

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

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## 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

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4 Organophosphorus compounds have been investigated for applications in agricultural,<sup>1</sup>  
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7 veterinary,<sup>2</sup> and medicinal<sup>3</sup> applications for decades, and a considerable number of  
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10 phosphorus-containing drugs have achieved commercial success.<sup>4,5</sup> The majority of  
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13 these approved phosphorus-containing pharmaceuticals contain a phosphate, a  
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16 phosphoramidate or a phosphonate group, while phosphines, phosphinates and phosphine  
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19 oxides are rare. Among the successful examples of organophosphorus drug research are  
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22 the phosphorodiamidate based anti-cancer drugs cyclophosphamide (1) and ifosfamide  
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25 (2),<sup>6</sup> as well as the phosphoramidate and phosphonate containing reverse transcriptase  
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28 inhibitors tenofovir alafenamide<sup>7</sup> (3) and adefovir dipivoxil<sup>8</sup> (4) to fight infectious diseases  
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31 like HIV and hepatitis B, respectively (Figure 1). Several so-called bisphosphonates  
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34 containing a phosphonic acid motif such as etidronate (5) are used for the treatment of  
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37 osteoporosis,<sup>9</sup> and the natural product fosfomycin (6) is a broad spectrum antibiotic.<sup>10</sup> The  
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40 ACE inhibitor fosinopril (7) is so far the only approved phosphinate based drug on the  
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43 market and used for the treatment of hypertension.<sup>11</sup>  
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52 A major obstacle associated with the use of acidic phosphorus-containing functional  
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55 groups such as phosphates, phosphonates and phosphinates in drug discovery is their  
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3 occurrence as charged species at physiological pH, which often leads to low cell permeability and  
4 poor oral bioavailability.<sup>12,13</sup> In most orally administered phosphate-containing drugs the  
5 phosphate constitutes a solubility-enhancing prodrug<sup>14</sup> and is not part of the pharmacophore of the  
6 active principle itself, as for example in case of antiretroviral protease inhibitor fosamprenavir  
7 **(8)**,<sup>15</sup> SYK inhibitor fostamatinib **(9)**<sup>16</sup> and fospropofol **(10)**,<sup>17</sup> a widely used anesthetic (Figure 1).  
8 Similarly, many of the drugs containing a phosphonate or phosphinate are employed as prodrugs  
9 as exemplified e.g. by the phosphonate and phosphinate esters in adefovir dipivoxil **(4)** and  
10 fosinopril **(7)**, respectively, or the phosphoramidate in tenofovir alafenamide **(3)**. Also Gilead's  
11 remdesivir **(11)**,<sup>18</sup> a phase III antiviral drug originally developed for the treatment of ebola virus  
12 that is currently tested in clinical trials for efficacy against Covid-19,<sup>19</sup> constitutes a  
13 phosphoramidate prodrug.  
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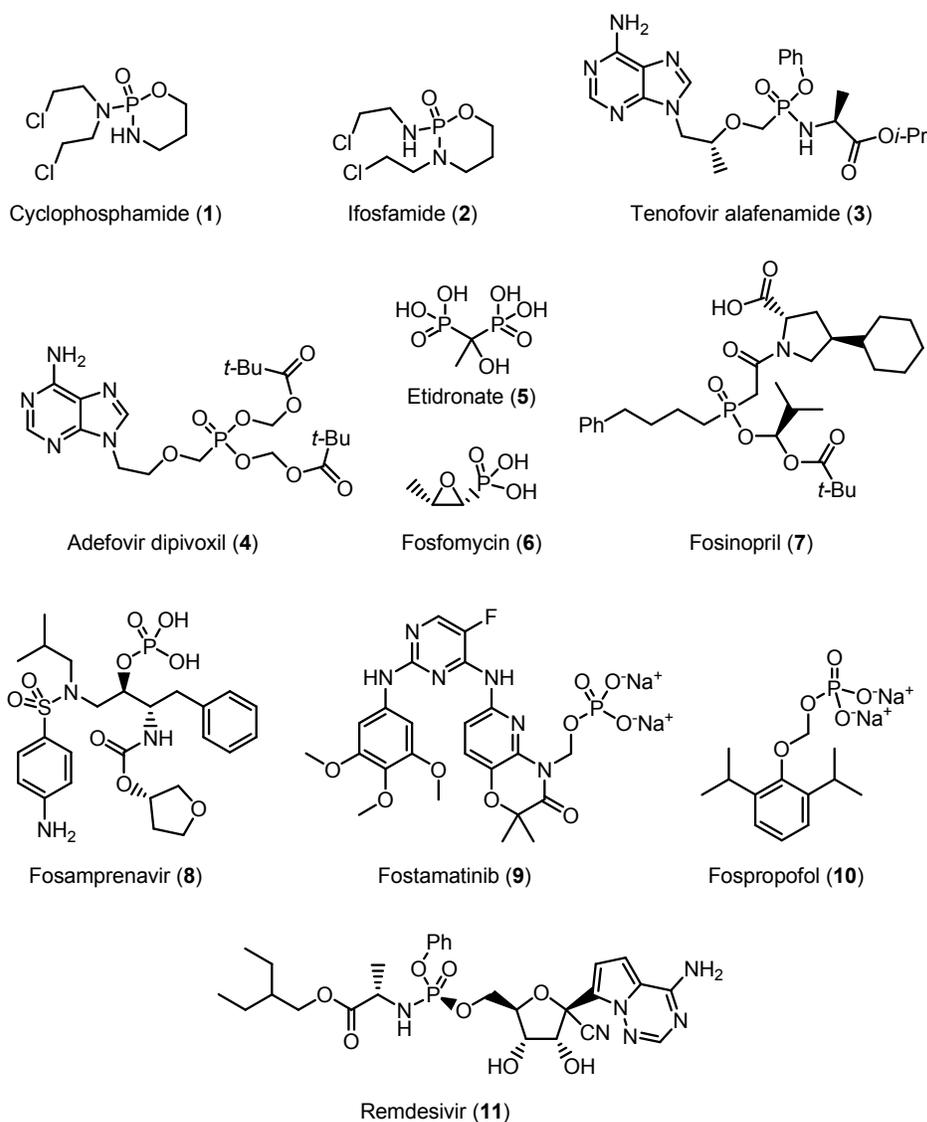


Figure 1: Selected examples of phosphorus-containing drugs.

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**,<sup>20</sup> progesterone receptor

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

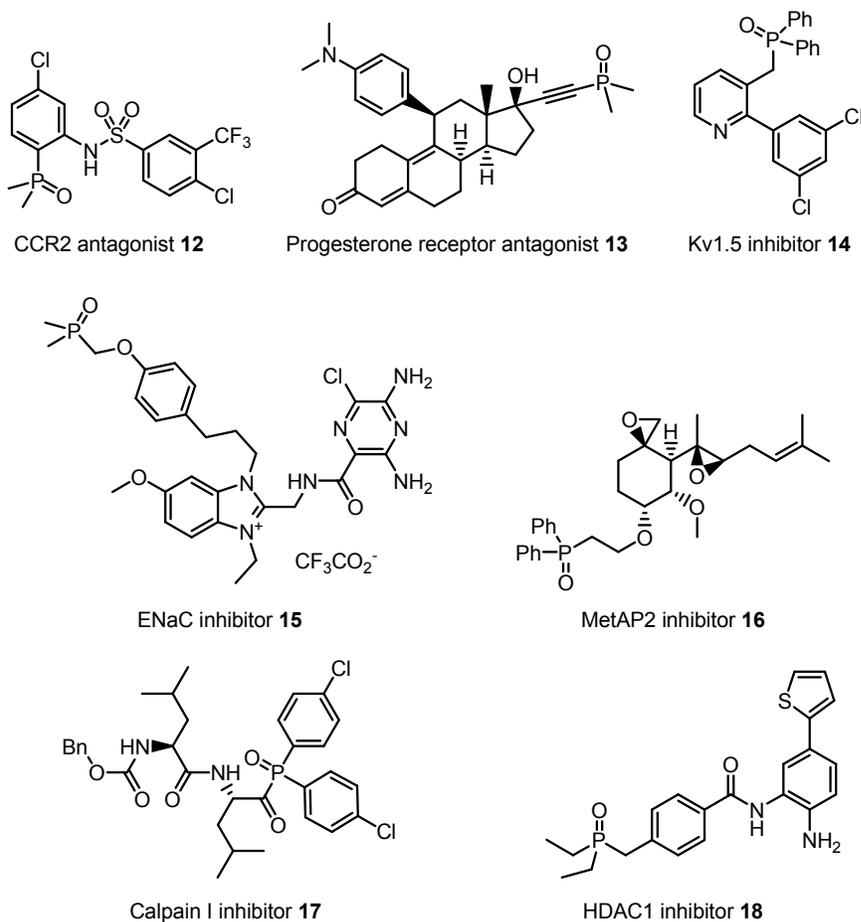


Figure 2: Recent examples for the application of phosphine oxides in medicinal chemistry.

