Journal of
Medicinal Chemistry

Article

Phosphine Oxides from a Medicinal Chemist's Perspective: Physicochemical and *in vitro* Parameters Relevant for Drug Discovery

Peter Finkbeiner, Joerg P. Hehn, and Christian Gnamm

J. Med. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.jmedchem.0c00407 • Publication Date (Web): 01 Jun 2020

Just Accepted

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Phosphine Oxides from a Medicinal Chemist's Perspective: Physicochemical and *in vitro* Parameters Relevant for Drug Discovery

Peter Finkbeiner,[§,†] Jörg P. Hehn[§] and Christian Gnamm[§,]*

[§] Boehringer Ingelheim Pharma GmbH & Co. KG, Birkendorfer Straße 65, 88397 Biberach an der Riß, Germany

KEYWORDS

Phosphine Oxides, Phosphonates, Phosphinates, Polarity, Solubility, Metabolic Stability, Permeability.

ABSTRACT

Phosphine oxides and related phosphorus-containing functional groups such as phosphonates and phosphinates are established structural motifs that are, still, underrepresented in today's drug discovery projects, and only few examples can be found amongst approved drugs. In this account, the physicochemical and *in vitro* properties of phosphine oxides and related phosphorus-containing functional groups are reported and compared to more commonly used structural motifs in drug discovery. Furthermore, the impact on the physicochemical properties of a real drug scaffold is exemplified by a series of phosphorus-containing analogs of imatinib. We demonstrate that phosphine oxides are highly polar functional groups leading to high solubility and metabolic stability, however, occasionally at the cost of reduced permeability. We conclude that phosphine oxides and related phosphorus-containing functional groups are valuable polar structural elements and that they deserve to be considered as routine part of every medicinal chemist's toolbox.

1. INTRODUCTION

Organophosphorus compounds have been investigated for applications in agricultural,[1] veterinary,[2] and medicinal[3] applications for decades, and a considerable number of phosphorus-containing drugs have achieved commercial success.[4,5] The majority of these approved phosphorus-containing pharmaceuticals contain a phosphate, a phosphoramide or a phosphonate group, while phosphines, phosphinates and phosphine oxides are rare. Among the successful examples of organophosphorus drug research are the phosphorodiamidate based anti-cancer drugs cyclophosphamide (**1**) and ifosfamide (**2**),[6] as well as the phosphonamidate and phosphonate containing reverse transcriptase inhibitors tenofovir alafenamide[7] (**3**) and adefovir dipivoxil[8] (**4**) to fight infectious diseases like HIV and hepatitis B, respectively (Figure 1). Several so-called bisphosphonates containing a phosphonic acid motif such as etidronate (**5**) are used for the treatment of osteoporosis,[9] and the natural product fosfomycin (**6**) is a broad spectrum antibiotic.[10] The ACE inhibitor fosinopril (**7**) is so far the only approved phosphinate based drug on the market and used for the treatment of hypertension.[11]

A major obstacle associated with the use of acidic phosphorus-containing functional groups such as phosphates, phosphonates and phosphinates in drug discovery is their

occurrence as charged species at physiological pH, which often leads to low cell permeability and poor oral bioavailability.[12,13] In most orally administered phosphate-containing drugs the phosphate constitutes a solubility-enhancing prodrug[14] and is not part of the pharmacophore of the active principle itself, as for example in case of antiretroviral protease inhibitor fosamprenavir (**8**),[15] SYK inhibitor fostamatinib (**9**)[16] and fospropofol (**10**),[17] a widely used anesthetic (Figure 1). Similarly, many of the drugs containing a phosphonate or phosphinate are employed as prodrugs as exemplified e.g. by the phosphonate and phosphinate esters in adefovir dipivoxil (**4**) and fosinopril (**7**), respectively, or the phosphonamidate in tenofovir alafenamide (**3**). Also Gilead's remdesivir (**11**),[18] a phase III antiviral drug originally developed for the treatment of ebola virus that is currently tested in clinical trials for efficacy against Covid-19,[19] constitutes a phosphoramidate prodrug.

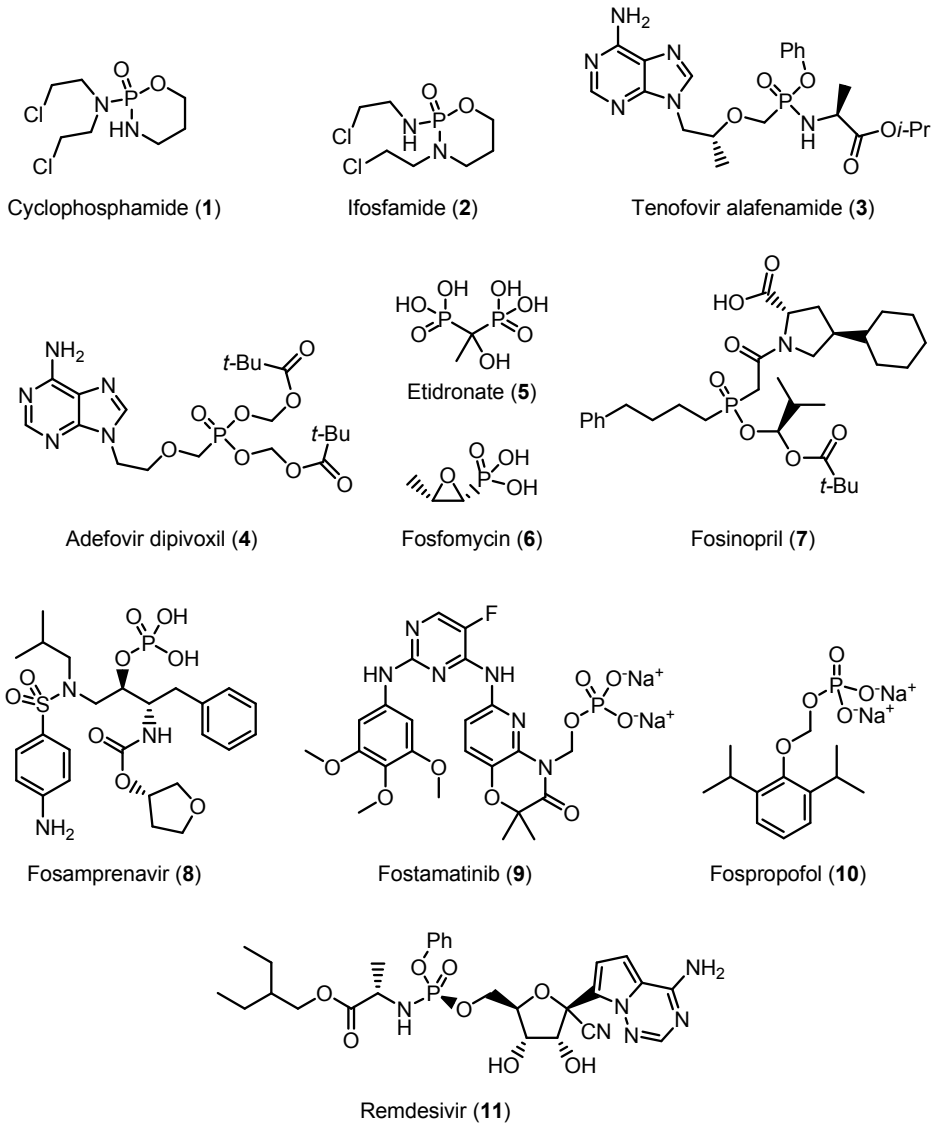


Figure 1: Selected examples of phosphorus-containing drugs.

In light of all the difficulties associated with the use of charged phosphorus-containing functionalities it is surprising that their uncharged counterparts, namely phosphine oxides but also *O*-substituted phosphonates and phosphinates, have been largely neglected in medicinal chemistry. Some recent examples for the application of phosphine oxides in medicinal chemistry are shown in Figure 2, including C-C chemokine receptor 2 (CCR2) antagonist **12**,[20] progesterone receptor

(PR) antagonist **13**,[21] potassium voltage-gated channel subfamily A member 5 (Kv1.5) inhibitor **14**,[22] epithelial sodium channel (ENaC) inhibitor **15**,[23] methionine aminopeptidase 2 (MetAP2) inhibitor **16**,[24] human calpain I inhibitor **17**,[25] and histone deacetylase 1 (HDAC1) inhibitor **18**.[26]

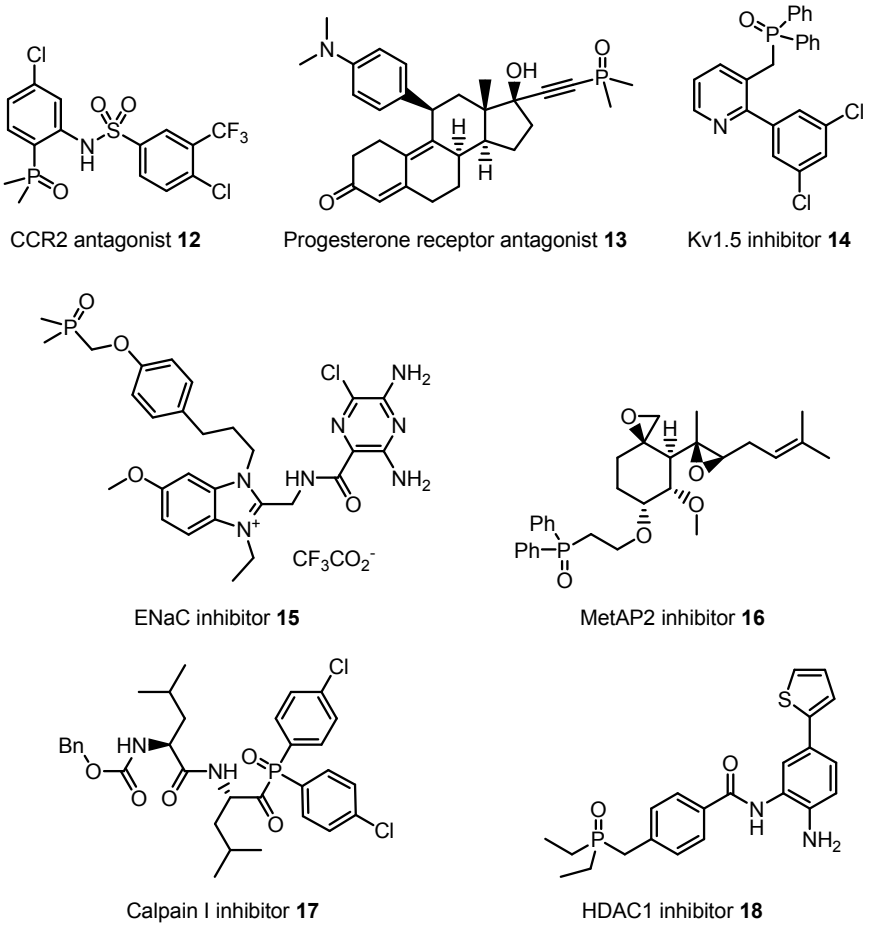
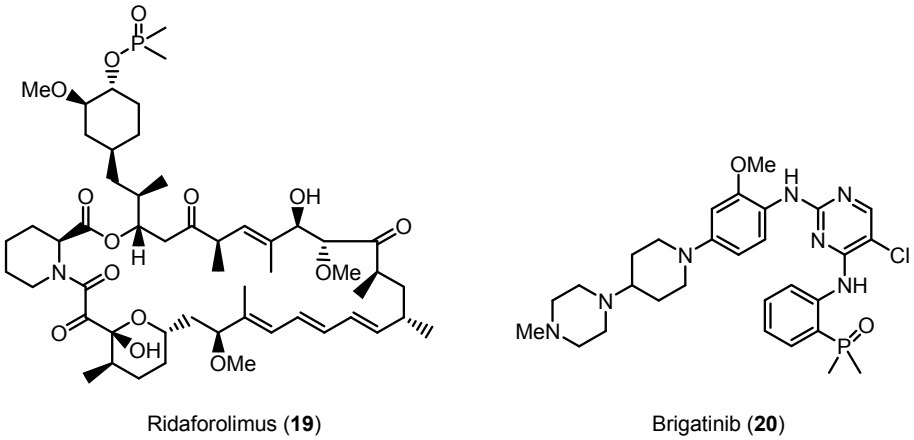


Figure 2: Recent examples for the application of phosphine oxides in medicinal chemistry.

It has been only recently that ridaforolimus (**19**), a dimethylphosphinic ester containing inhibitor of mammalian target of rapamycin (mTOR), progressed into Phase III clinical studies for the treatment of sarcoma,[27] and that the anaplastic lymphoma kinase (ALK) inhibitor brigatinib (**20**) became the very first drug containing a phosphine oxide motif that was approved by the U.S. FDA for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) (Figure 3).[28]



Ridaforolimus (**19**) Brigatinib (**20**)

Figure 3: Ridaforolimus (**19**) and brigatinib (**20**) as examples for investigational or approved drugs with a non-charged phosphorus-containing functional group.

The reasons for the rare appearance of phosphine oxides in drug discovery are not obvious, since they are chemically stable and their synthesis is well precedented. Additionally, they offer the unique feature of a very strong H-bond acceptor attached to a tetrahedral center with three potential vectors for derivatization.[29] Surprisingly, only few reports on the physicochemical properties and *in vitro* parameters of phosphine oxides and related phosphorus-containing functional groups are available today. [26,28a,30]

With the aim to provide a better understanding of phosphorus-containing functional groups from a medicinal chemist's perspective, we herein describe the design and synthesis of a larger set of phosphorus-containing tool compounds. In addition, we report selected physicochemical and *in vitro* parameters and rank the phosphorus-containing functional groups among related bioisosteres.[31] Furthermore, the effects of phosphorus-containing functional groups on the properties of analogs of the approved tyrosine kinase inhibitor imatinib (**36**) are presented.[32]

2. RESULTS AND DISCUSSION

2.1 Design of tool compounds 21-35 and drug-like analogs 37-45 derived from imatinib.

In order to measure the unbiased effect of the envisaged phosphorus-containing functional groups (Figure 4a), a 4-(trifluoromethyl)phenyl group was chosen as chemically robust and simple platform. Initially, acyclic phosphine oxides **21a-c** with increasingly sized aliphatic residues as well as cyclic phosphine oxides **22a-g** comprising different ring sizes and heteroatoms were designed. In addition, a variety of phospinates **23a-b** and phosphonates **24a-25d** was outlined and rounded off by cyclic phosphonamidates **26a-b** and cyclic phosphonamides **27a-c**. Pyridines **28a-c** were designed to measure the effects of the attached phosphorus-containing functional groups on their basicity. This set of phosphorus-containing tool compounds was then complemented by the corresponding bioisosteric structural motifs (Figure 4b),[31] comprising carboxylic acid and esters **29a-c**, carboxamides **30a-d**, sulfonamides **31a-c**, sulfoxide **32** and sulfone **33**, but also sulfoximines **34a-c** and sulfonimidamides **35a-c**.[33]

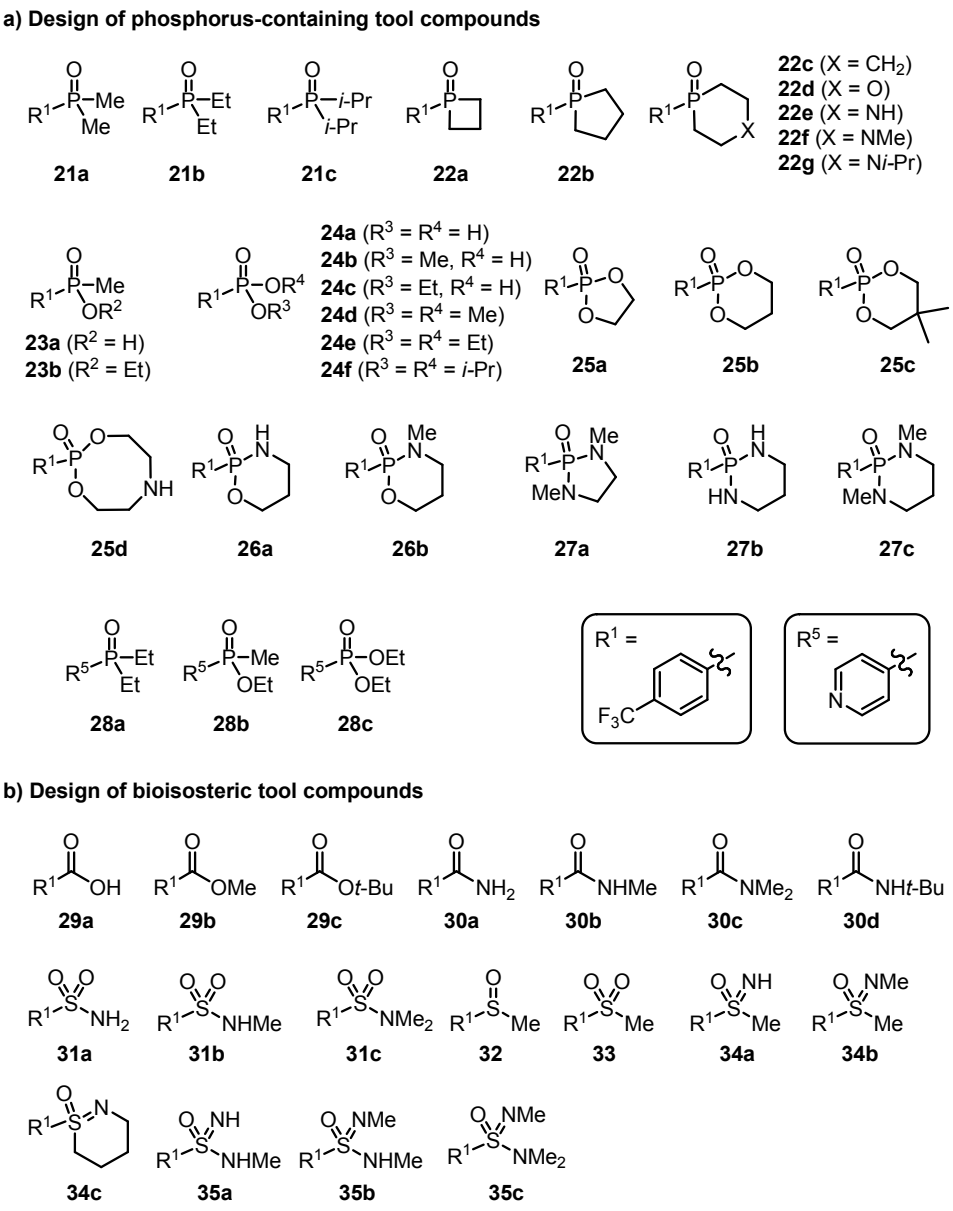


Figure 4: Design of a) tool compounds bearing phosphorus-containing functional groups and b) bioisosteric functional groups.

Finally, the effects of phosphorus-containing functional groups were explored in the context of a drug-like substrate. As small molecule kinase inhibitors with their usually flat

and polyaromatic core structures often lack aqueous solubility and bioavailability, they were considered to be an ideal showcase. To this end, tyrosine kinase inhibitor imatinib (**36**)[32] was selected as a reference and imatinib analogs **37a**-**45c** including phosphorus-containing or classical functional groups were designed (Figure 5).

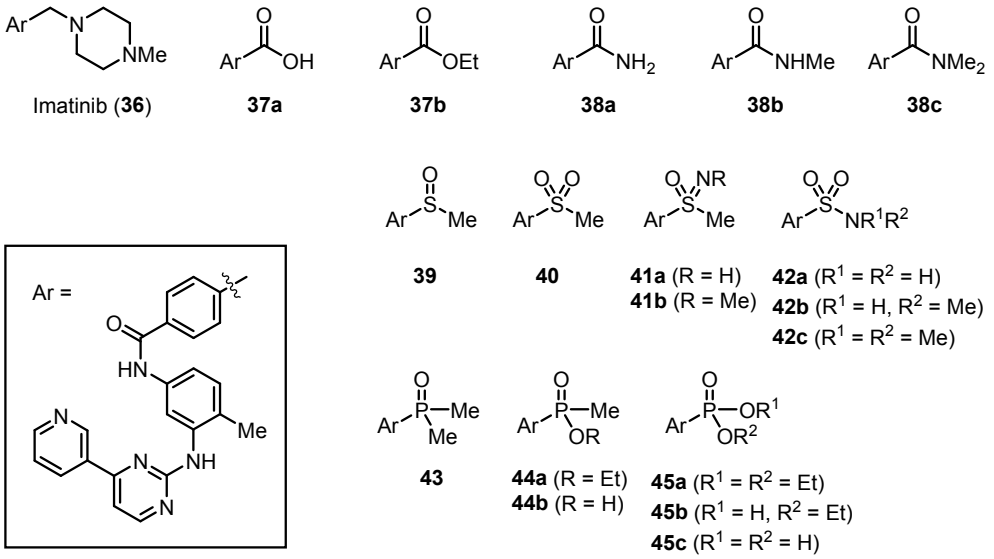
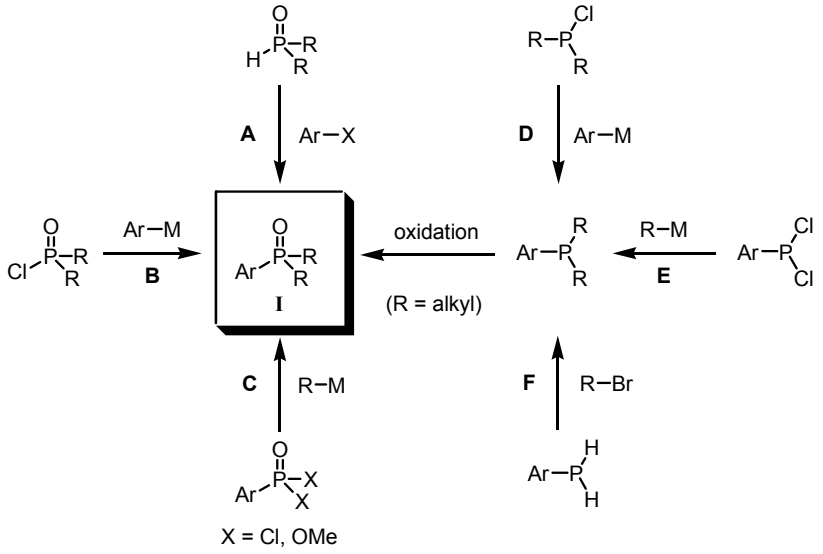


Figure 5: Design of imatinib analogs containing phosphorus-, sulfur- and carbon-based functional groups.

2.2 Chemistry. General synthesis of aryldialkylphosphine oxides and related arylphosphinates and -phosphonates. The synthesis of aryl-phosphorus compounds is well-precedented and still a thriving field of research.[34] Symmetric tertiary

aryldialkylphosphine oxides **I** can be synthesized in numerous ways, most conveniently starting from corresponding phosphorus(V) H-phosphine oxide precursors via transition metal catalyzed cross coupling methodologies (Scheme 1, A).[35] Alternatively, nucleophilic arylation of dialkylphosphinoyl chlorides[36] (Scheme 1, B) and double nucleophilic addition of organometallic species to arylphosphoryl dichlorides[37] and arylphosphonic acid esters[38] (Scheme 1, C) have been described. In addition, P(III)-precursors like dialkylphosphinyl chlorides[39] and aryldichlorophosphines are reported to react with C-nucleophiles[40] (Scheme 1, D and E), and arylphosphines can be alkylated using alkyl halides[41] (Scheme 1, F). However, when P(III) intermediates are employed, a subsequent oxidation of the intermediate tertiary phosphines to the phosphine oxides **I** is required.

Scheme 1: Synthetic pathways for the construction of aryldialkylphosphine oxides **I**.

