AABB}$ = 9.0 Hz, 2H), 3.97 (q, $^3J_{HH}$ = 6.9 Hz, 1H), 3.81 (q, $^3J_{HH}$ = 7.0 Hz, 1H), 1.95−2.05 (m, 2H), 1.30−1.50 (m, 2H), 1.20 (t, $^3J_{HH}$ = 6.8 Hz, 3H), 0.92 (t, $^3J_{HH}$ = 6.5 Hz, 3H). LC-MS: R_t = 3.22 min. (ESI): m/z = 258 $[M + H]^+$. Reduction of ethyl (4-nitrophenyl)propylphosphinate (1.30 g, 5.06 mmol) was carried out according to the nitro group reduction described for compound **26a**. The free base was prepared as a yellow oil (0.985 g, 86%). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.32 (dd, $^3J_{PH} \sim J_{AABB}$ = 9.0 Hz, 2H), 6.60 (d, J_{AABB} = 5.7 Hz, 2H), 5.70 (br, 2H), 3.80−3.85 (m, 1H), 3.60−3.75 (m, 1H), 1.70−1.80 (m, 2H), 1.25−1.40 (m, 2H), 1.16 (br, 3H), 0.90 (br, 3H). LC-MS: R_t = 2.53 min. (ESI): m/z = 228 $[M + H]^+$.

*Ethyl (4-Aminophenyl)phenylphosphinate (**64c**).* According to the general Pd-catalyzed coupling procedure, 4-bromo-nitrobenzene (2.02 g, 10.0 mmol) and ethyl phenylphosphinate **62c** (1.87 g, 11.0 mmol) were reacted, affording a yellow oil (1.849 g, 64%). ^{31}P NMR (DMSO-d_6, 242 MHz): δ 29.7 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.33 (d, J_{AABB} = 6.1 Hz, 2H), 8.04 (dd, $^3J_{PH} \sim J_{AABB}$ = 9.5 Hz, 2H), 7.81 (dd, $^3J_{PH} \sim J_{AABB}$ = 9.2 Hz, 2H), 7.60−7.65 (m, 1H), 7.50−7.65 (m, 2H), 4.00−4.10 (m, 2H), 1.31 (t, $^3J_{HH}$ = 6.7 Hz, 3H). LC-MS: R_t = 3.49 min. (ESI): m/z = 292 $[M + H]^+$. Reduction of ethyl (4-nitrophenyl)-phenylphosphinate (1.809 g, 6.22 mmol) was carried out according to the nitro group reduction described for compound **26a**. The free base was prepared as a yellow solid (1.435 g, 88%). ^{31}P NMR (DMSO-d_6, 242 MHz): δ 33.6 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.68 (dd, $^3J_{PH} \sim {}^3J_{HH}$ = 9.1 Hz, 2H), 7.40−7.60 (m, 3H), 7.37 (dd, $^3J_{PH} \sim J_{AABB}$ = 9.4 Hz, 2H), 6.60 (d, J_{AABB} = 5.9 Hz, 2H), 5.79 (br, 2H), 3.85−3.95 (m, 2H), 1.24 (br, 3H). LC-MS: R_t = 2.83 min. (ESI): m/z = 262 $[M + H]^+$.

*Diethyl (4-Aminophenyl)phosphonate (**64d**).* According to the general Pd-catalyzed coupling procedure, 4-bromo-nitrobenzene (5.05 g, 25.0 mmol) and diethyl phosphite **62d** (3.795 g, 27.5 mmol) were reacted, giving a yellow oil (3.948 g, 61%). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.35 (dd, J_{AABB} = 8.7 Hz, $^4J_{PH}$ = 3.1 Hz, 2H), 7.99 (dd, J_{AABB} = 8.7 Hz, $^3J_{PH}$ = 12.5 Hz, 2H), 4.00−4.10 (m, 4H), 1.25 (t, $^3J_{HH}$ = 7.0 Hz, 6H). LC-MS: R_t = 3.25 min. (ESI): m/z = 260 $[M + H]^+$. Reduction of diethyl (4-nitrophenyl)phosphonate (3.947 g, 15.2 mmol) was carried out according to the nitro group reduction described at compound **26a**. The free base was prepared as a yellow solid (1.807 g, 52%). ^{31}P NMR (DMSO-d_6, 242 MHz): δ 20.3 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.31 (dd, $^3J_{PH}$ = 12.5 Hz, J_{AABB} = 8.5 Hz, 2H), 6.60 (d, J_{AABB} = 8.5 Hz, $^4J_{PH}$ = 3.7 Hz, 2H), 5.77 (br, 2H), 3.80−4.00 (m, 4H), 1.18 (t, $^3J_{HH}$ = 7.0 Hz, 6H). LC-MS: R_t = 2.48 min. (ESI): m/z = 230 $[M + H]^+$.

*Ethyl Ethyl (3-{[6-(3-Methoxyphenyl)pyrimidin-4-yl]amino}-phenyl)phosphinate (**65**).* According to the general coupling procedure, 4-chloro-6-(2-methoxyphenyl)-pyrimidine **13a** (0.057 g, 0.26 mmol) and ethyl (3-aminophenyl)ethylphosphinate·HCl **63a** (0.077 g, 0.31 mmol) were reacted. The crude product was recrystallized from MeCN to give a yellow powder (0.035 g, 34%); mp = 155 °C (MeCN). ^{31}P NMR (DMSO-d_6, 242 MHz): δ 47.7 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.85 (s, 1H), 8.72 (s, 1H), 7.85−8.10 (m, 3H), 7.40−7.55 (m, 3H), 7.28−7.40 (m, 1H), 7.14−7.25 (m, 1H), 7.02−7.12 (m, 1H), 3.91 (s, 3H), 3.80−4.00 (m, 2H), 1.80−1.95 (m, 2H), 1.23 (br, 3H), 0.97 (dt, $^3J_{PH}$ = 17.3 Hz, $^3J_{HH}$ = 6.4 Hz, 3H). LC-MS: R_t = 2.56 min. (ESI): m/z = 398 $[M + H]^+$.

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*Ethyl Ethyl (3-{[6-(4-Nitrophenyl)pyrimidin-4-yl]amino}phenyl)-phosphinate (**66**).* According to the general coupling procedure, 4-chloro-6-(3-nitrophenyl)-pyrimidine **13b** (0.073 g, 0.31 mmol) and diethyl (3-aminophenyl)phosphonate·HCl **63d** (0.091 g, 0.37 mmol) were reacted. The crude product was recrystallized from MeCN to give a yellow powder (0.066 g, 52%); mp = 211 °C (MeCN). ^{31}P NMR (DMSO-d_6, 242 MHz): δ 47.5 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 10.07 (s, 1H), 8.83 (s, 1H), 8.81 (s, 1H), 8.47 (d, $^{3}J_{HH}$ = 6.6 Hz, 1H), 8.37 (d, $^{3}J_{HH}$ = 6.9 Hz, 1H), 8.00−8.10 (m, 2H), 7.85 (t, $^{3}J_{HH}$ = 7.2 Hz, 1H), 7.45−7.55 (m, 1H), 7.30−7.45 (m, 2H), 3.90−4.00 (m, 1H), 3.80−3.90 (m, 1H), 1.80−2.00 (m, 2H), 1.23 (br, 3H), 0.99 (dt, $^{3}J_{PH}$ = 18.3 Hz, $^{3}J_{HH}$ = 8.7 Hz, 3H). LC-MS: R_t = 3.55 min. (ESI): m/z = 413 $[M + H]^+$.

*Ethyl (3-{[6-(4-Aminophenyl)pyrimidin-4-yl]amino}phenyl)-ethylphosphinate (**67**).* Reduction of the nitro compound **66** (0.048 g, 0.12 mmol) was carried out according to the nitro group reduction described for compound **26a**, giving a yellow powder (0.04 g, 80%); mp = 213-214 °C (EtOH, Et_2O). ^{31}P NMR (DMSO-d_6, 242 MHz): δ 47.2 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 11.06 (s, 1H), 8.87 (s, 1H), 8.00−8.15 (m, 2H), 7.75−7.85 (m, 2H), 7.55−7.62 (m, 2H), 7.38−7.50 (m, 3H), 5.30 (br, 2H), 3.95−4.00 (m, 1H), 3.80−3.85 (m, 1H), 1.88−1.93 (m, 2H), 1.23 (br, 3H), 0.98 (dt, $^{3}J_{PH}$ = 18.7 Hz, $^{3}J_{HH}$ = 6.8 Hz, 3H). LC-MS: R_t = 2.37 min. (ESI): m/z = 383 $[M + H]^+$.