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,<sup>27</sup> 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).<sup>28</sup>

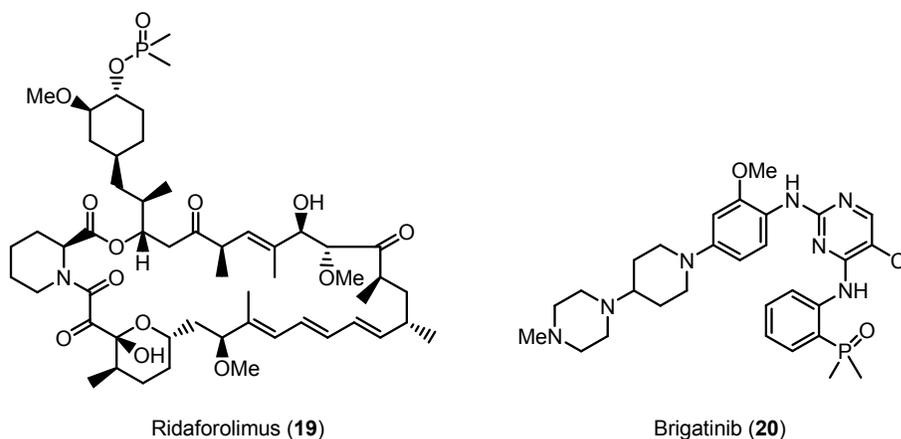


Figure 3: Ridaforolimus (19) and brigatinib (20) as examples for investigational or approved drugs with a non-charged phosphorus-containing functional group.

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 preceded. Additionally, they offer the unique feature of a very strong H-bond acceptor attached to a tetrahedral center with three potential vectors for derivatization.<sup>29</sup> Surprisingly, only few reports on the physicochemical properties and *in vitro* parameters of phosphine oxides and related phosphorus-containing functional groups are available today.<sup>26,28a,30</sup>

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.<sup>31</sup> Furthermore, the effects of phosphorus-containing functional groups on the properties of analogs of the approved tyrosine kinase inhibitor imatinib (36) are presented.<sup>32</sup>

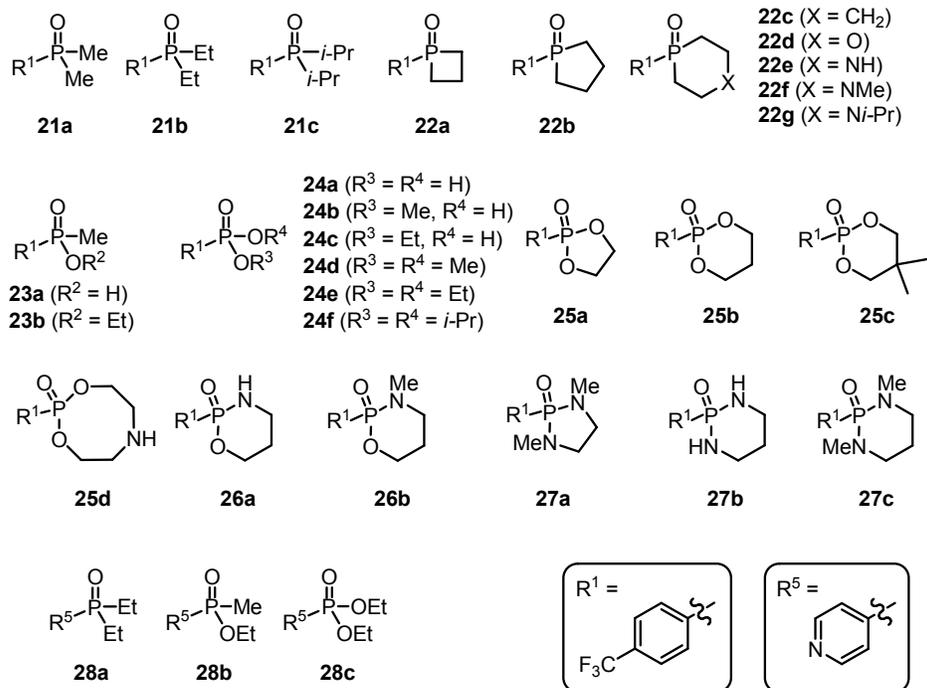
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## 2. RESULTS AND DISCUSSION

### 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 phosphinates **23a-b** and phosphonates **24a-25d** was outlined and rounded off by cyclic phosphoramidates **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),<sup>31</sup> 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**.<sup>33</sup>

## a) Design of phosphorus-containing tool compounds



## b) Design of bioisosteric tool compounds

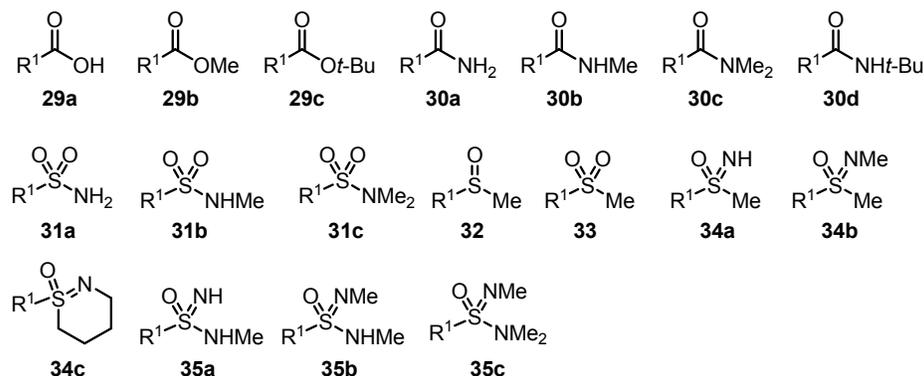


Figure 4: Design of a) tool compounds bearing phosphorus-containing functional groups and b) bioisosteric functional groups.

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**)<sup>32</sup> was selected as a reference and imatinib analogs **37a-45c** including phosphorus-containing or classical functional groups were designed (Figure 5).

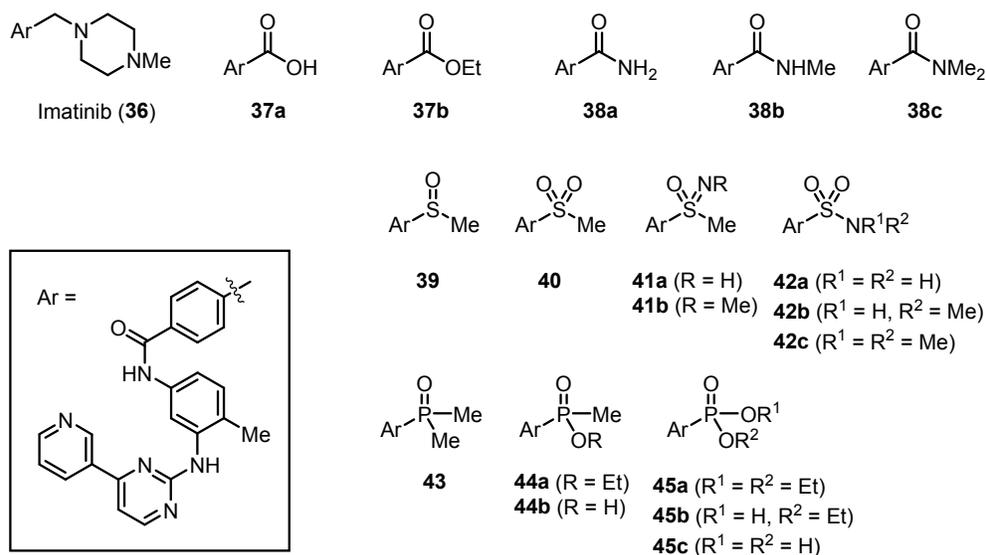
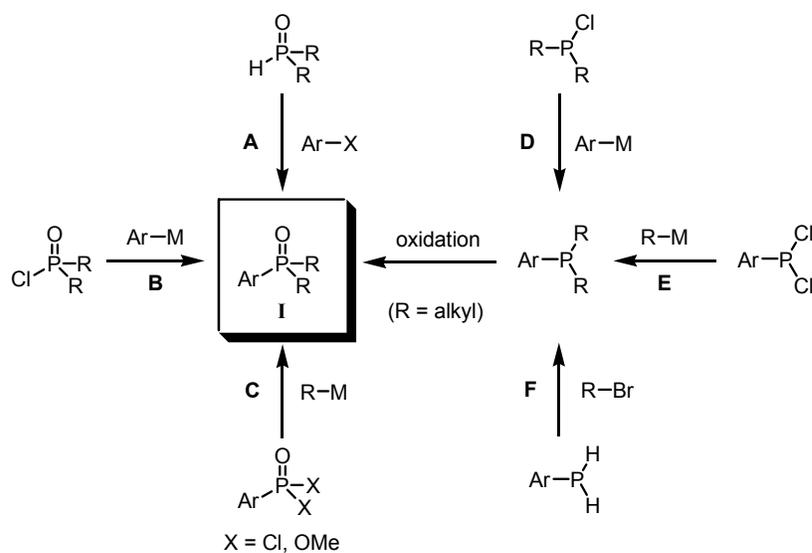


Figure 5: Design of imatinib analogs containing phosphorus-, sulfur- and carbon-based functional groups.