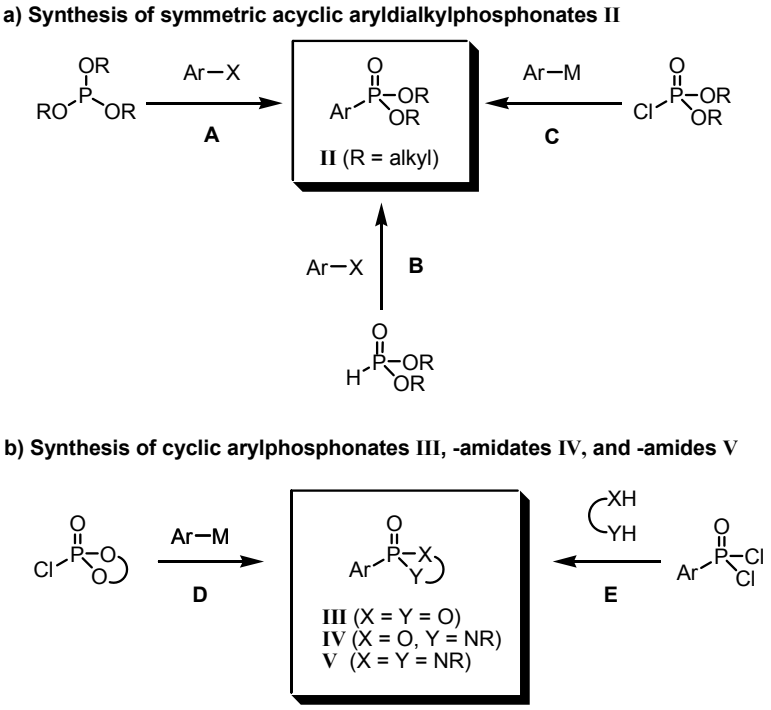


Similar to the preparation of phosphine oxides, a large number of methods exists for the synthesis of aryl phosphinates[42] and aryl phosphonates.[43] Acyclic dialkyl arylphosphonates **II** are accessed by the Arbuzov reaction between trialkylphosphites and aryl halides (Scheme 2, A). While electron-poor aryl halides can undergo direct S_NAr-type reaction with trialkylphosphites at elevated temperatures,[44] their electron-rich congeners require either radical initiators[45] or Ni-,[46] Pd-,[47] Cu-,[48] or photoredox-catalysis.[49] The Pd-catalyzed cross coupling of H-phosphonates and aryl halides was pioneered by Hirao and co-workers,[50] and is still inspiration to modern synthetic methodologies utilizing poorly activated aryl pseudohalides,[51] -amides and -esters (Scheme 2, B).[52] In addition,

H-phosphonates are capable to react with nucleophiles like arylboronic acids,[53] -sulfinates,[54] -silanes,[55] and C(aryl)-H bonds under oxidative coupling conditions.[56] C(aryl)-P bond construction via nucleophilic addition of aryl Grignard reagents to acyclic dialkyl chlorophosphates is well precedented (Scheme 2, C).[57]

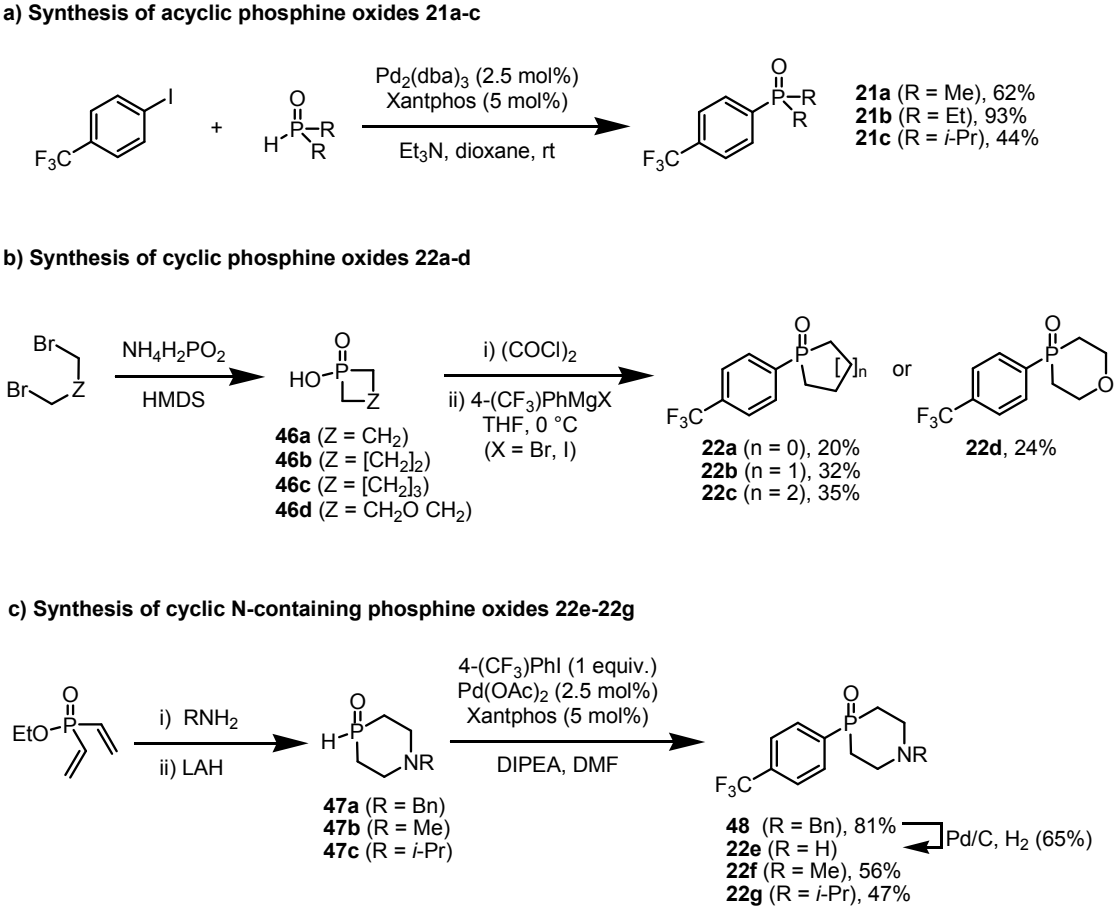
In contrast, the synthesis of cyclic alkyl arylphosphonates **III** by the reaction of a nucleophilic aryl-metal species with a corresponding cyclic chlorophosphate is rather challenging (Scheme 2, D).[58] However, cyclic alkyl arylphosphonates **III**,[59] -amidates **IV**,[60] and -amides **V**[61] are readily accessible by the reaction of arylphosphonyl dichlorides with diols, aminoalcohols, and diamines (Scheme 2, E).

Scheme 2: Synthetic pathways for the construction of a) aryldialkylphosphonates **II** and b) cyclic arylphosphonates **III**, -amidates **IV**, and -amides **V**.



Synthesis of acyclic and cyclic tertiary phosphine oxides 21 and 22. Our synthetic efforts aimed at the installation of the arene-phosphorus bond as the final step of every reaction sequence allowing an easy and modular exchange of aromatic moieties. The synthesis of tertiary acyclic phosphine oxides **21** was achieved through Pd-catalyzed coupling of 4-(trifluoromethyl)phenyl iodide with secondary phosphine oxides to deliver the desired products **21a-c** in 44-93% yield (Scheme 3a).[35c]

Scheme 3: Synthesis of a) acyclic, b) cyclic, and c) cyclic nitrogen-containing phosphine oxides.



Cyclic tertiary phosphine oxides are usually more challenging to synthesize. In view of the designed compounds **22a-g**, two distinct synthetic approaches were envisioned (Scheme 3b and 3c). The first route relies on the addition of aryl Grignard reagents to

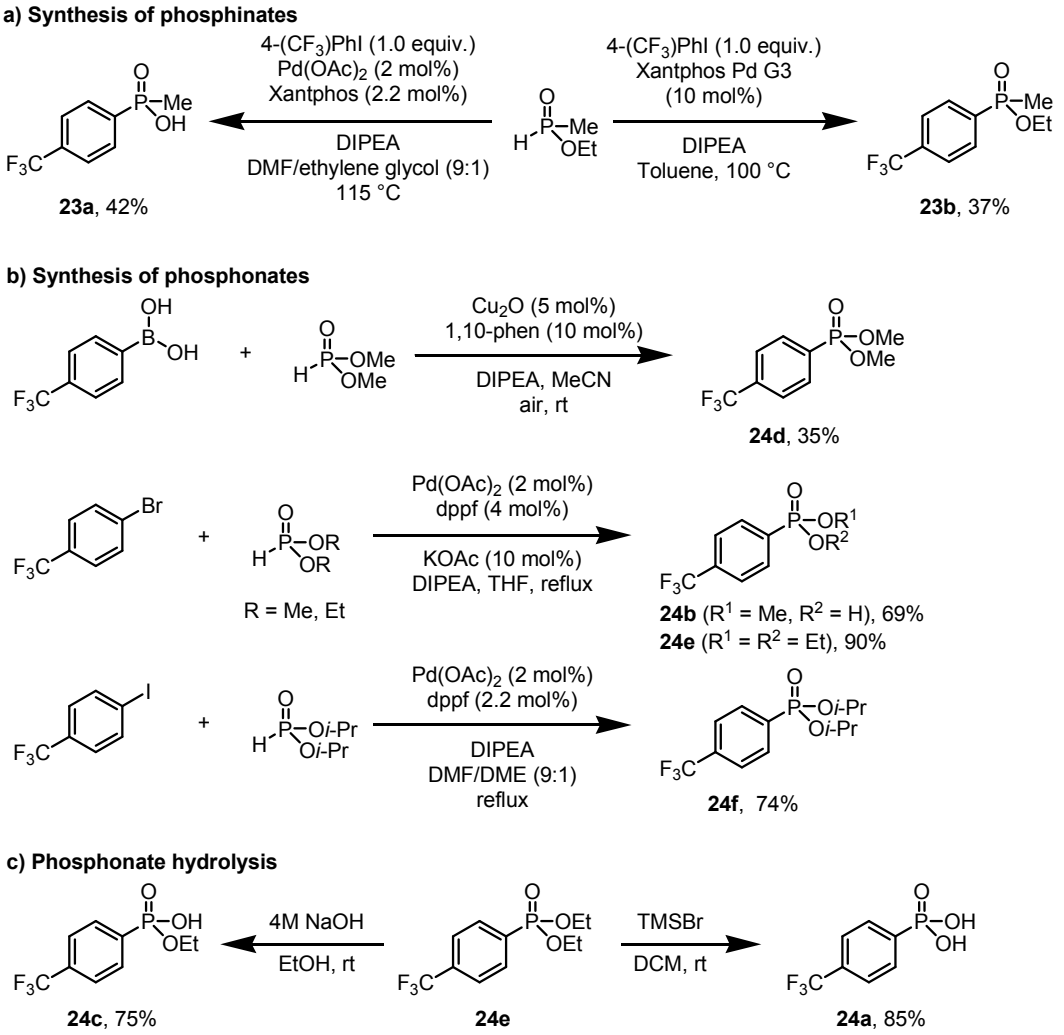
phosphinoyl chlorides derived from cyclic phosphinic acids (Scheme 3b).[62] In our case, the barely functionalized phosphinic acids **46a-d**[62b-c] were most conveniently accessed by a robust double-Arbuzov reaction of alkyldihalides with ammonium phosphinate and hexamethyldisilazane (HMDS). Activation of the phosphinic acids using oxalyl chloride gave the corresponding phosphinoyl chlorides which upon treatment with 4-(trifluoromethyl)phenylmagnesium halide[63] furnished cyclic aryl phosphine oxides **22a-d** in 20-35% yield (over 2 steps).

The second route provides nitrogen-containing cyclic phosphine oxides via Pd-mediated cross coupling of cyclic secondary phosphine oxides with aryl halides (Scheme 3c). Precursors for phosphine oxides **22e-g** were assembled by double-Michael addition of primary amines to ethyl divinylphosphinate.[64,65] Reduction of the corresponding cyclic ethyl phosphinates (structure not shown) using lithium aluminium hydride (LAH) afforded cyclic secondary phosphine oxides **47a-c**,[65b] which smoothly reacted in Pd-mediated cross coupling reactions with 4-(trifluoromethyl)phenyl iodide to give cyclic phosphine oxides **48** (and **22e** after subsequent hydrogenation), **22f** and **22g** in good yields (47-81%).

Synthesis of arylphosphinates 23 and acyclic arylphosphonates 24. Phosphinates can be synthesized by palladium-mediated cross coupling, occasionally accompanied by undesired transesterification events or base-promoted dealkylation.[42c,66] The reaction of ethyl methylphosphinate with 4-(trifluoromethyl)phenyl iodide directly delivered the phosphinic acid **23a** in 42% yield when a mixture of DMF and ethylene glycol was used as solvent, while similar conditions using toluene as solvent furnished ethyl phosphinate **23b** in 37% yield (Scheme 4a).

Dimethyl phosphonate **24d** was prepared by an Cu-catalyzed oxidative coupling of 4-(trifluoromethyl)phenylboronic acid and dimethyl phosphite in 35% yield (Scheme 4b).[53] Dialkyl phosphonates **24e** and **24f** were obtained through Pd-mediated cross coupling with 4-(trifluoromethyl)phenyl halides in 90% and 74% yield, respectively.[67,42c] However, when dimethyl phosphite was employed, the partially dealkylated methoxyphosphinic acid **24b** was obtained in 69% yield.[68] Diethyl phosphonate **24e** was selectively converted to the ethoxyphosphinic acid **24c** in 75% yield using aqueous NaOH, or to phosphonic acid **24a** in 85% yield upon treatment with trimethylsilyl bromide (Scheme 4c).[69]

Scheme 4: Synthesis of a) phosphinates **23** and b) phosphonates **24**, and c) selective hydrolysis of diethyl phosphonate **24e**.

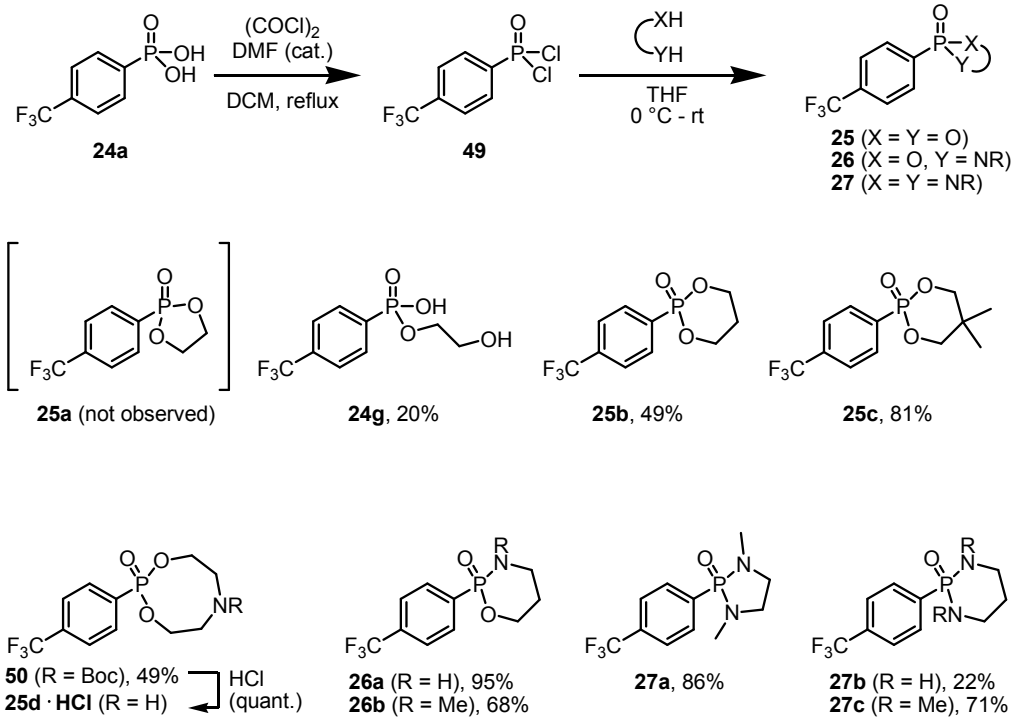


Synthesis of cyclic phosphonates 25, phosphonamidates 26, and phosphonamides 27.

For the synthesis of cyclic phosphonates **25a-d**, phosphonamidates **26a-b** and phosphonamides **27a-c**, arylphosphonic acid **24a** was converted into the corresponding

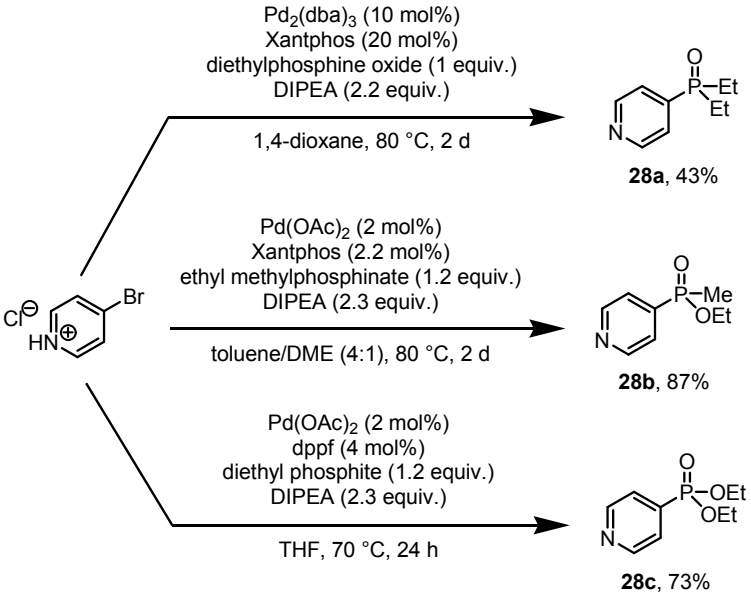
phosphonic acid dichloride **49** by treatment with oxalyl chloride, and the crude product was directly reacted with the selected diols, aminoalcohols, or diamines (Scheme 5). The attempted synthesis of arylphosphonic acid ethylene ester **25a**[38,70] however was sluggish and resulted in the isolation of hydrolyzed compound **24g** (20%) as the sole product.[71] In contrast, the dioxaphosphinane-2-ones **25b** and **25c** were obtained in good yields of 49% and 81%, respectively. Dioxazaphosphocan-2-one **50** was isolated in 49% yield and subsequent cleavage of the Boc protecting group (HCl/dioxane) afforded compound **25d** as a hydrochloride salt in quantitative yield. In the same manner, arylphosphonamidates **26a-b** and arylphosphonamides **27a-c** were prepared in 68-95% yield and 22-86%, respectively.

Scheme 5: Synthesis of cyclic phosphonates **25**, cyclic phosphonamidates **26** and -amides **27**.



Synthesis of pyridine derivatives 28a-c. Pyridine derivatives **28a-c** were synthesized by Pd-catalyzed coupling of 4-bromopyridine hydrochloride with diethylphosphine oxide, ethyl methylphosphinate or diethyl phosphite in moderate to excellent yields of up to 87% (Scheme 6).

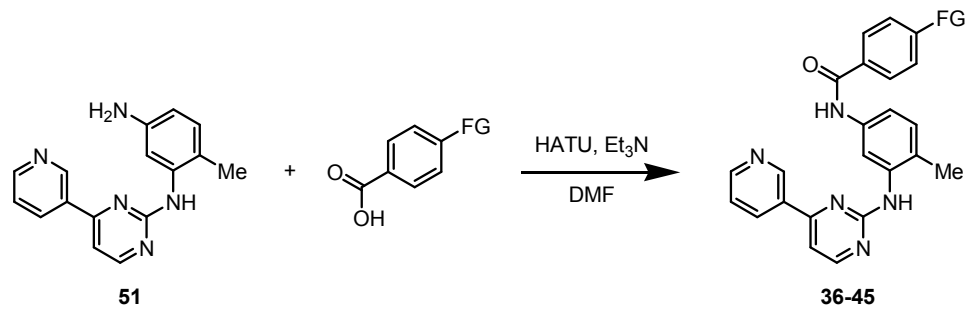
Scheme 6: Synthesis of pyridines bearing phosphorus-containing functional groups.

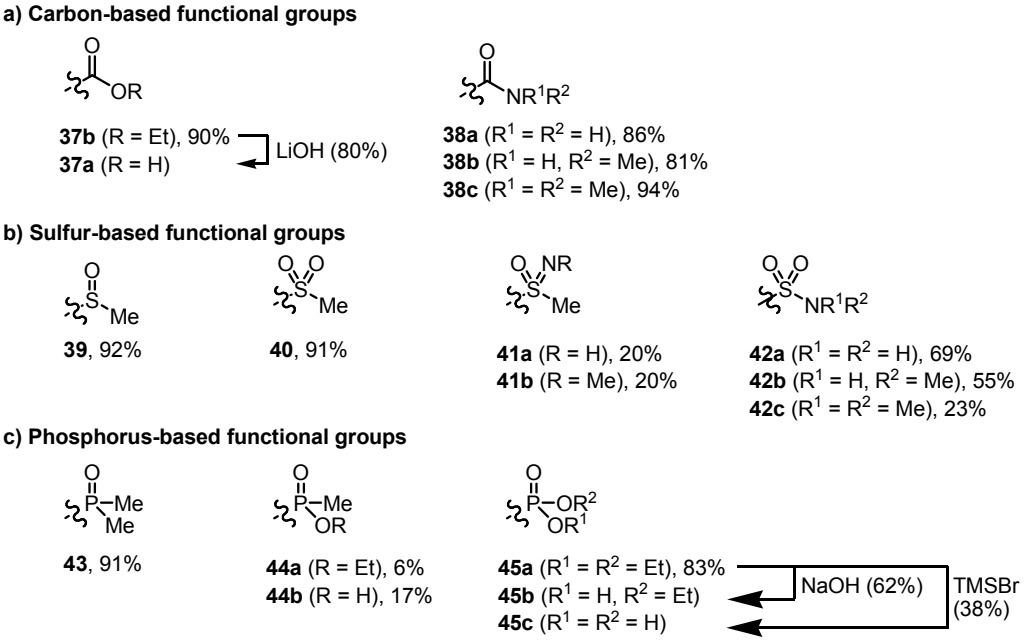


Synthesis of imatinib analogs 37-45. The imatinib analogs **37-45** were synthesized starting from a commercially available aniline building block **51**,[72] which was coupled (HATU) with the corresponding benzoic acids bearing the desired functional group (FG) in *para* position (Scheme 7). For carboxylate **37b** and carboxamides **38a-c** the coupling reactions proceeded smoothly with yields of up to 94% (Scheme 7a). However, mixed results were obtained for derivatives with sulfur containing functional groups (Scheme 7b). Sulfoxide **39** and sulfone **40**[73] were obtained in 92% and 91% yield, respectively, whereas sulfoximines **41a-b** and sulfonamides **42a-c** were isolated in lower yields of 20-

69% (conditions not optimized). Phosphine oxide analog **43**[74] was isolated in 91% yield after HATU coupling (Scheme 7c). The low yielding synthesis of ethyl phosphinate **44a** and phosphinic acid derivate **44b** is the result of an unselective hydrolysis of ethyl 4-[ethoxy(methyl)phosphoryl]benzoate and was not optimized.[75] Diethyl phosphonate **45a** was obtained in a good yield of 83%, and subsequently converted under standard conditions to the ethoxyphosphinic acid **45b** and phosphonic acid **45c** in 62% and 38% yield, respectively.

Scheme 7: Synthesis of imatinib analogs bearing a) carbon-, b) sulfur-, or c) phosphorus-based functional groups.

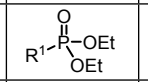
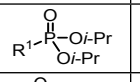
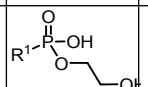
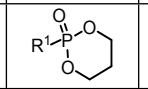
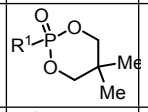
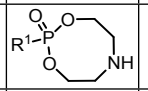
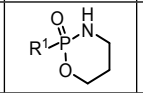
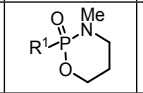
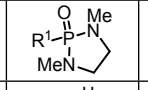
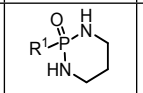
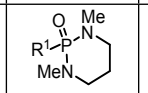
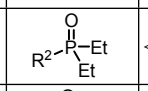
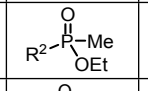
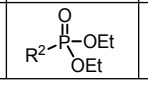




2.3 Physicochemical and *in vitro* properties of tool compounds 21-35. For all synthesized phosphorus-containing compounds the relevant physicochemical and *in vitro* pharmacokinetic parameters such as lipophilicity (logD), dissociation constants (pK_a/pK_b, where appropriate), aqueous solubility (HPLC and shake flask assay),[76] stability in human liver microsomes and Caco-2 permeability were measured (Table 1). The same set of data was also determined for the collection of compounds containing more classical functional groups (Table 2).

Table 1: Physicochemical and *in vitro* parameters of phosphorus-containing tool compounds **21**-**28**.[a]

Compound	*Structure*	*logD*		*pK_a or pK_b*	*Stability in human liver microsomes*		*Aqueous solubility (pH 6.8) [µg/mL]*		*Caco-2 permeability*		*Chemical stability: decomposition after 7 days [%]*	
		pH 2	*pH 11*		*$T_{1/2}$ [min]*	*$\%Q_H$*	*HPLC assay*	*Shake flask assay*	*$P_{A\rightarrow B}$ [10^{-6} cm/s]*	*Efflux ratio*	*pH <1*	*pH >10*
21a		1.5	1.1	n.d.	>130	<23	>52	>30,000	82	0.5	<10	<10
21b		2.3	2.0	n.d.	>130	<23	>60	22,500	88	0.7	<10	<10
21c		3.1	2.8	n.d.	>130	<23	>61	22,200	110	0.5	<10	<10
22a		1.8	1.6	n.d.	>130	<23	>53	24,500	78	0.8	<10	<10
22b		2.0	1.7	n.d.	>130	<23	>59	24,500	69	0.7	<10	<10
22c		2.4	2.0	n.d.	>130	<23	>66	7,700	49	1.1	<10	<10
22d		1.4	1.1	n.d.	>130	<23	>65	>30,000	65	0.7	<10	<10
22e		0.0	0.5	pK_b 6.9	>130	<23	>61	28,000	13	1.1	<10	<10
22f		0.0	0.9	pK_b 6.3	>130	<23	>66	>30,000	52	0.7	<10	<10
22g		0.2	2.0	pK_b 7.0	>130	<23	>68	23,000	84	0.5	<10	<10
23a		1.3	−1.3	pK_a 2.0	>130	<23	>49	>8,900[b#]	<5	-	<10	<10
23b		2.5	2.3	n.d.	>130	<23	n.v.	n.d.	69	1.0	n.d.	n.d.
24a		0.6	<−1.6	pK_{a1} <2.0 pK_{a2} 6.8	n.v.	n.v.	>54	17,800[b*]	n.v.	-	<10	<10
24b		1.3	n.v.	n.v.	>130	<23	>60	27,300[b§]	n.v.	-	<10	<10
24c		1.9	−0.8	n.v.	>130	<23	>64	28,000[b§]	10	<0.1	<10	<10
24d		2.5	2.2	n.d.	>130	<23	50	10,100	85	0.5	<10	<10

Compound	*Structure*	*logD*		*pK_a or pK_b*	*Stability in human liver microsomes*		*Aqueous solubility (pH 6.8) [µg/mL]*		*Caco-2 permeability*		*Chemical stability: decomposition after 7 days [%]*	
		pH 2	*pH 11*		*$T_{1/2}$ [min]*	*$\%Q_H$*	*HPLC assay*	*Shake flask assay*	*$P_{A\rightarrow B}$ [10^{-6} cm/s]*	*Efflux ratio*	*pH <1*	*pH >10*
24e		3.4	3.2	n.d.	>130	<23	>61	1,300	95	0.6	<10	<10
24f		4.3	4.2	n.d.	>130	<23	29	400	84	0.5	<10	<10
24g		n.v.	n.v.	n.d.	n.v.	n.v.	>63	>28,500[b$]	n.v.	-	<10	<10
25b		2.1	1.5	n.d.	>130	<23	>66	8,800	95	0.4	<10	>90[c]
25c		3.1	2.6	n.d.	>130	<23	>67	2,800	73	0.6	<10	>90[c]
25d		0.5	1.5	pK_b 6.0	>130	<23	66	>10,000	63	0.7	<10	70[d]
26a		2.0	1.3	n.v.	>130	<23	>60	n.v.	57	0.7	>90[c]	>90[c]
26b		2.5	1.9	n.d.	>130	<23	53	7,500	64	0.5	>90[c]	<10
27a		n.v.	2.0	n.d.	n.v.	n.v.	>64	>30,000	n.v.	-	>90[c]	<10
27b		n.v.	1.1	n.v.	>130	<23	>61	12,300	42	0.7	>90[c]	<10
27c		3.0	2.7	n.d.	>130	<23	>68	11,100	81	0.5	>90[c]	<10
28a		<−1.8	−1.0	pK_b <2	>130	<23	>46	11,600	19	0.6	n.d.	n.d.
28b		−1.1	−0.7	pK_b <2	>130	<23	>45	>30,000	54	0.6	n.d.	n.d.
28c		0.0	0.2	pK_b <2	>130	<23	>50	29,500	66	0.7	n.d.	n.d.