*Ethyl Ethyl (4-{[6-(2-Methoxyphenyl)pyrimidin-4-yl]amino}-phenyl)phosphinate (**68a**).* According to the general coupling procedure, 4-chloro-6-(2-methoxyphenyl)-pyrimidine **13a** (0.11 g, 0.5 mmol) and ethyl (4-aminophenyl)ethylphosphinate·HCl **64a** (0.15 g, 0.6 mmol) were reacted. The crude product was purified by preparative TLC with 100% EtOAc and 1 v/v% AcOH as eluent. The pure product was extracted with MeOH from the silica. After evaporation, **68a** was obtained as a yellow powder (0.075 g, 38%); mp = 151−153 °C (MeOH). ^{31}P NMR (DMSO-d_6, 242 MHz): δ 47.3 ppm. ^{1}H NMR (DMSO-d_6, 600 MHz): δ 9.95 (s, 1H), 8.74 (s, 1H), 7.94 (dd, $^{3}J_{HH}$ = 7.8 Hz, $^{4}J_{HH}$ = 2.0 Hz, 1H), 7.88 (dd, J_{AABB} = 8.4 Hz, $^{4}J_{PH}$ = 2.4 Hz, 2H), 7.65 (dd, J_{AABB} = 8.4 Hz, $^{3}J_{PH}$ = 10.8 Hz, 2H), 7.51 (s, 1H), 7.44 (t, $^{3}J_{HH}$ = 7.2 Hz, 1H), 7.17 (d, $^{3}J_{HH}$ = 8.4 Hz, 1H), 7.06 (t, $^{3}J_{HH}$ = 7.2 Hz, 1H), 3.88 (s, 3H), 3.85−3.92 (m, 1H), 3.70−3.78 (m, 1H), 1.77−1.90 (m, 2H), 1.17 (t, $^{3}J_{HH}$ = 7.2 Hz, 3H), 0.93 (dt, $^{3}J_{PH}$ = 18.6 Hz, $^{3}J_{HH}$ = 7.8 Hz, 3H). LC-MS: R_t = 2.60 min. (ESI): m/z = 398 $[M + H]^+$.

*Ethyl (4-{[6-(2-Methoxyphenyl)pyrimidin-4-yl]amino}phenyl)-propylphosphinate (**68b**).* According to the general coupling procedure, 4-chloro-6-(2-methoxyphenyl)-pyrimidine **13a** (0.11 g, 0.5 mmol) and ethyl (4-aminophenyl)propylphosphinate·HCl **64b** (0.132 g, 0.6 mmol) were reacted. The crude product was purified by preparative TLC with 100% EtOAc as eluent. The product was extracted with MeOH from the silica. After evaporation, **68b** was isolated as a yellow powder (0.041 g, 20%); mp = 85 °C (MeOH). ^{31}P NMR (DMSO-d_6, 242 MHz): δ 45.7 ppm. ^{1}H NMR (DMSO-d_6, 600 MHz): δ 9.94 (s, 1H), 8.74 (s, 1H), 7.94 (dd, $^{3}J_{HH}$ = 7.8 Hz, $^{4}J_{HH}$ = 1.2 Hz, 1H), 7.88 (dd, J_{AABB} = 8.4 Hz, $^{4}J_{PH}$ = 2.4 Hz, 2H), 7.65 (dd, J_{AABB} = 9.0 Hz, $^{3}J_{PH}$ = 10.8 Hz, 2H), 7.51 (s, 1H), 7.44 (t, $^{3}J_{HH}$ = 7.8 Hz, 1H), 7.17 (d, $^{3}J_{HH}$ = 8.4 Hz, 1H), 7.06 (t, $^{3}J_{HH}$ = 7.8 Hz, 1H), 3.88 (s, 3H), 3.84−3.90 (m, 1H), 3.68−3.76 (m, 1H), 1.76−1.88 (m, 2H), 1.30−1.48 (m, 2H), 1.17 (t, $^{3}J_{HH}$ = 7.2 Hz, 3H), 0.89 (t, $^{3}J_{HH}$ = 7.8 Hz, 3H). LC-MS: R_t = 2.82 min. (ESI): m/z = 412 $[M + H]^+$.

*Ethyl (4-{[6-(2-Methoxyphenyl)pyrimidin-4-yl]amino}phenyl)-phenylphosphinate (**68c**).* According to the general coupling procedure, 4-chloro-6-(2-methoxyphenyl)-pyrimidine **13a** (0.11 g, 0.5 mmol) and ethyl (4-aminophenyl)phenylphosphinate·HCl **64c** (0.179 g, 0.6 mmol) were reacted. The crude product was recrystallized from MeCN, providing a pale-yellow powder (0.129 g, 58%); mp = 197−198 °C (MeCN). ^{31}P NMR (DMSO-d_6, 242 MHz): δ 32.0 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.97 (s, 1H), 8.77 (s, 1H), 7.96 (d, $^{3}J_{HH}$ = 7.4 Hz, 1H), 7.85−7.95 (m, 2H), 7.70−7.80 (m, 4H), 7.40−7.60 (m, 5H), 7.19 (d, $^{3}J_{HH}$ = 7.7 Hz, 1H), 7.09 (t, $^{3}J_{HH}$ = 7.2 Hz, 1H), 3.90−3.80 (m, 2H), 3.90 (s, 3H), 1.29 (t, $^{3}J_{HH}$ = 7.0 Hz, 3H). LC-MS: R_t = 3.06 min. (ESI): m/z = 446 $[M + H]^+$.

*Ethyl Ethyl (4-{[6-(3-Nitrophenyl)pyrimidin-4-yl]amino}phenyl)-phosphinate (**69a**).* According to the general coupling procedure, 4-chloro-6-(3-nitrophenyl)-pyrimidine **13b** (0.118 g, 0.5 mmol) and ethyl (4-aminophenyl)ethylphosphinate·HCl **64a** (0.15 g, 0.6 mmol) were reacted. The crude product was recrystallized from MeCN, providing a yellow powder (0.135 g, 66%); mp = 241−242 °C (MeCN). ^{31}P NMR (DMSO-d_6, 242 MHz): δ 47.4 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 10.20 (s, 1H), 8.85 (s, 2H), 8.48 (d, $^{3}J_{HH}$ = 6.3 Hz, 1H), 8.37 (d, $^{3}J_{HH}$ = 5.7 Hz, 1H), 7.30−7.70 (m, 3H), 7.60−7.70 (m, 2H),7.40−7.50 (m, 1H), 3.90−3.93 (m, 1H), 3.76−3.79 (m, 1H), 1.83−1.87 (m, 2H), 1.20 (br, 3H), 0.96 (dt, $^{3}J_{PH}$ = 18.3 Hz, $^{3}J_{HH}$ = 9.3 Hz, 3H). LC-MS: R_t = 3.57 min. (ESI): m/z = 413 $[M + H]^+$.

*Ethyl (4-{[6-(3-Nitrophenyl)pyrimidin-4-yl]amino}phenyl)-propylphosphinate (**69b**).* According to the general coupling procedure, 4-chloro-6- 3-nitrophenyl)-pyrimidine **13b** (0.118 g, 0.5 mmol) and ethyl (4-aminophenyl)propylphosphinate·HCl **64b** (0.167 g, 0.6 mmol) were reacted. The crude product was recrystallized from MeCN, providing a yellow powder (0.059 g, 28%); mp = 207−209 °C (MeCN). ^{31}P NMR (DMSO-d_6, 242 MHz): δ 45.9 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 10.20 (s, 1H), 8.85 (s, 2H), 8.48 (d, $^{3}J_{HH}$ = 6.5 Hz, 1H), 8.37 (d, $^{3}J_{HH}$ = 7.3 Hz, 1H), 7.75−7.95 (m, 3H), 7.65−7.75 (m, 2H), 7.48 (s, 1H), 3.90−3.95 (m, 1H), 3.75−3.80 (m, 1H), 1.83−1.89 (m, 2H), 1.40−1.45 (m, 2H), 1.20 (br, 3H), 0.92 (br, 3H). LC-MS: R_t = 3.87 min. (ESI): m/z = 427 $[M + H]^+$.

*Ethyl (4-{[6-(3-Nitrophenyl)pyrimidin-4-yl]amino}phenyl)-phenylphosphinate (**69c**).* According to the general coupling procedure, 4-chloro-6-(3-nitrophenyl)-pyrimidine **13b** (0.118 g, 0.5 mmol) and ethyl (4-aminophenyl)phenylphosphinate·HCl **64c** (0.179 g, 0.6 mmol) were reacted. The crude product was recrystallized from MeCN, providing a pale-yellow powder (0.149 g, 65%); mp = 243 °C (MeCN). ^{31}P NMR (DMSO-d_6, 242 MHz): δ 32.1 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 10.37 (s, 1H), 8.84 (s, 2H), 8.47 (d, $^{3}J_{HH}$ = 5.7 Hz, 1H), 8.36 (d, $^{3}J_{HH}$ = 6.3 Hz, 1H), 7.90−8.00 (m, 2H), 7.60−7.90 (m, 5H), 7.40−7.60 (m, 4H), 3.80−4.05 (m, 2H), 1.30 (t, $^{3}J_{HH}$ = 7.5 Hz, 3H). LC-MS: R_t = 4.02 min. (ESI): m/z = 461 $[M + H]^+$.

*Ethyl (4-{[6-(3-Aminophenyl)pyrimidin-4-yl]amino}phenyl)-ethylphosphinate (**70a**).* Reduction of the nitro compound **69a** (0.108 g, 0.26 mmol) was carried out according to the nitro group reduction described for compound **26a**, giving a yellow powder (0.084 g, 77%); mp = 136−138 °C (EtOH, Et_2O). ^{31}P NMR (DMSO-d_6, 242 MHz): δ 47.7 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 10.88 (s, 1H), 8.87 (s, 1H), 7.92−7.96 (m, 2H), 7.83−7.87 (m, 2H), 7.70−7.75 (m, 2H), 7.59−7.62 (m, 1H), 7.42−7.47 (m, 2H), 4.00 (br, 2H), 3.90−4.00 (m, 1H), 3.80−3.90 (m, 1H), 1.85−1.89 (m, 2H), 1.21 (br, 3H), 0.96 (dt, $^{3}J_{PH}$ = 18.5 Hz, $^{3}J_{HH}$ = 8.0 Hz, 3H). LC-MS: R_t = 2.23 and 2.39 min. (ESI): m/z = 383 $[M + H]^+$.