**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.<sup>34</sup> Symmetric tertiary

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4 aryldialkylphosphine oxides I can be synthesized in numerous ways, most conveniently  
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7 starting from corresponding phosphorus(V) H-phosphine oxide precursors via transition  
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10 metal catalyzed cross coupling methodologies (Scheme 1, A).<sup>35</sup> Alternatively, nucleophilic  
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13 arylation of dialkylphosphinoyl chlorides<sup>36</sup> (Scheme 1, B) and double nucleophilic addition  
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16 of organometallic species to arylphosphoryl dichlorides<sup>37</sup> and arylphosphonic acid  
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19 esters<sup>38</sup> (Scheme 1, C) have been described. In addition, P(III)-precursors like  
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22 dialkylphosphinyl chlorides<sup>39</sup> and aryldichlorophosphines are reported to react with  
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25 C-nucleophiles<sup>40</sup> (Scheme 1, D and E), and arylphosphines can be alkylated using alkyl  
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28 halides<sup>41</sup> (Scheme 1, F). However, when P(III) intermediates are employed, a subsequent  
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35 oxidation of the intermediate tertiary phosphines to the phosphine oxides I is required.  
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42 Scheme 1: Synthetic pathways for the construction of aryldialkylphosphine oxides I.  
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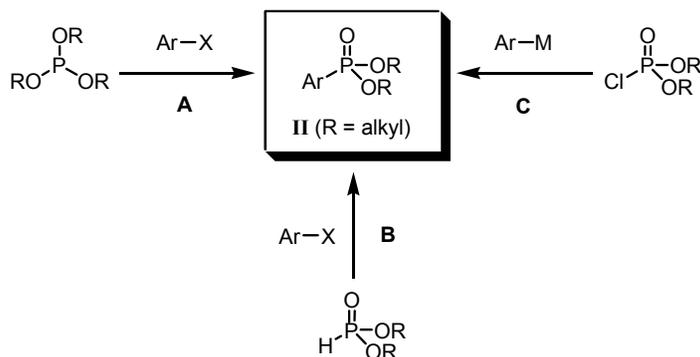
Similar to the preparation of phosphine oxides, a large number of methods exists for the synthesis of aryl phosphinates<sup>42</sup> and aryl phosphonates.<sup>43</sup> Acyclic dialkyl arylphosphonates **II** are accessed by the Arbuzov reaction between trialkylphosphites and aryl halides (Scheme 2, A). While electron-poor aryl halides can undergo direct  $S_NAr$ -type reaction with trialkylphosphites at elevated temperatures,<sup>44</sup> their electron-rich congeners require either radical initiators<sup>45</sup> or Ni-,<sup>46</sup> Pd-,<sup>47</sup> Cu-,<sup>48</sup> or photoredox-catalysis.<sup>49</sup> The Pd-catalyzed cross coupling of H-phosphonates and aryl halides was pioneered by Hirao and co-workers,<sup>50</sup> and is still inspiration to modern synthetic methodologies utilizing poorly activated aryl pseudohalides,<sup>51</sup> -amides and -esters (Scheme 2, B).<sup>52</sup> In addition,

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3 H-phosphonates are capable to react with nucleophiles like arylboronic acids,<sup>53</sup> -  
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7 sulfinates,<sup>54</sup> -silanes,<sup>55</sup> and C(aryl)-H bonds under oxidative coupling conditions.<sup>56</sup>  
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10 C(aryl)-P bond construction via nucleophilic addition of aryl Grignard reagents to acyclic  
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14 dialkyl chlorophosphates is well precedented (Scheme 2, C).<sup>57</sup>  
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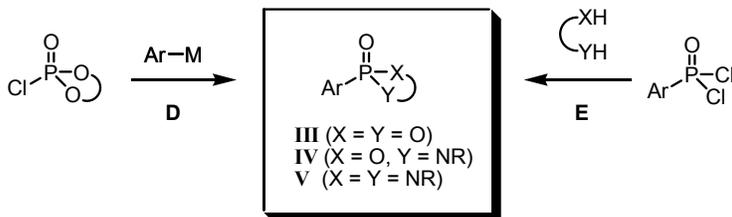
17 In contrast, the synthesis of cyclic alkyl arylphosphonates III by the reaction of a  
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20 nucleophilic aryl-metal species with a corresponding cyclic chlorophosphate is rather  
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24 challenging (Scheme 2, D).<sup>58</sup> However, cyclic alkyl arylphosphonates III,<sup>59</sup> -amidates IV,<sup>60</sup>  
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27 and -amides V<sup>61</sup> are readily accessible by the reaction of arylphosphonyl dichlorides with  
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31 diols, aminoalcohols, and diamines (Scheme 2, E).  
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Scheme 2: Synthetic pathways for the construction of a) aryldialkylphosphonates **II** and b) cyclic arylphosphonates **III**, -amidates **IV**, and -amides **V**.

a) Synthesis of symmetric acyclic aryldialkylphosphonates **II**



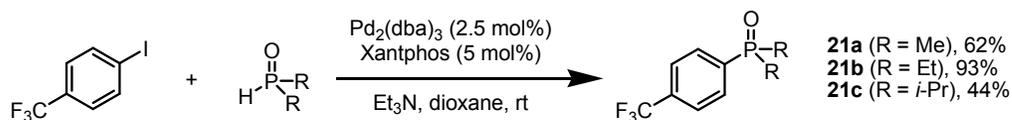
b) Synthesis of cyclic arylphosphonates **III**, -amidates **IV**, and -amides **V**



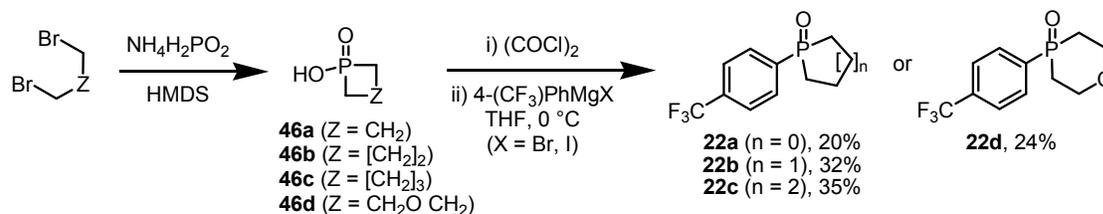
**Synthesis of acyclic and cyclic tertiary phosphine oxides **21** and **22**.** Our synthetic efforts aimed at the installation of the arene-phosphorus bond as the final step of every reaction sequence allowing an easy and modular exchange of aromatic moieties. The synthesis of tertiary acyclic phosphine 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).<sup>35c</sup>

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

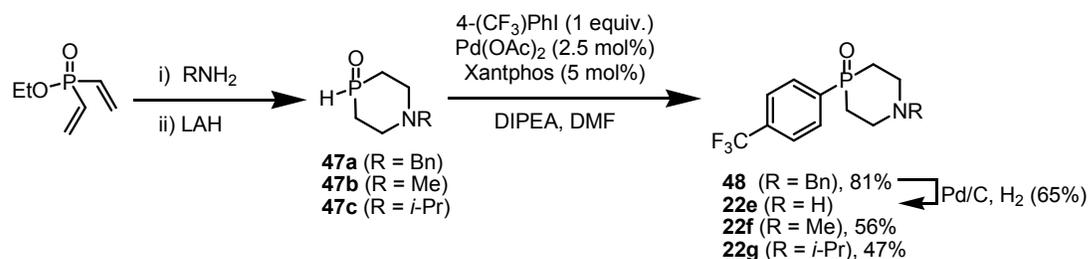
**a) Synthesis of acyclic phosphine oxides 21a-c**



**b) Synthesis of cyclic phosphine oxides 22a-d**



**c) Synthesis of cyclic N-containing phosphine oxides 22e-22g**



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

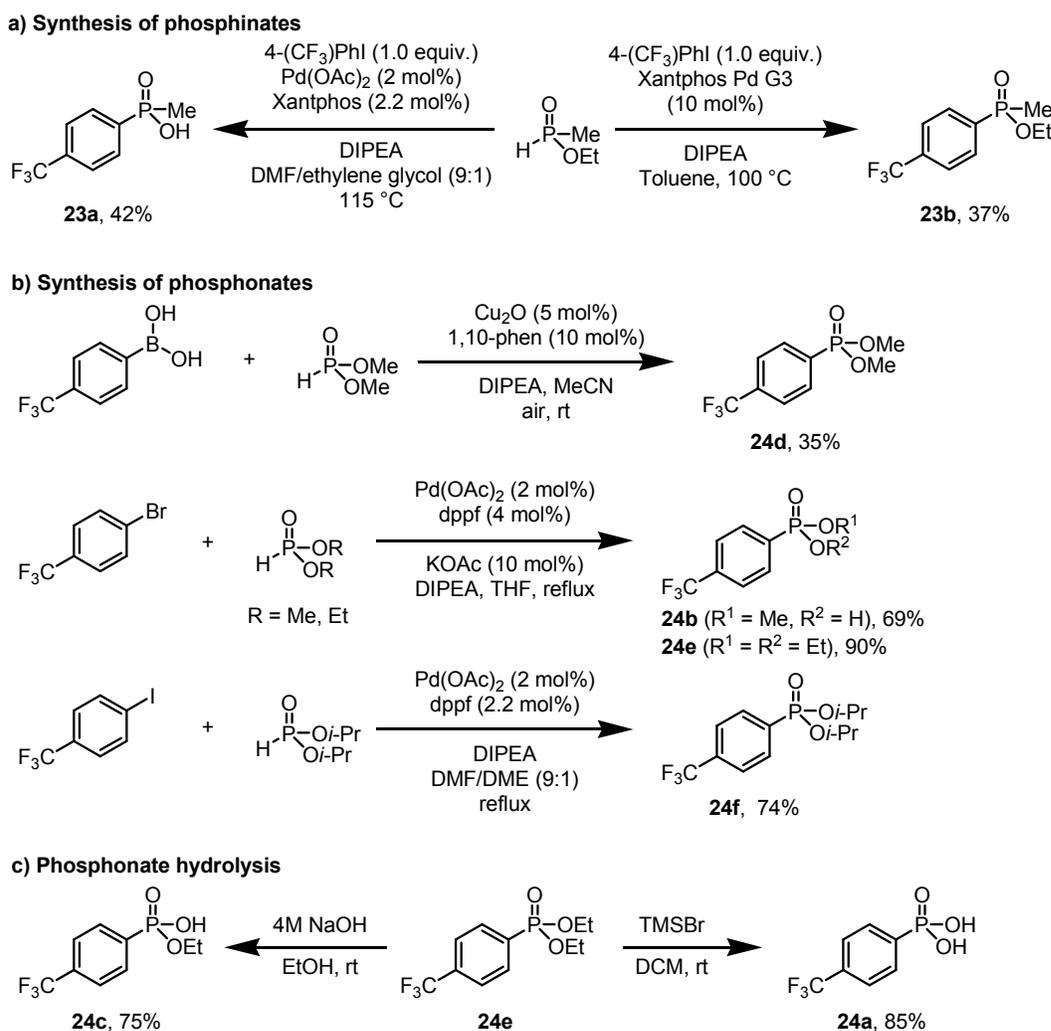
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3 phosphinoyl chlorides derived from cyclic phosphinic acids (Scheme 3b).<sup>62</sup> In our case,  
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7 the barely functionalized phosphinic acids **46a-d**<sup>62b-c</sup> were most conveniently accessed by  
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10 a robust double-Arbuzov reaction of alkyldihalides with ammonium phosphinate and  
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13 hexamethyldisilazane (HMDS). Activation of the phosphinic acids using oxalyl chloride  
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17 gave the corresponding phosphinoyl chlorides which upon treatment with 4-  
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20 (trifluoromethyl)phenylmagnesium halide<sup>63</sup> furnished cyclic aryl phosphine oxides **22a-d**  
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24 in 20-35% yield (over 2 steps).  
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28 The second route provides nitrogen-containing cyclic phosphine oxides via  
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31 Pd-mediated cross coupling of cyclic secondary phosphine oxides with aryl halides  
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34 (Scheme 3c). Precursors for phosphine oxides **22e-g** were assembled by double-Michael  
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37 addition of primary amines to ethyl divinylphosphinate.<sup>64,65</sup> Reduction of the  
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41 corresponding cyclic ethyl phosphinates (structure not shown) using lithium aluminium  
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45 hydride (LAH) afforded cyclic secondary phosphine oxides **47a-c**,<sup>65b</sup> which smoothly  
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49 reacted in Pd-mediated cross coupling reactions with 4-(trifluoromethyl)phenyl iodide to  
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52 give cyclic phosphine oxides **48** (and **22e** after subsequent hydrogenation), **22f** and **22g**  
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56 in good yields (47-81%).  
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3       **Synthesis of arylphosphinates 23 and acyclic arylphosphonates 24.** Phosphinates can  
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7 be synthesized by palladium-mediated cross coupling, occasionally accompanied by  
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10 undesired transesterification events or base-promoted dealkylation.<sup>42c,66</sup> The reaction of  
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13 ethyl methylphosphinate with 4-(trifluoromethyl)phenyl iodide directly delivered the  
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17 phosphinic acid **23a** in 42% yield when a mixture of DMF and ethylene glycol was used  
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20 as solvent, while similar conditions using toluene as solvent furnished ethyl phosphinate  
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24 **23b** in 37% yield (Scheme 4a).