[a]R^1 = 4-(CF_3)-phenyl; R^2 = 4-pyridyl; n.d.: not determined; n.v.: no valid data; color-coding: green: desirable, yellow: acceptable, red: undesirable. [b]Buffer capacity exceeded: sample measured at #pH 5.9, *pH 2.3, §pH 2.0 and $pH 2.1. [c]Result after one day. [d]20% decomposition observed under neutral conditions.

Table 2: Physicochemical and *in vitro* parameters of bioisosteric tool compounds **29**-**35**.[a]

Compound	*Structure*	*logD*		*pK_a or pK_b*	*Stability in human liver microsomes*		*Aqueous solubility (pH 6.8) [µg/mL]*		*Caco-2 permeability*	
		pH 2	*pH 11*		*$T_{1/2}$ [min]*	*$\%Q_H$*	*HPLC assay*	*Shake flask assay*	*$P_{A\rightarrow B}$ [10^{-6} cm/s]*	*Efflux ratio*
29a		n.v.	n.v.	pK_a 3.5	>130	<23	>48	>10,000	15	1.3
29b		n.v.	n.v.	n.d.	n.v.	n.v.	<1	20	n.v.	-
29c		n.v.	n.v.	n.d.	n.v.	n.v.	7	20	n.v.	-
30a		1.5	n.v.	n.d.	n.v.	n.v.	>44	300	68	1.0
30b		1.9	1.6	n.d.	>130	<23	>51	200	56	0.9
30c		2.3	2.1	n.d.	>130	<23	>54	700	83	0.6
30d		3.8	3.7	n.d.	>130	<23	14	10	56	0.7
31a		n.v.	n.v.	pK_a 9.4	>130	<23	>48	800	83	0.6
31b		n.v.	n.v.	pK_a 10.7	>130	<23	>49	900	36	0.9
31c		3.4	n.v.	n.d.	n.v.	n.v.	47	90	n.v.	-
32		1.7	1.4	n.d.	n.v.	n.v.	>46	11,100	n.v.	-
33		n.v.	n.v.	n.d.	n.v.	n.v.	>47	300	n.v.	-
34a		0.8	0.9	pK_b 2.5	>130	<23	>50	9,100	88	0.7
34b		0.7	1.7	n.d.	>130	<23	>54	2,400	67	1.0
34c		0.1	1.8	pK_b 3.8	>130	<23	>59	4,700	84	0.7
35a		0.8	1.0	pK_b 2.4	47	45	>54	6,900	70	0.9
35b		0.7	1.8	n.d.	>130	<23	>57	1,200	81	0.5
35c		2.2	2.9	n.d.	>130	<23	49	1,200	70	0.8

[a]R^1 = 4-(CF_3)-phenyl; n.d.: not determined; n.v.: no valid data; color-coding: green: desirable, yellow: acceptable, red: undesirable.

Lipophilicity (logD). Amongst the phosphorus-containing compounds that are not ionized at physiological pH, phosphine oxides such as **21a** and **22a** are the most polar ones, exhibiting a polarity comparable to sulfoxide **32**, sulfoximine **34a** and sulfonimidamide **35a** (Figure 6).[77] As expected, the lipophilicity of phosphine oxides can be fine-tuned by the size of the aliphatic residues (**21b-c**, **22b-c**) and polarity can be increased by introduction of additional heteroatoms like in ether **22d** or amines that are considerably protonated at physiological pH, such as **22e-g**. Dialkyl phosphonates **24d-f** are about one log unit more lipophilic than their phosphine oxide congeners **21a-c**, while the cyclic phosphonate **25b** is more polar than the corresponding phosphine oxide of identical ring size **22c**. In comparison to the cyclic phosphine oxide **22c** (logD 2.0 at pH 11), the corresponding phosphonamidate **26a** and phosphonamide **27b** are more polar with logD values of 1.3 and 1.1, respectively, while the methylated analogs **26b**, **27a** and **27c** show comparable or higher lipophilicity with logD values of 1.9 - 2.7. The phosphinic and phosphonic acid derivatives **23a** and **24a** are predominantly ionized at physiological pH and represent the most polar phosphorus-containing functional groups covered by this study as indicated by their low logD values at pH 2 (1.3 and 0.6) and at pH 11 (–1.3 and <–1.6), respectively.

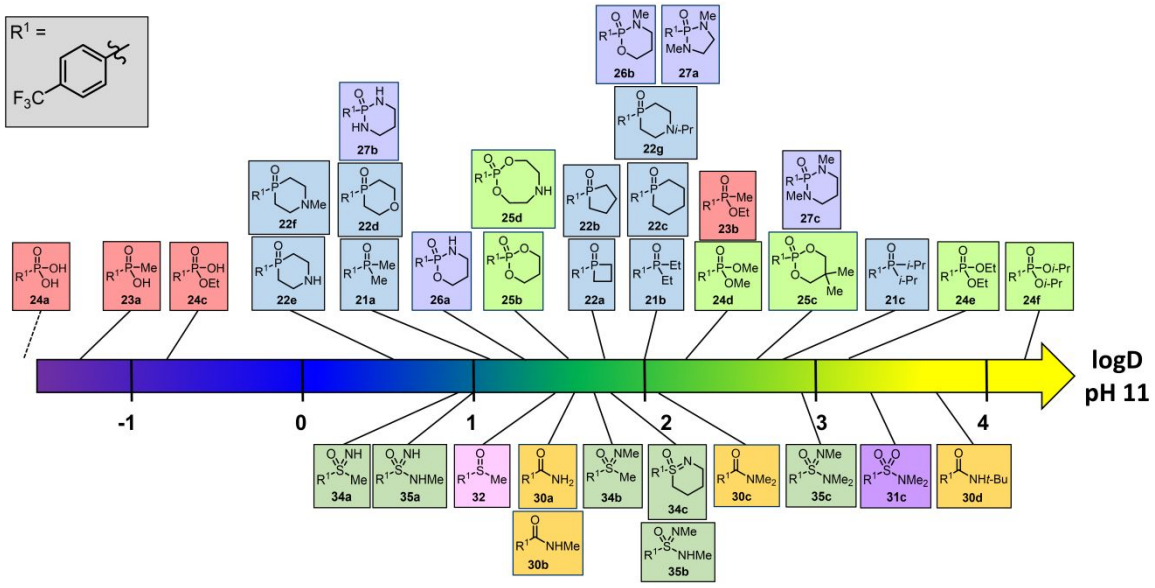


Figure 6: Graphical depiction of logD values of phosphorus-containing compounds and bioisosteres at pH 11.[77]

Dissociation constants (pK_a/pK_b). Tertiary phosphine oxides are not expected to be protonated/deprotonated at physiological pH values and were therefore not tested.[78] Derivatives containing amine functionalities such as phosphine oxides **22e-g** and phosphonate **25d** exhibit pK_b values ranging from 6.0 to 7.0, reflecting an attenuated basicity in the range between morpholine (pK_b 8.5) and thiomorpholine-1,1-dioxide (pK_b 5.4).[79] Pyridine derivatives **28a-c** bearing in 4-position a phosphine oxide (**28a**), a phosphinate (**28b**) or a phosphonate (**28c**) did not exhibit pK_a/pK_b values between 2-12. This indicates an electron-withdrawing effect of the phosphorus-containing functional groups comparable to sulfones, in line with the basicity of 4-methylsulfonyl-pyridine (pK_b <2).[80] Phosphinic acid **23a** and phosphonic acid **24a** were found to be considerably

more acidic than benzoic acid (two log units) with pK_a values of 2.0 (**23a**) and <2.0 (**24a**),[81] respectively, while the second dissociation of phosphonic acid **24a** was detected at pK_a 6.8.[82]

Aqueous solubility. Only limited conclusions can be drawn from the solubility data measured in the high-throughput HPLC assay, as most of the compounds are soluble beyond the upper detection limit of the assay (≈250 μM). The majority of the compounds measured in the shake flask solubility assay show very high aqueous solubility >10 mg/mL with up to >30 mg/mL for the most soluble compounds, such as phosphine oxides **21a**, **22d**, **22f** and phosphonamide **27a**. Only the most lipophilic derivatives, namely the dialkyl phosphonates **24e** and **24f** with logD values of 3.4 and 4.3, respectively, show more attenuated solubilities of 1.3 and 0.4 mg/mL, respectively. The phosphorus-containing compounds investigated in this study are considerably more soluble than most of the more commonly used functional groups represented by the bioisosteric tool compounds, such as esters **29b-c**, carboxamides **30a-c**, sulfonamides **31a-c** and sulfone **33**, which all have solubilities <1 mg/mL. Only the carboxylic acid **29a**, the sulfoxide **32**, the sulfoximines **34a-c** and the sulfonimidamides **35a-c** show comparably high solubilities between 1-10 mg/mL.

Metabolic stability. All phosphorus-containing compounds tested were found to be stable in human liver microsomes beyond the scope of the assay ($t_{1/2}$ > 130 min), notably also the comparatively lipophilic diethyl and diisopropyl phosphonates **24e** and **24f** with logD values of 3.4 and 4.3, respectively. This consistent dataset allows to conclude that none of these phosphorus-containing functional groups is an intrinsic metabolic weak spot.

Permeability. As expected for compounds of comparatively low molecular weight, most phosphorus-containing compounds show (very) high Caco-2 permeability, even those that are very polar (cyclic and acyclic phosphine oxides **21** and **22**) and/or contain an ionizable group (ethoxyphosphinic acid **24c**).

Chemical Stability. To assess the chemical stability of the functional groups, we studied their degradation in methanolic solution after addition of aqueous HCl (pH<1) and NH_3 (pH>10), respectively, for seven days ($MeOH/H_2O$: 15/1, for details see the supporting information). All tested phosphine oxides **21-22**, phosphinic and phosphonic acid **23a** and **24a**, alkoxyphosphinic acids **24b-c** and **24g** as well as acyclic dialkylphosphonates **24d-f** were found to be stable under both, acidic and basic conditions. Interestingly, cyclic phosphonates **25b-d** were less stable than their acyclic congeners **24d-f** and decomposed under basic conditions.[83] The cyclic NH-phosphonamidate **26a** decomposed quickly under both acidic and basic conditions, while the methylated analog **26b** is stable at pH 11. In contrast to the cyclic phosphonates **25b-d**, their aza-analogs, namely the cyclic phosphonamides **27a-c** were stable under basic conditions but decomposed under acidic conditions.

2.4 Physicochemical and *in vitro* properties of imatinib 36 and imatinib analogs 37-45.

Having evaluated the properties of phosphorus-containing functional groups in small tool compounds based on a 4-CF_3-phenyl core, we sought to investigate their effect on the

physicochemical properties of more drug-like molecules. To that end, we replaced the methylpiperazine motif in imatinib (**36**) with different functional groups (cf. Figure 5 and Scheme 7) and measured the physicochemical properties of these imatinib analogs (Table 3). In comparison to imatinib (**36**) and its analogs containing more classical functional groups like carboxylic acid **37a**, and ester **37b**, carboxamides **38**, sulfoxide **39**, sulfone **40**, sulfoximines **41** and sulfonamides **42**, the phosphorus-containing analogs **43-45** cover a larger and more polar range of polarity as can be seen from their logD values at different pH (Table 3, Figure 7).

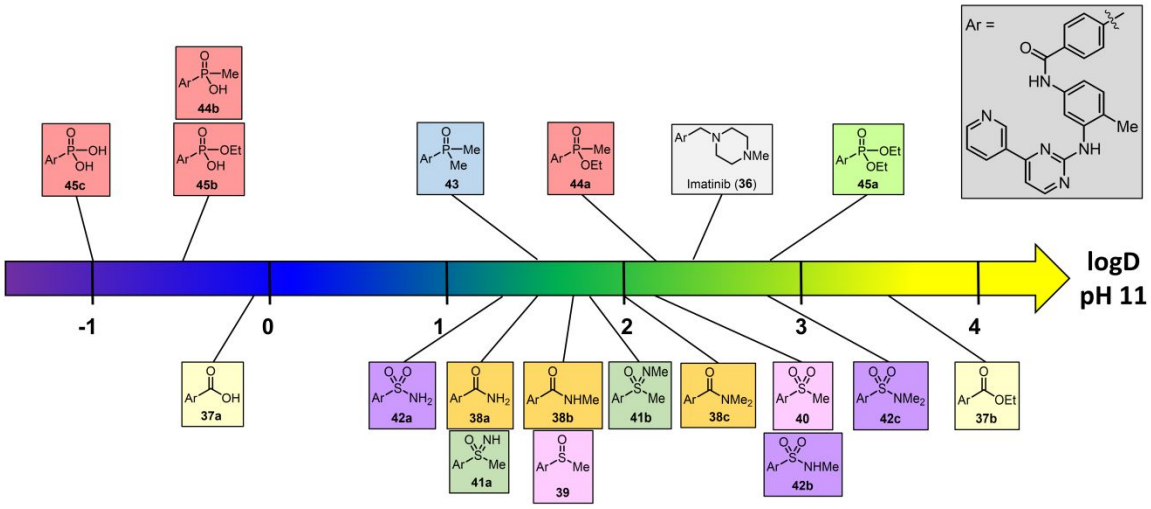
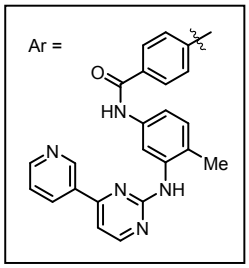
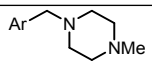


Figure 7: Graphical depiction of logD values of imatinib analogs at pH 11.

Table 3: Physicochemical and *in vitro* parameters of imatinib (**36**) and imatinib analogs **37-45**.[a,85]



Compound[85]	*Structure*	*logD (HPLC assay)*		*Stability in human liver microsomes*		*Aqueous solubility (pH 6.8) [µg/mL]*		*Caco-2 permeability*		*human PPB*
		pH 2	*pH 11*	*$T_{1/2}$ [min]*	*$\%Q_H$*	*HPLC assay*	*Shake flask assay*	*$P_{A\rightarrow B}$ [10^{-6} cm/s]*	*Efflux ratio*	*[%]*
36		−0.1	2.4	38	50	>122	2	20	1.6	96.9
37a		0.8	−0.1	>130	<23	>135	n.v.	0.1	54	94.9
37b		1.9	3.5	<5	>88	<1	n.d.	n.v.	-	n.d.
38a		0.4	1.5	117	25	<1	n.d.	3	8.1	n.d.
38b		0.5	1.7	>130	<23	<1	n.d.	8	4.9	n.d.
38c		0.7	2.0	67	37	<1	n.d.	19	2.2	n.d.
39		0.4	1.7	97	29	<1	n.d.	7	5.3	n.d.
40		0.8	2.2	78	33	<1	n.d.	18	1.1	n.d.
41a		0.2	1.5	>130	<23	1	n.d.	<5	-	85.4
41b		0.2	1.8	26	60	<1	n.d.	17	2.4	n.d.
42a		0.5	1.3	45	46	<1	n.d.	<2	-	n.d.
42b		0.9	2.2	6	87	<1	n.d.	7	4.9	n.d.
42c		1.4	2.8	<5	>89	<1	n.d.	42	0.5	n.d.
43		0.4	1.5	>130	<23	77	20	0.1	16	83.7
44a		0.9	2.2	48	45	51	n.v.	5	9.9	n.v.

Compound[85]	*Structure*	*logD (HPLC assay)*		*Stability in human liver microsomes*		*Aqueous solubility (pH 6.8) [µg/mL]*		*Caco-2 permeability*		*human PPB*
		pH 2	*pH 11*	$T_{1/2}$ *[min]*	$\%Q_H$	*HPLC assay*	*Shake flask assay*	$P_{A\rightarrow B}$ *[10^{-6} cm/s]*	*Efflux ratio*	*[%]*
44b		0.6	−0.6	>130	<23	>115	>10,000	<0.1	-	88.1
45a		1.5	2.8	17	70	1	< 1	18	1.6	98.1
45b		1.0	−0.6	>130	<23	>122	1,100	<0.1	-	95.4
45c		0.4	−1.0	>130	<23	>115	700	<0.3	-	97.9

[a]n.d.: not determined; n.v.: no valid data; color-coding: green: desirable, yellow: acceptable, red: undesirable.

It is not surprising that the increased polarity of the phosphorus-containing analogs leads to improved metabolic stability, i.e. increased half-life in human liver microsomes. In comparison to the *N*-methylpiperazine motif of imatinib ($t_{1/2}$ = 26 min), the more polar phosphorus-containing analogs like phosphine oxide **43**, phosphinic acid **44b**, ethoxy phosphinic acid **45b** and the phosphonic acid **45c** clearly show improved metabolic stability ($t_{1/2}$ >130 min). More lipophilic variants such as ethyl phosphinate **44a** and diethylphosphonate **45a** show microsomal stability comparable to that of imatinib. A marked improvement of metabolic stability can also be seen for for carboxylic acid **37a**, methylamide **38b** and sulfoximine **41a**.

Kinase inhibitors tend to exhibit poor solubility and the methylpiperazine moiety of imatinib (**36**) was incorporated to improve both solubility and oral bioavailability.[32,84] The aqueous solubility of imatinib and its analogs was first determined by an HPLC-based high-throughput assay starting from DMSO stock solution.[85] However, as the solubility of imatinib (**36**) (>122 µg/mL) and several analogs was beyond the scope of this assay, we decided to analyze and compare the data from a shake-flask assay, which uses solid material and is not restricted by an upper limit for quantification of high solubilities. In the shake flask assay, imatinib (**36**) showed poor solubility of only 2 µg/mL, however, this strong discrepancy in comparison to the HPLC assay is likely due to the high crystallinity of the applied material. Amongst the classical functional groups tested only carboxylic acid **37a** led to a similarly high solubility (HPLC assay), but at the cost of very poor Caco-2 permeability. All other compounds with more classical functional groups (**37b**, **38-42**) showed very poor solubility.

Amongst the uncharged phosphorus-containing analogs, lipophilic diethyl phosphonate **45a** showed poor solubility while phosphine oxide **43** and ethyl phosphinate **44a** were moderately more soluble. In striking contrast, phosphinic acid **44b**, ethoxyphosphinic acid

45b and phosphonic acid 45c (i.e. those phosphorus-containing analogs that are ionized at physiological pH), exhibited a very high solubility up to >10 mg/mL.

Some of the highly polar phosphorus-containing analogs still show moderate or even high Caco-2 permeability, such as ethyl phosphinate 44a and diethyl phosphonate 45a. Notably, the former represents an optimal compromise of polarity and acceptable microsomal stability, solubility and permeability.

In comparison to methylpiperazine imatinib (36) and its carboxylic acid analog 37a, which both show high binding to human plasma protein (hPPB) of 96.9% and 94.9%, the corresponding phosphine oxide 43 and sulfoximine 41a have a reduced hPPB of 83.7% and 85.4%, respectively. Interestingly, phosphinic acid 44b exhibits a comparatively low hPPB of 88.1%, while diethyl phosphonate 45a, ethoxyphosphinic acid 45b and phosphonic acid 45c show a high hPPB between 95.4% and 98.1%.

Although it was beyond the scope of this study on the properties of phosphorus-containing functional groups, all imatinib analogs 37-45 were tested towards their inhibition of PDGFRβ, ABL1, LCK and KIT and found to show no or significantly reduced activity (see Table S2 in the supporting information for details).

3. CONCLUSION

In conclusion, a series of phosphorus-containing tool compounds comprising phosphine oxides, phosphonates, phosphinates, phosphonamidates and phosphonamides were synthesized and their physicochemical properties (logD, dissociation constant, aqueous solubility, chemical stability) and behavior in selected *in vitro* assays (microsomal stability, Caco-2 permeability) were explored. The impact of these functional groups on the scaffold of a real drug molecule was further evaluated in a series of phosphorus-containing analogs of imatinib.

As a rule of thumb for the lipophilicity of uncharged phosphorus-containing functional groups, phosphine oxides exhibit the highest polarity in a comparable range to sulfoxides and sulfoximines. They are more polar than dialkyl phosphonates and classical functional groups such as amides or sulfonamides. Phosphinic and phosphonic acids, which were found to be significantly more acidic than benzoic acid (two log units), are predominantly ionized at physiological pH and represent the most polar functional groups within this study.[86]

Reflecting their high polarity, phosphine oxides and the other phosphorus-containing functional groups exhibited very high aqueous solubility and were found to be stable in human liver microsomes without revealing a metabolically weak spot. As expected for compounds of comparable low molecular weight, high permeability was found even for the most polar and some ionized phosphorus-containing tool compounds.

Phosphine oxides, acyclic dialkyl phosphonates as well as phosphinic and phosphonic acids were found to be stable under both acidic and basic conditions, while cyclic phosphonates, phosphonamidates and phosphonamides showed reduced stability under either acidic or basic conditions.

Our analysis of the phosphorus-containing analogs of imatinib showed that also on a real drug scaffold the high polarity of the tested phosphorus-containing functional groups can lead to improved metabolic stability and aqueous solubility. However, this comes at the cost of reduced permeability, and only ethyl phosphinate **44a** represents a compromise between cell permeability and polarity.

In summary, the results from our study demonstrate that phosphine oxides and related phosphorus-containing functional groups are valuable polar structural elements without

principal flaws, at least as long as a reduced permeability is acceptable. They deserve to be considered as a routine part of every medicinal chemist's toolbox and to be employed in medicinal chemistry just like other more commonly used functional groups.

4. EXPERIMENTAL SECTION

General Information. All commercially available chemicals were used as received from their commercial supplier. Anhydrous solvents were either purchased or prepared according to standard procedures[87] and stored over molecular sieves under argon. Unless stated otherwise, all reactions were carried out using Schlenk technique under argon atmosphere. Flash column chromatography was performed on Biotage® SNAP KP-Sil cartridges (50 μm silica particle) using a Biotage Isolera Four system. Thin layer chromatography was performed with TLC Silica gel 60 F_{254} glass plates and products were visualized by either UV detection (254 nm) or a basic aqueous solution of potassium permanganate. Nuclear magnetic resonance (NMR) spectra were recorded at room temperature on a Bruker Avance 400 or Bruker Avance 600 spectrometer with

tetramethylsilane as an internal reference. Chemical shifts δ are reported in parts per million (ppm). ^{1}H NMR spectra were referenced to the residual partially non-deuterated solvent signal of $CHCl_3$ (δ = 7.27 ppm) or DMSO (δ = 2.50 ppm). ^{13}C NMR spectra were referenced to the deuterated solvent signal of $CDCl_3$ (δ = 77.00 ppm) or DMSO-d_6 (δ = 39.51 ppm). ^{19}F NMR and ^{31}P NMR spectra are referenced according to the unified chemical shift scale as recommended by the IUPAC.[88] Collection of ^{13}C, ^{19}F and ^{31}P NMR data was done with complete ^{1}H decoupling. Coupling constants J are reported in Hz, and splitting patterns are described as br = broad, s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet. Infrared spectra were recorded on a Thermo Nicolet iS10 FT-IR Spectrometer using attenuated total reflectance (ATR) technique. Wave numbers of absorptions are reported in cm^{-1}. Low resolution mass spectra were recorded on a Waters ZQ or Waters Acquity QDa, and high-resolution mass spectra were recorded on a Thermo Scientific LTQ Orbitrap XL or Waters Synapt G2-Si spectrometer using electrospray ionization in positive ion mode (ESI^+). Unless specified otherwise, the purity of all final compounds was determined to be ≥95% by ^{1}H NMR.

Dimethyl(4-(trifluormethyl)phenyl)phosphine oxide (21a). A solution of $Pd_2(dba)_3$ (45.8 mg, 50.0 µmol, 2.5 mol%) and Xantphos (57.9 mg, 100 µmol, 5.0 mol%) in 1,4-dioxane (1.00 mL) is stirred at rt for 5 min and then added to a solution of 4-(trifluoromethyl)phenyl iodide (544 mg, 2.00 mmol, 1.0 equiv.), dimethylphosphine oxide (208 mg, 2.40 mmol, 1.2 equiv.) and Et_3N (335 µL, 2.40 mmol, 1.2 equiv.) in 1,4-dioxane (4.00 mL). The reaction mixture is stirred at rt for 6 h. The reaction mixture is diluted with saturated aqueous $NaHCO_3$ (40 mL) and the aqueous phase is extracted with DCM (3 x 25 mL). The combined organic phases are dried over $MgSO_4$ and concentrated. The residue is purified by flash chromatography on silica gel (gradient of MeOH in DCM; 2% – 20% MeOH) to give 276 mg (62%) of the title compound as a white solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 7.97 – 8.05 (m, 2H), 7.86 – 7.92 (m, 2H), 1.70 (d, J = 13.5 Hz, 6H) ppm. ^{13}C NMR (DMSO-d_6, 101 MHz) δ = 141.0 (br d, J = 91 Hz), 131.0 – 131.9 (m), 130.7 (d, J = 10 Hz), 124.8 – 125.4 (m), 123.8 (q, J = 273 Hz), 17.5 (d, J = 71 Hz) ppm. ^{19}F NMR (DMSO-d_6, 565 MHz): δ = −61.57 ppm. ^{31}P NMR (DMSO-d_6, 162 MHz): δ = 32.42 ppm. IR (ATR): 2976, 2906, 1400, 1325, 1298, 1177, 1165, 1134, 1103, 1061, 942,

826, 721 cm^{-1}. HRMS (ESI^+) calculated for $C_9H_{11}F_3OP$ $[M+H]^+$ m/z 223.0494, found 223.0499.