*Ethyl (4-{[6-(3-Aminophenyl)pyrimidin-4-yl]amino}phenyl)-propylphosphinate (**70b**).* Reduction of the nitro compound **69b** (0.039 g, 0.09 mmol) was carried out according to the nitro group reduction described for compound **26a**, affording a yellow powder (0.035 g, 90%); mp = 140−142 °C (EtOH, DEE). ^{31}P NMR (DMSO-d_6, 242 MHz): δ 45.7 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 10.75 (s, 1H), 8.87 (s, 1H), 7.90−7.93 (m, 2H), 7.69−7.82 (m, 4H), 7.55−7.60 (m, 1H), 7.35−7.44 (m, 2H), 3.68 (br, 4H), 1.83−1.87 (m, 2H), 1.40−1.44 (m, 2H), 1.21 (t, $^{3}J_{HH}$ = 7.0 Hz, 3H), 0.92 (t, $^{3}J_{HH}$ = 7.0 Hz, 3H). LC-MS: R_t = 2.61 min. (ESI): m/z = 397 $[M + H]^+$.

*Ethyl (4-{[6-(3-Aminophenyl)pyrimidin-4-yl]amino}phenyl)-phenylphosphinate (**70c**).* Reduction of the nitro compound **69c** (0.132 g, 0.29 mmol) was carried out according to the nitro group reduction described for compound **26a**, giving a yellow powder (0.073 g, 59%); mp = 131−134 °C (EtOH, Et_2O). ^{31}P NMR (DMSO-d_6, 242 MHz): δ 33.0 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.98 (s, 1H), 8.73 (s, 1H), 7.99 (d, $^{3}J_{HH}$ = 5.4 Hz, 1H), 7.71−7.76 (m, 5H), 7.55−7.60 (m, 3H), 7.10−7.35 (m, 4H), 6.70−6.75 (m, 1H), 5.29 (br, 2H), 3.97−4.01 (m, 2H), 1.29 (t, $^{3}J_{HH}$ = 6.7 Hz, 3H). LC-MS: R_t = 2.81 min. (ESI): m/z = 431 $[M + H]^+$.

*Diethyl (3-{[6-(2-Methoxyphenyl)pyrimidin-4-yl]amino}phenyl)-phosphonate (**71**).* According to the general coupling procedure, 4-chloro-6-(2-methoxyphenyl)-pyrimidine **13a** (0.121 g, 0.55 mmol) and diethyl (3-aminophenyl)phosphonate·HCl **63d** (0.218 g, 0.82 mmol) were reacted. The crude product was suspended in diisoprpylether, and filtration gave a pale-yellow powder (0.132 g, 58%); mp = 122−123 °C (DIPE). ^{31}P NMR (DMSO-d_6, 242 MHz): δ 17.0 ppm. ^{1}H NMR

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(DMSO-d_6, 300 MHz): δ 9.87 (s, 1H), 8.74 (s, 1H), 8.10 (d, $^3J_{PH}$ = 15.4 Hz, 1H), 8.06 (d, $^3J_{HH}$ = 8.4 Hz, 1H), 7.97 (d, $^3J_{HH}$ = 7.5 Hz, 1H), 7.44−7.55 (m, 3H), 7.32 (dd, $^3J_{PH}$ = 12.6 Hz, $^3J_{HH}$ = 7.4 Hz, 1H), 7.19 (d, $^3J_{HH}$ = 8.3 Hz, 1H), 7.09 (t, $^3J_{HH}$ = 7.4 Hz, 1H), 3.98−4.09 (m, 4H), 3.91 (s, 3H), 1.26 (t, $^3J_{HH}$ = 7.0 Hz, 6H). LC-MS: R_t = 2.70 min. (ESI): m/z = 414 $[M + H]^+$.

*Diethyl (3-{[6-(3-Nitrophenyl)pyrimidin-4-yl]amino}phenyl)-phosphonate (**72**).* According to the general coupling procedure, 4-chloro-6-(3-nitrophenyl)-pyrimidine **13b** (0.249 g, 1.06 mmol) and diethyl (3-aminophenyl)phosphonate·HCl **63d** (0.421 g, 1.59 mmol) were reacted. The crude product was suspended in DIPE, and filtration gave a yellow powder (0.364 g, 80%); mp = 206−208 °C (DIPE). ^{31}P NMR (DMSO-d_6, 242 MHz): δ 16.9 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 10.04 (s, 1H), 8.84 (s, 1H), 8.82 (s, 1H), 8.47 (d, $^3J_{HH}$ = 7.8 Hz, 1H), 8.37 (d, $^3J_{HH}$ = 7.2 Hz, 1H), 8.13 (d, $^3J_{PH}$ = 14.7 Hz, 1H), 8.04 (d, $^3J_{HH}$ = 8.1 Hz, 1H), 7.86 (t, $^3J_{HH}$ = 8.1 Hz, 1H), 7.53 (dt, $^3J_{HH}$ = 7.8 Hz, $^4J_{PH}$ = 5.2 Hz, 1H), 7.40 (s, 1H), 7.19 (dd, $^3J_{PH}$ = 12.9 Hz, $^3J_{HH}$ = 7.4 Hz, 1H), 4.00−4.10 (m, 4H), 1.26 (t, $^3J_{HH}$ = 6.9 Hz, 6H). LC-MS: R_t = 3.85 min. (ESI): m/z = 429 $[M + H]^+$.

*Diethyl (4-{[6-(2-Methoxyphenyl)pyrimidin-4-yl]amino}phenyl)-phosphonate (**73**).* According to the general coupling procedure, 4-chloro-6- (2-methoxyphenyl)-pyrimidine **13a** (0.097 g, 0.44 mmol) and diethyl (4-aminophenyl)phosphonate·HCl **64d** (0.174 g, 0.66 mmol) were reacted. The crude product was suspended in DIPE, and filtration gave a yellow powder (0.106 g, 58%); mp = 151 °C (DIPE). ^{31}P NMR (DMSO-d_6, 242 MHz): δ 17.9 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.97 (s, 1H), 8.78 (s, 1H), 7.98 (dd, $^3J_{HH}$ = 7.7 Hz, $^4J_{HH}$ = 1.5 Hz, 1H), 7.92 (dd, J_{AABB} = 8.5 Hz, $^4J_{PH}$ = 3.5 Hz, 2H), 7.67 (dd, $^3J_{PH}$ = 12.6 Hz, J_{AABB} = 8.5 Hz, 2H), 7.55 (s, 1H), 7.47 (dd, $^3J_{HH}$ = 7.7 Hz, $^3J_{HH}$ = 7.2 Hz, 1H), 7.19 (d, $^3J_{HH}$ = 8.3 Hz, 1H), 7.09 (t, $^3J_{HH}$ = 7.2 Hz, 1H), 3.94−4.05 (m, 4H), 3.92 (s, 3H), 1.24 (t, $^3J_{HH}$ = 7.0 Hz, 6H). LC-MS: R_t = 2.82 min. (ESI): m/z = 414 $[M + H]^+$.

*Diethyl (4-{[6-(3-Nitrophenyl)pyrimidin-4-yl]amino}phenyl)-phosphonate (**74**).* According to the general coupling procedure, 4-chloro-6-(3-nitrophenyl)-pyrimidine **13b** (0.25 g, 1.06 mmol) and diethyl (4-aminophenyl)phosphonate·HCl **64d** (0.422 g, 1.59 mmol) were reacted. The crude product was suspended in Et_2O, and precipitate was filtered. Recrystallization from MeCN gave a yellow powder (0.209 g, 46%); mp = 219 °C (MeCN). ^{31}P NMR (DMSO-d_6, 242 MHz): δ 17.7 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 10.30 (s, 1H), 8.85 (s, 2H), 8.48 (d, $^3J_{HH}$ = 7.7 Hz, 1H), 8.37 (d, $^3J_{HH}$ = 7.9 Hz, 1H), 7.94 (dd, J_{AABB} = 8.2 Hz, $^4J_{PH}$ = 3.1 Hz, 2H), 7.85 (t, $^3J_{HH}$ = 8.0 Hz, 1H), 7.68 (dd, $^3J_{PH}$ = 12.5 Hz, J_{AABB} = 8.4 Hz, 2H), 7.51 (s, 1H), 3.94−4.05 (m, 4H), 1.24 (t, $^3J_{HH}$ = 7.0 Hz, 6H). LC-MS: R_t = 3.87 min. (ESI): m/z = 429 $[M + H]^+$.

*Diethyl (4-{[6-(3-Aminophenyl)pyrimidin-4-yl]amino}phenyl)-phosphonate (**75**).* Reduction of the nitro compound **74** (0.14 g, 0.33 mmol) was carried out according to the nitro group reduction described for compound **26a**. The free base was prepared as a yellow powder (0.127 g, 97%); mp = 174−175 °C (EtOH). ^{31}P NMR (DMSO-d_6, 242 MHz): δ 17.8 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.99 (s, 1H), 8.75 (s, 1H), 7.91 (dd, J_{AABB} = 8.5 Hz, $^4J_{PH}$ = 3.5 Hz, 2H), 7.67 (dd, $^3J_{PH}$ = 12.5 Hz, J_{AABB} = 8.5 Hz, 2H), 7.31 (s, 1H), 7.23 (s, 1H), 7.10−7.20 (m, 2H), 6.65−6.71 (m, 1H), 5.30 (br, 2H; 3.94−4.04 (m, 4H), 1.23 (t, $^3J_{HH}$ = 7.0 Hz, 6H). LC-MS: R_t = 2.56 min. (ESI): m/z = 399 $[M + H]^+$.