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27       Dimethyl phosphonate **24d** was prepared by an Cu-catalyzed oxidative coupling of  
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31 4-(trifluoromethyl)phenylboronic acid and dimethyl phosphite in 35% yield (Scheme 4b).<sup>53</sup>  
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35 Dialkyl phosphonates **24e** and **24f** were obtained through Pd-mediated cross coupling  
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38 with 4-(trifluoromethyl)phenyl halides in 90% and 74% yield, respectively.<sup>67,42c</sup> However,  
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41 when dimethyl phosphite was employed, the partially dealkylated methoxyphosphinic  
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45 acid **24b** was obtained in 69% yield.<sup>68</sup> Diethyl phosphonate **24e** was selectively converted  
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48 to the ethoxyphosphinic acid **24c** in 75% yield using aqueous NaOH, or to phosphinic  
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52 acid **24a** in 85% yield upon treatment with trimethylsilyl bromide (Scheme 4c).<sup>69</sup>  
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Scheme 4: Synthesis of a) phosphinates **23** and b) phosphonates **24**, and c) selective hydrolysis of diethyl phosphonate **24e**.

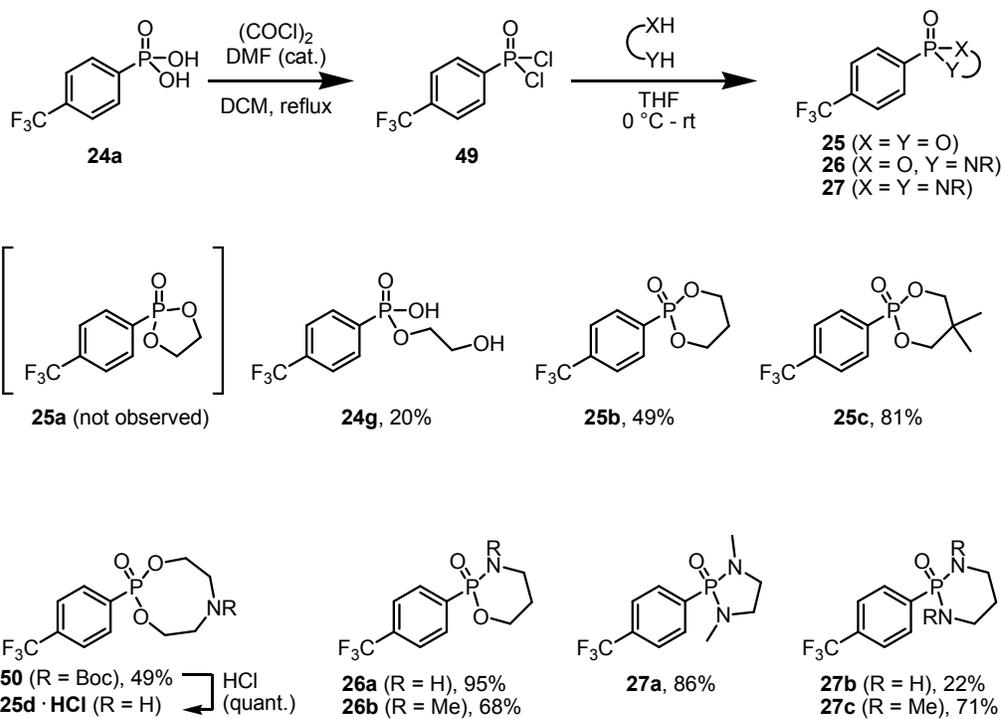


Synthesis of cyclic phosphonates **25**, phosphoramidates **26**, and phosphonamides **27**.

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

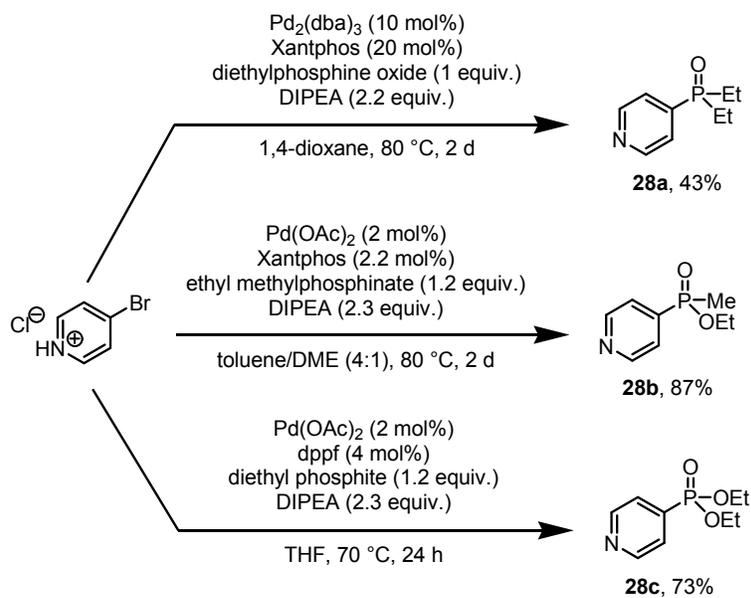
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4 phosphonic acid dichloride **49** by treatment with oxalyl chloride, and the crude product  
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7 was directly reacted with the selected diols, aminoalcohols, or diamines (Scheme 5). The  
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10 attempted synthesis of arylphosphonic acid ethylene ester **25a**<sup>38,70</sup> however was sluggish  
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13 and resulted in the isolation of hydrolyzed compound **24g** (20%) as the sole product.<sup>71</sup> In  
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16 contrast, the dioxaphosphinane-2-ones **25b** and **25c** were obtained in good yields of 49%  
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19 and 81%, respectively. Dioxazaphosphocan-2-one **50** was isolated in 49% yield and  
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22 subsequent cleavage of the Boc protecting group (HCl/dioxane) afforded compound **25d**  
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25 as a hydrochloride salt in quantitative yield. In the same manner, arylphosphonamidates  
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31 **26a-b** and arylphosphonamides **27a-c** were prepared in 68-95% yield and 22-86%,  
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35 respectively.

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



31      **Synthesis of pyridine derivatives 28a-c.** Pyridine derivatives **28a-c** were synthesized by  
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34      Pd-catalyzed coupling of 4-bromopyridine hydrochloride with diethylphosphine oxide,  
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37      ethyl methylphosphinate or diethyl phosphite in moderate to excellent yields of up to 87%  
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41      (Scheme 6).  
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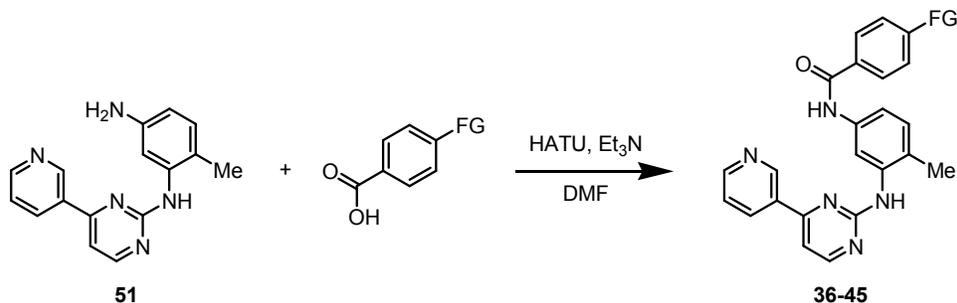
## Scheme 6: Synthesis of pyridines bearing phosphorus-containing functional groups.