Diethyl(4-(trifluormethyl)phenyl)phosphine oxide (21b). A solution of $Pd_2(dba)_3$ (45.8 mg, 50.0 µmol, 2.5 mol%) and Xantphos (57.9 mg, 100 µmol, 5.0 mol%) in 1,4-dioxane (1.00 mL) is stirred at rt for 5 min and then added to a solution of 4-(trifluoromethyl)phenyl iodide (544 mg, 2.00 mmol, 1.0 equiv.), diethylphosphine oxide (255 mg, 2.40 mmol, 1.2 equiv.) and Et_3N (335 µL, 2.40 mmol, 1.2 equiv.) in 1,4-dioxane (4.00 mL). The reaction mixture is stirred at rt for 20 h. The reaction mixture is diluted with saturated aqueous $NaHCO_3$ (40 mL), and the aqueous phase is extracted with DCM (3 x 25 mL). The combined organic phases are dried over $MgSO_4$ and concentrated. The residue is purified by flash chromatography on silica gel (gradient of MeOH in DCM; 2% – 20% MeOH) to give 465 mg (93%) of the title compound as a brown solid. ^1H NMR (DMSO-d_6, 400 MHz): δ = 7.92 – 8.00 (m, 2H), 7.86 – 7.92 (m, 2H), 1.86 – 2.09 (m, 4H), 0.93 (dt, J = 16.9, 7.7 Hz, 6H) ppm. ^{13}C NMR (DMSO-d_6, 101 MHz): δ = 137.9 (br d, J = 85 Hz), 131.6 (d, J = 9 Hz), 130.8 – 131.8 (m), 124.9 – 125.3 (m), 123.8 (q, J = 272 Hz), 21.3 (d, J = 69 Hz), 5.2 (d, J = 6 Hz) ppm. ^{19}F NMR (DMSO-d_6, 565 MHz) δ

= −61.6 ppm. ^{31}P NMR (DMSO-d_6, 162 MHz) δ = 42.1 ppm. IR (ATR): 2972, 2943, 1400, 1326, 1315, 1167, 1100, 1060, 840, 774, 706 cm^{-1}. HRMS (ESI$^+$) calculated for $C_{11}H_{15}F_3OP$ $[M+H]^+$ m/z 251.0807, found 251.0810.

Diisopropyl(4-(trifluormethyl)phenyl)phosphine oxide (21c). A solution of $Pd_2(dba)_3$ (45.8 mg, 50.0 µmol, 2.5 mol%) and Xantphos (57.9 mg, 100 µmol, 5.0 mol%) in 1,4-dioxane (1.00 mL) is stirred at rt for 5 min and then added to a solution of 4-(trifluoromethyl)phenyl iodide (544 mg, 2.00 mmol, 1.0 equiv.), diisopropylphosphine oxide (322 mg, 2.40 mmol, 1.2 equiv.) and Et_3N (335 µL, 2.40 mmol, 1.2 equiv.) in 1,4-dioxane (7.00 mL). The reaction mixture is stirred at rt for 2 d. The reaction mixture is filtered over a plug of celite, and the filter cake is washed with EtOAc (60 mL). The combined organic filtrates are washed with saturated aqueous $NaHCO_3$ (40 mL) and brine (40 mL), dried over $MgSO_4$ and concentrated. The residue is repeatedly purified by flash chromatography on silica gel (gradient of MeOH in DCM; 2% – 20% MeOH, and gradient of MeOH in EtOAc; 2% – 20% MeOH) to give 247 mg (44%) of the title compound as a colorless solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 7.87 – 7.96 (m, 4H), 2.34 – 2.48 (m, 2H), 1.07 (dd, *J* = 14.9, 7.1 Hz, 6H), 0.90 (dd, *J* = 15.9, 7.1 Hz, 6H) ppm. ^{13}C NMR

(DMSO-d_6, 101 MHz): δ = 135.5 (d, *J* = 79 Hz), 132.3 (d, *J* = 8 Hz), 130.7 – 131.9 (m), 124.7 – 125.1 (m), 123.8 (q, *J* = 273 Hz), 24.3 (d, *J* = 67 Hz), 15.8 (d, *J* = 2 Hz), 14.7 (d, *J* = 3 Hz) ppm. ^{19}F NMR (DMSO-d_6, 565 MHz): δ = −61.5 ppm. ^{31}P NMR (DMSO-d_6, 162 MHz): δ = 49.7 ppm. IR (ATR): 2959, 2925, 2870, 1330, 1322, 1175, 1156, 1122, 1102, 1062, 1017, 839, 713, 690 cm^{-1}. HRMS (ESI$^+$) calculated for $C_{13}H_{19}F_3OP$ $[M+H]^+$ m/z 279.1120, found 279.1123.

1-[4-(Trifluoromethyl)phenyl]-1λ^5-phosphetan-1-one (22a). Oxalyl chloride (609 µL, 7.20 mmol, 3.0 equiv.) is added dropwise at 0 °C to a solution of 1-hydroxy-1λ^5-phosphetan-1-one (**46a**)[62b,c] (255 mg, 2.40 mmol, 1.0 equiv.) in anhydrous DCM (12.0 mL). The ice-bath is removed, and the reaction mixture is stirred at rt for 1 h. The reaction mixture is concentrated to dryness, and the residue is dissolved in THF (12.0 mL). The solution is cooled to 0 °C, before a freshly prepared solution of 4-trifluoromethylphenylmagnesium bromide[63] (0.5 M in THF; 5.04 mL, 2.52 mmol, 1.05 equiv.) is added dropwise. The reaction mixture is allowed to warm to rt overnight and treated with saturated aqueous NH_4Cl (40 mL). The aqueous phase is extracted with EtOAc (3 x 75 mL), and the combined organic phases are dried over Na_2SO_4 and

concentrated. The residue is repeatedly purified by preparative RP-HPLC (Waters SunFire™ C_{18}, gradient of acetonitrile in water, 0.1% TFA) and flash chromatography on silica gel (gradient of MeOH in DCM; 0% – 5% MeOH) to give 112 mg (20%) of the title compound as a colorless solid. R_f (DCM:MeOH, 10:1) = 0.77. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 8.06 – 8.13 (m, 2H), 7.90 – 7.95 (m, 2H), 2.70 – 2.85 (m, 4H), 1.97 – 2.22 (m, 1H), 1.49 – 1.65 (m, 1H) ppm. ^{13}C NMR (DMSO-d_6, 101 MHz) δ = 138.9 (d, J = 71 Hz), 131.0 – 132.2 (m), 130.6 (d, J = 11 Hz), 125.3 – 125.9 (m), 123.8 (q, J = 272 Hz), 34.7 (d, J = 55 Hz), 8.3 (d, J = 22 Hz) ppm. ^{31}P NMR (DMSO-d_6, 162 MHz): δ = 38.4 ppm. IR (ATR): 1395, 1321, 1221, 1120, 1108, 1059, 931, 906, 848, 754, 713 cm^{-1}. HRMS (ESI$^+$) calculated for $C_{10}H_{11}F_3OP$ $[M+H]^+$ m/z 235.0494, found 235.0493.

1-[4-(Trifluoromethyl)phenyl]-1λ^5-phospholan-1-one (22b). Oxalyl chloride (508 µL, 6.00 mmol, 3.0 equiv.) is added dropwise at 0 °C to a solution of 1-hydroxy-1λ^5-phospholan-1-one (**46b**)[62b,c] (240 mg, 2.00 mmol, 1.0 equiv.) in anhydrous DCM (10.0 mL). The ice-bath is removed, and the reaction mixture is allowed to stir at rt for 1 h. The reaction mixture is concentrated to dryness, and the residue is dissolved in THF (10.0 mL). The solution is cooled to 0 °C, before a freshly prepared solution of

4-trifluoromethylphenylmagnesium halide[63] (0.5 M in THF; 4.20 mL, 2.10 mmol, 1.05 equiv.) is added dropwise. The reaction mixture is allowed to warm to rt overnight and treated with saturated aqueous NH_4Cl (20 mL). The aqueous phase is extracted with EtOAc (3 x 30 mL), and the combined organic phases are dried over Na_2SO_4 and concentrated. The residue is repeatedly purified by preparative RP-HPLC (Waters SunFire™ C_{18}, gradient of acetonitrile in water, 0.1% TFA) and flash chromatography on silica gel (gradient of MeOH in DCM; 2% – 5%) to give 172 mg (35%) of the title compound as a colorless solid. R_f (DCM:MeOH, 10:1) = 0.80. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 7.95 – 8.02 (m, 2H), 7.87 – 7.91 (m, 2H), 1.97 – 2.11 (m, 4H), 1.81 – 1.97 (m, 4H) ppm. ^{13}C NMR (DMSO-d_6, 101 MHz) δ = 140.1 (br d, J = 83 Hz), 131.3 – 131.6 (m), 131.0 (d, J = 10 Hz), 124.9 – 125.5 (m), 123.8 (q, J = 273 Hz), 28.8 (d, J = 68 Hz), 24.5 (d, J = 8 Hz) ppm. ^{31}P NMR (DMSO-d_6, 162 MHz): δ = 57.7 ppm. IR (ATR): 2966, 1322, 1177, 1163, 1125, 1104, 1060, 1010, 842, 718, 707 cm^{-1}. HRMS (ESI$^+$) calculated for $C_{11}H_{13}F_3OP$ $[M+H]^+$ m/z 249.0651, found 249.0650.

1-[4-(Trifluoromethyl)phenyl]-1λ^5-phosphinan-1-one (22c). Oxalyl chloride (169 µL, 2.00 mmol, 2.0 equiv.) is added dropwise at 0 °C to a solution of 1-hydroxy-1λ^5-

phosphinan-1-one (**46c**)[62c] (134 mg, 1.00 mmol, 1.0 equiv.) in anhydrous DCM (5.00 mL). The ice-bath is removed, and the reaction mixture is allowed to stir at rt for 1 h. The reaction mixture is concentrated to dryness, and the residue is dissolved in THF (5.00 mL). The solution is cooled to 0 °C, before a freshly prepared solution of 4-trifluoromethylphenylmagnesium halide[63] (1.0 M in THF; 1.20 mL, 1.20 mmol, 1.2 equiv.) is added dropwise. The reaction mixture is allowed to warm to rt overnight and treated with of saturated aqueous NH_4Cl (20 mL). The aqueous phase is extracted with EtOAc (3 x 30 mL), and the combined organic phases are dried over Na_2SO_4 and concentrated. The residue is repeatedly purified by preparative RP-HPLC (Waters SunFire™ C_{18}, gradient of acetonitrile in water, 0.1% TFA) and flash chromatography on silica gel (gradient of MeOH in DCM; 0% – 7% MeOH) to give 82.5 mg (32%) of the title compound as a colorless solid. R_f (DCM:MeOH, 10:1) = 0.55. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.86 – 7.94 (m, 2H), 7.73 – 7.78 (m, 2H), 1.78 – 2.23 (m, 9H), 1.45 – 1.57 (m, 1H) ppm. ^{13}C NMR ($CDCl_3$, 101 MHz) δ = 137.7 (br d, J = 91 Hz), 133.6 (br d, J = 35 Hz), 130.6 (d, J = 9 Hz), 125.2 – 125.7 (m), 123.5 (q, J = 273 Hz), 28.3 (d, J = 65 Hz), 26.6 (d, J = 7 Hz), 21.9 (d, J = 6 Hz) ppm. ^{31}P NMR ($CDCl_3$, 162 MHz): δ = 32.0 ppm. IR (ATR):

2934, 1324, 1168, 1157, 1126, 1061, 1017, 937, 850, 813, 804, 713, 691, 681 cm^{-1}. HRMS (ESI^+) calculated for $C_{12}H_{15}F_3OP$ $[M+H]^+$ m/z 263.0807, found 263.0811.

4-[4-(Trifluoromethyl)phenyl]-1,4λ^5-oxaphosphinan-4-one (22d). Oxalyl chloride (169 µL, 2.00 mmol, 2.0 equiv.) is added dropwise at 0 °C to a solution of 4-hydroxy-1,4λ^5-oxaphosphinan-4-one (**46d**)[62b] (136 mg, 1.00 mmol, 1.0 equiv.) in anhydrous DCM (5.00 mL). The ice-bath is removed, and the reaction mixture is allowed to stir at rt for 1 h. The reaction mixture is concentrated to dryness, and the residue is dissolved in THF (5.00 mL). The solution is cooled to 0 °C, before a freshly prepared solution of 4-trifluoromethylphenylmagnesium halide[63] (0.5 M in THF; 2.00 mL, 1.00 mmol, 1 equiv.) is added dropwise. The reaction mixture is allowed to warm to rt overnight and treated with saturated aqueous NH_4Cl (40 mL). The aqueous phase is extracted with EtOAc (3 x 20 mL) and the combined organic phases are dried over Na_2SO_4 and concentrated. The residue is repeatedly purified by flash chromatography on silica gel (gradient of MeOH in DCM; 0% – 5% MeOH) and preparative RP-HPLC (Waters XBridge™ C_{18}, gradient of acetonitrile in water, 0.1% TFA) to give 64.1 mg (24%) of the title compound as a colorless solid. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.89 – 7.96 (m, 2H), 7.77 – 7.82 (m,

2H), 4.10 – 4.27 (m, 4H), 2.22 – 2.33 (m, 2H), 2.01 – 2.13 (m, 2H) ppm. ^{13}C NMR ($CDCl_3$, 101 MHz) δ = 136.5 (br d, *J* = 95 Hz), 133.2 – 134.6 (m), 130.8 (d, *J* = 9 Hz), 125.6 – 126.0 (m), 123.4 (q, *J* = 273 Hz), 64.6 (d, *J* = 8 Hz), 29.6 (d, *J* = 65 Hz) ppm. ^{31}P NMR ($CDCl_3$, 162 MHz): δ = 25.1 ppm. IR (ATR): 2861, 1329, 1318, 1199, 1166, 1159, 1156, 1126, 1104, 1085, 1062, 1017, 809, 720 cm^{-1}. HRMS (ESI^+) calculated for $C_{11}H_{13}F_3O_2P$ $[M+H]^+$ m/z 265.0600, found 265.0605.

4-[4-(Trifluoromethyl)phenyl]-1,4λ^5-azaphosphinan-4-one (22e). A suspension of 1-benzyl-4-[4-(trifluoromethyl)phenyl]-1,4λ^5-azaphosphinan-4-one (**48**) (282 mg, 0.800 mmol, 1.0 equiv.) and Pd/C (10% Pd; 16.8 mg, 2.0 mol %) in EtOH (4.00 mL) is stirred under an atmosphere of H_2 (60 psi) at 50 °C for 24 h. The reaction mixture is filtered, and the filtrate is concentrated. The residue is purified by preparative RP-HPLC (Waters XBridge™ Phenyl, gradient of acetonitrile in water, 0.1% NH_4OH) to give 136 mg (65%) of the title compound as a colorless solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.88 – 7.95 (m, 2H), 7.75 – 7.79 (m, 2H), 3.36 – 3.47 (m, 2H), 3.18 – 3.32 (m, 2H), 2.00 – 2.18 (m, 4H) ppm. ^{13}C NMR ($CDCl_3$, 101 MHz) δ = 137.2 (br d, *J* = 93 Hz), 133.4 – 134.5 (m), 130.7 (d, *J* = 10 Hz), 125.4 – 125.9 (m), 123.5 (q, *J* = 273 Hz), 42.8 (d, *J* = 7 Hz), 29.9 (d,

J = 65 Hz) ppm. ^{31}P NMR ($CDCl_3$, 162 MHz): δ = 28.7 ppm. IR (ATR): 3274, 1399, 1323, 1156, 1140, 1104, 1060, 1013, 947, 808, 717 cm^{-1}. HRMS (ESI^+) calculated for $C_{11}H_{14}F_3NOP$ $[M+H]^+$ m/z 264.0760, found 264.0765.

1-Methyl-4-[4-(trifluoromethyl)phenyl]-1,4λ^5-azaphosphinan-4-one (22f). 4-(Trifluoromethyl)phenyl iodide (272 mg, 1.00 mmol, 1.0 equiv.) is added to a solution of $Pd_2(dba)_3$ (11.4 mg, 12.5 µmol, 2.5 mol%), Xantphos (14.5 mg, 25.0 µmol, 5.0 mol%), and 1-methyl-1,4λ^5-azaphosphinan-4-one (**47b**) (9.9 mg, 600 µmol, 1.2 equiv.) in DIPEA (128 µL, 750 µmol, 1.5 equiv.) and DMF (2.00 mL). The reaction mixture is sealed in a microwave vial and heated at 80 °C for 3 d. The reaction mixture is filtered and directly purified by preparative RP-HPLC (Waters XBridge^{TM} C_{18}, gradient of acetonitrile in water, 0.1% NH_4OH) to give 78.0 mg (56%) of the title compound as light-yellow oil. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 8.00 – 8.09 (m, 2H), 7.87 – 7.93 (m, 2H), 2.65 – 2.83 (m, 4H), 2.23 – 2.34 (m, 5H), 1.89 – 2.02 (m, 2H) ppm. ^{13}C NMR (DMSO-d_6, 101 MHz) δ = 138.1 (br d, *J* = 91 Hz), 131.4 – 132.2 (m), 131.3 (d, *J* = 10 Hz), 125.2 – 125.8 (m), 123.7 (q, *J* = 272 Hz), 51.0 (d, *J* = 7 Hz), 45.7, 27.1 (d, *J* = 66 Hz) ppm. ^{31}P NMR (DMSO-d_6, 162 MHz): δ = 26.1 ppm. IR (ATR): 2790, 1322, 1254, 1170, 1156, 1128, 1105, 1062, 1013,

922, 812, 721, 605 cm^{-1}. HRMS (ESI^+) calculated for $C_{12}H_{16}F_3NOP$ $[M+H]^+$ m/z 278.0916, found 278.0922.

1-Isopropyl-4-[4-(trifluoromethyl)phenyl]-1,4λ^5-azaphosphinan-4-one (22g). 4-(Trifluoromethyl)phenyl iodide (272 mg, 1.00 mmol, 1.0 equiv.) is added to a solution of $Pd_2(dba)_3$ (11.4 mg, 12.5 µmol, 2.5 mol%), Xantphos (14.5 mg, 25.0 µmol, 5.0 mol%), and 1-isopropyl-1,4λ^5-azaphosphinan-4-one (**47c**) (79.9 mg, 600 µmol, 1.2 equiv.) in DIPEA (128 µL, 750 µmol, 1.5 equiv.) and DMF (2.00 mL). The reaction mixture is sealed in a microwave vial and heated at 80 °C for 3 d. The reaction mixture is filtered and directly purified by preparative RP-HPLC (Waters XBridge™ C_{18}, gradient of acetonitrile in water, 0.1% NH_4OH) to give 72.0 mg (47%) of the title compound as a colorless solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 7.99 – 8.08 (m, 2H), 7.87 – 7.92 (m, 2H), 2.75 – 2.95 (m, 5H), 2.15 – 2.27 (m, 2H), 1.87 – 2.00 (m, 2H), 0.98 (d, *J* = 6.6 Hz, 6H) ppm. ^{13}C NMR (DMSO-d_6, 101 MHz) δ = 138.3 (br d, *J* = 90 Hz), 131.4 – 131.8 (m), 131.3 (d, *J* = 9 Hz), 125.2 – 125.6 (m), 123.7 (q, *J* = 273 Hz), 54.3, 44.5 (d, *J* = 7 Hz), 28.2 (d, *J* = 66 Hz), 17.9 ppm. ^{31}P NMR (DMSO-d_6, 162 MHz): δ = 28.3 ppm. IR (ATR): 2968, 2814, 1330, 1318, 1257,

1205, 1160, 1127, 1104, 1062, 1015, 922, 816, 720, 699 cm^{-1}. HRMS (ESI^+) calculated for $C_{14}H_{20}F_3NOP$ $[M+H]^+$ m/z 306.1229, found 306.1234.

Methyl(4-(trifluoromethyl)phenyl)phosphinic acid (23a). 4-(Trifluoromethyl)phenyl iodide (136 mg, 500 µmol, 1.0 equiv.), ethyl methylphosphinate (64.8 mg, 600 µmol, 1.2 equiv.) and DIPEA (111 µL, 650 µmol, 1.3 equiv.) is added to a solution of $Pd(OAc)_2$ (2.25 mg, 10.0 µmol, 2.0 mol%) and Xantphos (6.36 mg, 11.0 µmol, 2.2 mol%) in DMF (1.80 mL) and DME (200 µL). The reaction mixture is sealed in a microwave vial and heated at 115 °C overnight. The reaction mixture is acidified with TFA and purified by preparative RP-HPLC (Waters XBridge™ Phenyl, gradient of acetonitrile in water, 0.1% TFA) to give 47.0 mg (42%) of the title compound as a colorless solid. ^1H NMR (DMSO-d_6, 400 MHz): δ = 7.95 (br dd, *J* = 11.0, 8.3 Hz, 2H), 7.82 – 7.90 (m, 2H), 1.56 (d, *J* = 14.6 Hz, 3H) ppm. ^{13}C NMR (DMSO-d_6, 101 MHz) δ = 140.3 (br d, *J* = 124 Hz), 131.5 (br d, *J* = 3 Hz), 131.2 (br d, *J* = 11 Hz), 125.0 - 125.2 (m), 123.8 (q, *J* = 273 Hz), 16.5 (d, *J* = 100 Hz) ppm. ^{31}P NMR (DMSO-d_6, 162 MHz): δ = 32.7 ppm. IR (ATR): 2156, 1688, 1399, 1322, 1306, 1161, 1123, 1104, 1061, 1021, 968, 885, 836, 763 cm^{-1}. HRMS (ESI^+) calculated for $C_8H_9F_3O_2P$ $[M+H]^+$ m/z 225.0287, found 225.0293.

Ethyl methyl[4-(trifluoromethyl)phenyl]phosphinate (23b). A mixture of 4-(trifluoromethyl)phenyl iodide (272 mg, 1.0 mmol, 1.0 equiv.), ethyl methylphosphinate (216 mg, 2.0 mmol, 2.0 equiv.), *N*,*N*-diisopropylamine (226 µL, 1.3 mmol, 1.3 equiv.) and XantphosPd G3 (95 mg, 0.10 mmol, 10 mol%) in toluene (4 mL) is stirred at 100 °C for 2 h. The mixture is allowed to cool to rt, and Palladium scavenger SiliaMetS-DMT (Dimercaptotriazine, R79030B) (200 mg) is added, and stirring is continued for 15 min. The reaction mixture is filtered, and the filtrate is concentrated under reduced pressure. The residue is repeatedly purified by preparative RP-HPLC (Waters XBridge™ C_{18}, gradient of acetonitrile in water, 0.15% NH_4OH) and flash chromatography on silica gel (gradient of EtOAc in cyclohexane: 10% – 90% EtOAc) to give 95 mg (37%) of the title compound as colorless oil. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 7.99 (dd, *J* = 11.4, 8.3 Hz, 2H), 7.91 (dd, *J* =8.3, 2.2 Hz, 2H), 3.96 (ddq, *J* = 10.2, 8.1, 7.1 Hz, 1 H), 3.79 (ddq, *J* = 10.2, 8.1, 7.1 Hz, 2 H), 1.71 (d, *J* = 14.7 Hz, 3H), 1.20 (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C NMR (DMSO-d_6, 101 MHz) δ = 137.1 (d, *J* = 123.5 Hz), 131.8 (d, *J* = 10.3 Hz), 131.7-132.0 (m), 125.3 (dq, *J* = 12.3, 3.7 Hz), 123.7 (br. q, *J* = 272.3 Hz), 60.2 (d, *J* = 6.0 Hz), 16.2 (d, *J* = 6.0 Hz), 14.7 (d, *J* = 101.1 Hz) ppm. ^{31}P NMR (DMSO-d_6, 162 MHz): δ = 39.8 ppm.

[4-(Trifluoromethyl)phenyl]phosphonic acid (24a). Bromotrimethylsilane (7.16 mL, 54.2 mmol, 3.0 equiv.) is added slowly at 0 °C to a solution of diethyl [4-(trifluoromethyl)phenyl]phosphonate (**24e**) (5.10 g, 18.1 mmol, 1.0 equiv.) in MeCN (100 mL), and the reaction mixture is allowed to warm to rt overnight. Water (50 mL) is added, and the mixture is concentrated to dryness. The residue is purified by preparative RP-HPLC (Waters SunFire^{TM} C_{18}, gradient of acetonitrile in water, 0.1% TFA) to give 3.49 g (85%) of the title compound as a colorless solid. The spectral data is in accordance with literature reports.[82]

Methoxy[4-(trifluoromethyl)phenyl]phosphinic acid (24b). According to a procedure reported in the literature,[67] 4-bromobenzotrifluoride (280 µL, 2.00 mmol, 1.0 equiv.) and dimethyl phosphite (222 µL, 2.40 mmol, 1.2 equiv.) is added to a suspension of $Pd(OAc)_2$ (8.98 mg, 40.0 µmol, 2 mol%), dppf (44.4 mg, 80.0 µmol 4 mol%), KOAc (19.6 mg, 200 µmol, 10 mol%) and DIPEA (453 µL, 2.60 mmol, 1.3 equiv.) in THF (10.0 mL). The reaction mixture is sealed in a microwave vial and heated at 75 °C overnight. The reaction mixture is filtered over a plug of celite and concentrated. The residue is purified by preparative RP-HPLC (Waters XBridge^{TM} C_{18}, gradient of acetonitrile in water, 0.1% TFA)

to give 330 mg (69%) of the title compound as a light-yellow oil. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 7.84 – 7.92 (m, 4H), 3.55 ppm (s, 3H) ppm. ^{13}C NMR (DMSO-d_6, 101 MHz) δ = 135.6 (br d, *J* = 181 Hz), 131.9 (d, *J* = 10 Hz), 130.8 – 131.8 (m), 125.2 (br dd, *J* = 14, 4 Hz), 123.9 (q, *J* = 273 Hz), 51.9 (d, *J* = 5 Hz) ppm. ^{31}P NMR (DMSO-d_6, 162 MHz): δ = 13.7 ppm. IR (ATR): 1400, 1321, 1167, 1124, 1106, 1061, 1040, 1017, 981, 837, 807, 774, 705 cm^{-1}. HRMS (ESI^{+}) calculated for $C_8H_9F_3O_3P$ $[M+H]^{+}$ m/z 241.0236, found 241.0234.