*(3-{[6-(2-Methoxyphenyl)pyrimidin-4-yl]amino}phenyl)-phosphonic Acid (**76**).* **76** was prepared with the method described for compound **45a** starting from diethyl phosphonate **71** (0.05 g, 0.12 mmol). The reaction yielded a yellow powder (0.03 g, 69%); mp = 250−253 °C (dec, EtOH). ^{31}P NMR (DMSO-d_6, 242 MHz): δ 10.9 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 11.41 (s, 1H), 8.91 (s, 1H), 8.00 (d, $^3J_{PH}$ = 14.0 Hz, 1H), 7.91 (d, $^3J_{HH}$ = 4.9 Hz, 1H), 7.77 (d, $^3J_{HH}$ = 7.4 Hz, 1H), 7.61 (t, $^3J_{HH}$ = 7.6 Hz, 1H), 7.40−7.55 (m, 2H), 7.45 (s, 1H), 7.27 (d, $^3J_{HH}$ = 8.2 Hz, 1H), 7.17 (t, $^3J_{HH}$ = 7.4 Hz, 1H), 5.75 (br, 2H), 3.91 (s, 3H). LC-MS: R_t = 0.47 and 1.92 min. (ESI): m/z = 358 $[M + H]^+$.

*(3-{[6-(3-Nitrophenyl)pyrimidin-4-yl]amino}phenyl)phosphonic Acid (**77**).* **77** was prepared with the method described for compound **45a** starting from diethyl phosphonate **72** (0.15 g, 0.35 mmol). The reaction yielded a yellow powder (0.039 g, 30%); mp> 350 °C (EtOH). ^{31}P NMR (DMSO-d_6, 242 MHz): δ 11.6 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 10.16 (s, 1H), 8.82 (s, 2H), 8.43 (d, $^3J_{HH}$ = 7.7 Hz, 1H), 8.38 (d, $^3J_{HH}$ = 8.1 Hz, 1H), 8.00 (d, $^3J_{PH}$ = 14.7 Hz, 1H), 7.94 (d, $^3J_{HH}$ = 7.8 Hz, 1H), 7.86 (t, $^3J_{HH}$ = 8.0 Hz, 1H), 7.33−7.49 (m, 3H), 5.27 (br, 2H). LC-MS: R_t = 2.50 min. (ESI): m/z = 373 $[M + H]^+$.

*(4-{[6-(2-Methoxyphenyl)pyrimidin-4-yl]amino}phenyl)-phosphonic Acid (**78**).* **78** was prepared with the method described for compound **45a** starting from diethyl phosphonate **73** (0.077 g, 0.19 mmol). The reaction yielded a yellow powder (0.015 g, 22%); mp> 350 °C (EtOH). ^{31}P NMR (DMSO-d_6, 242 MHz): δ 10.7 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.85 (s, 1H), 8.74 (s, 1H), 7.90 (d, $^3J_{HH}$ = 6.5 Hz, 1H), 7.52−7.80 (m, 4H), 7.40−7.50 (m, 2H), 7.19 (d, $^3J_{HH}$ = 8.0 Hz, 1H), 7.09 (dd, $^3J_{HH}$ = 7.0 Hz, $^3J_{HH}$ = 6.6 Hz, 1H), 4.60 (br, 2H), 3.91 (s, 3H). LC-MS: R_t = 0.46 and 1.83 min. (ESI): m/z = 358 $[M + H]^+$.

*(4-{[6-(3-Aminophenyl)pyrimidin-4-yl]amino}phenyl)phosphonic Acid (**79**).* **79** was prepared with the method described at compound **45a** starting from diethyl phosphonate **75** (0.086 g, 0.22 mmol). The reaction yielded a yellow powder (0.046 g, 61%); mp > 350 °C (EtOH). ^{31}P NMR (DMSO-d_6, 242 MHz): δ 12.0 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 10.63 (s, 1H), 8.83 (s, 1H), 7.83 (dd, J_{AABB} = 8.4 Hz, $^4J_{PH}$ = 2.7 Hz, 2H), 7.64−7.72 (m, 4H), 7.51 (t, $^3J_{HH}$ = 7.9 Hz, 1H), 7.37 (s, 1H), 7.26 (t, $^3J_{HH}$ = 7.5 Hz, 1H), 5.70 (br, 4H). LC-MS: R_t = 0.45 and 1.07 min. (ESI): m/z = 343 $[M + H]^+$.

General Method for the Suzuki Coupling. To the solution of 4,6-dichloropyridine (0.373 g; 2.5 mmol) in dimethoxyethane (40 mL) tetrakis (triphenylphosphine)palladium (0) (0.145 g; 0.13 mmol; 0.05 equiv) was added under inert atmosphere. The mixture was stirred at RT for 1.5 h then the boronic acid or the boronic acid pinacolate ester (2.5 mmol; 1 equiv), Na_2CO_3 (0.53 g; 5.0 mmol; 2 equiv), and 0.5 mL of degassed water were added. The reaction mixture was refluxed for 20 h under inert atmosphere. Volatiles were evaporated under reduced pressure then the residue was suspended in 1 M NaH_2PO_4. The suspension was extracted 3 times with EtOAc, combined organics were washed with satd Na_2CO_3 and with brine and dried with $MgSO_4$. After evaporation of the volatiles under reduced pressure, the crude product was purified by column chromatography in hexane:EtOAc (4:1). For further purifications, yields, and analytical data see the exact examples.

*4-Chloro-6-(2-ethoxyphenyl)pyrimidine (**13c**).* Yellow crystals (0.267 g, 46%); mp = 75−76 °C (EtOAc, hexane). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.5−7.7 (m, 4H), 7.3−7.4 (m, 1H), 6.9−7.0 (m, 1H), 4.09 (q, $^3J_{HH}$ = 6.9 Hz, 2H), 1.36 (t, $^3J_{HH}$ = 6.7 Hz, 3H). LC-MS: R_t = 4.31 min. (ESI): m/z = 234 $[M + H]^+$.

*4-Chloro-6-(2-propoxyphenyl)pyrimidine (**13d**).* White crystals (0.159 g, 26%). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.1 (s, 1H), 8.19 (s, 1H), 8.01 (d, $^3J_{HH}$ = 5.8 Hz, 1H), 7.53 (s, 1H), 7.21 (d, $^3J_{HH}$ = 6.6 Hz, 1H), 7.12 (s, 1H), 4.1 (t, $^3J_{HH}$ = 7.0 Hz, 2H), 1.73−1.8 (m, 2H), 1.02 (t, $^3J_{HH}$ = 7.3 Hz, 3H). LC-MS: R_t = 4.68 min. (ESI): m/z = 248 $[M + H]^+$.

*4-Chloro-6-(2-isopropoxyphenyl)pyrimidine (**13e**).* Colorless liquid (0.258 g, 42%). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.09 (s, 1H), 8.17 (s, 1H), 8.01 (d, $^3J_{HH}$ = 7.1 Hz, 1H), 7.52 (t, $^3J_{HH}$ = 7.0 Hz, 1H), 7.23 (d, $^3J_{HH}$ = 7.2 Hz, 1H), 7.1 (t, $^3J_{HH}$ = 7.1 Hz, 1H), 3.42−3.51 (m, 1H), 1.32 (d, $^3J_{HH}$ = 6.9 Hz, 6H). LC-MS: R_t = 4.55 min. (ESI): m/z = 248 $[M + H]^+$.

*4-Chloro-6-(2-phenoxyphenyl)pyrimidine (**13f**).* White crystals (0.44 g, 63%); mp = 73 °C (EtOAc, hexane), ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.12 (s, 1H), 8.08 (s, 1H), 8.03 (d, $^3J_{HH}$ = 7.3 Hz, 1H), 7.54 (t, $^3J_{HH}$ = 6.8 Hz, 1H), 7.3−7.5 (m, 3H), 7.16 (t, $^3J_{HH}$ = 6.7 Hz, 1H), 7.0−7.1 (m, 3H). LC-MS: R_t = 4.73 min. (ESI): m/z = 282 $[M + H]^+$.

*4-[2-(Benzyloxy)phenyl]-6-chloropyrimidine (**13g**).* White crystals (0.388 g, 52%); mp = 87−88 °C (EtOAc, hexane), ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.1 (s, 1H), 8.19 (s, 1H), 8.01 (d, $^3J_{HH}$ = 6.8 Hz, 1H), 7.3−7.6 (m, 7H), 7.15 (t, $^3J_{HH}$ = 5.6 Hz, 1H), 5.27 (s, 2H). LC-MS: R_t = 4.74 min. (ESI): m/z = 296 $[M + H]^+$.

*4-Chloro-6-(3-methoxyphenyl)pyrimidine (**13h**).* White crystals (0.34 g, 62%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.02 (s, 1H), 7.23 (s, 1H), 7.65 (s, 1H), 7.61 (d, $^3J_{HH}$ = 8 Hz, 1H), 7.42 (t, $^3J_{HH}$ = 8.0 Hz, 1H), 7.08 (d, J_{HH} = 6.5 Hz, 1H), 3.90 (s, 3H).

*4-Chloro-6-(4-methoxyphenyl)pyrimidine (**13i**).* White crystals (0.21 g, 38%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.96 (s, 1H), 8.06 (d,

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J_{HH} = 8.5 Hz, 2H), 7.67 (s, 1H), 7.02 (d, J_{HH} = 8.5 Hz, 2H_{AR}), 3.89 (s, 3H).

*4-Chloro-6-(2,3-dimethoxyphenyl)pyrimidine (**13j**).* White crystals (0.24 g, 38%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.05 (s, 1H), 8.02 (s, 1H), 7.52 (d, J_{HH} = 6.5 Hz, 1H), 7.19 (t, J_{HH} = 8 Hz, 1H), 7.07 (d, J_{HH} = 8 Hz, 1H), 3.93 (s, 3H), 3.80 (s, 3H).