**Synthesis of imatinib analogs 37-45.** The imatinib analogs **37-45** were synthesized starting from a commercially available aniline building block **51**,<sup>72</sup> 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**<sup>73</sup> were obtained in 92% and 91% yield, respectively, whereas sulfoximines **41a-b** and sulfonamides **42a-c** were isolated in lower yields of 20-

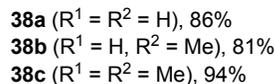
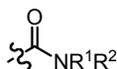
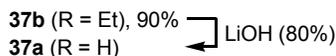
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4 69% (conditions not optimized). Phosphine oxide analog **43**<sup>74</sup> was isolated in 91% yield  
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7 after HATU coupling (Scheme 7c). The low yielding synthesis of ethyl phosphinate **44a**  
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9  
10 and phosphinic acid derivate **44b** is the result of an unselective hydrolysis of ethyl  
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12  
13 4-[ethoxy(methyl)phosphoryl]benzoate and was not optimized.<sup>75</sup> Diethyl phosphonate  
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15  
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17 **45a** was obtained in a good yield of 83%, and subsequently converted under standard  
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20 conditions to the ethoxyphosphinic acid **45b** and phosphonic acid **45c** in 62% and 38%  
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24 yield, respectively.  
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31 Scheme 7: Synthesis of imatinib analogs bearing a) carbon-, b) sulfur-, or c) phosphorus-  
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34 based functional groups.  
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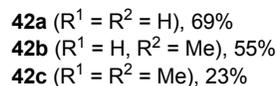
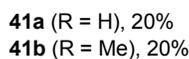
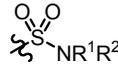
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**a) Carbon-based functional groups**



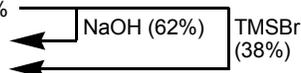
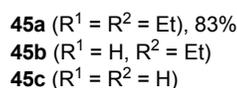
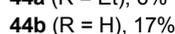
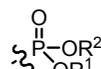
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**b) Sulfur-based functional groups**



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**c) Phosphorus-based functional groups**



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**2.3 Physicochemical and *in vitro* properties of tool compounds 21-35.** For all synthesized

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phosphorus-containing compounds the relevant physicochemical and *in vitro* pharmacokinetic parameters such as lipophilicity (logD), dissociation constants (pK<sub>a</sub>/pK<sub>b</sub>, where appropriate), aqueous solubility (HPLC and shake flask assay),<sup>76</sup> 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**.<sup>a</sup>

Compound	Structure	logD		pK <sub>a</sub> or pK <sub>b</sub>	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 <sub>1/2</sub> [min]	%Q <sub>H</sub>	HPLC assay	Shake flask assay	P <sub>A→B</sub> [10 <sup>-6</sup> cm/s]	Efflux ratio	pH <1	pH >10
<b>21a</b>		1.5	1.1	n.d.	>130	<23	>52	>30,000	82	0.5	<10	<10
<b>21b</b>		2.3	2.0	n.d.	>130	<23	>60	22,500	88	0.7	<10	<10
<b>21c</b>		3.1	2.8	n.d.	>130	<23	>61	22,200	110	0.5	<10	<10
<b>22a</b>		1.8	1.6	n.d.	>130	<23	>53	24,500	78	0.8	<10	<10
<b>22b</b>		2.0	1.7	n.d.	>130	<23	>59	24,500	69	0.7	<10	<10
<b>22c</b>		2.4	2.0	n.d.	>130	<23	>66	7,700	49	1.1	<10	<10
<b>22d</b>		1.4	1.1	n.d.	>130	<23	>65	>30,000	65	0.7	<10	<10
<b>22e</b>		0.0	0.5	pK <sub>b</sub> 6.9	>130	<23	>61	28,000	13	1.1	<10	<10
<b>22f</b>		0.0	0.9	pK <sub>b</sub> 6.3	>130	<23	>66	>30,000	52	0.7	<10	<10
<b>22g</b>		0.2	2.0	pK <sub>b</sub> 7.0	>130	<23	>68	23,000	84	0.5	<10	<10
<b>23a</b>		1.3	-1.3	pK <sub>a</sub> 2.0	>130	<23	>49	>8,900 <sup>b#</sup>	<5	-	<10	<10
<b>23b</b>		2.5	2.3	n.d.	>130	<23	n.v.	n.d.	69	1.0	n.d.	n.d.
<b>24a</b>		0.6	<-1.6	pK <sub>a1</sub> <2.0 pK <sub>a2</sub> 6.8	n.v.	n.v.	>54	17,800 <sup>b*</sup>	n.v.	-	<10	<10
<b>24b</b>		1.3	n.v.	n.v.	>130	<23	>60	27,300 <sup>b§</sup>	n.v.	-	<10	<10
<b>24c</b>		1.9	-0.8	n.v.	>130	<23	>64	28,000 <sup>b§</sup>	10	<0.1	<10	<10
<b>24d</b>		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) [ $\mu\text{g/mL}$ ]		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 <sup>bs</sup>	n.v.	-	<10	<10
25b		2.1	1.5	n.d.	>130	<23	>66	8,800	95	0.4	<10	>90 <sup>c</sup>
25c		3.1	2.6	n.d.	>130	<23	>67	2,800	73	0.6	<10	>90 <sup>c</sup>
25d		0.5	1.5	$pK_b$ 6.0	>130	<23	66	>10,000	63	0.7	<10	70 <sup>d</sup>
26a		2.0	1.3	n.v.	>130	<23	>60	n.v.	57	0.7	>90 <sup>c</sup>	>90 <sup>c</sup>
26b		2.5	1.9	n.d.	>130	<23	53	7,500	64	0.5	>90 <sup>c</sup>	<10
27a		n.v.	2.0	n.d.	n.v.	n.v.	>64	>30,000	n.v.	-	>90 <sup>c</sup>	<10
27b		n.v.	1.1	n.v.	>130	<23	>61	12,300	42	0.7	>90 <sup>c</sup>	<10
27c		3.0	2.7	n.d.	>130	<23	>68	11,100	81	0.5	>90 <sup>c</sup>	<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.

<sup>a</sup>R<sup>1</sup> = 4-(CF<sub>3</sub>)-phenyl; R<sup>2</sup> = 4-pyridyl; n.d.: not determined; n.v.: no valid data; color-coding: green: desirable, yellow: acceptable, red: undesirable. <sup>b</sup>Buffer capacity exceeded: sample measured at #pH 5.9, \*pH 2.3, §pH 2.0 and \$pH 2.1. <sup>c</sup>Result after one day. <sup>d</sup>20% decomposition observed under neutral conditions.

Table 2: Physicochemical and *in vitro* parameters of bioisosteric tool compounds 29-35.<sup>a</sup>

Compound	Structure	logD		pK <sub>a</sub> or pK <sub>b</sub>	Stability in human liver microsomes		Aqueous solubility (pH 6.8) [μg/mL]		Caco-2 permeability	
		pH 2	pH 11		T <sub>1/2</sub> [min]	%Q <sub>H</sub>	HPLC assay	Shake flask assay	P <sub>A→B</sub> [10 <sup>-6</sup> cm/s]	Efflux ratio
29a		n.v.	n.v.	pK <sub>a</sub> 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 <sub>a</sub> 9.4	>130	<23	>48	800	83	0.6
31b		n.v.	n.v.	pK <sub>a</sub> 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 <sub>b</sub> 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 <sub>b</sub> 3.8	>130	<23	>59	4,700	84	0.7
35a		0.8	1.0	pK <sub>b</sub> 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

<sup>a</sup>R<sup>1</sup> = 4-(CF<sub>3</sub>)-phenyl; n.d.: not determined; n.v.: no valid data; color-coding: green: desirable, yellow: acceptable, red: undesirable.