Ethoxy[4-(trifluoromethyl)phenyl]phosphinic acid (24c). Aqueous NaOH (4 M, 2.5 mL, 10.0 mmol, 20.0 equiv.) is added to a solution of diethyl [4-(trifluoromethyl)phenyl]phosphonate (**24e**, 141 mg, 500 µmol, 1.0 equiv.) in EtOH (2.50 mL), and the reaction mixture is stirred at rt for 5 d. Aqueous HCl (1 M, 20 mL) is added, and the aqueous phase is extracted with DCM (4 x 15 mL). The combined organic phases are dried over $MgSO_4$ and concentrated. The residue is purified by RP-HPLC (Waters XBridge^{TM} C_{18}, gradient of acetonitrile in water, 0.1% TFA) to give 95.0 mg (75%) of the title compound as a colorless solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 7.83 – 7.94 (m, 4H), 3.91 (dq, *J* = 8.1, 7.1 Hz, 2H), 1.18 (t, *J* = 7.0 Hz, 3H) ppm. ^{13}C NMR (DMSO-d_6,

101 MHz) δ = 136.3 (br d, J = 181 Hz), 131.8 (d, J = 10 Hz), 131.2 – 131.7 (m), 124.9 – 125.5 (m), 121.1 (q, J = 273 Hz), 61.0 (d, J = 5 Hz), 16.2 (d, J = 6 Hz) ppm. ^{31}P NMR (DMSO-d_6, 162 MHz): δ = 12.3 ppm. IR (ATR): 2501, 2228, 1399, 1320, 1216, 1162, 1125, 1107, 1063, 1040, 1007, 967, 836, 805, 708 cm^{-1}. HRMS (ESI$^+$) calculated for $C_9H_{11}F_3O_3P$ $[M+H]^+$ m/z 255.0392, found 255.0390.

Dimethyl [4-(trifluoromethyl)phenyl]phosphonate (24d). The reaction was performed following a literature report.[53] Copper(I) oxide (14.3 mg, 100 µmol, 5.0 mol%) and 1,10-phenanthroline (36.0 mg, 200 µmol, 10 mol%) is added to a solution of 4-(trifluoro-methyl)phenylboronic acid (380 mg, 2.00 mmol, 1.0 equiv.), dimethyl phosphite (242 mg, 2.20 mmol, 1.1 equiv.) and DIPEA (511 µL, 3.00 mmol, 1.5 equiv.) in MeCN (5.00 mL), and the reaction mixture is stirred open to air for 3 d. The reaction mixture is diluted with saturated aqueous $NaHCO_3$ (50 mL) and EtOAc (40 mL). The organic phase is dried over $MgSO_4$ and concentrated. The residue is purified by flash chromatography on silica gel (gradient of EtOAc in cyclohexane; 10% – 50% EtOAc) to give 180 mg (35%) of the title compound as a colorless oil. The spectral data is in accordance with literature reports.[45]

Diethyl [4-(trifluoromethyl)phenyl]phosphonate (24e). The reaction was performed using an adopted literature report.[67] 4-Bromobenzotrifluoride (4.50 mL, 20.0 mmol, 1.0 equiv.) and diethyl phosphite (3.31 mL, 24.0 mmol, 1.2 equiv.) is added to a suspension of $Pd(OAc)_2$ (89.8 mg, 400 µmol, 2.0 mol%), dppf (444 mg, 800 µmol 4.0 mol%), KOAc (196 mg, 2.00 mmol, 10 mol%) and DIPEA (4.42 mL, 3.00 mmol, 1.3 equiv.) in THF (100 mL), and the reaction mixture is refluxed overnight. The mixture is filtered over a plug of celite and concentrated. The residue is dissolved in water (100 mL) and brine (100 mL), and the aqueous phase is extracted with EtOAc (3 x 100 mL). The combined organic phases are dried over Na_2SO_4 and concentrated. The residue is purified by preparative RP-HPLC (Waters SunFire^{TM} C_{18}, gradient of acetonitrile in water, 0.1% TFA) to give 5.10 g (90%) of the title compound as colorless oil. The spectral data is in accordance with literature reports.[53]

Diisopropyl [4-(trifluoromethyl)phenyl]phosphonate (24f). The reaction was performed using an adopted literature report.[42c] $Pd(OAc)_2$ (4.49 mg, 20.0 µmol, 2.0 mol%) and dppf (12.2 mg, 22.0 µmol 2.2 mol%) is added to a solution of 4-(trifluoromethyl)phenyl iodide (147 µL, 1.0 mmol, 1.0 equiv.), diisopropyl phosphite (199 mg, 1.20 mmol, 1.2 equiv.)

and DIPEA (226 µL, 1.30 mmol, 1.3 equiv.) in DMF (9.00 mL) and DME (1.00 mL). The reaction mixture is sealed in a microwave vial and heated at 115 °C overnight. The reaction mixture is diluted with EtOAc (30 mL) and the organic phase is extracted with water (2 x 20 mL) and brine (20 mL), dried over Na_2SO_4 and concentrated. The residue is purified by flash chromatography on silica gel (gradient of EtOAc in cyclohexane; 0% – 3% EtOAc) to give 230 mg (74%) of the title compound as a yellow oil. The spectral data is in accordance with literature reports.[42c]

2-Hydroxyethoxy(4-(trifluoromethyl)phenyl)phosphinic acid (24g). A solution of [4-(trifluoromethyl)phenyl]phosphonic dichloride (**49**) (263 mg, 1.00 mmol, 1.0 equiv.) in THF (3.00 mL) is added dropwise at 0 °C to a solution of ethylene glycol (55.9 µL, 1.05 mmol, 1.05 equiv.) and Et_3N (278 µL, 2.00 mmol, 2.0 equiv.) in THF (20.0 mL), and the reaction mixture is allowed to warm to rt overnight. The reaction mixture is filtered over a plug of celite, and the filter cake is rinsed with EtOAc (20 mL). The combined filtrates are concentrated and purified by flash chromatography on silica gel (gradient of MeOH in DCM; 0% – 15% MeOH) to give 51.0 mg (20%) of the title compound as colorless oil. R_f (DCM:MeOH, 20:1) = 0.10. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 7.88 –

7.96 (m, 2H), 7.81 – 7.88 (m, 2H), 3.83 (dt, J = 7.5, 5.2 Hz, 2H), 3.52 (t, J = 5.2 Hz, 2H) ppm. ^{13}C NMR (DMSO-d_6, 101 MHz) δ = 136.0 (br d, J = 182 Hz), 131.9 (d, J = 10 Hz), 131.2 – 131.8 (m), 124.8 – 125.4 (m), 123.8 (q, J = 273 Hz), 66.6 (d, J = 6 Hz), 60.3 (d, J = 7 Hz) ppm. ^{31}P NMR (DMSO-d_6, 162 MHz): δ = 12.8 ppm. IR (ATR): 3284, 1653, 1400, 1322, 1168, 1125, 1062, 1017, 987, 951, 837, 706 cm^{-1}. HRMS (ESI$^+$) calculated for $C_9H_{11}F_3O_4P$ $[M+H]^+$ m/z 271.0342, found 271.0343.

2-[4-(Trifluoromethyl)phenyl]-1,3,2λ^5-dioxaphosphinan-2-one (25b). A solution of [4-(trifluoromethyl)phenyl]phosphonic dichloride (**49**) (263 mg, 1.00 mmol, 1.0 equiv.) in THF (3.00 mL) is added dropwise at 0 °C to a solution of 1,3-propandiol (79.9 mg, 1.05 mmol, 1.05 equiv.) and Et_3N (278 µL, 2.00 mmol, 2.0 equiv.) in THF (20.0 mL), and the reaction mixture is allowed to warm to rt overnight. The reaction mixture is filtered over a plug of celite and the filter cake is rinsed with EtOAc (20 mL). The combined filtrates are concentrated and repeatedly purified by flash chromatography on silica gel (gradient of MeOH in DCM; 0% – 5% MeOH and gradient of EtOAc in cyclohexane; 50% – 100% EtOAc) to give 130 mg (49%) of the title compound as colorless oil. R_f (DCM:MeOH, 20:1) = 0.45. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 7.90 – 7.98 (m, 4H), 4.45

– 4.56 (m, 2H), 4.21 – 4.31 (m, 2H), 2.09 – 2.21 (m, 1H), 1.88 – 1.98 (m, 1H) ppm. ^{13}C NMR (DMSO-d_6, 101 MHz) δ = 133.6, 132.0 (d, *J* = 11 Hz), 131.5 – 132.9 (m), 125.5 – 126.2 (m), 123.6 (q, *J* = 273 Hz), 68.1 (d, *J* = 6 Hz), 25.8 (d, *J* = 8 Hz) ppm. ^{31}P NMR (DMSO-d_6, 162 MHz): δ = 9.5 ppm. IR (ATR): 2901, 1400, 1321, 1125, 1049, 1018, 932, 875, 808, 754, 708, 698 cm^{-1}. HRMS (ESI$^+$) calculated for $C_{10}H_{11}F_3O_3P$ $[M+H]^+$ m/z 267.0392, found 267.0392.

5,5-Dimethyl-2-[4-(trifluoromethyl)phenyl]-1,3,2λ^5-dioxaphosphinan-2-one (25c). A solution of [4-(trifluoromethyl)phenyl]phosphonic dichloride (**49**) (263 mg, 1.00 mmol, 1.0 equiv.) in THF (3.00 mL) is added dropwise to a solution of 2,2-dimethyl-1,3-propandiol (109 mg, 1.05 mmol, 1.05 equiv.) and Et_3N (278 µL, 2.00 mmol, 2.0 equiv.) in THF (20.0 mL) at 0 °C, and the reaction mixture is allowed to warm to rt overnight. The reaction mixture is filtered over a plug of celite and the filter cake is rinsed with EtOAc (20 mL). The combined filtrates are concentrated, and the residue is purified by flash chromatography on silica gel (gradient of MeOH in DCM; 0% – 5% MeOH) to give 238 mg (81%) of the title compound as a colorless solid. R_f (DCM:MeOH, 20:1) = 0.25. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 7.91 – 7.99 (m, 4H), 4.15 (dd, *J* = 15.5, 11.2 Hz, 2H), 3.98 (dd,

J = 11.2, 7.7 Hz, 2H), 1.15 (s, 3H), 0.92 (s, 3H) ppm. ^{13}C NMR (DMSO-d_6, 101 MHz) δ = 132.2 – 132.8 (m), 131.9 (d, *J* = 11 Hz), 132.0 (br d, *J* = 182 Hz), 125.5 – 126.2 (m), 123.6 (q, *J* = 273 Hz), 76.3 (d, *J* = 6 Hz), 32.1 (d, *J* = 6 Hz), 21.0, 20.0 ppm. ^{31}P NMR (DMSO-d_6, 162 MHz): δ = 9.4 ppm. IR (ATR): 2977, 1472, 1397, 1325, 1241, 1163, 1121, 1053, 1001, 961, 910, 826, 815, 710, 630 cm^{-1}. HRMS (ESI$^+$) calculated for $C_{12}H_{15}F_3O_3P$ [M+H]$^+$ m/z 295.0705, found 295.0707.

2-[4-(Trifluoromethyl)phenyl]-1,3,6,2λ^5-dioxazaphosphocan-2-one hydrochloride (25d). *Tert*-butyl 2-oxo-2-[4-(trifluoromethyl)phenyl]-1,3,6,2λ^5-dioxazaphosphocan-6-carboxylate (**50**) (39.5 mg, 100 µmol, 1 equiv.) is dissolved in anhydrous HCl (4 M in 1,4-dioxane; 0.200 mL), and the reaction mixture is stirred at rt for 1 h. The solution is concentrated to give 33.0 mg (quant.) of the title compound as a colorless solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 9.73 (br s, 2H), 8.01 – 8.08 (m, 2H), 7.95 – 8.01 (m, 2H), 4.45 – 4.55 (m, 2H), 4.29 – 4.42 (m, 2H), 3.38 – 3.52 (m, 4H) ppm. ^{13}C NMR (DMSO-d_6, 101 MHz) δ = 132.5 – 133.1 (m), 132.0 (d, *J* = 10 Hz), 131.2 (br d, *J* = 189 Hz), 125.4 – 126.0 (m), 123.5 (q, *J* = 273 Hz), 62.8 (br d, *J* = 7 Hz), 46.3 ppm. ^{31}P NMR (DMSO-d_6, 162 MHz): δ = 14.7 ppm. IR (ATR): 2807, 1575, 1399, 1323, 1267, 1046, 1107, 1063, 1033,

990, 923, 840, 817, 737, 703 cm^{-1}. HRMS (ESI^+) calculated for $C_{11}H_{14}F_3NO_3P$ $[M+H]^+$ m/z 296.0658, found 296.0659.

2-[4-(Trifluoromethyl)phenyl]-1,3,2λ^5-oxazaphosphinan-2-one (26a). A solution of [4-(trifluoromethyl)phenyl]phosphonic dichloride (**49**) (263 mg, 1.00 mmol, 1.0 equiv.) in THF (3.00 mL) is added dropwise to a solution of 3-amino-1-propanol (78.9 mg, 1.05 mmol, 1.05 equiv.) and Et_3N (278 µL, 2.00 mmol, 2.0 equiv.) in THF (20.0 mL) at 0 °C, and the reaction mixture is allowed to warm to rt overnight. The reaction mixture is filtered through a plug of celite and the filter cake is rinsed with EtOAc (20 mL). The combined filtrates are concentrated and purified by flash chromatography on silica gel (gradient of MeOH in DCM; 0% – 5% MeOH) to give 251 mg (95%) of the title compound as colorless oil. R_f (DCM:MeOH, 20:1) = 0.31. ^1H NMR (DMSO-d_6, 400 MHz): δ = 7.84 – 7.93 (m, 4H), 5.53 – 5.62 (m, 1H), 4.27 – 4.39 (m, 1H), 3.97 (dddd, *J* = 11.3, 10.2, 6.4, 2.8 Hz, 1H), 3.16 – 3.28 (m, 1H), 2.97 – 3.07 (m, 1H), 1.85 – 1.97 (m, 1H), 1.59 – 1.69 (m, 1H) ppm. ^{13}C NMR (DMSO-d_6, 101 MHz) δ = 137.6 (br d, *J* = 162 Hz), 131.5 (d, *J* = 10 Hz), 130.6 – 131.8 (m), 125.2 – 125.6 (m), 123.8 (q, *J* = 273 Hz), 67.9 (d, *J* = 7 Hz), 40.3 (d, *J* = 2 Hz), 25.7 (d, *J* = 8 Hz) ppm. ^{31}P NMR (DMSO-d_6, 162 MHz): δ = 14.2 ppm.

IR (ATR): 3226, 1322, 1233, 1167, 1123, 1106, 1062, 1045, 1019, 982, 945, 871, 834, 789, 758 cm^{-1}. HRMS (ESI^+) calculated for $C_{10}H_{12}F_3NO_2P$ $[M+H]^+$ m/z 266.0552, found 266.0551.

3-Methyl-2-[4-(trifluoromethyl)phenyl]-1,3,2λ^5-oxazaphosphinan-2-one (26b). A solution of [4-(trifluoromethyl)phenyl]phosphonic dichloride (**49**) (263 mg, 1.00 mmol, 1.0 equiv.) in THF (3.00 mL) is added dropwise to a solution of 3-methylamino-1-propanol (93.6 mg, 1.05 mmol, 1.05 equiv.) and Et_3N (278 µL, 2.00 mmol, 2.0 equiv.) in THF (20.0 mL) at 0 °C, and the reaction mixture is allowed to warm to rt overnight. The reaction mixture is filtered over a plug of celite, and the filter cake is rinsed with EtOAc (20 mL). The combined filtrates are concentrated and purified by flash chromatography on silica gel (gradient of MeOH in DCM+0.1% Et_3N; 0% – 5% MeOH) to give 189 mg (68%) of the title compound as a colorless oil. R_f (DCM+0.1% Et_3N:MeOH, 20:1) = 0.48. ^1H NMR (DMSO-d_6, 400 MHz): δ = 7.84 – 7.92 (m, 4H), 4.28 – 4.38 (m, 1H), 4.12 – 4.22 (m, 1H), 3.14 – 3.26 (m, 2H), 2.58 (d, *J* = 9.9 Hz, 3H), 1.99 – 2.11 (m, 1H), 1.88 – 1.99 (m, 1H) ppm. ^{13}C NMR (DMSO-d_6, 101 MHz) δ = 136.5 (br d, *J* = 168 Hz), 132.0 (d, *J* = 10 Hz), 130.9 – 131.8 (m), 125.2 – 125.7 (m), 123.8 (q, *J* = 273 Hz), 67.3 (d, *J* = 7 Hz), 48.7, 35.1 (d,

J = 4 Hz), 25.5 (d, J = 5 Hz) ppm. ^{31}P NMR (DMSO-d_6, 162 MHz): δ = 14.9 ppm. IR (ATR): 2900, 1322, 1233, 1166, 1122, 1105, 1061, 1043, 1017, 975, 926, 875, 837, 793, 783 cm^{-1}. HRMS (ESI$^+$) calculated for $C_{11}H_{14}F_3NO_2P$ $[M+H]^+$ m/z 280.0709, found 280.0718.

1,3-Dimethyl-2-[4-(trifluoromethyl)phenyl]-1,3,2λ^5-diazaphospholan-2-one (27a). A solution of [4-(trifluoromethyl)phenyl]phosphonic dichloride (**49**) (263 mg, 1.00 mmol, 1.0 equiv.) in THF (3.00 mL) is added dropwise to a solution of *N,N'*-dimethylethylenediamine (113 µL, 1.05 mmol, 1.05 equiv.) and Et_3N (278 µL, 2.00 mmol, 2.0 equiv.) in THF (20.0 mL) at 0 °C, and the reaction mixture is allowed to warm to rt overnight. The reaction mixture is filtered over a plug of celite, and the filter cake is rinsed with EtOAc (20 mL). The combined filtrates are concentrated and purified by flash chromatography on silica gel (gradient of MeOH in DCM; 0% – 5% MeOH) to give 238 mg (86%) of the title compound as a colorless oil. R_f (DCM:MeOH, 20:1) = 0.39. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 7.79 – 7.87 (m, 4H), 3.26 – 3.30 (m, 2H), 3.18 – 3.25 (m, 2H), 2.38 (d, J = 9.9 Hz, 6H) ppm. ^{13}C NMR (DMSO-d_6, 101 MHz) δ = 136.9 (br d, J = 151 Hz), 132.8 (d, J = 10 Hz), 130.9 – 131.6 (m), 124.8 – 125.5 (m), 124.4 (q, J = 273 Hz), 47.6 (d,

J = 9 Hz), 31.0 (d, *J* = 6 Hz) ppm. ^{31}P NMR (DMSO-d_6, 162 MHz): δ = 26.0 ppm.IR (ATR): 1397, 1321, 1266, 1212, 1158, 1119, 1103, 1061, 1035, 1016, 941, 837, 727, 719 cm^{-1}. HRMS (ESI$^+$) calculated for $C_{11}H_{15}F_3N_2OP$ $[M+H]^+$ m/z 279.0869, found 279.0874.

2-[4-(Trifluoromethyl)phenyl]-1,3,2λ^5-diazaphosphinan-2-one (27b). A solution of [4-(trifluoromethyl)phenyl]phosphonic dichloride (**49**) (263 mg, 1.00 mmol, 1.0 equiv.) in THF (3.00 mL) is added dropwise to a solution of 1,3-propanediamine (77.8 mg, 1.05 mmol, 1.05 equiv.) and Et_3N (278 µL, 2.00 mmol, 2.0 equiv.) in THF (20.0 mL) at 0 °C, and the reaction mixture is allowed to warm to rt overnight. The reaction mixture is filtered over a plug of celite, and the filter cake is rinsed with EtOAc (20 mL). The combined filtrates are concentrated and purified by flash chromatography on silica gel (gradient of MeOH in DCM+0.1% Et_3N; 0% – 10% MeOH) to give 58.0 mg (22%) of the title compound as a colorless solid. R_f (DCM+0.1% Et_3N:MeOH, 20:1) = 0.27. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 7.87 – 7.95 (m, 2H), 7.79 – 7.84 (m, 2H), 4.84 – 4.92 (m, 2H), 3.08 – 3.22 (m, 2H), 2.83 – 2.93 (m, 2H), 1.64 – 1.77 (m, 1H), 1.47 – 1.57 (m, 1H) ppm. ^{13}C NMR (DMSO-d_6, 101 MHz) δ = 141.7 (br d, *J* = 143 Hz), 131.2 (d, *J* = 10 Hz), 129.4 – 130.8 (m), 124.5 – 125.2 (m), 124.0 (q, *J* = 272 Hz), 41.2 (d, *J* = 3 Hz), 26.2 (d,

J = 6 Hz) ppm. ^{31}P NMR (DMSO-d_6, 162 MHz): δ = 13.5 ppm. IR (ATR): 3181, 1395, 1314, 1185, 1159, 1113, 1100, 1058, 1016, 998, 960, 868, 828, 797, 701 cm^{-1}. HRMS (ESI$^+$) calculated for $C_{10}H_{13}F_3N_2OP$ $[M+H_2O+H]^+$ m/z 283.0818, found 283.0818.

1,3-Dimethyl-2-[4-(trifluoromethyl)phenyl]-1,3,2λ^5-diazaphosphinan-2-one (27c). A solution of [4-(trifluoromethyl)phenyl]phosphonic dichloride (**49**) (263 mg, 1.00 mmol, 1.0 equiv.) in THF (3.00 mL) is added dropwise to a solution of *N,N'*-dimethyl-1,3-propanediamine (107 mg, 1.05 mmol, 1.05 equiv.) and Et_3N (278 µL, 2.00 mmol, 2.0 equiv.) in THF (20.0 mL) at 0 °C, and the reaction mixture is allowed to warm to rt overnight. The reaction mixture is filtered over a plug of celite, and the filter cake is rinsed with EtOAc (20 mL). The combined filtrates are concentrated and purified by flash chromatography on silica gel (gradient of MeOH in DCM; 0% – 5% MeOH) to give 207 mg (71%) of the title compound as a colorless oil. R_f (DCM+0.1% Et_3N:MeOH, 20:1) = 0.30. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 7.79 – 7.88 (m, 4H), 3.05 – 3.21 (m, 4H), 2.39 (d, J = 10.0 Hz, 6H), 1.97 – 2.09 (m, 1H), 1.83 – 1.93 (m, 1H) ppm. ^{13}C NMR (DMSO-d_6, 101 MHz) δ = 138.1 (br d, J = 146 Hz), 132.2 (d, J = 9 Hz), 130.0 – 131.4 (m), 124.8 – 125.3 (m), 123.9 (q, J = 272 Hz), 49.8, 34.5 (d, J = 4 Hz), 25.0 (d, J = 3 Hz) ppm. ^{31}P NMR

(DMSO-d_6, 162 MHz): δ = 16.1 ppm. IR (ATR): 2932, 1322, 1260, 1164, 1121, 1103, 1059, 1017, 979, 874, 747, 711, 658 cm^{-1}. HRMS (ESI^+) calculated for $C_{12}H_{17}F_3N_2OP$ $[M+H]^+$ m/z 293.1025, found 293.1025.

4-(Diethylphosphoryl)pyridine (28a). A solution of $Pd_2(dba)_3$ (45.7 mg, 50.0 µmol, 5 mol%) and Xantphos (57.9 mg, 100 µmol, 10 mol%) in 1,4-dioxane (2.00 mL) is stirred at rt for 10 min and then added to a solution of 4-bromopyridine hydrochloride (194 mg, 1.00 mmol, 1.0 equiv.), diethylphosphine oxide (106 mg, 1.00 mmol, 1.0 equiv.) and DIPEA (383 µL, 2.20 mmol, 2.2 equiv.) in 1,4-dioxane (4.00 mL). The reaction mixture is heated at 80 °C for 2 days, allowed to cool to room temperature and diluted with saturated aqueous $NaHCO_3$ solution. The mixture is extracted with dichloromethane (4 x 20 mL), and the combined organic layers are dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue is purified by flash chromatography on silica gel (gradient of MeOH in DCM; 0% – 10% MeOH) to give 79.0 mg (43%) of the title compound as a colorless solid. ^1H NMR (DMSO-d_6, 400 MHz): δ = 8.72 – 8.77 (m, 2H), 7.66 – 7.72 (m, 2H), 1.85 – 2.08 (m, 4H), 0.95 (t, J = 7.7 Hz, 3H), 0.91 (t, J = 7.7 Hz, 3H) ppm. MS (ESI^+) $[M+H]^+$ m/z 184.19.