*4-Chloro-6-(4-fluoro-2-methoxyphenyl)pyrimidine (**13k**).* White crystals (0.12 g, 20%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.00 (s, 1H), 8.13 (t, J_{HH} = 7 Hz, 1H), 8.05 (s, 1H), 6.82 (t, J_{HH} = 8 Hz, 1H), 6.75 (d, J_{HH} = 8.5 Hz, 1H), 3.94 (s, 3H).

*4-[3-(Benzyloxy)phenyl]-6-chloropyrimidine (**13l**).* Yellow oil (0.592 g, 80%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.09 (s, 1H), 8.36 (s, 1H), 7.8−7.92 (m, 2H), 7.27.7.55 (m, 6H), 7.24 (d, J_{HH} = 7.2 Hz, 1H), 5.22 (s, 2H). LC-MS: R_t = 4.79 min. (ESI): m/z = 296 $[M + H]^+$.

*4-Chloro-6-(2-ethylphenyl)pyrimidine (**13m**).* White crystals were prepared (0.058 g, 11%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.12 (s, 1H), 7.24−7.49 (m, 5H), 2.68−2.78 (m, 2H), 1.08 (t, J_{HH} = 7.5 Hz, 3H).

*Ethyl (3-{[6-(2-Ethoxyphenyl)pyrimidin-4-yl]amino}benzyl)-propylphosphinate (**80**).* According to the general coupling procedure, 4-chloro-6-(2-ethoxyphenyl)-pyrimidine **13c** (0.262 g, 1.12 mmol) and ethyl (3-aminophenyl)propylphosphinate·HCl **48** (0.326 g, 1.23 mmol) were reacted. The crude product was purified by chromathography in hexane:EtOAc (9:1). Evaporation of the fractions under reduced pressure provided a pale-yellow oil (0.05 g, 10%). ^{31}P NMR ($CDCl_3$, 121 MHz): δ 54.2 ppm. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.76 (s, 1H), 7.98 (q, J_{HH} = 4 Hz, 1H), 7.41−7.46 (m, 3H), 7.27−7.38 (m, 3H), 7.06 (t, J_{HH} = 7 Hz, 2H), 6.95 (d, J_{HH} = 8.5 Hz, 1H), 4.01−4.06 (m, 2H), 3.94−4.01 (m, 2H), 3.12 (d, J_{PH} = 16.5 Hz, 2H), 1.59−1.63 (m, 4H), 1.33 (t, J_{HH} = 7.0 Hz, 3H), 1.24 (t, J_{HH} = 7.0 Hz, 3H), 0.96 (t, J_{HH} = 7 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 162.0 (s, 1C), 161.0 (s, 1C), 158.5 (s, 1C), 157.2 (s, 1C), 139.2 (d, J_{PC} = 2.6 Hz, 1C), 133.6 (d, J_{PC} = 7.1 Hz, 1C), 131.3 (s, 1C), 131.0 (s, 1C), 129.7 (d, J_{PC} = 2.6 Hz, 1C), 126.8 (s, 1C), 125.8 (d, J_{PC} = 5.5 Hz, 1C), 123.5 (d, J_{PC} = 5.5 Hz, 1C),15.0 (s, 1C), 121.0 (s, 1C), 120.4 (d, J_{PC} = 9.3 Hz, 1C), 112.6 (s, 1C), 105.4 (s, 1C), 64.3 (s, 1C), 60.8 (d, J_{PC} = 6.7 Hz, 1C), 36.6 (d, J_{PC} = 83.0 Hz, 1C), 29.9 (d, J_{PC} = 92.0 Hz, 1C), 16.8 (d, J_{PC} = 5.6 Hz, 1C), 15.6 (s, 1C), 15.5 (s, 1C). LC-MS: R_t = 2.91 min. (ESI): m/z = 440 $[M + H]^+$.

*Ethyl (3-{[6-(2-Propoxyphenyl)pyrimidin-4-yl]amino}benzyl)-propylphosphinate (**81**).* According to the general coupling procedure, 4-chloro-6-(2-propoxyphenyl)-pyrimidine **13d** (0.15 g, 0.6 mmol) and ethyl (3-aminophenyl)propylphosphinate·HCl **48** (0.175 g, 0.66 mmol) were reacted. The crude product was purified by chromathography in hexane:EtOAc (9:1). Evaporation of the fractions under reduced pressure provided a pale-yellow oil (0.1 g, 37%). ^{31}P NMR ($CDCl_3$, 121 MHz): δ 52.5 ppm. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.74 (s, 1H), 7.90−7.95 (m, 2H), 7.41 (s, 1H), 7.27−7.39 (m, 4H), 7.02 (t, J_{HH} = 8 Hz, 2H), 6.92 (d, J_{HH} = 8.5 Hz, 1H), 3.91−4.18 (m, 4H), 3.11 (d, J_{PH} = 16.5 Hz, 2H), 1.45−1.79 (m, 6H), 1.21 (t, J_{HH} = 7.0 Hz, 3H), 0.93 (t, J_{HH} = 7.5 Hz, 3H), 0.87 (t, J_{HH} = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 162.0 (s, 1C), 161.0 (s, 1C), 158.4 (s, 1C), 157.2 (s, 1C), 139.3 (d, J_{PC} = 2.6 Hz, 1C), 133.5 (d, J_{PC} = 7.1 Hz, 1C), 131.1 (s, 1C), 130.9 (s, 1C), 129.6 (d, J_{PC} = 2.6 Hz, 1C), 126.9 (s, 1C), 125.7 (d, J_{PC} = 5.5 Hz, 1C), 123.5 (d, J_{PC} = 5.5 Hz, 1C), 121.0 (s, 1C), 120.5 (d, J_{PC} = 3.0 Hz, 1C), 112.6 (s, 1C), 105.3 (s, 1C), 70.3 (s, 1C), 60.7 (d, J_{PC} = 6.7 Hz, 1C), 36.5 (d, J_{PC} = 83.5 Hz, 1C), 29.8 (d, J_{PC} = 92.6 Hz, 1C), 22.7 (s, 1C), 16.8 (d, J_{PC} = 5.6 Hz, 1C), 15.7 (d, J_{PC} = 5.7 Hz, 1C), 15.5 (d, J_{PC} = 5.6 Hz, 1C), 10.7 (s, 1C). LC-MS: R_t = 3.09 min. (ESI): m/z = 454 $[M + H]^+$.

*Ethyl (3-{[6-(2-Isopropoxyphenyl)pyrimidin-4-yl]amino}benzyl)-propylphosphinate (**82**).* According to the general coupling procedure, 4-chloro-6-(2-isopropoxyphenyl)-pyrimidine **13e** (0.243 g, 0.98 mmol) and ethyl (3-aminophenyl)propylphosphinate·HCl **48** (0.286 g, 1.08 mmol) were reacted. The crude product was purified by chromathography in hexane:EtOAc (9:1). After evaporation of the fractions under reduced pressure, the product was crystallized from hexane:*i*-PrOH (9:1), affording white crystals (0.17 g, 38%). ^{31}P NMR ($CDCl_3$, 121 MHz): δ 52.4 ppm. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.77 (s, 1H), 7.43−7.46 (m, 2H), 7.33−7.37 (m, 2H), 7.27−7.29 (m, 2H), 7.04−7.09 (m, 3H), 6.97 (d, J = 8.0 Hz, 1H), 4.54−4.63 (m, 1H), 3.95−4.07 (m, 2H), 3.13 (d, J_{PH} = 16.5 Hz, 2H), 1.61−1.64 (m, 4H), 1.26 (t, J_{HH} = 6.0 Hz, 9H), 0.97 (t, J_{HH} = 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 162.0 (s, 1C), 160.7 (s, 1C), 158.4 (s, 1C), 155.9 (s, 1C), 139.0 (d, J_{PC} = 2.7 Hz, 1C), 133.6 (d, J_{PC} = 7.1 Hz, 1C), 131.0 (d, J_{PC} = 8.2 Hz, 2C), 129.5 (d, J_{PC} = 2.6 Hz, 1C), 127.6 (s, 1C), 125.7 (d, J_{PC} = 5.6 Hz, 1C), 123.4 (d, J_{PC} = 5.5 Hz, 1C), 121.0 (s, 1C), 120.4 (d, J_{PC} = 3.0 Hz, 1C), 114.3 (s, 1C), 105.1 (s, 1C), 70.9 (s, 1C), 60.6 (d, J_{PC} = 6.6 Hz, 1C), 36.4 (d, J_{PC} = 82.9 Hz, 1C), 29.2 (s, 1C), 22.1 (s, 1C), 16.6 (d, J_{PC} = 5.5 Hz, 1C), 15.5 (d, J_{PC} = 5.8 Hz, 1C), 15.4 (d, J_{PC} = 5.5 Hz, 1C). LC-MS: R_t = 3.05 min; (ESI): m/z = 454 $[M + H]^+$.