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4       **Lipophilicity (logD)**. Amongst the phosphorus-containing compounds that are not ionized at  
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7 physiological pH, phosphine oxides such as **21a** and **22a** are the most polar ones, exhibiting a  
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9 polarity comparable to sulfoxide **32**, sulfoximine **34a** and sulfonimidamide **35a** (Figure 6).<sup>77</sup> As  
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11 expected, the lipophilicity of phosphine oxides can be fine-tuned by the size of the aliphatic  
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13 residues (**21b-c**, **22b-c**) and polarity can be increased by introduction of additional heteroatoms  
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15 like in ether **22d** or amines that are considerably protonated at physiological pH, such as **22e-g**.  
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17 Dialkyl phosphonates **24d-f** are about one log unit more lipophilic than their phosphine oxide  
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19 congeners **21a-c**, while the cyclic phosphonate **25b** is more polar than the corresponding  
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21 phosphine oxide of identical ring size **22c**. In comparison to the cyclic phosphine oxide **22c** (logD  
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23 2.0 at pH 11), the corresponding phosphonamidate **26a** and phosphonamide **27b** are more polar  
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25 with logD values of 1.3 and 1.1, respectively, while the methylated analogs **26b**, **27a** and **27c** show  
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27 comparable or higher lipophilicity with logD values of 1.9 - 2.7. The phosphinic and phosphonic  
28  
29 acid derivatives **23a** and **24a** are predominantly ionized at physiological pH and represent the most  
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31 polar phosphorus-containing functional groups covered by this study as indicated by their low  
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33 logD values at pH 2 (1.3 and 0.6) and at pH 11 (-1.3 and <-1.6), respectively.  
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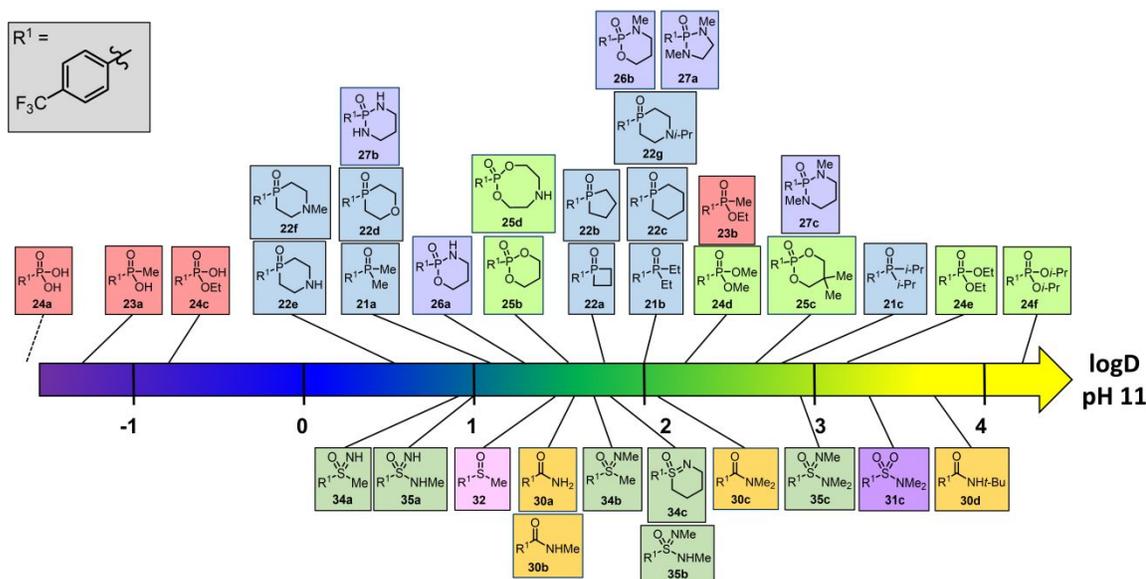


Figure 6: Graphical depiction of logD values of phosphorus-containing compounds and bioisosteres at pH 11.<sup>77</sup>

**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.<sup>78</sup> 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).<sup>79</sup> 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-methylsulfonylpyridine ( $pK_b < 2$ ).<sup>80</sup> Phosphinic acid **23a** and phosphonic acid **24a** were found to be considerably

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3 more acidic than benzoic acid (two log units) with pK<sub>a</sub> values of 2.0 (**23a**) and <2.0 (**24a**),<sup>81</sup>  
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5 respectively, while the second dissociation of phosphonic acid **24a** was detected at pK<sub>a</sub> 6.8.<sup>82</sup>  
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10 **Aqueous solubility.** Only limited conclusions can be drawn from the solubility data measured  
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12 in the high-throughput HPLC assay, as most of the compounds are soluble beyond the upper  
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14 detection limit of the assay (≈250 μM). The majority of the compounds measured in the shake  
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16 flask solubility assay show very high aqueous solubility >10 mg/mL with up to >30 mg/mL for  
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18 the most soluble compounds, such as phosphine oxides **21a**, **22d**, **22f** and phosphonamide **27a**.  
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20 Only the most lipophilic derivatives, namely the dialkyl phosphonates **24e** and **24f** with logD  
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22 values of 3.4 and 4.3, respectively, show more attenuated solubilities of 1.3 and 0.4 mg/mL,  
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24 respectively. The phosphorus-containing compounds investigated in this study are considerably  
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26 more soluble than most of the more commonly used functional groups represented by the  
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28 bioisosteric tool compounds, such as esters **29b-c**, carboxamides **30a-c**, sulfonamides **31a-c** and  
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30 sulfone **33**, which all have solubilities <1 mg/mL. Only the carboxylic acid **29a**, the sulfoxide **32**,  
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32 the sulfoximines **34a-c** and the sulfonimidamides **35a-c** show comparably high solubilities  
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34 between 1-10 mg/mL.  
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44 **Metabolic stability.** All phosphorus-containing compounds tested were found to be stable in  
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46 human liver microsomes beyond the scope of the assay (*t*<sub>1/2</sub> > 130 min), notably also the  
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48 comparatively lipophilic diethyl and diisopropyl phosphonates **24e** and **24f** with logD values of  
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50 3.4 and 4.3, respectively. This consistent dataset allows to conclude that none of these phosphorus-  
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52 containing functional groups is an intrinsic metabolic weak spot.  
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6 **Permeability.** As expected for compounds of comparatively low molecular weight, most  
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9 phosphorus-containing compounds show (very) high Caco-2 permeability, even those that are very  
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11 polar (cyclic and acyclic phosphine oxides **21** and **22**) and/or contain an ionizable group  
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13 (ethoxyphosphinic acid **24c**).  
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18 **Chemical Stability.** To assess the chemical stability of the functional groups, we studied their  
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21 degradation in methanolic solution after addition of aqueous HCl (pH<1) and NH<sub>3</sub> (pH>10),  
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23 respectively, for seven days (MeOH/H<sub>2</sub>O: 15/1, for details see the supporting information). All  
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25 tested phosphine oxides **21-22**, phosphinic and phosphonic acid **23a** and **24a**, alkoxyphosphinic  
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27 acids **24b-c** and **24g** as well as acyclic dialkylphosphonates **24d-f** were found to be stable under  
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29 both, acidic and basic conditions. Interestingly, cyclic phosphonates **25b-d** were less stable than  
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31 their acyclic congeners **24d-f** and decomposed under basic conditions.<sup>83</sup> The cyclic NH-  
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33 phosphonamidate **26a** decomposed quickly under both acidic and basic conditions, while the  
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35 methylated analog **26b** is stable at pH 11. In contrast to the cyclic phosphonates **25b-d**, their aza-  
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37 analogs, namely the cyclic phosphonamides **27a-c** were stable under basic conditions but  
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39 decomposed under acidic conditions.  
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## 46 **2.4 Physicochemical and *in vitro* properties of imatinib 36 and imatinib analogs 37-45.**

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50 Having evaluated the properties of phosphorus-containing functional groups in small tool  
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54 compounds based on a 4-CF<sub>3</sub>-phenyl core, we sought to investigate their effect on the  
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4 physicochemical properties of more drug-like molecules. To that end, we replaced the  
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7 methylpiperazine motif in imatinib (**36**) with different functional groups (cf. Figure 5 and  
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10 Scheme 7) and measured the physicochemical properties of these imatinib analogs  
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13 (Table 3). In comparison to imatinib (**36**) and its analogs containing more classical  
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15 functional groups like carboxylic acid **37a**, and ester **37b**, carboxamides **38**, sulfoxide **39**,  
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17 sulfone **40**, sulfoximines **41** and sulfonamides **42**, the phosphorus-containing analogs **43-**  
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21 sulfone **40**, sulfoximines **41** and sulfonamides **42**, the phosphorus-containing analogs **43-**  
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24 **45** cover a larger and more polar range of polarity as can be seen from their logD values  
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28 at different pH (Table 3, Figure 7).

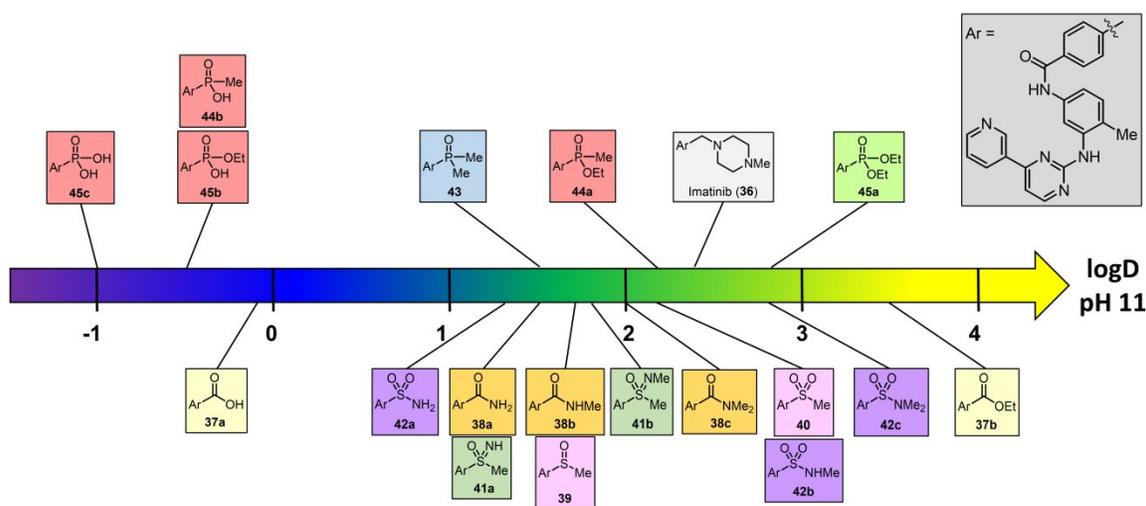
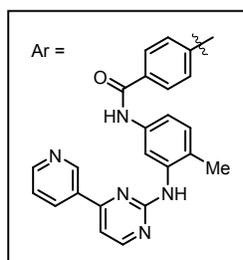


Figure 7: Graphical depiction of logD values of imatinib analogs at pH 11.