Ethyl methyl(pyridin-4-yl)phosphinate (28b). $Pd(OAc)_2$ (4.49 mg, 20.0 µmol, 2.0 mol%) and Xantphos (12.7 mg, 22.0 µmol, 2.2 mol%) is added to a solution of 4-bromopyridine hydrochloride (194 mg, 1.00 mmol, 1.0 equiv.), ethyl methylphosphinate (130 mg, 1.20 mmol, 1.2 equiv.) and DIPEA (401 µL, 1.30 mmol, 2.3 equiv.) in toluene (1.60 mL) and DME (400 µL). The reaction mixture is sealed in a microwave vial and heated at 80 °C for 2 d. The reaction mixture is diluted with saturated aqueous $NaHCO_3$ (30 mL) and extracted with DCM (4 x 20 mL). The combined organic phases are dried over Na_2SO_4 and concentrated. The residue is purified by flash chromatography on silica gel (gradient of MeOH in DCM; 0% – 10% MeOH) to give 161 mg (87%) of the title compound as a yellow oil. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 8.76 – 8.80 (m, 2H), 7.66 – 7.73 (m, 2H), 3.97 (ddq, J = 10.3, 8.2, 7.0 Hz, 1H), 3.81 (ddq, J = 10.3, 8.2, 7.0 Hz, 1H), 1.71 (d, J = 14.8 Hz, 3H), 1.20 (t, J = 7.0 Hz, 3H) ppm. ^{13}C NMR (DMSO-d_6, 101 MHz) δ = 150.0 (d, J = 10 Hz), 140.9 (d, J = 120 Hz), 124.6 (d, J = 9 Hz), 60.5 (d, J = 6 Hz), 16.2 (d, J = 6 Hz), 14.4 (d, J = 101 Hz) ppm. ^{31}P NMR (DMSO-d_6, 162 MHz): δ = 39.2 ppm. IR (ATR): 3445, 2985, 1401, 1219, 1205, 1132, 1026, 956, 834, 785, 756 cm^{-1}. HRMS (ESI$^+$) calculated for $C_8H_{13}NO_2P$ $[M+H]^+$ m/z 186.0678, found 186.0684.

Diethyl (pyridin-4-yl)phosphonate (28c). The reaction was performed according to a literature report.[67] To a suspension of $Pd(OAc)_2$ (17.9 mg, 80.0 µmol, 2.0 mol%), dppf (88.7 mg, 160 µmol 4.0 mol%), KOAc (39.3 mg, 400 µmol, 10 mol%) and DIPEA (1.60 mL, 9.20 mmol, 2.3 equiv.) in THF (20.0 mL) is added 4-bromopyridine hydrochloride (778 mg, 4.00 mmol, 1.0 equiv.) and diethyl phosphite (618 µL, 4.80 mmol, 1.2 equiv.). The reaction mixture is sealed in a microwave vial and heated at 70 °C for 24 h. The reaction mixture is filtered through a plug of celite, and the filtrate is concentrated. The residue is purified by preparative RP-HPLC (Waters SunFire™ C_{18}, gradient of acetonitrile in water, 0.1% TFA), and the appropriate fractions are combined and diluted with saturated aqueous $NaHCO_3$ (100 mL). The aqueous phase is extracted with EtOAc (3 x 75 mL), and the combined organic phases are dried over Na_2SO_4 and concentrated to give 629 mg (73%) of the title compound as light-yellow oil. The spectral data is in accordance with the literature.[67]

4-((4-Methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzoic acid trifluoroacetate salt (37a·TFA). LiOH (59.9 mg, 2.00 mmol, 10.0 equiv.) is added to a solution of ethyl 4-((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-

yl)amino)phenyl)carbamoyl)benzoate trifluoroacetate salt (**37b**·TFA, 90.7 mg, 200 µmol, 1.0 equiv.) in a solvent mixture of THF/MeOH/H_2O (*v:v:v*, 2:1:1; 4 mL), and the reaction mixture is stirred at rt overnight. Aqueous HCl (1M, 5 mL) is added, and the mixture is concentrated. The residue is dissolved in DMF, filtered and purified by preparative RP-HPLC (Waters SunFire™ C_{18}, gradient of acetonitrile in water, 0.1% TFA) to give 84.0 mg (80%) of the title compound as a yellow solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 10.36 (s, 1H), 9.32 – 9.37 (m, 1H), 9.03 (s, 1H), 8.77 (dd, *J* = 5.0, 1.6 Hz, 1H), 8.67 (ddd, *J* = 8.2, 1.8, 1.8 Hz, 1H), 8.55 (d, *J* = 5.1 Hz, 1H), 8.13 (d, *J* = 2.0 Hz, 1H), 8.03 – 8.09 (m, 4H), 7.66 – 7.72 (m, 1H), 7.45 – 7.50 (m, 2H), 7.23 (d, *J* = 8.5 Hz, 1H), 2.24 (s, 3H) ppm. ^{13}C NMR (DMSO-d_6, 101 MHz) δ = 166.7, 164.6, 161.0, 160.8, 159.6, 149.4, 146.4, 138.8, 137.7, 136.9, 136.6, 133.2, 133.0, 130.1, 129.2, 127.8, 124.6, 117.2, 116.8, 107.7, 17.6 ppm. IR (ATR): 1674, 1575, 1530, 1423, 1406, 1300, 1286, 1199, 1183, 1125, 796, 719, 674, 654 cm^{-1}. HRMS (ESI$^+$) calculated for $C_{24}H_{20}N_5O_3$ $[M+H]^+$ m/z 426.1561, found 426.1558.

Ethyl 4-((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzoate trifluoroacetate salt (37b·TFA). HATU (384 mg, 1.00 mmol, 1.0 equiv.) is added to a

solution of ethyl terephthalate (194 mg, 1.00 mmol, 1.0 equiv.) and DIPEA (518 µL, 3.00 mmol, 3.0 equiv.) in DMF (5.00 mL), and the reaction mixture is stirred at rt for 10 min. Then 6-methyl-*N*^{1}-(4-(pyridin-3-yl)pyrimidin-2-yl)benzene-1,3-diamine (**51**) (277 mg, 1.00 mmol, 1.0 equiv.) is added, and the reaction mixture is heated at 50 °C for 1 h. The reaction mixture is acidified using TFA and directly purified by preparative RP-HPLC (Waters SunFire^{TM} C_{18}, gradient of acetonitrile in water, 0.1% TFA) to give 509 mg (90%) of the title compound as a yellow solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 10.39 (s, 1H), 9.34 (d, *J* = 2.1 Hz, 1H), 9.03 (s, 1H), 8.77 (dd, *J* = 5.0, 1.6 Hz, 1H), 8.66 (ddd, *J* = 8.1, 1.8, 1.8 Hz, 1H), 8.55 (d, *J* = 5.1 Hz, 1H), 8.12 (d, *J* = 2.0 Hz, 1H), 8.08 (s, 4H), 7.69 (dd, *J* = 8.0, 5.0 Hz, 1H), 7.45 – 7.50 (m, 2H), 7.23 (d, *J* = 8.4 Hz, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 2.24 (s, 3H), 1.35 (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C NMR (DMSO-d_6, 101 MHz) δ = 165.2, 164.5, 161.0, 160.8, 159.6, 149.4, 146.4, 139.1, 137.7, 136.8, 136.5, 132.9, 132.2, 130.1, 129.1, 128.0, 127.8, 124.6, 117.2, 116.8, 107.6, 61.1, 17.6, 14.1 ppm.

IR (ATR): 1696, 1669, 1581, 1527, 1452, 1404, 1280, 1175, 1130, 1112, 832, 803, 794, 721, 672 cm^{-1}. HRMS (ESI$^+$) calculated for $C_{26}H_{24}N_5O_3$ $[M+H]^+$ m/z 454.1874, found 454.1873.

N^1-(4-Methyl-3-{[4-(pyridin-3-yl)pyrimidin-2-yl]amino}phenyl)benzene-1,4-dicarboxamide trifluoroacetate salt (38a·TFA). HATU (384 mg, 1.00 mmol, 1.0 equiv.) is added to a solution of terephthalic acid monoamide (165 mg, 1.00 mmol, 1.0 equiv.) and DIPEA (518 µL, 3.00 mmol, 3.0 equiv.) in DMF (5.00 mL), and the reaction mixture is stirred at rt for 10 min. Then 6-methyl-N^1-(4-(pyridin-3-yl)pyrimidin-2-yl)benzene-1,3-diamine (**51**) (277 mg, 1.00 mmol, 1.0 equiv.) is added, and the reaction mixture is heated at 50 °C for 1 h. The reaction mixture is acidified using TFA and directly purified by preparative RP-HPLC (Waters XBridge^{TM} C_{18}, gradient of acetonitrile in water, 0.1% TFA) to give 462 mg (86%) of the title compound as a yellow solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 10.30 (s, 1H), 9.35 (dd, J = 2.2, 0.6 Hz, 1H), 9.04 (s, 1H), 8.79 (dd, J = 5.0, 1.6 Hz, 1H), 8.70 (ddd, J = 8.2, 1.8, 1.8 Hz, 1H), 8.56 (d, J = 5.2 Hz, 1H), 8.13 (d, J = 2.0 Hz, 1H), 8.10 (br s, 1H), 7.97 – 8.05 (m, 4H), 7.71 (br dd, J = 8.0, 5.1 Hz, 1H), 7.44 – 7.54 (m, 3H), 7.23 (d, J = 8.5 Hz, 1H), 2.24 (s, 3H) ppm. ^{13}C NMR (DMSO-d_6, 101 MHz) δ = 167.1, 164.7, 161.0, 160.7, 159.6, 149.1, 146.1, 137.6, 137.3, 137.0, 136.7, 133.1, 130.1, 127.7, 127.5, 127.4, 124.7, 117.2, 116.8, 107.7, 17.6 ppm. IR (ATR): 3312,

1664, 1578, 1532, 1404, 1198, 1126, 801, 721, 670 cm^{-1}. HRMS (ESI^+) calculated for $C_{24}H_{21}N_6O_2$ $[M+H]^+$ m/z 425.1741, found 425.1726.

***N*¹-Methyl-*N*⁴-(4-methyl-3-{[4-(pyridin-3-yl)pyrimidin-2-yl]amino}phenyl)benzene-1,4-dicarboxamide trifluoroacetate salt (38b·TFA).** HATU (384 mg, 1.00 mmol, 1.0 equiv.) is added to a solution of *N*-methyl terephthalic acid monoamide (179 mg, 1.00 mmol, 1.0 equiv.) and DIPEA (518 µL, 3.00 mmol, 3.0 equiv.) in DMF (5.00 mL), and the reaction mixture is stirred at rt for 10 min. Then 6-methyl-*N*¹-(4-(pyridin-3-yl)pyrimidin-2-yl)benzene-1,3-diamine (**51**) (277 mg, 1.00 mmol, 1.0 equiv.) is added, and the reaction mixture is heated at 50 °C for 1 h. The reaction mixture is acidified using TFA and directly purified by preparative RP-HPLC (Waters SunFire™ C_{18}, gradient of acetonitrile in water, 0.1% TFA) to give 450 mg (81%) of the title compound as an orange solid. ^1H NMR (DMSO-d_6, 400 MHz): δ = 10.31 (s, 1H), 9.38 (d, *J* = 1.8 Hz, 1H), 9.07 (s, 1H), 8.82 (dd, *J* = 5.1, 1.4 Hz, 1H), 8.77 (ddd, *J* = 8.1, 1.8, 1.8 Hz, 1H), 8.57 (d, *J* = 5.1 Hz, 2H), 8.14 (d, *J* = 2.0 Hz, 1H), 8.00 – 8.06 (m, 2H), 7.93 – 7.99 (m, 2H), 7.77 (dd, *J* = 8.0, 5.1 Hz, 1H), 7.50 (d, *J* = 5.1 Hz, 1H), 7.47 (dd, *J* = 8.3, 2.2 Hz, 1H), 7.23 (d, *J* = 8.5 Hz, 1H), 2.81 (d, *J* = 4.4 Hz, 3H), 2.24 (s, 3H) ppm. ^{13}C NMR (DMSO-d_6, 101 MHz) δ = 165.9, 164.7, 161.0,

160.4, 159.6, 148.4, 145.5, 137.7, 137.6, 137.1, 137.0, 136.9, 130.1, 127.7, 127.6, 127.0, 125.1, 117.2, 116.9, 107.7, 26.3, 17.6 ppm. IR (ATR): 3321, 1630, 1576, 1530, 1198, 1185, 1135, 807, 720, 704, 671 cm^{-1}. HRMS (ESI^+) calculated for $C_{25}H_{23}N_6O_2$ $[M+H]^+$ m/z 439.1877, found 439.1876.

***N*¹,*N*¹-Dimethyl-*N*⁴-(4-methyl-3-{[4-(pyridin-3-yl)pyrimidin-2-yl]amino}phenyl)benzene-1,4-dicarboxamide trifluoroacetate salt (38c·TFA).** HATU (384 mg, 1.00 mmol, 1.0 equiv.) is added to a solution of *N,N*-dimethyl terephthalic acid monoamide (193 mg, 1.00 mmol, 1.0 equiv.) and DIPEA (518 µL, 3.00 mmol, 3.0 equiv.) in DMF (5.00 mL), and the reaction mixture is stirred at rt for 10 min. Then 6-methyl-*N*¹-(4-(pyridin-3-yl)pyrimidin-2-yl)benzene-1,3-diamine (**51**) (277 mg, 1.00 mmol, 1.0 equiv.) is added, and the reaction mixture is heated at 50 °C for 1 h. The reaction mixture is acidified using TFA and directly purified by preparative RP-HPLC (Waters SunFire™ C_{18}, gradient of acetonitrile in water, 0.1% TFA) to give 530 mg (94%) of the title compound as a yellow solid. ^1H NMR (DMSO-d_6, 400 MHz): δ = 10.28 (s, 1H), 9.36 (d, *J* = 1.6 Hz, 1H), 9.05 (s, 1H), 8.79 (dd, *J* = 5.0, 1.5 Hz, 1H), 8.72 (ddd, *J* = 8.1, 1.7, 1.7 Hz, 1H), 8.56 (d, *J* = 5.1 Hz, 1H), 8.13 (d, *J* = 2.1 Hz, 1H), 8.01 (d, *J* = 8.4 Hz, 2H), 7.73 (dd, *J* = 8.0, 5.1 Hz, 1H), 7.51 – 7.57 (m,

2H), 7.44 – 7.51 (m, 2H), 7.22 (d, *J* = 8.5 Hz, 1H), 3.01 (br s, 3H), 2.91 (br s, 3H), 2.23 (s, 3H) ppm. ^{13}C NMR (DMSO-d_6, 101 MHz): δ = 169.4, 164.8, 161.0, 160.6, 159.6, 149.0, 146.0, 139.3, 137.6, 137.1, 137.0, 135.6, 133.2, 130.1, 127.7, 127.6, 126.8, 124.8, 117.2, 116.8, 107.7, 34.7, 29.4, 17.6 ppm. IR (ATR): 1606, 1578, 1532, 1453, 1406, 1180, 1129, 837, 799, 720, 672 cm^{-1}. HRMS (ESI$^+$) calculated for $C_{26}H_{25}N_6O_2$ $[M+H]^+$ m/z 453.2034, found 453.2034.

4-Methanesulfinyl-*N*-(4-methyl-3-{[4-(pyridin-3-yl)pyrimidin-2-yl]amino}phenyl)-benzamide trifluoroacetate salt (39·TFA). HATU (384 mg, 1.00 mmol, 1.0 equiv.) is added to a solution of 4-methanesulfinylbenzoic acid (184 mg, 1.00 mmol, 1.0 equiv.) and DIPEA (518 µL, 3.00 mmol, 3.0 equiv.) in DMF (5.00 mL), and the reaction mixture is stirred at rt for 10 min. Then 6-methyl-*N*^{1}-(4-(pyridin-3-yl)pyrimidin-2-yl)benzene-1,3-diamine (**51**) (277 mg, 1.00 mmol, 1.0 equiv.) is added, and the reaction mixture is heated at 50 °C for 1 h. The reaction mixture is acidified using TFA and purified by preparative RP-HPLC (Waters SunFire^{TM} C_{18}, gradient of acetonitrile in water, 0.1% TFA) to give 512 mg (92%) of the title compound as an orange solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 10.35 (s, 1H), 9.36 (d, *J* = 1.6 Hz, 1H), 9.05 (s, 1H), 8.80 (dd, *J* = 5.0, 1.5 Hz, 1H),

8.71 – 8.76 (m, 1H), 8.57 (d, *J* = 5.1 Hz, 1H), 8.10 – 8.16 (m, 3H), 7.81 – 7.86 (m, 2H), 7.75 (dd, *J* = 8.0, 5.0 Hz, 1H), 7.45 – 7.51 (m, 2H), 7.23 (d, *J* = 8.5 Hz, 1H), 2.80 (s, 3H), 2.24 (s, 3H) ppm. ^{13}C NMR (DMSO-d_6, 101 MHz): δ = 164.6, 161.0, 160.6, 159.6, 149.7, 148.8, 145.8, 137.6, 137.3, 137.1, 136.9, 133.2, 130.1, 128.4, 127.8, 124.9, 123.6, 117.2, 116.8, 107.7, 43.1, 17.6 ppm. IR (ATR): 1667, 1603, 1575, 1530, 1451, 1405, 1185, 1133, 843, 798, 720 cm^{-1}. HRMS (ESI$^+$) calculated for $C_{24}H_{22}N_5O_2S$ $[M+H]^+$ m/z 444.1489, found 444.1490.

4-Methanesulfonyl-*N*-(4-methyl-3-{[4-(pyridin-3-yl)pyrimidin-2-yl]amino}phenyl)-benzamide trifluoroacetate salt (40·TFA). HATU (384 mg, 1.00 mmol, 1.0 equiv.) is added to a solution of 4-methanesulfonylbenzoic acid (200 mg, 1.00 mmol, 1.0 equiv.) and DIPEA (518 µL, 3.00 mmol, 3.0 equiv.) in DMF (5.00 mL), and the reaction mixture is stirred at rt for 10 min. Then 6-methyl-*N*^{1}-(4-(pyridin-3-yl)pyrimidin-2-yl)benzene-1,3-diamine (**51**) (277 mg, 1.00 mmol, 1.0 equiv.) is added, and the reaction mixture is heated at 50 °C for 1 h. The reaction mixture is acidified using TFA and purified by preparative RP-HPLC (Waters SunFire^{TM} C_{18}, gradient of acetonitrile in water, 0.1% TFA) to give 522 mg (91%) of the title compound as an orange solid.[73] ^{1}H NMR (DMSO-d_6, 400 MHz):

δ = 10.45 (s, 1H), 9.36 (d, *J* = 1.6 Hz, 1H), 9.05 (s, 1H), 8.79 (dd, *J* = 5.0, 1.5 Hz, 1H), 8.71 (ddd, *J* = 8.1, 1.8, 1.8 Hz, 1H), 8.57 (d, *J* = 5.1 Hz, 1H), 8.12 – 8.23 (m, 3H), 8.03 – 8.11 (m, 2H), 7.73 (dd, *J* = 8.0, 5.0 Hz, 1H), 7.44 – 7.52 (m, 2H), 7.24 (d, *J* = 8.4 Hz, 1H), 3.29 (s, 3H), 2.24 (s, 3H) ppm. ^{13}C NMR (DMSO-d_6, 101 MHz): δ = 164.1, 161.0, 160.6, 159.6, 149.0, 146.0, 143.0, 139.5, 137.7, 137.0, 136.7, 133.1, 130.2, 128.6, 127.9, 127.0, 124.8, 117.1, 116.8, 107.7, 43.3, 17.6 ppm. IR (ATR): 1668, 1575, 1529, 1452, 1295, 1184, 1150, 799, 784, 720 cm^{-1}. HRMS (ESI$^+$) calculated for $C_{24}H_{22}N_5O_3S$ $[M+H]^+$ m/z 460.1438, found 460.1432.

4-[Imino(methyl)oxo-λ^6-sulfanyl]-*N*-(4-methyl-3-{[4-(pyridin-3-yl)pyrimidin-2-yl]amino}-phenyl)benzamide (41a). Step 1: Synthesis of 4-[imino(methyl)oxo-λ^6-sulfanyl]benzoic acid. LiOH (239 mg, 10.0 mmol, 10.0 equiv.) is added to a solution of methyl 4-[imino(methyl)oxo-λ^6-sulfanyl]benzoate[89] (213 mg, 1.00 mmol, 1.0 equiv.) in THF/MeOH/H_2O (*v:v:v*, 2:1:1; 4.00 mL), and the reaction mixture is stirred at rt overnight. Aqueous HCl (1M, 35 mL) is added, and the aqueous phase is extracted with EtOAc (10 x 30 mL). The combined organic phases are dried over Na_2SO_4 and concentrated. The residue is purified by RP-HPLC (Waters XBridge^{TM}-C_{18}, gradient of

acetonitrile in water, 0.1% TFA) to give 299 mg of a crude reaction product which is used directly in the next reaction step.

Step 2: Synthesis of 4-[imino(methyl)oxo-λ^6-sulfanyl]-*N*-(4-methyl-3-{[4-(pyridin-3-yl)pyrimidin-2-yl]amino}phenyl)benzamide (41a). HATU (576 mg, 1.50 mmol, 1.5 equiv.) is added to a solution of the crude 4-[imino(methyl)oxo-λ^6-sulfanyl]benzoic acid (Step 1, assumption: 1.00 mmol), 6-methyl-*N*^{1}-(4-(pyridin-3-yl)pyrimidin-2-yl)benzene-1,3-diamine (**51**) (333 mg, 1.20 mmol, 1.2 equiv.) and DIPEA (518 µL, 3.00 mmol, 3.0 equiv.) in DMF (5.00 mL), and the reaction mixture is stirred at rt overnight. The reaction mixture is acidified using TFA and repeatedly purified by preparative RP-HPLC (Waters XBridge^{TM} C_{18}, gradient of acetonitrile in water, 0.1% TFA; Waters XBridge^{TM} C_{18}, gradient of methanol in water, 0.1% NH_4OH) to give 90.0 mg (20%) of the title compound as light-yellow solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 10.39 (s, 1H), 9.28 (dd, *J* = 2.2, 0.7 Hz, 1H), 8.97 (s, 1H), 8.68 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.52 (d, *J* = 5.2 Hz, 1H), 8.48 (ddd, *J* = 8.2, 1.9, 1.8 Hz, 1H), 8.09 – 8.15 (m, 3H), 8.04 – 8.09 (m, 2H), 7.52 (ddd, *J* = 8.0, 4.8, 0.8 Hz, 1H), 7.49 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.43 (d, *J* = 5.2 Hz, 1H), 7.23 (d, *J* = 8.5 Hz, 1H), 4.37 (s, 1H), 3.12 (d, *J* = 0.6 Hz, 3H), 2.23 (s, 3H) ppm. ^{13}C NMR (DMSO-

d_6, 151 MHz) δ = 164.3, 161.6, 161.1, 159.4, 151.3, 148.1, 146.6, 138.5, 137.8, 136.8, 134.4, 132.2, 130.1, 128.2, 127.9, 127.2, 123.7, 117.1, 116.7, 107.5, 45.5, 17.6 ppm. IR (ATR): 3230, 2987, 1668, 1585, 1559, 1524, 1415, 996, 813, 755, 708, 688, 650 cm^{-1}. HRMS (ESI^+) calculated for $C_{24}H_{23}N_6O_2S$ $[M+H]^+$ m/z 459.1598, found 459.1593.

4-[Methyl(methylimino)oxo-λ⁶-sulfanyl]-*N*-(4-methyl-3-{[4-(pyridine-3-yl)pyrimidin-2-yl]-amino}phenyl)benzamide (41b). Step 1: Synthesis of 4-[methyl(methylimino)oxo-λ⁶-sulfanyl]benzoic acid. A solution of methyl 4-[imino(methyl)oxo-λ⁶-sulfanyl]benzoate[89] (213 mg, 1.00 mmol, 1.0 equiv.) in aqueous formaldehyde solution (37%; 2.00 mL) and formic acid (8.00 mL) is refluxed for 36 h. The reaction mixture is cooled to rt and carefully treated with saturated aqueous $NaHCO_3$ (40 mL) and solid $NaHCO_3$. The basic aqueous phase is extracted with EtOAc (3 x 20 mL), and the combined organic phases are dried over $MgSO_4$ and concentrated. The residue is purified by RP-HPLC (Waters XBridge™ C_{18}, gradient of acetonitrile in water, 0.1% NH_4OH) to give 135 mg (~60%, ~70% purity) of a crude reaction product which is directly dissolved in aqueous HCl (4 M; 2.00 mL) and heated at 80 °C overnight. The reaction mixture is concentrated, and the residue is used in the next step without further purification.

Step 2: Synthesis of 4-[methyl(methylimino)oxo-λ^6-sulfanyl]-*N*-(4-methyl-3-{[4-(pyridine-3-yl)pyrimidin-2-yl]amino}phenyl)benzamide (41b). HATU (346 mg, 900 µmol, 1.5 equiv.) is added to a solution of crude 4-[methyl(methylimino)oxo-λ^6-sulfanyl]benzoic acid (Step 1, approx. 600 µmol, 1.0 equiv.), 6-methyl-*N*^{1}-(4-(pyridin-3-yl)pyrimidin-2-yl)benzene-1,3-diamine (**51**) (200 mg, 720 µmol, 1.2 equiv.) and DIPEA (311 µL, 1.80 mmol, 3.0 equiv.) in DMF (3.00 mL), and the reaction mixture is stirred at rt for 2 h. The reaction mixture is acidified using TFA and repeatedly purified by preparative RP-HPLC (Waters SunFire^{TM} C_{18}, gradient of acetonitrile in water, 0.1% TFA; Waters XBridge^{TM} Phenyl, gradient of methanol in water, 0.1% NH_4OH) to give 57.0 mg (20%) of the title compound as light-yellow solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 10.42 (s, 1H), 9.28 (dd, *J* = 2.3, 0.8 Hz, 1H), 8.97 (s, 1H), 8.69 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.52 (d, *J* = 5.1 Hz, 1H), 8.48 (ddd, *J* = 8.2, 1.8, 1.8 Hz, 1H), 8.12 – 8.17 (m, 2H), 8.10 (d, *J* = 2.0 Hz, 1H), 7.93 – 8.00 (m, 2H), 7.53 (ddd, *J* = 8.0, 4.8, 0.8 Hz, 1H), 7.49 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.43 (d, *J* = 5.2 Hz, 1H), 7.23 (d, *J* = 8.5 Hz, 1H), 3.18 (s, 3H), 2.49 (s, 3H), 2.24 (s, 3H) ppm. ^{13}C NMR (DMSO-d_6, 151 MHz): δ = 164.4, 161.6, 161.1, 159.4, 151.3, 148.2, 141.7, 138.9, 137.8, 136.8, 134.4, 132.2, 130.1, 128.6, 128.3, 127.9, 123.7, 117.1,

116.7, 107.5, 43.4, 29.1, 17.6 ppm. IR (ATR): 3414, 1674, 1578, 1518, 1479, 1423, 1395, 1239, 1146, 847, 799, 746, 702 cm^{-1}. HRMS (ESI^+) calculated for $C_{25}H_{25}N_6O_2S$ $[M+H]^+$ m/z 473.1760, found 473.1750.