*Ethyl (3-{[6-(2-Phenoxyphenyl)pyrimidin-4-yl]amino}benzyl)-propylphosphinate (**83**).* According to the general coupling procedure, 4-chloro-6-(2-phenoxyphenyl)-pyrimidine **13f** (0.23 g, 0.81 mmol) and ethyl (3-aminophenyl)propylphosphinate·HCl **48** (0.236 g, 0.89 mmol) were reacted. The crude product was purified by chromathography in hexane:EtOAc (9:1). After evaporation of the fractions under reduced pressure, the product was crystallized from MeCN to give white crystals (0.12 g, 30%). ^{31}P NMR ($CDCl_3$, 121 MHz): δ 53.3 ppm. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.73 (s, 1H), 8.25 (s, 1H), 8.03 (d, J_{HH} = 6.5 Hz, 1H), 7.40 (s, 1H), 7.21−7.35 (m, 6H), 7.14 (t, J_{HH} = 9.0 Hz, 1H), 7.06 (t, J_{HH} = 7.5 Hz, 1H), 6.97 (d, J_{HH} = 7.5 Hz, 1H), 6.92 (d, J_{HH} = 8.0 Hz, 3H), 3.94−4.08 (m, 2H), 3.01 (d, J_{PH} = 16.5 Hz, 2H), 1.59−1.65 (m, 4H), 1.22 (t, J_{HH} = 7.3 Hz, 3H), 0.94 (t, J_{HH} = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 160.9 (s, 1C), 160.8 (s, 1C), 158.5 (s, 1C), 156.9 (s, 1C), 154.9 (s, 1C), 139.2 (d, J_{PC} = 2.7 Hz, 1C), 133.2 (d, J_{PC} = 7.1 Hz, 1C), 131.1 (d, J_{PC} = 3.6 Hz, 1C), 129.9 (s, 1C), 129.7 (s, 1C), 129.5 (s, 1C), 129.4 (s, 1C), 125.3 (d, J_{PC} = 5.4 Hz, 1C), 124.1 (s, 1C), 123.5 (s, 1C), 122.8 (d, J_{PC} = 5.6 Hz, 2C), 120.0 (d, J_{PC} = 2.9 Hz, 2C), 119.6 (s, 1C), 118.6 (s, 1C), 105.4 (s, 1C), 60.7 (d, J_{PC} = 6.7 Hz, 1C), 36.4 (d, J_{PC} = 83.0 Hz, 1C), 29.8 (d, J_{PC} = 92.0 Hz, 1C), 16.7 (d, J_{PC} = 5.6 Hz, 1C), 15.6 (d, J_{PC} = 8.6 Hz, 1C), 15.5 (d, J_{PC} = 2.7 Hz, 1C). LC-MS: R_t = 3.48 min. (ESI): m/z = 488 $[M + H]^+$.

*Ethyl [3-({6-[2-(Benzyloxy)phenyl]pyrimidin-4-yl}amino)benzyl]-propylphosphinate (**84**).* According to the general coupling procedure, 4-[2-(benzyloxy)phenyl]-6-chloropyrimidine **13g** (0.369 g, 1.25 mmol) and ethyl (3-aminophenyl)propylphosphinate·HCl **48** (0.363 g, 1.37 mmol) were reacted. The crude product was purified by chromathography in hexane:EtOAc (9:1). After evaporation of the fractions under reduced pressure, the product was crystallized from Et_2O to give white crystals (0.23 g, 37%). ^{31}P NMR ($CDCl_3$, 121 MHz): δ 52.5 ppm. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.74 (s, 1H), 8.24 (d, J_{HH} = 4.5 Hz, 1H), 7.87 (d, J_{HH} = 7.5 Hz, 1H), 7.37 (s, 1H), 7.19−7.33 (m, 8H), 7.09 (t, J = 8.0 Hz, 1H), 7.02 (t, J = 7.5 Hz, 1H), 6.92−6.97 (m, 2H), 5.05 (s, 2H), 3.89−4.01 (m, 2H), 3.00 (d, J_{PH} = 16.5 Hz, 2H), 1.42−1.59 (m, 4H), 1.17 (t, J_{HH} = 7.5 Hz, 3H), 0.89 (t, J_{HH} = 6.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 161.6 (s, 1C), 160.7 (s, 1C), 158.3 (s, 1C), 156.6 (s, 1C), 139.3 (d, J_{PC} = 2.6 Hz, 1C), 136.7 (s, 1C), 133.2 (d, J_{PC} = 7.1 Hz, 1C), 130.9 (d, J_{PC} = 5.4 Hz, 1C), 129.4 (d, J_{PC} = 2.5 Hz, 1C), 128.6 (s, 1C), 127.9 (s, 2C), 127.6 (s, 1C), 127.1 (s, 1C), 125.1 (d, J_{PC} = 5.4 Hz, 2C), 122.6 (d, J_{PC} = 5.6 Hz, 1C), 121.4 (s, 1C), 119.8 (s, 1C), 119.77 (s, 1C), 113.3 (s, 1C), 105.8 (s, 1C), 70.8 (s, 1C), 60.6 (d, J_{PC} = 6.8 Hz, 1C), 36.3 (d, J_{PC} = 83.0 Hz, 1C), 29.6 (d, J_{PC} = 92.0 Hz, 1C), 16.6 (d, J_{PC} = 5.6 Hz, 1C), 15.5 (d, J_{PC} = 7.9 Hz, 1C), 15.4 (d, J_{PC} = 3.5 Hz, 1C). LC-MS: R_t = 3.28 min. (ESI): m/z = 502 $[M + H]^+$.

*Ethyl (3-{[6-(3-Methoxyphenyl)pyrimidin-4-yl]amino}benzyl)-propylphosphinate (**85**).* According to the general coupling procedure, 4-chloro-6-(3-methoxyphenyl)-pyrimidine **13h** (0.33 g, 1.5 mmol) and ethyl (3-aminophenyl)propylphosphinate·HCl **48** (0.437 g, 1.65 mmol) were reacted. The crude product was purified by chromathography in hexane:EtOAc (9:1). Evaporation of the fractions under reduced pressure provided a pale-yellow oil (0.18 g, 28%). ^{31}P NMR ($CDCl_3$, 121 MHz): δ 53.2 ppm. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.81 (s, 1H), 8.70 (s, 1H), 7.59 (s, 1H), 7.55 (s, 1H), 7.46 (d, J_{HH} = 8.0 Hz, 1H), 7.35 (d, J_{HH} = 8.0 Hz, 1H), 7.3 (t, J_{HH} = 8.0 Hz, 1H), 7.23 (t, J_{HH} = 8.0 Hz, 1H), 7.07 (s, 1H), 6.95 (t, J_{HH} = 8.0 Hz, 2H), 3.9−4.1 (m, 2H), 3.82 (s, 3H), 3.13 (d, J_{PH} = 16.0 Hz, 2H), 1.59−1.63 (m, 4H), 1.24 (t, 7.0 Hz, 3H), 0.97 (t, J_{HH} = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 162.7 (s, 1C), 161.4 (s, 1C), 159.9 (s, 1C), 158.4 (s, 1C), 139.6 (d, J_{PC} = 2.7 Hz, 1C), 132.9 (d, J_{PC} = 7.3 Hz, 1C), 129.7 (s, 1C), 129.3 (d, J_{PC} = 2.4 Hz, 1C), 124.8 (d, J_{PC} = 5.6 Hz, 1C), 122.4 (d, J_{PC} = 5.3 Hz, 1C), 119.6 (d, J_{PC} = 2.8 Hz, 1C), 119.2 (s, 1C), 116.1 (s, 1C), 112.2 (s, 1C), 105.7 (s, 1C), 101.7 (s, 1C), 60.7 (d, J_{PC} = 6.7 Hz, 1C), 55.3 (s, 1C), 36.4 (d, J_{PC} =

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82.5 Hz, 1C), 29.8 (d, J_{PC} = 92.5 Hz, 1C), 16.7 (d, J_{PC} = 5.6 Hz, 1C), 15.7 (d, J_{PC} = 6.9 Hz, 1C), 15.5 (d, J_{PC} = 8.9 Hz, 1C). LC-MS: R_t = 3.06 min. (ESI): m/z = 426 $[M + H]^+$.

*Ethyl (3-{[6-(4-Methoxyphenyl)pyrimidin-4-yl]amino}benzyl)-propylphosphinate (**86**).* According to the general coupling procedure, 4-chloro-6-(4-methoxyphenyl)-pyrimidine **13i** (0.21 g, 0.95 mmol) and ethyl (3-aminophenyl)propylphosphinate·HCl **48** (0.278 g, 1.05 mmol) were reacted. The crude product was purified by chromathography in hexane:EtOAc (9:1). Evaporation of the fractions under reduced pressure provided a pale-yellow oil (0.27 g, 67%). ^{31}P NMR ($CDCl_3$, 121 MHz): δ 52.8 ppm. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.69 (s, 1H), 8.19 (s, 1H), 7.93 (d, J_{HH} = 9.0 Hz, 2H), 7.48 (s, 1H), 7.34 (d, J_{HH} = 8.0 Hz, 1H), 7.28 (t, J_{HH} = 7.5 Hz, 1H), 7.02 (t, J_{HH} = 8.5 Hz, 2H), 6.94 (d, J_{HH} = 9.0 Hz, 2H), 4.05 (m, 2H), 3.83 (s, 3H), 3.14 (d, J_{PH} = 16.5 Hz, 2H), 1.59−1.62 (m, 4H), 1.25 (t, J_{HH} = 7.0 Hz, 3H), 0.98 (t, J_{HH} = 7.3 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 163.0 (s, 1C), 161.5 (d, J_{PC} = 9.5 Hz, 1C), 158.7 (s, 1C), 139.5 (d, J_{PC} = 2.8 Hz, 1C), 133.3 (d, J_{PC} = 7.2 Hz, 1C), 130.0 (s, 1C), 129.6 (d, J_{PC} = 2.5 Hz, 1C), 128.5 (s, 1C), 125.3 (d, J_{PC} = 5.6 Hz, 2C), 122.9 (d, J_{PC} = 5.4 Hz, 2C), 120.1 (d, J_{PC} = 2.9 Hz, 2C), 114.2 (s, 1C), 99.9 (s, 1C), 60.8 (d, J_{PC} = 6.7 Hz, 1C), 55.5 (s, 1C), 36.6 (d, J_{PC} = 82.9 Hz, 1C), 29.9 (d, J_{PC} = 91.8 Hz, 1C), 16.8 (d, J_{PC} = 5.6 Hz, 1C), 15.7 (d, J_{PC} = 4.4 Hz, 1C), 15.6 (d, J_{PC} = 6.9 Hz, 1C). LC-MS: R_t = 2.90 min. (ESI): m/z = 426 $[M + H]^+$.