Table 3: Physicochemical and *in vitro* parameters of imatinib (**36**) and imatinib analogs**37-45.**<sup>a,85</sup>

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

Compound <sup>85</sup>	Structure	logD (HPLC assay)		Stability in human liver microsomes		Aqueous solubility (pH 6.8) [ $\mu\text{g/mL}$ ]		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	[%]
<b>44b</b>		0.6	-0.6	>130	<23	>115	>10,000	<0.1	-	88.1
<b>45a</b>		1.5	2.8	17	70	1	< 1	18	1.6	98.1
<b>45b</b>		1.0	-0.6	>130	<23	>122	1,100	<0.1	-	95.4
<b>45c</b>		0.4	-1.0	>130	<23	>115	700	<0.3	-	97.9

<sup>a</sup>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**.

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2  
3 Kinase inhibitors tend to exhibit poor solubility and the methylpiperazine moiety of  
4 imatinib (**36**) was incorporated to improve both solubility and oral bioavailability.<sup>32,84</sup> The  
5  
6 aqueous solubility of imatinib and its analogs was first determined by an HPLC-based  
7  
8 high-throughput assay starting from DMSO stock solution.<sup>85</sup> However, as the solubility of  
9  
10 imatinib (**36**) (>122 µg/mL) and several analogs was beyond the scope of this assay, we  
11  
12 decided to analyze and compare the data from a shake-flask assay, which uses solid  
13  
14 material and is not restricted by an upper limit for quantification of high solubilities. In the  
15  
16 shake flask assay, imatinib (**36**) showed poor solubility of only 2 µg/mL, however, this  
17  
18 strong discrepancy in comparison to the HPLC assay is likely due to the high crystallinity  
19  
20 of the applied material. Amongst the classical functional groups tested only carboxylic  
21  
22 acid **37a** led to a similarly high solubility (HPLC assay), but at the cost of very poor Caco-2  
23  
24 permeability. All other compounds with more classical functional groups (**37b**, **38-42**)  
25  
26 showed very poor solubility.  
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49 Amongst the uncharged phosphorus-containing analogs, lipophilic diethyl phosphonate  
50  
51 **45a** showed poor solubility while phosphine oxide **43** and ethyl phosphinate **44a** were  
52  
53 moderately more soluble. In striking contrast, phosphinic acid **44b**, ethoxyphosphinic acid  
54  
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4 **45b** and phosphonic acid **45c** (i.e. those phosphorus-containing analogs that are ionized at  
5  
6  
7 physiological pH), exhibited a very high solubility up to >10 mg/mL.  
8  
9

10 Some of the highly polar phosphorus-containing analogs still show moderate or even  
11  
12 high Caco-2 permeability, such as ethyl phosphinate **44a** and diethyl phosphonate **45a**.  
13  
14  
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16  
17 Notably, the former represents an optimal compromise of polarity and acceptable  
18  
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20  
21 microsomal stability, solubility and permeability.  
22  
23

24 In comparison to methylpiperazine imatinib (**36**) and its carboxylic acid analog **37a**,  
25  
26  
27 which both show high binding to human plasma protein (hPPB) of 96.9% and 94.9%, the  
28  
29  
30  
31 corresponding phosphine oxide **43** and sulfoximine **41a** have a reduced hPPB of 83.7%  
32  
33  
34 and 85.4%, respectively. Interestingly, phosphinic acid **44b** exhibits a comparatively low  
35  
36  
37  
38 hPPB of 88.1%, while diethyl phosphonate **45a**, ethoxyphosphinic acid **45b** and  
39  
40  
41  
42 phosphonic acid **45c** show a high hPPB between 95.4% and 98.1%.  
43  
44

45 Although it was beyond the scope of this study on the properties of phosphorus-  
46  
47  
48 containing functional groups, all imatinib analogs **37-45** were tested towards their  
49  
50  
51  
52 inhibition of PDGFR $\beta$ , ABL1, LCK and KIT and found to show no or significantly reduced  
53  
54  
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56 activity (see Table S2 in the supporting information for details).  
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### 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.<sup>86</sup>

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3 Reflecting their high polarity, phosphine oxides and the other phosphorus-containing  
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7 functional groups exhibited very high aqueous solubility and were found to be stable in  
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9  
10 human liver microsomes without revealing a metabolically weak spot. As expected for  
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13  
14 compounds of comparable low molecular weight, high permeability was found even for  
15  
16  
17 the most polar and some ionized phosphorus-containing tool compounds.  
18  
19

20  
21 Phosphine oxides, acyclic dialkyl phosphonates as well as phosphinic and phosphonic  
22  
23  
24 acids were found to be stable under both acidic and basic conditions, while cyclic  
25  
26  
27 phosphonates, phosphonamidates and phosphonamides showed reduced stability under  
28  
29  
30  
31 either acidic or basic conditions.  
32  
33

34  
35 Our analysis of the phosphorus-containing analogs of imatinib showed that also on a  
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37  
38 real drug scaffold the high polarity of the tested phosphorus-containing functional groups  
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40  
41  
42 can lead to improved metabolic stability and aqueous solubility. However, this comes at  
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44  
45 the cost of reduced permeability, and only ethyl phosphinate **44a** represents a  
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48  
49 compromise between cell permeability and polarity.  
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52 In summary, the results from our study demonstrate that phosphine oxides and related  
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56 phosphorus-containing functional groups are valuable polar structural elements without  
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3 principal flaws, at least as long as a reduced permeability is acceptable. They deserve to  
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7 be considered as a routine part of every medicinal chemist's toolbox and to be employed  
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9  
10 in medicinal chemistry just like other more commonly used functional groups.  
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#### 19 4. EXPERIMENTAL SECTION 20 21

22 **General Information.** All commercially available chemicals were used as received from  
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24 their commercial supplier. Anhydrous solvents were either purchased or prepared  
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26 according to standard procedures<sup>87</sup> and stored over molecular sieves under argon.  
27  
28  
29 Unless stated otherwise, all reactions were carried out using Schlenk technique under  
30  
31 argon atmosphere. Flash column chromatography was performed on Biotage® SNAP  
32  
33 KP-Sil cartridges (50 µm silica particle) using a Biotage Isolera Four system. Thin layer  
34  
35 chromatography was performed with TLC Silica gel 60 F<sub>254</sub> glass plates and products  
36  
37 were visualized by either UV detection (254 nm) or a basic aqueous solution of potassium  
38  
39 permanganate. Nuclear magnetic resonance (NMR) spectra were recorded at room  
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41 temperature on a Bruker Avance 400 or Bruker Avance 600 spectrometer with  
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3 tetramethylsilane as an internal reference. Chemical shifts  $\delta$  are reported in parts per  
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6  
7 million (ppm).  $^1\text{H}$  NMR spectra were referenced to the residual partially non-deuterated  
8  
9  
10 solvent signal of  $\text{CHCl}_3$  ( $\delta = 7.27$  ppm) or DMSO ( $\delta = 2.50$  ppm).  $^{13}\text{C}$  NMR spectra were  
11  
12  
13 referenced to the deuterated solvent signal of  $\text{CDCl}_3$  ( $\delta = 77.00$  ppm) or DMSO- $\text{d}_6$  ( $\delta =$   
14  
15  
16  
17 39.51 ppm).  $^{19}\text{F}$  NMR and  $^{31}\text{P}$  NMR spectra are referenced according to the unified  
18  
19  
20 chemical shift scale as recommended by the IUPAC.<sup>88</sup> Collection of  $^{13}\text{C}$ ,  $^{19}\text{F}$  and  $^{31}\text{P}$  NMR  
21  
22  
23 data was done with complete  $^1\text{H}$  decoupling. Coupling constants  $J$  are reported in Hz,  
24  
25  
26  
27 and splitting patterns are described as br = broad, s = singlet, d = doublet, t = triplet, q =  
28  
29  
30  
31 quartet and m = multiplet. Infrared spectra were recorded on a Thermo Nicolet iS10 FT-  
32  
33  
34 IR Spectrometer using attenuated total reflectance (ATR) technique. Wave numbers of  
35  
36  
37 absorptions are reported in  $\text{cm}^{-1}$ . Low resolution mass spectra were recorded on a Waters  
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39  
40  
41 ZQ or Waters Acquity QDa, and high-resolution mass spectra were recorded on a Thermo  
42  
43  
44 Scientific LTQ Orbitrap XL or Waters Synapt G2-Si spectrometer using electrospray  
45  
46  
47 ionization in positive ion mode (ESI<sup>+</sup>). Unless specified otherwise, the purity of all final  
48  
49  
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52 compounds was determined to be  $\geq 95\%$  by  $^1\text{H}$  NMR.  
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1  
2  
3 **Dimethyl(4-(trifluoromethyl)phenyl)phosphine oxide (21a).** A solution of Pd<sub>2</sub>(dba)<sub>3</sub>  
4 (45.8 mg, 50.0 μmol, 2.5 mol%) and Xantphos (57.9 mg, 100 μmol, 5.0 mol%) in 1,4-  
5  
6  
7 dioxane (1.00 mL) is stirred at rt for 5 min and then added to a solution of 4-  
8  
9  
10  
11 (trifluoromethyl)phenyl iodide (544 mg, 2.00 mmol, 1.0 equiv.), dimethylphosphine oxide  
12  
13  
14 (208 mg, 2.40 mmol, 1.2 equiv.) and Et<sub>3</sub>N (335 μL, 2.40 mmol, 1.2 equiv.) in 1,4-dioxane  
15  
16  
17 (4.00 mL). The reaction mixture is stirred at rt for 6 h. The reaction mixture is diluted with  
18  
19  
20  
21 saturated aqueous NaHCO<sub>3</sub> (40 mL) and the aqueous phase is extracted with DCM  
22  
23  
24  
25  
26  
27  
28 (3 x 25 mL). The combined organic phases are dried over MgSO<sub>4</sub> and concentrated. The  
29  
30  
31 residue is purified by flash chromatography on silica gel (gradient of MeOH in DCM; 2%  
32  
33  
34 – 20% MeOH) to give 276 mg (62%) of the title compound as a white solid. <sup>1</sup>H NMR  
35  
36  
37 (DMSO-d<sub>6</sub>, 400 MHz): δ = 7.97 – 8.05 (m, 2H), 7.86 – 7.92 (m, 2H), 1.70 (d, *J* = 13.5 Hz,  
38  
39  
40  
41 6H) ppm. <sup>13</sup>C NMR (DMSO-d<sub>6</sub>, 101 MHz) δ = 141.0 (br d, *J* = 91 Hz), 131.0 – 131.9 (m),  
42  
43  
44  
45 130.7 (d, *J* = 10 Hz), 124.8 – 125.4 (m), 123.8 (q, *J* = 273 Hz), 17.5 (d, *J* = 71 Hz) ppm.  
46  
47  
48  
49 <sup>19</sup>F NMR (DMSO-d<sub>6</sub>, 565 MHz): δ = –61.57 ppm. <sup>31</sup>P NMR (DMSO-d<sub>6</sub>, 162 MHz): δ =  
50  
51  
52  
53 32.42 ppm. IR (ATR): 2976, 2906, 1400, 1325, 1298, 1177, 1165, 1134, 1103, 1061, 942,  
54  
55  
56  
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826, 721  $\text{cm}^{-1}$ . HRMS (ESI<sup>+</sup>) calculated for  $\text{C}_9\text{H}_{11}\text{F}_3\text{OP}$   $[\text{M}+\text{H}]^+$   $m/z$  223.0494, found 223.0499.