***N*-(4-Methyl-3-{[4-(pyridine-3-yl)pyrimidin-2-yl]amino}phenyl)-4-sulfamoylbenzamide trifluoroacetate salt (42a·TFA).** HATU (384 mg, 1.00 mmol, 1.0 equiv.) is added to a solution of 4-sulfamoylbenzoic acid (201 mg, 1.00 mmol, 1.0 equiv.) and DIPEA (518 µL, 3.00 mmol, 3.0 equiv.) in DMF (5.00 mL), and the reaction mixture is stirred at rt for 10 min. Then 6-methyl-*N*^{1}-(4-(pyridin-3-yl)pyrimidin-2-yl)benzene-1,3-diamine (**51**) (277 mg, 1.00 mmol, 1.0 equiv.) is added, and the reaction mixture is heated at 50 °C overnight. The reaction mixture is acidified using TFA and purified by preparative RP-HPLC (Waters SunFire^{TM} C_{18}, gradient of acetonitrile in water, 0.1% TFA) to give 395 mg (69%) of the title compound as a yellow solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 10.37 (s, 1H), 9.31 (dd, *J* = 2.2, 0.7 Hz, 1H), 9.00 (s, 1H), 8.73 (dd, *J* = 4.9, 1.6 Hz, 1H), 8.57 (ddd, *J* = 8.1, 1.9, 1.9 Hz, 1H), 8.53 (d, *J* = 5.1 Hz, 1H), 8.08 – 8.13 (m, 3H), 7.93 – 7.97 (m, 2H), 7.60 (br dd, *J* = 8.0, 4.8 Hz, 1H), 7.44 – 7.54 (m, 4H), 7.23 (d, *J* = 8.5 Hz, 1H), 2.24 (s, 3H) ppm. ^{13}C NMR (DMSO-d_6, 151 MHz): δ = 164.3, 161.0, 161.0, 159.5, 149.8,

146.7, 146.4, 137.9, 137.7, 136.8, 136.2, 132.8, 130.1, 128.3, 127.8, 125.6, 124.4, 117.1, 116.8, 107.6, 17.6 ppm. IR (ATR): 3335, 1647, 1578, 1531, 1416, 1404, 1289, 1165, 1157, 797, 610 cm^{-1}. HRMS (ESI^+) calculated for $C_{23}H_{21}N_6O_3$ $[M+H]^+$ m/z 461.1390, found 461.1380.

***N*-(4-Methyl-3-{[4-(pyridine-3-yl)pyrimidin-2-yl]amino}phenyl)-4-(methylsulfamoyl)-benzamide trifluoroacetate salt (42b·TFA).** HATU (384 mg, 1.00 mmol, 1.0 equiv.) is added to a solution of 4-methylsulfamoylbenzoic acid (215 mg, 1.00 mmol, 1.0 equiv.) and DIPEA (518 µL, 3.00 mmol, 3.0 equiv.) in DMF (5.00 mL), and the reaction mixture is stirred at rt for 10 min. Then 6-methyl-*N*^{1}-(4-(pyridin-3-yl)pyrimidin-2-yl)benzene-1,3-diamine (**51**) (277 mg, 1.00 mmol, 1.0 equiv.) is added, and the reaction mixture is heated at 50 °C overnight. The reaction mixture is acidified using TFA and purified by preparative RP-HPLC (Waters SunFire^{TM} C_{18}, gradient of acetonitrile in water, 0.1% TFA) to give 325 mg (55%) of the title compound as a yellow solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 10.41 (s, 1H), 9.33 (dd, *J* = 2.2, 0.6 Hz, 1H), 9.03 (s, 1H), 8.75 (dd, *J* = 4.9, 1.5 Hz, 1H), 8.63 (ddd, *J* = 8.0, 1.9, 1.9 Hz, 1H), 8.55 (d, *J* = 5.2 Hz, 1H), 8.10 – 8.16 (m, 3H), 7.88 – 7.94 (m, 2H), 7.66 (dd, *J* = 8.0, 4.9 Hz, 1H), 7.57 – 7.63 (m, 1H), 7.44 – 7.49 (m, 2H), 7.23

(d, J = 8.5 Hz, 1H), 2.45 (d, J = 4.9 Hz, 3H), 2.24 (s, 3H) ppm. ^{13}C NMR (DMSO-d_6, 151 MHz): δ = 164.3, 161.0, 160.7, 159.6, 149.1, 146.1, 141.7, 138.5, 137.7, 136.9, 136.8, 133.1, 130.1, 128.5, 127.9, 126.7, 124.7, 117.1, 116.8, 107.7, 28.6, 17.6 ppm. IR (ATR): 1671, 1575, 1531, 1451, 1199, 1161, 1133, 798, 721, 603 cm^{-1}. HRMS (ESI$^+$) calculated for $C_{24}H_{23}N_6O_3S$ $[M+H]^+$ m/z 475.1547, found 475.1541.

4-(Dimethylsulfamoyl)-*N*-(4-methyl-3-{[4-(pyridine-3-yl)pyrimidin-2-yl]amino}phenyl)-benzamide (42c). HATU (384 mg, 1.00 mmol, 1.0 equiv.) is added to a solution of 4-dimethylsulfamoylbenzoic acid (229 mg, 1.00 mmol, 1.0 equiv.) and DIPEA (518 µL, 3.00 mmol, 3.0 equiv.) in DMF (5.00 mL), and the reaction mixture is stirred at rt for 10 min. Then 6-methyl-*N*^{1}-(4-(pyridin-3-yl)pyrimidin-2-yl)benzene-1,3-diamine (**51**) (277 mg, 1.00 mmol, 1.0 equiv.) is added, and the reaction mixture is heated at 50 °C overnight. The reaction mixture is acidified using TFA and repeatedly purified by preparative RP-HPLC (Waters SunFire™ C_{18}, gradient of acetonitrile in water, 0.1% TFA; Waters XBridge™ C_{18}, gradient of acetonitrile in water, 0.1% NH_4OH) to give 111 mg (23%) of the title compound as a colorless solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 10.45 (s, 1H), 9.27 (dd, J = 2.3, 0.8 Hz, 1H), 8.97 (s, 1H), 8.68 (dd, J = 4.7, 1.6 Hz, 1H), 8.51

(d, J = 5.2 Hz, 1H), 8.45 – 8.50 (m, 1H), 8.14 – 8.19 (m, 2H), 8.09 (d, J = 2.0 Hz, 1H), 7.86 – 7.92 (m, 2H), 7.53 (ddd, J = 8.0, 4.8, 0.8 Hz, 1H), 7.48 (dd, J = 8.2, 2.2 Hz, 1H), 7.43 (d, J = 5.2 Hz, 1H), 7.23 (d, J = 8.6 Hz, 1H), 2.65 (s, 6H), 2.23 (s, 3H) ppm. ^{13}C NMR (DMSO-d_6, 101 MHz) δ = 164.1, 161.6, 161.1, 159.4, 151.3, 148.1, 139.0, 137.8, 137.2, 136.7, 134.4, 132.2, 130.1, 128.6, 128.0, 127.5, 123.7, 117.2, 116.7, 107.5, 37.5, 17.6 ppm. IR (ATR): 1670, 1583, 1527, 1412, 1335, 1312, 1163, 1154, 753, 736, 704, 601 cm^{-1}. HRMS (ESI$^+$) calculated for $C_{25}H_{25}N_6O_3S$ $[M+H]^+$ m/z 489.1703, found 489.1692.

4-(Dimethylphosphoryl)-*N*-(4-methyl-3-{[4-(pyridin-3-yl)pyrimidin-2-yl]amino}phenyl)-benzamide trifluoroacetate salt (43·TFA).[74] HATU (384 mg, 1.00 mmol, 1.0 equiv.) is added to a solution of 4-(dimethylphosphoryl)benzoic acid[90] (164 mg, 830 µmol, 1.0 equiv.) and DIPEA (428 µL, 3.00 mmol, 3.0 equiv.) in DMF (5.00 mL), and the reaction mixture is stirred at rt for 10 min. Then 6-methyl-*N*^{1}-(4-(pyridin-3-yl)pyrimidin-2-yl)benzene-1,3-diamine (**51**) (277 mg, 1.00 mmol, 1.0 equiv.) is added, and the reaction mixture is heated at 50 °C for 1 h. The reaction mixture is acidified using TFA and purified by preparative RP-HPLC (Waters SunFire™ C_{18}, gradient of acetonitrile in water, 0.1%

TFA) to give 522 mg (91%) of the title compound as an orange solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 10.33 (s, 1H), 9.38 – 9.42 (m, 1H), 9.09 (s, 1H), 8.80 – 8.88 (m, 2H), 8.59 (d, *J* = 5.1 Hz, 1H), 8.15 (d, *J* = 2.1 Hz, 1H), 8.04 – 8.09 (m, 2H), 7.89 – 7.96 (m, 2H), 7.80 – 7.85 (m, 1H), 7.51 (d, *J* = 5.1 Hz, 1H), 7.47 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.23 (d, *J* = 8.5 Hz, 1H), 2.24 (s, 3H), 1.70 (d, *J* = 13.4 Hz, 6H) ppm. ^{13}C NMR (DMSO-d_6, 101 MHz) δ = 164.8, 160.9, 160.2, 159.7, 147.8, 145.0, 139.2 (d, *J* = 93 Hz), 138.4, 137.5, 136.9, 133.6, 130.1, 129.8 (d, *J* = 10 Hz), 127.8, 127.6 (d, *J* = 12 Hz), 125.3, 117.2, 116.9, 107.8, 17.6, 17.6 (d, *J* = 71 Hz) ppm. ^{31}P NMR (DMSO-d_6, 162 MHz): δ = 32.8 ppm. IR (ATR): 1662, 1576, 1528, 1189, 1139, 937, 836, 799, 752, 721, 706, 671 cm^{-1}. HRMS (ESI^{+}) calculated for $C_{25}H_{25}N_5O_2P$ $[M+H]^+$ m/z 458.1740, found 458.1738.

4-(Dimethylphosphoryl)-*N*-(4-methyl-3-{[4-(pyridin-3-yl)pyrimidin-2-yl]amino}phenyl)-benzamide (43). Concentrated aqueous NH_4OH (2 drops) is added to a solution of 4-(dimethylphosphoryl)-*N*-(4-methyl-3-{[4-(pyridin-3-yl)pyrimidin-2-yl]amino}phenyl)-benzamide trifluoroacetate salt (**43·TFA**, 100 mg) in EtOH (5 mL), and the mixture is purified by preparative RP-HPLC (Waters XBridge^{TM} C_{18}, gradient of acetonitrile in water, 0.1% NH_4OH) to give 64 mg (80%) of a colorless solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ

= 10.33 (s, 1H) 9.28 (d, *J* = 2.2 Hz, 1H), 8.97 (s, 1H), 8.69 (dd, *J* = 4.8, 1.5 Hz, 1H), 8.52 (d, *J* = 5.1 Hz, 1H), 8.48 (ddd, *J* = 8.0, 2.2, 1.5 Hz, 1H), 8.11 (d, *J* = 2.2 Hz, 1H), 8.04 - 8.09 (m, 2H), 7.89 - 7.96 (m, 2H), 7.52 (ddd, *J* = 8.0, 4.8, 0.7 Hz, 1H), 7.50 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.43 (d, *J* = 5.1 Hz, 1H), 7.23 (dd, *J* = 8.2, 0.5 Hz, 1H), 2.24 (s, 3H), 1.70 (d, *J* = 13.4 Hz, 6H) ppm. ^{13}C NMR (DMSO-d_6, 101 MHz) δ = 164.8, 161.6, 161.1, 159.4, 151.3, 148.1, 139.2 (d, *J* = 93 Hz), 137.8, 137.5 (d, *J* = 2 Hz), 136.9, 134.4, 132.2, 130.0, 129.8 (d, *J* = 10 Hz), 127.8, 127.5 (d, *J* = 12 Hz), 123.7, 117.1, 116.7, 107.5, 17.6, 17.6 (d, *J* = 70 Hz) ppm. ^{31}P NMR (DMSO-d_6, 162 MHz): δ = 32.4 ppm.

Ethyl methyl({4-[(4-methyl-3-{[4-(pyridin-3-yl)pyrimidin-2-yl]amino}phenyl)carbamoyl]-phenyl})phosphinate trifluoroacetate salt (44a·TFA) and methyl({4-[(4-methyl-3-{[4-(pyridin-3-yl)pyrimidin-2-yl]amino}phenyl)carbamoyl]phenyl})phosphinic acid trifluoro-acetate salt (44b·TFA). Step 1: Synthesis of methyl 4-[ethoxy(methyl)phosphoryl]benzoate.[26] Ethyl methylphosphinate (259 mg, 2.4 mmol, 1.2 equiv.), methyl 4-bromobenzoate (430 mg, 2.00 mmol, 1.0 equiv.) and DIPEA (453 µL, 650 µmol, 1.3 equiv.) is added to a solution of $Pd(OAc)_2$ (8.98 mg, 40.0 µmol, 2.0 mol%) and Xantphos (25.5 mg, 44.0 µmol, 2.2 mol%) in DMF (3.06 mL) and DME

(400 µL), and the mixture is sealed in a microwave vial and heated at 110 °C for 5 h. The reaction mixture is acidified with TFA and purified by preparative RP-HPLC (Waters SunFire™ C_{18}, gradient of acetonitrile in water, 0.1% TFA) to give 392 mg (81%) of the title compound as colorless oil. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 8.05-8.11 (m, 2H), 7.86 – 7.94 (m, 2H), 3.89 – 4.00 (m, 1H), 3.91 (s, 3H) 3.72 – 3.84 (m, 1H), 1.69 (d, *J* = 14.6 Hz, 3H), 1.18 (t, *J* = 7.0 Hz, 3H) ppm. ^{13}C NMR (DMSO-d_6, 101 MHz) δ = 165.6, 137.3 (d, *J* = 123 Hz), 132.6 (d, *J* = 3 Hz), 131.3 (d, *J* = 10 Hz), 129.1 (d, *J* = 12 Hz), 60.2 (d, *J* = 6 Hz), 52.4, 16.2 (d, *J* = 6 Hz), 14.8 (d, *J* = 101 Hz) ppm. ^{31}P NMR (DMSO-d_6, 162 MHz): δ = 40.3 ppm. IR (ATR): 2988, 1724, 1276, 1193, 1158, 1102, 1030, 1018, 957, 884, 789, 761, 749, 696 cm^{-1}. HRMS (ESI^{+}) calculated for $C_{11}H_{16}O_4P$ $[M+H]^{+}$ m/z 243.0781, found 243.0775.

Step 2: Synthesis of ethyl methyl({4-[(4-methyl-3-{[4-(pyridin-3-yl)pyrimidin-2-yl]amino}-phenyl)-carbamoyl]phenyl})phosphinate trifluoroacetate salt (44a·TFA) and methyl({4-[(4-methyl-3-{[4-(pyridin-3-yl)pyrimidin-2-yl]amino}phenyl)carbamoyl]phenyl})phosphinic acid trifluoroacetate salt (44b·TFA). LiOH (365 mg, 15.2 mmol, 10.0 equiv.) is added to a mixture of methyl 4-[ethoxy(methyl)phosphoryl]benzoate (369 mg, 1.52 mmol, 1.0 equiv.)

and THF/MeOH/H_2O (*v:v:v*, 2:1:1; 20.0 mL), and the reaction mixture is stirred at rt for 30 min. Aqueous HCl (1 M, 25 mL) and brine (20 mL) is added, and the aqueous phase is extracted with EtOAc (10 x 25 mL). The combined organic layers are dried over $MgSO_4$ and concentrated under reduced pressure. The residue is dissolved in DMF (7.00 mL), and the mixture is treated with DIPEA (682 µL, 3.95 mmol, 3.0 equiv.). HATU (1.52 g, 3.95 mmol, 3.0 equiv.) is added in three equal portions (1.0 equiv. each) over a period of 30 min. Then 6-methyl-*N*^{1}-(4-(pyridin-3-yl)pyrimidin-2-yl)benzene-1,3-diamine (**51**) (365 mg, 1.32 mmol, 1.0 equiv.) is added, and the reaction mixture is heated at 50 °C for 1 h. The reaction mixture is acidified using TFA and repeatedly purified by preparative RP-HPLC (Waters XBridge™ C_{18}, gradient of acetonitrile in water, 0.1% TFA; Waters SunFire™ C_{18}, gradient of acetonitrile in water, 0.1% TFA) to give 47.0 mg (6%) of the ethyl phosphinate **44a·TFA** and 130 mg (17%) of the corresponding phosphinic acid **44b·TFA** both as yellow-orange solids.

Ethyl methyl({4-[(4-methyl-3-{[4-(pyridin-3-yl)pyrimidin-2-yl]amino}phenyl)carbamoyl]-phenyl})phosphinate trifluoroacetate salt (44a·TFA). ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 10.36 (s, 1H), 9.35 (d, *J* = 1.6 Hz, 1H), 9.04 (s, 1H), 8.78 (dd, *J* = 5.0, 1.6 Hz, 1H), 8.68

(ddd, *J* = 8.1, 1.9, 1.8 Hz, 1H), 8.56 (d, *J* = 5.2 Hz, 1H), 8.13 (d, *J* = 2.0 Hz, 1H), 8.04 – 8.10 (m, 2H), 7.86 – 7.94 (m, 2H), 7.70 (dd, *J* = 7.9, 5.2 Hz, 1H), 7.45 – 7.50 (m, 2H), 7.23 (d, *J* = 8.5 Hz, 1H), 3.89 – 4.02 (m, 1H), 3.73 – 3.85 (m, 1H), 2.24 (s, 3H), 1.70 (d, *J* = 14.6 Hz, 3H), 1.20 (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C NMR (DMSO-d_6, 101 MHz) δ = 164.7, 161.0, 160.7, 159.6, 149.3, 146.3, 138.3, 137.7, 136.9, 136.7, 135.3 (d, *J* = 123 Hz), 133.0, 130.9 (d, *J* = 11 Hz), 130.1, 127.8 (br s), 127.7 (br d, *J* = 12 Hz), 124.7, 117.2, 116.8, 107.7, 60.1 (d, *J* = 6 Hz), 17.6, 16.3 (d, *J* = 6 Hz), 14.9 (d, *J* = 101 Hz) ppm. ^{31}P NMR (DMSO-d_6, 162 MHz): δ = 40.5 ppm. IR (ATR): 3273, 3090, 1667, 1573, 1530, 1452, 1198, 1576, 1530, 1452, 1198, 1131, 1034, 797 cm^{-1}. HRMS (ESI$^+$) calculated for $C_{26}H_{27}N_5O_3P$ $[M+H]^+$ m/z 488.1846, found 488.1832.

Methyl({4-[(4-methyl-3-{[4-(pyridin-3-yl)pyrimidin-2-yl]amino}phenyl)carbamoyl]-phenyl})phosphinic acid trifluoroacetate salt (44b·TFA). ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 10.32 (s, 1H), 9.32 – 9.39 (m, 1H), 9.05 (s, 1H), 8.79 (dd, *J* = 5.1, 1.5 Hz, 1H), 8.71 (ddd, *J* = 8.1, 1.8, 1.8 Hz, 1H), 8.56 (d, *J* = 5.2 Hz, 1H), 8.11 – 8.16 (m, 1H), 8.02 – 8.07 (m, 2H), 7.83 – 7.91 (m, 2H), 7.72 (dd, *J* = 7.9, 5.3 Hz, 1H), 7.45 – 7.51 (m, 2H), 7.23 (d, *J* = 8.5 Hz, 1H), 2.24 (s, 3H), 1.56 (d, *J* = 14.6 Hz, 3H) ppm. ^{13}C NMR (DMSO-d_6, 101

MHz) δ = 164.8, 161.0, 160.6, 159.6, 149.0, 146.0, 138.6 (d, *J* = 125 Hz), 137.6, 137.5 (d, *J* = 2 Hz), 137.1, 136.9, 133.2, 130.3 (d, *J* = 10 Hz), 130.1, 127.8, 127.5 (d, *J* = 12 Hz), 124.8, 117.2, 116.8, 107.7, 17.6, 16.7 (d, *J* = 99 Hz) ppm. ^{31}P NMR (DMSO-d_6, 162 MHz): δ = 33.8 ppm. IR (ATR): 1665, 1602, 1575, 1528, 1451, 1182, 1132, 962, 877, 797, 719, 671, 608 cm^{-1}. HRMS (ESI$^+$) calculated for $C_{24}H_{23}N_5O_3P$ $[M+H]^+$ m/z 460.1533, found 460.1523.

Methyl({4-[(4-methyl-3-{[4-(pyridin-3-yl)pyrimidin-2-yl]amino}phenyl)carbamoyl]-phenyl})phosphinic acid (44b). Aqueous NaOH (0.1 M, 0.140 mmol, 1 equiv.) is added to a solution of methyl({4-[(4-methyl-3-{[4-(pyridin-3-yl)pyrimidin-2-yl]amino}phenyl)carbamoyl]phenyl})phosphinic acid trifluoroacetate salt (**44b·TFA**, 80.0 mg, 0.140 mmol, 1 equiv.) in minimal amounts of EtOH, and the neutralized sample is purified by flash chromatography on silica gel (gradient of MeOH in DCM; 10% – 50% MeOH, then isocratic DCM:MeOH:H_2O, 1:1:0.1). Appropriate fractions are collected and concentrated. The residue is triturated with MTBE to give a quantitative yield of the title compound as light-yellow solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 10.30 (s, 1H), 9.26 (d, *J* = 1.9 Hz, 1H), 8.94 (s, 1H), 8.67 (dd, *J* = 4.8, 1.4 Hz, 1H), 8.50 (d, *J* = 5.1 Hz, 1H),

8.47 (dt, *J* = 8.0, 1.9 Hz, 1H), 8.11 (d, *J* = 1.3 Hz, 1H), 7.94 (br d, *J* = 6.8 Hz, 2H), 7.82 (br t, *J* = 8.0 Hz, 2H), 7.49 - 7.53 (m, 1H), 7.49 - 7.52 (m, 1H), 7.41 (d, *J* = 5.1 Hz, 1H), 7.18 (d, *J* = 8.5 Hz, 1H), 2.22 (s, 3H), 1.22 (br d, *J* = 13.4 Hz, 3H) ppm. ^{13}C NMR (DMSO-d_6, 101 MHz) δ = 165.3, 161.6, 161.1, 159.4, 151.3, 148.1, 137.7, 137.1, 135.6, 134.4, 132.2, 130.3 (d, *J* = 8 Hz), 129.9, 127.6, 126.8 (d, *J* = 10 Hz), 123.7, 117.2, 116.8, 107.4, 18.9 (br d, *J* = 101 Hz), 17.6 ppm. ^{31}P NMR (DMSO-d_6, 162 MHz): δ = 21.8 ppm.

Diethyl {4-[(4-Methyl-3-{[4-(pyridin-3-yl)pyrimidin-2-yl]amino}phenyl)carbamoyl]-phenyl}phosphonate trifluoroacetate salt (45a·TFA). HATU (384 mg, 1.00 mmol, 1.0 equiv.) is added to a solution of diethyl (4-carboxyphenyl)phosphonate (258 mg, 1.00 mmol, 1.0 equiv.) and DIPEA (519 µL, 3.00 mmol, 3.0 equiv.) in DMF (5.00 mL), and the reaction mixture is stirred at rt for 10 min. Then 6-methyl-*N*^{1}-(4-(pyridin-3-yl)pyrimidin-2-yl)benzene-1,3-diamine (**51**) (277 mg, 1.00 mmol, 1.0 equiv.) is added, and the reaction mixture is heated at 50 °C overnight. The reaction mixture is acidified using TFA and purified by preparative RP-HPLC (Waters XBridge^{TM} C_{18}, gradient of acetonitrile in water, 0.1% TFA) to give 522 mg (83%) of the title compound as a yellow solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 10.37 (s, 1H), 9.33 (dd, *J* = 2.3, 0.8 Hz, 1H), 9.02 (s, 1H), 8.76 (dd,

J = 5.0, 1.6 Hz, 1H), 8.64 (ddd, *J* = 8.2, 1.8, 1.8 Hz, 1H), 8.55 (d, *J* = 5.2 Hz, 1H), 8.12 (d, *J* = 2.0 Hz, 1H), 8.05 – 8.10 (m, 2H), 7.82 – 7.90 (m, 2H), 7.67 (ddd, *J* = 8.0, 4.9, 0.7 Hz, 1H), 7.44 – 7.49 (m, 2H), 7.23 (d, *J* = 8.6 Hz, 1H), 4.00 – 4.11 (m, 4H), 2.24 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 6H) ppm. ^{13}C NMR (DMSO-d_6, 101 MHz) δ = 164.6, 161.0, 160.9, 159.5, 149.7, 146.6, 138.6 (d, *J* = 3 Hz), 137.3 (d, *J* = 86 Hz), 136.3, 132.9, 132.3, 131.3 (d, *J* = 10 Hz), 130.5, 130.1, 127.8 (br s), 127.8 (br d, *J* = 15 Hz), 124.5, 117.1, 116.8, 107.6, 61.9 (d, *J* = 5 Hz), 17.6, 16.1 (d, *J* = 6 Hz) ppm. ^{31}P NMR (DMSO-d_6, 162 MHz): δ = 16.7 ppm. IR (ATR): 3293, 1575, 1529, 1453, 1243, 1178, 1134, 1046, 1019, 967, 959, 798, 720 cm^{-1}. HRMS (ESI$^+$) calculated for $C_{27}H_{29}N_5O_3P$ $[M+H]^+$ m/z 518.1952, found 518.1956.