*Ethyl (3-{[6-(2,3-Dimethoxyphenyl)pyrimidin-4-yl]amino}benzyl)-propylphosphinate (**87**).* According to the general coupling procedure, 4-chloro-6-(2,3-dimethoxyphenyl)-pyrimidine **13j** (0.24 g, 0.96 mmol) and ethyl (3-aminophenyl)propylphosphinate·HCl **48** (0.278 g, 1.05 mmol) were reacted. The crude product was purified by chromathography in hexane:EtOAc (9:1). After evaporation of the fractions under reduced pressure, the product was crystallized from Et_2O to give white crystals (0.16 g, 37%). ^{31}P NMR ($CDCl_3$, 121 MHz): δ 53.9 ppm. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.66 (s, 1H), 8.49 (s, 1H), 7.41 (s, 1H), 7.33 (d, J_{HH} = 8.0 Hz, 1H), 7.27 (dd, J_{HH} = 8.0 Hz, 2H), 7.15 (t, J_{HH} = 7.5 Hz, 1H), 7.03 (t, J_{HH} = 8.0 Hz, 1H), 6.89 (dd, J_{HH} = 9.5 Hz, 2H), 3.95 (m, 2H), 3.77 (s, 3H), 3.62 (s, 3H), 3.04 (d, J_{PH} = 16.5 Hz, 2H), 1.52−1.59 (m, 4H), 1.45 (t, J_{HH} = 7.0 Hz, 3H), 0.86 (t, J_{HH} = 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 161.4 (s, 1C), 161.0 (s, 1C), 158.3 (s, 1C), 153.0 (s, 1C), 147.6 (s, 1C), 139.5 (d, J_{PC} = 2.7 Hz, 1C), 133.1 (d, J_{PC} = 7.1 Hz, 1C), 132.4 (s, 1C), 129.3 (d, J_{PC} = 2.5 Hz, 1C), 124.9 (d, J_{PC} = 5.3 Hz, 1C), 124.3 (s, 1C), 122.4 (d, J_{PC} = 5.5 Hz, 1C), 122.1 (s, 1C), 119.6 (d, J_{PC} = 2.8 Hz, 1C), 113.6 (s, 1C), 105.9 (s, 1C), 60.9 (s, 1C), 60.6 (d, J_{PC} = 6.7 Hz, 1C), 55.9 (s, 1C), 36.5 (d, J_{PC} = 83.0 Hz, 1C), 29.6 (d, J_{PC} = 91.9 Hz, 1C), 16.6 (d, J_{PC} = 5.7 Hz, 1C), 15.5 (d, J_{PC} = 5.9 Hz, 1C), 15.3 (d, J_{PC} = 6.1 Hz, 1C). LC-MS: R_t = 2.83 min. (ESI): m/z = 456 $[M + H]^+$.

*Ethyl (3-{[6-(4-Fluoro-2-methoxyphenyl)pyrimidin-4-yl]amino}-benzyl)propylphosphinate (**88**).* According to the general coupling procedure, 4-chloro-6-(4-fluoro-2-methoxyphenyl)-pyrimidine **13k** (0.12 g, 0.5 mmol) and ethyl (3-aminophenyl)propylphosphinate·HCl **48** (0.146 g, 0.55 mmol) were reacted. The crude product was purified by chromathography in hexane:EtOAc (9:1). Evaporation of the fractions under reduced pressure provided a pale-yellow oil (0.05 g, 23%). ^{31}P NMR ($CDCl_3$, 121 MHz): δ 52.6 ppm. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.76 (s, 1H), 7.98 (t, J_{HH} = 7.8 Hz, 1H), 7.78 (s, 1H), 7.44 (s, 2H), 7.04−7.35 (m, 2H), 6.81 (d, J_{HH} = 7.5 Hz, 1H), 6.83 (t, J_{HH} = 8.5 Hz, 1H), 6.71 (d, J_{HH} = 8.5 Hz, 1H), 3.9−4.1 (m, 2H), 3.87 (s, 3H), 3.15 (d, J_{PH} = 16.0 Hz, 2H), 1.59−1.64 (m, 4H), 1.3 (t, J_{HH} = 7.0 Hz, 3H), 1.0 (t, J_{HH} = 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 164.7 (d, J_{FC} = 249.7 Hz, 1C), 160.8 (d, J_{PC} = 8.4 Hz, 1C), 159.1 (d, J_{PC} = 10.0 Hz, 1C), 158.4 (s, 1C), 139.4 (d, J_{PC} = 2.7 Hz, 1C), 133.4 (d, J_{PC} = 7.2 Hz, 1C), 132.4 (d, J_{PC} = 10.3 Hz, 1C), 129.5 (d, J_{PC} = 2.6 Hz, 1C), 125.3 (d, J_{PC} = 2.6 Hz, 1C), 122.9 (d, J_{PC} = 3.3 Hz, 1C), 122.7 (s, 1C), 122.6 (s, 1C), 119.8 (d, J_{FC} = 3.1 Hz, 1C), 107.8 (d, J_{FC} = 21.2 Hz, 1C), 105.7 (s, 1C), 99.7 (d, J_{PC} = 25.8 Hz, 1C), 60.8 (d, J_{PC} = 6.8 Hz, 1C), 56.1 (s, 1C), 36.6 (d, J_{PC} = 83.6 Hz, 1C), 29.8 (d, J_{PC} = 92.5 Hz, 1C), 16.8 (d, J_{PC} = 5.6 Hz, 1C), 15.7 (d, J_{PC} = 5.6 Hz, 1C), 15.6 (d, J_{PC} = 5.6 Hz, 1C). LC-MS: R_t = 2.89 min. (ESI): m/z = 444 $[M + H]^+$.

*Ethyl [3-({6-[3-(Benzyloxy)phenyl]pyrimidin-4-yl}amino)benzyl]-propylphosphinate (**89**).* According to the general coupling procedure, 4-[3-(benzyloxy)phenyl]-6-chloropyrimidine **13l** (0.241 g, 0.81 mmol) and ethyl (3-aminophenyl)propylphosphinate·HCl **48** (0.235 g, 0.89 mmol) were reacted. The crude product was purified by chromathography in hexane:EtOAc (9:1). Evaporation of the fractions under reduced pressure provided a pale-yellow oil (0.08 g, 20%). ^{31}P NMR ($CDCl_3$, 121 MHz): δ 52.4 ppm. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.73 (s, 1H), 8.04 (s, 1H), 7.67 (s, 1H), 7.43−7.52 (m, 4H), 7.26−7.39 (m, 6H), 7.01−7.07 (m, 3H), 5.11 (s, 2H), 4.0 (m, 2H), 3.13 (d, J_{PH} = 16.0 Hz, 2H), 1.59−1.62 (m, 4H), 1.25 (t, J_{HH} = 8.0 Hz, 3H), 0.97 (t, J_{HH} = 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 163.2 (s, 1C), 161.6 (s, 1C), 159.4 (s, 1C), 158.8 (s, 1C), 139.3 (s, 1C), 139.2 (s, 1C), 139.1 (s, 1C), 136.9 (s, 1C), 133.4 (d, J_{PC} = 7.3 Hz, 1C), 129.9 (s, 1C), 129.7 (s, 1C), 129.7 (s, 1C), 128.7 (s, 2C), 128.2 (s, 1C), 127.7 (s, 2C), 125.5 (d, J_{PC} = 5.6 Hz, 1C), 122.9 (d, J_{PC} = 5.3 Hz, 1C), 120.2 (d, J_{PC} = 2.9 Hz, 1C), 119.7 (s, 1C), 117.1 (s, 1C), 113.4 (s, 1C), 101.2 (s, 1C), 70.3 (s, 1C), 60.8 (d, J_{PC} = 6.8 Hz, 1C), 36.6 (d, J_{PC} = 83.0 Hz, 1C), 30.4 (d, J_{PC} = 91.8 Hz, 1C), 16.8 (d, J_{PC} = 5.6 Hz, 1C), 15.8 (d, J_{PC} = 2.7 Hz, 1C), 15.6 (d, J_{PC} = 8.6 Hz, 1C). LC-MS: R_t = 3.58 min. (ESI): m/z = 502 $[M + H]^+$.

*Ethyl (3-{[6-(2-Ethylphenyl)pyrimidin-4-yl]amino}benzyl)-propylphosphinate (**90**).* According to the general coupling procedure, 4-chloro-6-(2-ethylphenyl)pyrimidine **13m** (0.053 g, 0.24 mmol) and ethyl (3-aminophenyl)propylphosphinate·HCl **48** (0.067 g, 0.24 mmol) were reacted. The crude product was purified by preparative TLC with two elutions (100% EtOAc then EtOAc:EtOH (8:1)). The pure product was extracted from the silica with MeOH. After evaporation of the volatiles under reduced pressure, a white powder was obtained (0.016 g, 16%). ^{31}P NMR (DMSO-d_6, 121 MHz): δ 56.7 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.65 (s, 1H), 8.67 (s, 1H), 7.5−7.7 (m, 2H), 7.2−7.45 (m, 5H), 6.94 (d, J_{HH} = 7.2 Hz, 1H), 6.83 (s, 1H), 3.85−4.00 (m, 2H), 3.16 (d, J_{PH} = 16.8 Hz, 2H), 2.73 (q, J_{HH} = 7.2 Hz, 2H), 1.35−1.70 (m, 4H), 1.17 (t, J_{HH} = 6.9 Hz, 3H), 1.1 (t, J_{HH} = 7.5 Hz, 3H), 0.92 (t, J_{HH} = 6.9 Hz, 3H). LC-MS: R_t = 3.05 min. (ESI): m/z = 423 $[M + H]^+$.