Diethyl {4-[(4-methyl-3-{[4-(pyridin-3-yl)pyrimidin-2-yl]amino}phenyl)carbamoyl]-phenyl}phosphonate (45a). Concentrated aqueous NH_4OH solution (2 drops) is added to a solution of diethyl {4-[(4-Methyl-3-{[4-(pyridin-3-yl)pyrimidin-2-yl]amino}phenyl)carbamoyl]phenyl}phosphonate trifluoroacetate salt (**45a·TFA**, 100 mg) in EtOH (5 mL), and the mixture is purified by preparative RP-HPLC (Waters XBridge™ C_{18}, gradient of acetonitrile in water, 0.1% NH_4OH) to give 62 mg (76%) of a colorless

solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 10.38 (s, 1H), 9.29 (d, *J* = 1.8 Hz, 1H), 8.97 (s, 1H), 8.69 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.52 (d, *J* = 5.2 Hz, 1H), 8.48 (ddd, *J* = 8.0, 2.3, 1.7 Hz, 1H), 8.12 (d, *J* = 2.2 Hz, 1H), 8.06 - 8.11 (m, 2H), 7.83 - 7.91 (m, 2H), 7.53 (ddd, *J* = 8.0, 4.8, 0.8 Hz, 1H), 7.50 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.43 (d, *J* = 5.2 Hz, 1H), 7.23 (d, *J* = 8.5 Hz, 1H), 4.08 (ddq, *J* = 10.3, 8.2, 7.1 Hz, 2H), 4.04 (ddq, *J* = 10.3, 8.4, 7.1 Hz, 2H), 2.25 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 6H) ppm. ^{13}C NMR (DMSO-d_6, 101 MHz) δ = 164.6, 161.6, 161.1, 159.4, 151.3, 148.1, 138.6 (d, *J* = 3 Hz), 137.8, 136.8, 134.4, 132.2, 131.3 (d, *J* = 10 Hz), 131.4 (d, *J* = 185 Hz), 130.1, 127.9, 127.8 (d, *J* = 15 Hz), 123.7, 117.1, 116.7, 107.5, 61.9 (d, *J* = 5 Hz), 17.6, 16.1 (d, *J* = 6 Hz) ppm. ^{31}P NMR (DMSO-d_6, 162 MHz): δ = 16.7 ppm.

Ethoxy{4-[(4-methyl-3-{[4-(pyridin-3-yl)pyrimidin-2-yl]amino}phenyl)carbamoyl]-phenyl}phosphinic acid trifluoroacetate salt (45b·TFA). A solution of diethyl {4-[(4-methyl-3-{[4-(pyridin-3-yl)pyrimidin-2-yl]amino}phenyl)carbamoyl]phenyl}phosphonate trifluoroacetate salt (**45a·TFA**) (47.4 mg, 75.1 µmol, 1.0 equiv.) in MeOH (2.00 mL) and aqueous NaOH (4 M; 1.04 mL) is stirred at rt for 48 h. The reaction mixture is concentrated, and the residue is dissolved in DMF. The solution is acidified with TFA and

purified by preparative RP-HPLC (Waters XBridge^{TM} C_{18}, gradient of acetonitrile in water, 0.1% TFA) to give 28.0 mg (62%) of the title compound as a yellow-orange solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 10.32 (s, 1H), 9.30 (d, *J* = 1.6 Hz, 1H), 8.99 (s, 1H), 8.72 (dd, *J* = 4.8, 1.5 Hz, 1H), 8.56 (ddd, *J* = 8.1, 1.8, 1.8 Hz, 1H), 8.53 (d, *J* = 5.2 Hz, 1H), 8.11 (d, *J* = 1.9 Hz, 1H), 8.01 – 8.06 (m, 2H), 7.82 (dd, *J* = 12.6, 8.3 Hz, 2H), 7.60 (dd, *J* = 8.0, 4.9 Hz, 1H), 7.47 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.45 (d, *J* = 5.2 Hz, 1H), 7.22 (d, *J* = 8.5 Hz, 1H), 3.88 – 3.96 (m, 3H), 2.23 (s, 3H), 1.20 ppm (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C NMR (DMSO-d_6, 101 MHz) δ = 164.8, 161.0, 161.0 (br s), 159.5, 149.8, 146.8, 137.8 (br d, *J* = 3 Hz), 137.3 (d, *J* = 79 Hz), 136.1, 135.3, 133.5, 132.8, 131.0 (br d, *J* = 10 Hz), 130.1, 127.8, 127.5 (br d, *J* = 14 Hz), 124.4 (br s), 117.2, 116.8, 107.6, 60.8 (d, *J* = 5 Hz), 17.6, 16.2 (d, *J* = 6 Hz) ppm. ^{31}P NMR (DMSO-d_6, 162 MHz): δ = 13.7 ppm. IR (ATR): 1635, 1579, 1532, 1172, 1138, 1114, 1035, 1017, 952, 796, 757, 720, 695 cm^{-1}. HRMS (ESI^{+}) calculated for $C_{25}H_{25}N_5O_4P$ $[M+H]^+$ m/z 490.1639, found 490.1632.

Ethoxy{4-[(4-methyl-3-{[4-(pyridin-3-yl)pyrimidin-2-yl]amino}phenyl)carbamoyl]-phenyl}phosphinic acid (45b). A solution of ethoxy{4-[(4-methyl-3-{[4-(pyridin-3-yl)-pyrimidin-2-yl]amino}phenyl)carbamoyl]phenyl}phosphinic acid trifluoroacetate salt

(**45a·TFA**) (500 mg, 96.6 µmol, 1.0 equiv.) in EtOH (10 mL) and aqueous NaOH (4 M, 9.67 mL) is stirred at 50 °C for 2 h. The mixture is cooled to room temperature, neutralized with 4 M aqueous HCl solution and purified by preparative RP-HPLC (Waters XBridge™ C_{18}, gradient of acetonitrile in water, 0.1% NH_4OH) to give 240 mg of the title compound as a 20:80 mixture of its free acid and its ammonium salt. The crude product is dissolved in acetonitrile and water at elevated temperature and freeze-dried to obtain 200 mg of the title compound as a 61:39 mixture of its free acid and its ammonium salt. This material is then triturated in aqueous HCl solution (0.1 N, 3.9 mL) overnight. The solids are collected by filtration, washed with water and dried in vacuo to give 150 mg (31%) of the title compound as a yellowish solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 10.32 (s, 1H), 9.28 (d, *J* = 1.8 Hz, 1H), 8.95 (s, 1H), 8.69 (dd, *J* = 4.8, 1.5 Hz, 1H), 8.52 (d, *J* = 5.2 Hz, 1H), 8.48 (ddd, *J* = 8.1, 1.9, 1.9 Hz, 1H), 8.10 (d, *J* = 2.0 Hz, 1H), 8.01 – 8.05 (m, 2H), 7.84 (d, *J* = 8.2 Hz, 1H), 7.81 (d, *J* = 8.2 Hz, 1H), 7.52 (dd, *J* = 8.0, 4.9 Hz, 1H), 7.48 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.43 (d, *J* = 5.2 Hz, 1H), 7.22 (d, *J* = 8.5 Hz, 1H), 3.88 – 3.95 (m, 3H), 2.23 (s, 3H), 1.19 ppm (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C NMR (DMSO-d_6, 101 MHz) δ = 164.7, 161.6, 161.1 (br s), 159.4, 151.3, 148.1, 137.8 (br d, *J* = 3 Hz), 137.7 (d, *J* = 79 Hz),

136.9, 134.4, 134.4, 132.2, 130.9 (br d, J = 10 Hz), 130.0, 127.8, 127.5 (br d, J = 14 Hz), 123.7 (br s), 117.2, 116.8, 107.5, 60.8 (d, J = 5 Hz), 17.6, 16.2 (d, J = 6 Hz) ppm. ^{31}P NMR (DMSO-d_6, 162 MHz): δ = 13.6 ppm.

{4-[(4-Methyl-3-{[4-(pyridin-3-yl)pyrimidin-2-yl]amino}phenyl)carbamoyl]phenyl}-phosphonic acid (45c). Bromotrimethylsilane (380 µL, 2.90 mmol, 6.04 equiv.) is added to a suspension of diethyl {4-[(4-methyl-3-{[4-(pyridin-3-yl)pyrimidin-2-yl]amino}phenyl)-carbamoyl]phenyl}phosphonate (**45a·TFA**) (250 mg, 0.48 mmol, 1.00 equiv.) in DCM (10 mL), and the reaction mixture is stirred at room temperature overnight. Another portion of bromotrimethylsilane (380 µL, 2.90 mmol, 6.04 equiv.) is added, and the mixture is stirred for 8 h. Water is added, and the aqueous mixture is concentrated under reduced pressure. The residue is dissolved in water and basified with aqueous NH_4OH. The precipitate is collected by filtration, washed with H_2O and dried in vacuo to give 140 mg of the title compound as its mono-ammonium salt. A portion of this material (115 mg, 0.24 mmol) is triturated with aqueous hydrogen chloride solution (0.1 M, 2.4 mL), and the precipitate is filtered, washed with water and dried in vacuo to obtain 95 mg (42%) of the title compound as yellowish solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 10.28 (s, 1H), 9.28 (d, J = 1.7 Hz,

1H), 8.95 (s, 1H), 8.69 (dd, *J* = 4.6, 1.2 Hz, 1H), 8.52 (d, *J* = 5.2 Hz, 1H), 8.49 (ddd, *J* = 7.6, 1.8, 1.8 Hz, 1H), 8.10 (s, 1H), 8.01 (dd, *J* = 8.1, 3.0 Hz, 2H), 7.78-7.83 (m, 2H), 7.52 (br dd, *J* = 7.7, 4.9 Hz, 1H), 7.49 (br d, *J* = 8.0 Hz, 1H), 7.43 (d, *J* = 5.1 Hz, 1H), 7.22 (br d, *J* = 8.2 Hz, 1H), 2.23 (s, 3H) ppm. ^{13}C NMR (101 MHz, DMSO-d_6) δ = 164.8, 161.6, 161.1, 159.4, 151.3, 148.1, 137.8, 137.3 (br d, *J* = 3 Hz), 137.0 (br d, *J* = 86 Hz), 136.9, 134.4, 132.2, 130.4 (br d, *J* = 10 Hz), 130.0, 127.7, 127.2 (br d, *J* = 14 Hz), 123.7, 117.2, 116.7, 107.5, 17.6 ppm. ^{31}P NMR (DMSO-d_6, 162 MHz): δ = 11.4 ppm.

1-Methyl-1,4λ^5-azaphosphinan-4-one (47b). The synthesis is performed according to an adopted literature protocol.[65b] LAH (1.0 M in THF; 16.9 mL, 16.9 mmol, 2.0 equiv.) is added dropwise at 0 °C to a solution of 4-ethoxy-1-methyl-1,4λ^5-azaphosphinan-4-one[65a] (1.50 g, 8.45 mmol, 1.0 equiv.) in THF (50.0 mL), and the reaction mixture is stirred at 0 °C for 45 min. Water (300 µL), aqueous NaOH (15%; 300 µL) and again water (900 µL) is added, and the slurry is stirred at rt for 1 h, filtered and concentrated. The residue is repeatedly purified by flash chromatography on silica gel to give 500 mg (44%) of the title compound as a pale-yellow semi-solid. R_f (EtOAc) = 0.30. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 6.14 – 7.37 (m, 1H), 2.74 – 2.93 (m, 2H), 2.31 – 2.44 (m, 2H), 2.15 – 2.24 (m, 3H),

1.99 – 2.13 (m, 2H), 1.80 – 1.98 (m, 2H) ppm. ^{13}C NMR (DMSO-d_6, 101 MHz) δ = 51.2 (d, J = 6 Hz), 45.3, 26.3 (d, J = 62 Hz) ppm. ^{31}P NMR (DMSO-d_6, 162 MHz): δ = 22.4 ppm. IR (ATR): 3399, 2945, 2797, 2338, 1665, 1258, 1158, 1109, 1018, 956, 921, 765, 688 cm^{-1}. HRMS (ESI$^+$) calculated for $C_5H_{13}NOP$ $[M+H]^+$ m/z 134.0729, found 134.0728.

1-Isopropyl-1,4λ^5-azaphosphinan-4-one (47c). According to an adopted literature protocol,[65b] a solution of $LiAlH_4$ (1.0 M in THF; 19.5 mL, 19.5 mmol, 2.0 equiv.) is added to a solution of 4-ethoxy-1-isopropyl-1,4λ^5-azaphosphinan-4-one (2.00 g, 9.75 mmol, 1.0 equiv.) in THF (100 mL) at 0 °C, and the mixture is stirred at 0 °C for 45 min. Water (0.5 mL), aqueous sodium hydroxide (15%, 0.5 mL) and again water (1.5 mL) are added to the reaction mixture, and the slurry is stirred at room temperature for 1 h. The mixture is filtered, and the filtrate is concentrated under reduced pressure. The residue is purified by flash chromatography on silica (gradient ethyl acetate/cyclohexane 4:1 to ethyl acetate), appropriate fractions are concentrated and the obtained material is used without further purification in the next step.

1-Benzyl-4-[4-(trifluoromethyl)phenyl]-1,4λ^5-azaphosphinan-4-one (48). 4-(Trifluoromethyl)phenyl iodide (272 mg, 1.00 mmol, 1.0 equiv.) is added to a solution of $Pd_2(dba)_3$ (23.0 mg, 25.0 µmol, 2.5 mol%), Xantphos (29.0 mg, 50 µmol, 5.0 mol%), and 1-benzyl-1,4λ^5-azaphosphinan-4-one (**47a**)[65b] (251 mg, 1.20 mmol, 1.2 equiv.) in DIPEA (255 µL, 1.50 mmol, 1.5 equiv.) and DMF (4.00 mL). The reaction mixture is sealed in a microwave vial and heated at 110 °C overnight. The reaction mixture is diluted with saturated aqueous $NaHCO_3$ (20 mL) and the aqueous phase is extracted with EtOAc (3 x 20 mL). The combined organic phases are dried over Na_2SO_4 and concentrated. The residue is purified by preparative RP-HPLC (Waters XBridge^{TM} C_{18}, gradient of acetonitrile in water, 0.1% NH_4OH) to give 283 mg (81%) of the title compound as light-yellow oil. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 8.02 – 8.09 (m, 2H), 7.90 (dd, *J* = 8.4, 1.4 Hz, 2H), 7.31 – 7.38 (m, 4H), 7.23 – 7.29 (m, 1H), 3.64 (s, 2H), 2.74 – 2.92 (m, 4H), 2.23 – 2.34 (m, 2H), 1.89 – 2.02 (m, 2H) ppm. MS (ESI$^+$) calculated for $C_{18}H_{20}F_3NOP$ $[M+H]^+$ m/z 354.12, found 354.12.

[4-(Trifluoromethyl)phenyl]phosphonic dichloride (49). The reaction was performed using an adopted literature report.[91] Oxalyl chloride (1.59 g, 12.5 mmol, 2.5 equiv.) is

added dropwise to a refluxing suspension of [4-(trifluoromethyl)phenyl]phosphonic acid (**24a**) (1.13 g, 5.00 mmol, 1.0 equiv.) in DCM (10.0 mL) and DMF (10.0 µL), and the reaction mixture is heated at reflux for 1 h. The reaction mixture is concentrated, and the yellow solid is used directly in the next step without further purification.

***Tert*-butyl 2-oxo-2-[4-(trifluoromethyl)phenyl]-1,3,6,2λ^5-dioxazaphosphocan-6-carboxyl-ate (50).** A solution of [4-(trifluoromethyl)phenyl]phosphonic dichloride (**49**) (263 mg, 1.00 mmol, 1.0 equiv.) in THF (3.00 mL) is added dropwise to a solution of *tert*-butyl *N,N*-bis(2-hydroxyethyl)carbamate (216 mg, 1.05 mmol, 1.05 equiv.) and Et_3N (278 µL, 2.00 mmol, 2.0 equiv.) in THF (20.0 mL) at 0 °C, and the reaction mixture is allowed to warm to rt overnight. The reaction mixture is filtered over a plug of celite and the filter cake is rinsed with EtOAc (20 mL). The combined filtrates are concentrated and purified by flash chromatography on silica gel (gradient of MeOH in DCM; 0% – 5% MeOH) to give 157 mg (40%) of the title compound as a colorless oil. R_f (DCM:MeOH, 20:1) = 0.25. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 7.86 – 7.98 (m, 4H), 4.52 – 4.63 (m, 2H), 3.98 – 4.12 (m, 2H), 3.72 – 3.87 (m, 2H), 3.16 – 3.29 (m, 2H), 1.45 (s, 9H) ppm. ^{13}C NMR (DMSO-d_6, 101 MHz) δ = 154.1, 133.6 (br d, J = 199 Hz), 132.1 – 132.2 (m), 131.5 (d,

J = 10 Hz), 125.3 – 125.5 (m), 123.6 (q, *J* = 273 Hz), 79.5, 65.9 (br d, *J* = 8 Hz), 65.4 (br d, *J* = 7 Hz) 50.4, 50.2, 28.0 ppm. ^{31}P NMR (DMSO-d_6, 162 MHz): δ = 14.5 ppm. IR (ATR): 1692, 1367, 1324, 1240, 1129, 1091, 1030, 1017, 903, 730, 702 cm^{-1}. HRMS (ESI$^+$) calculated for $C_{16}H_{21}F_3NNaO_5P$ $[M+Na]^+$ m/z 418.1002, found 418.1003.

ASSOCIATED CONTENT

Supporting Information.

Spectroscopic data for all new compounds, descriptions of the physicochemical and *in vitro* assays, data for the biological activity of imatinib analogs in selected kinase assays as well as molecular formula strings can be found at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*Email: christian.gnamm@boehringer-ingelheim.com. Phone : (+49)7351-5498297.

Fax : (+49)7351-545181

Present Addresses

† Syngenta Crop Protection AG, Schaffhauserstrasse, 4332 Stein, Switzerland.

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

ORCID

Peter Finkbeiner: 0000-0001-7161-6388

Jörg P. Hehn: 0000-0002-1819-9623

Christian Gnamm: 0000-0001-7392-9513

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

We thank P. Sieger and K. Klinder for the measurement of the physicochemical and in vitro pharmacokinetic data and fruitful discussions. J. Willwacher, C. Kuttruff and K. Young are acknowledged for careful proofreading of the manuscript and helpful discussions.

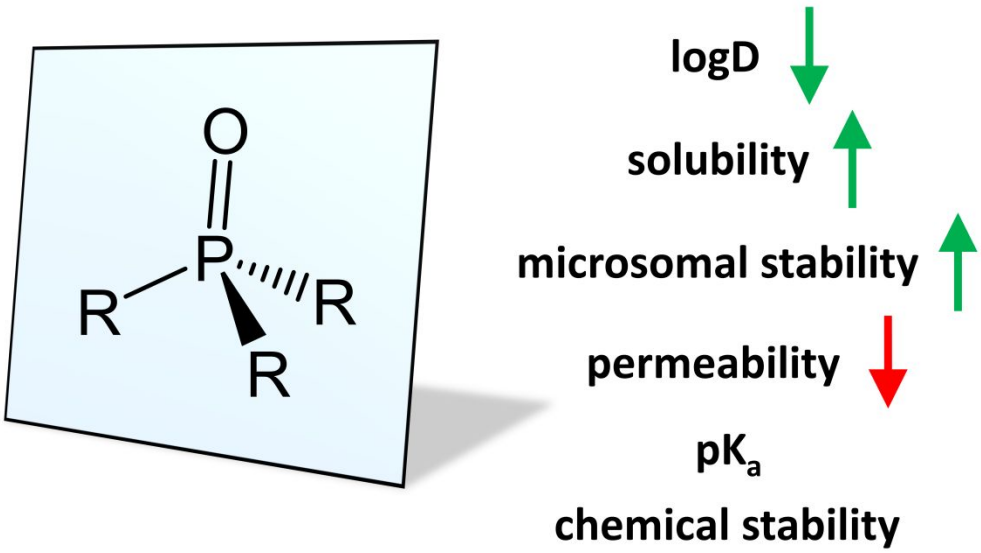
ABBREVIATIONS

ABL1, Abelson murine leukemia viral oncogene homolog 1; ALK, anaplastic lymphoma kinase; CCR2, C-C chemokine receptor 2; dba, dibenzylideneacetone; DIPEA, diisopropylethylamine; dppf, 1,1′-ferrocenediyl-bis(diphenylphosphine); EG, ethylene glycol; ENaC, epithelial sodium channel; FG, functional group; HATU, *N*-[(dimethylamino)-1*H*-1,2,3-triazolo-[4,5-b]pyridin-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide; HDAC1, histone deacetylase 1; HMDS, hexamethyldisilazane; HPLC, high-performance liquid chromatography; IUPAC, International Union of Pure and Applied Chemistry, KIT, proto-oncogene c-KIT; LCK,

lymphocyte-specific protein tyrosine kinase; MetAP2, methionine aminopeptidase 2; mTOR, mammalian target of Rapamycin; PDGFRb, platelet-derived growth factor receptor beta; PR, progesterone receptor; SYK, spleen tyrosine kinase; TMS, trimethylsilyl.

REFERENCES

For Table of Contents Only:



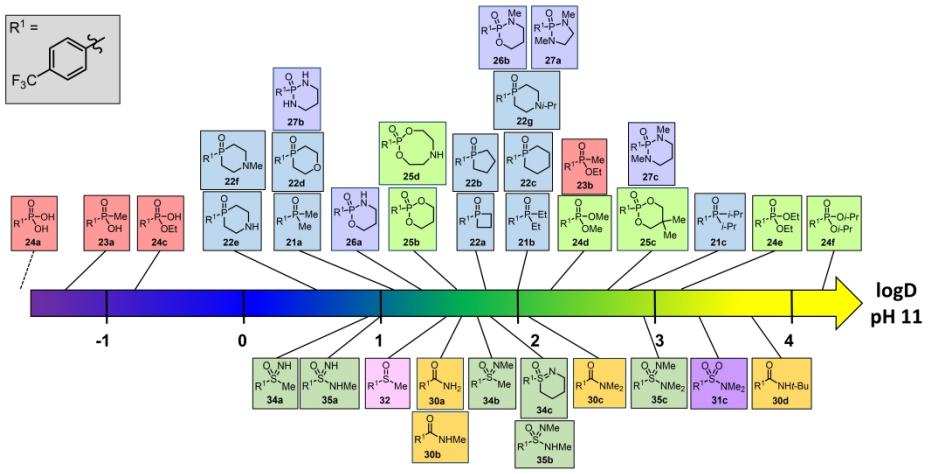


Figure 6: Graphical depiction of logD values of phosphorus-containing compounds and bioisosteres at pH 11.[77]

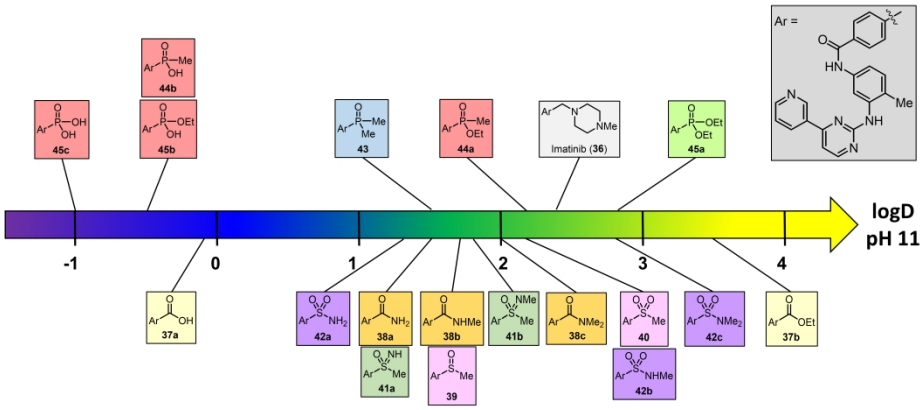
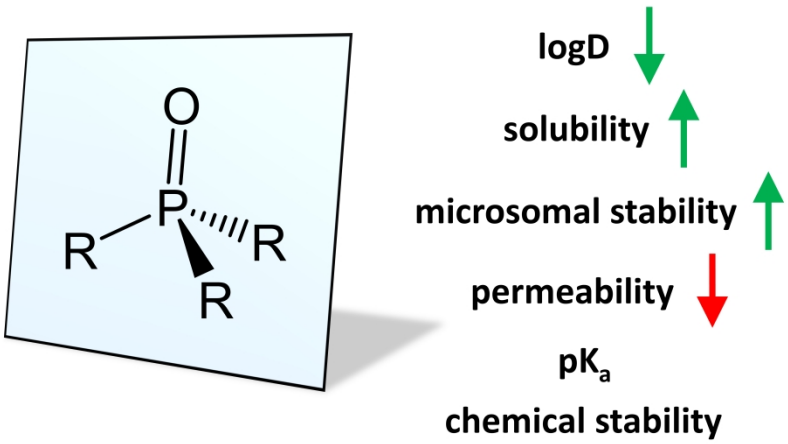


Figure 7: Graphical depiction of logD values of imatinib analogs at pH 11.


O
P
R
R
R
logD
solubility
microsomal stability
permeability
pK$_a$
chemical stability

TOC graphic