*Ethyl [3-({6-[2-(Benzyloxy)phenyl]pyrimidin-4-yl}amino)benzyl]-ethylphosphinate (**91**).* According to the general coupling procedure, 4-[2-(benzyloxy)phenyl]-6-chloropyrimidine **13g** (0.593 g, 2.0 mmol) and ethyl (3-aminophenyl)ethylphosphinate·HCl **47** (0.553 g, 2.1 mmol) were reacted. The crude product was purified by flash chromathography in 100% EtOAc. After evaporation of the fractions under reduced pressure, the desired compound was isolated as white crystals (0.312 g, 32%); mp = 61−62 °C (EtOAc). ^{31}P NMR (DMSO-d_6, 121 MHz): δ 53.9 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.6 (s, 1H), 8.69 (s, 1H), 7.84 (d, J_{HH} = 6.9 Hz, 1H), 7.5−7.6 (m, 2H), 7.15−7.5 (m, 9H), 7.08 (t, J_{HH} = 7.2 Hz, 1H), 6.94 (d, J_{HH} = 7.2 Hz, 1H), 5.26 (s, 2H), 3.85−4.0 (m, 2H), 3.15 (d, J_{PH} = 16.5 Hz, 2H), 1.55−1.7 (m, 2H), 1.17 (t, J_{HH} = 7.2 Hz, 3H), 0.99 (dt, J_{PH} = 17.7 Hz, J_{HH} = 7.7 Hz, 3H). LC-MS: R_t = 3.11 min. (ESI): m/z = 487 $[M + H]^+$.

*[3-({6-[2-(Benzyloxy)phenyl]pyrimidin-4-yl}amino)benzyl]-ethylphosphinic Acid (**92**).* Hydrolysis of the ester **91** (0.136 g, 0.28 mmol) was carried out according to the method described for compound **61**, providing a yellow oil (0.025 g, 19%). ^{31}P NMR (DMSO-d_6, 121 MHz): δ 29.8 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.99 (s, 1H), 8.63 (s, 1H), 7.79 (d, J_{HH} = 6.9 Hz, 1H), 7.59 (d, J_{HH} = 7.2 Hz, 1H), 7.2−7.5 (m, 8H), 7.16 (d, J_{HH} = 8.4 Hz, 1H), 7.0−7.1 (m, 2H), 6.85 (d, J_{HH} = 6.9 Hz, 1H), 5.24 (s, 2H), 2.62 (d, J_{PH} = 16.2 Hz, 2H), 1.0−1.15 (m, 2H), 0.88 (dt, J_{PH} = 15.3 Hz, J_{HH} = 6.9 Hz, 3H). LC-MS: R_t = 0.44 and 2.79 min. (ESI): m/z = 459 $[M + H]^+$.

*[3-({6-[2-(Benzyloxy)phenyl]pyrimidin-4-yl}amino)benzyl]-propylphosphinic Acid (**93**).* Hydrolysis of the ester **84** (0.14 g, 0.28 mmol) was carried out according to the method described for compound **61**, yielding a yellow oil (0.06 g, 45%). It crystallizes upon standing; mp = 238−240 °C. ^{31}P NMR (DMSO-d_6, 121 MHz): DMSO, δ 32.3 ppm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 10.08 (s, 1H), 8.63 (s, 1H), 7.78 (d, J_{HH} = 7.8 Hz, 1H), 7.61 (d, J_{HH} = 6.9 Hz, 1H), 7.2−7.6 (m, 8H), 7.17 (d, J_{HH} = 8.1 Hz, 1H), 7.0−7.1 (m, 2H), 6.84 (d, J_{HH} = 7.2 Hz, 1H), 5.24 (s, 2H), 2.64 (d, J_{PH} = 15.6 Hz, 2H), 1.3−1.5 (m, 2H), 1.0−1.2 (m, 2H), 0.8 (t, J_{HH} = 6.6 Hz, 3H). LC-MS: R_t = 2.90 min. (ESI): m/z = 473 $[M + H]^+$.

Biology. *Protocol for CDK9/Cyclin T1 Kinase Assay.* CDK9/CycT1 kinase assays were performed in low protein binding 384-well plates (Corning 3676). Test compounds were diluted in 100% DMSO to 5

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mM stock concentration, and then further dilutions were made in H_2O or 100% DMSO to desirable concentrations. Each reaction consisted of 5 nM enzyme: CDK9/CyclinT1 (Proqinase catalogue no. 0371-0345-1), 400 nM TAMRA-Rbtide (synthetic 15-mer peptide derived from human retinoblastoma tumor suppressor protein labeled with TAMRA dye, Genecust Europe), 12 μM ATP (= Kmapp, Sigma-Aldrich) and kinase buffer: 20 mM MOPS pH 7 (Sigma-Aldrich), 1 mM DTT (Sigma-Aldrich), 10 mM $MgCl_2$ (Sigma-Aldrich), 0.01% Tween 20 (Sigma-Aldrich). For each reaction, 4 or 6 μL containing TAMRA-Rbtide, ATP, and kianse buffer were combined with 2 μL of diluted compound in H_2O or 0.028 μL of compound in 100% DMSO. The kinase reaction was started by the addition of 2 μL of diluted enzyme. The reaction was allowed to run for 1 h at room temperature. The reaction was stopped by adding 15 μL of IMAP beads (1:400 beads in progressive (100% buffer A) 1× buffer). After an additional 1 h, fluorescent polarization (Ex, 550−10 nm; Em, 590−10 nm; Dich, 561 nm) was measured using an Analyst GT (Molecular devices). IC_{50} curves were fitted with XLfit curve fitting software.

Protocol for CDK2/Cyclin E and CDK4/Cyclin D1 Kinase Assays. The percentage of inhibition for CDK2/CycE; CDK4/CycD1 were determined by our partners under contract work. These CDK/cyclin protein kinase complexes were assayed using IMAP FAM FP assay method. Assays were performed in low protein binding 384-well plates (Corning 3676). Test compounds were diluted in 100% DMSO to 10 mM stock concentration, and then further dilutions were made in 100% DMSO to desirable concentrations in 384-well polypropylene plate (Falcon, 3995). Kinase specific FAM labeled peptide substrate was used in 400 nM. Optimal kinase buffer conditions were determined for each CDK kinase. ATP concentration was used at the KmATP, app. Kinase concentration used to yield 50% substrate turnover as determined in titration experiment. Optimal kinase incubation time was determined for each kinase: 6 μL of specific FAM-substrate + ATP in reaction buffer were added to each well. Then 10.8 nL of test compound in 100% DMSO was added to wells using Pintool. Then 2 μL of reaction buffer was added to C-wells, and 2 μL of kinase in reaction buffer were added to wells except C-wells. After kinase incubation period, 15 μL of IMAP binding solution were added to each well. After IMAP incubation period, fluorescence polarization (Ex, 485−20 nm; Em, 530−25 nm; Dich, 505 nm) was measured on Analyst GT (Molecular Devices)

Protocol for Viability of MT4 Cell Lines Assay (MTT Assay). The cytotoxic effect of selected compounds was measured by means of the colorimetric assay (MTT). Briefly, 2−3 × 10^4 MT4 cells per well were cultured in 96-well plates containing RPMI1640 medium supplemented with 10% FCS and antibiotics (100 IU/mL penicillin (SIGMA), 100 μg/mL streptomycin (SIGMA)), and two concentrations of the compounds to be tested (2500 and 1250 nM). After 7 days of incubation (37 °C, 5% CO_2 atmosphere), 20 μL of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide (MTT; 5 mg/mL dissolved in PBS) was added to each well. After incubation for 4 h, the cell supernatant was removed and (according our modification) 100 μL of DMSO was added, and the contents were mixed thoroughly. The absorbance was measured at 540 nm.

Determination of the Viability of HIV-1 Infected MT4 cells. To assess the anti-HIV-1 effects of selected compounds, MT4 cells were cultivated as described above, treated with test compounds (1250 nM), and infected with HIV-1 (strain HTLV-IIIB; 3400 $TCID_{50}$/mL HIV-1/well was used). The $TCID_{50}$ (50% tissue culture infectious dose) of HIV-1 was determined by a virus yield assay. The effects of HIV-1 on the viability of infected MT4 cells were measured by MTT assay in the presence or absence of test compounds.

■ ASSOCIATED CONTENT

Supporting Information

Predicted and measured ADME-T properties of selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS USED

ATP, adenosine triphosphate; AZT, azidothymidine; CDK, cyclin dependent kinase; Ctrl, control; Cyc, cyclin; FDA, U.S. Food and Drug Administration; HIV, human immunodeficiency virus; IC_{50}, half-maximal inhibitory concentration; KI, potassium iodide; K_i, binding affinity; K_{mATP}, dissociation constant of the kinase and the ATP; Pd/C, palladium on charcoal; RNA, ribonucleic acid; SAR, structure−activity relationship; TMSCl, trimethylsilyl chloride

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NOTE ADDED AFTER ASAP PUBLICATION

This paper was published ASAP on May 2, 2014. The spelling of an author's name was corrected and the revised version was reposted on May 6, 2014. A change was made to Scheme 10 and the revised version was reposted on May 22, 2014.