**Diethyl(4-(trifluoromethyl)phenyl)phosphine oxide (21b).** A solution of  $\text{Pd}_2(\text{dba})_3$  (45.8 mg, 50.0  $\mu\text{mol}$ , 2.5 mol%) and Xantphos (57.9 mg, 100  $\mu\text{mol}$ , 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  $\text{Et}_3\text{N}$  (335  $\mu\text{L}$ , 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  $\text{NaHCO}_3$  (40 mL), and the aqueous phase is extracted with DCM (3 x 25 mL). The combined organic phases are dried over  $\text{MgSO}_4$  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.  $^1\text{H}$  NMR (DMSO- $d_6$ , 400 MHz):  $\delta$  = 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.  $^{13}\text{C}$  NMR (DMSO- $d_6$ , 101 MHz):  $\delta$  = 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.  $^{19}\text{F}$  NMR (DMSO- $d_6$ , 565 MHz)  $\delta$

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3  
4 = -61.6 ppm.  $^{31}\text{P}$  NMR (DMSO- $d_6$ , 162 MHz)  $\delta$  = 42.1 ppm. IR (ATR): 2972, 2943, 1400,  
5  
6  
7 1326, 1315, 1167, 1100, 1060, 840, 774, 706  $\text{cm}^{-1}$ . HRMS (ESI $^+$ ) calculated for  
8  
9  
10  $\text{C}_{11}\text{H}_{15}\text{F}_3\text{OP}$  [M+H] $^+$   $m/z$  251.0807, found 251.0810.

11  
12  
13  
14 **Diisopropyl(4-(trifluoromethyl)phenyl)phosphine oxide (21c)**. A solution of  $\text{Pd}_2(\text{dba})_3$   
15  
16  
17 (45.8 mg, 50.0  $\mu\text{mol}$ , 2.5 mol%) and Xantphos (57.9 mg, 100  $\mu\text{mol}$ , 5.0 mol%) in 1,4-  
18  
19  
20 dioxane (1.00 mL) is stirred at rt for 5 min and then added to a solution of 4-  
21  
22  
23 (trifluoromethyl)phenyl iodide (544 mg, 2.00 mmol, 1.0 equiv.), diisopropylphosphine  
24  
25  
26  
27 oxide (322 mg, 2.40 mmol, 1.2 equiv.) and  $\text{Et}_3\text{N}$  (335  $\mu\text{L}$ , 2.40 mmol, 1.2 equiv.) in 1,4-  
28  
29  
30 dioxane (7.00 mL). The reaction mixture is stirred at rt for 2 d. The reaction mixture is  
31  
32  
33  
34 filtered over a plug of celite, and the filter cake is washed with EtOAc (60 mL). The  
35  
36  
37 combined organic filtrates are washed with saturated aqueous  $\text{NaHCO}_3$  (40 mL) and  
38  
39  
40  
41 brine (40 mL), dried over  $\text{MgSO}_4$  and concentrated. The residue is repeatedly purified by  
42  
43  
44  
45 flash chromatography on silica gel (gradient of MeOH in DCM; 2% – 20% MeOH, and  
46  
47  
48  
49 gradient of MeOH in EtOAc; 2% – 20% MeOH) to give 247 mg (44%) of the title compound  
50  
51  
52 as a colorless solid.  $^1\text{H}$  NMR (DMSO- $d_6$ , 400 MHz):  $\delta$  = 7.87 – 7.96 (m, 4H), 2.34 – 2.48  
53  
54  
55 (m, 2H), 1.07 (dd,  $J$  = 14.9, 7.1 Hz, 6H), 0.90 (dd,  $J$  = 15.9, 7.1 Hz, 6H) ppm.  $^{13}\text{C}$  NMR  
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4 (DMSO-d<sub>6</sub>, 101 MHz):  $\delta$  = 135.5 (d,  $J$  = 79 Hz), 132.3 (d,  $J$  = 8 Hz), 130.7 – 131.9 (m),  
5  
6  
7 124.7 – 125.1 (m), 123.8 (q,  $J$  = 273 Hz), 24.3 (d,  $J$  = 67 Hz), 15.8 (d,  $J$  = 2 Hz), 14.7 (d,  
8  
9  
10  $J$  = 3 Hz) ppm. <sup>19</sup>F NMR (DMSO-d<sub>6</sub>, 565 MHz):  $\delta$  = -61.5 ppm. <sup>31</sup>P NMR (DMSO-d<sub>6</sub>, 162  
11  
12  
13 MHz):  $\delta$  = 49.7 ppm. IR (ATR): 2959, 2925, 2870, 1330, 1322, 1175, 1156, 1122, 1102,  
14  
15  
16  
17 1062, 1017, 839, 713, 690 cm<sup>-1</sup>. HRMS (ESI<sup>+</sup>) calculated for C<sub>13</sub>H<sub>19</sub>F<sub>3</sub>OP [M+H]<sup>+</sup> m/z  
18  
19  
20  
21 279.1120, found 279.1123.  
22  
23

24 **1-[4-(Trifluoromethyl)phenyl]-1 $\lambda$ <sup>5</sup>-phosphetan-1-one (22a)**. Oxalyl chloride (609  $\mu$ L,  
25  
26  
27 7.20 mmol, 3.0 equiv.) is added dropwise at 0 °C to a solution of 1-hydroxy-1 $\lambda$ <sup>5</sup>-  
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1-**(46a)**<sup>62b,c</sup> (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<sup>63</sup> (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<sub>4</sub>Cl (40 mL). The aqueous phase is extracted with  
EtOAc (3 x 75 mL), and the combined organic phases are dried over Na<sub>2</sub>SO<sub>4</sub> and

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3 concentrated. The residue is repeatedly purified by preparative RP-HPLC (Waters  
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5  
6 SunFire™ C<sub>18</sub>, gradient of acetonitrile in water, 0.1% TFA) and flash chromatography on  
7  
8  
9 silica gel (gradient of MeOH in DCM; 0% – 5% MeOH) to give 112 mg (20%) of the title  
10  
11  
12 compound as a colorless solid. R<sub>f</sub> (DCM:MeOH, 10:1) = 0.77. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400  
13  
14 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,  
15  
16 1H), 1.49 – 1.65 (m, 1H) ppm. <sup>13</sup>C NMR (DMSO-d<sub>6</sub>, 101 MHz) δ = 138.9 (d, *J* = 71 Hz),  
17  
18 131.0 – 132.2 (m), 130.6 (d, *J* = 11 Hz), 125.3 – 125.9 (m), 123.8 (q, *J* = 272 Hz), 34.7 (d,  
19  
20 *J* = 55 Hz), 8.3 (d, *J* = 22 Hz) ppm. <sup>31</sup>P NMR (DMSO-d<sub>6</sub>, 162 MHz): δ = 38.4 ppm. IR  
21  
22 (ATR): 1395, 1321, 1221, 1120, 1108, 1059, 931, 906, 848, 754, 713 cm<sup>-1</sup>. HRMS (ESI<sup>+</sup>)  
23  
24 calculated for C<sub>10</sub>H<sub>11</sub>F<sub>3</sub>OP [M+H]<sup>+</sup> m/z 235.0494, found 235.0493.  
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38 **1-[4-(Trifluoromethyl)phenyl]-1λ<sup>5</sup>-phospholan-1-one (22b)**. Oxalyl chloride (508 μL,  
39  
40 6.00 mmol, 3.0 equiv.) is added dropwise at 0 °C to a solution of 1-hydroxy-1λ<sup>5</sup>-  
41  
42 phospholan-1-one (**46b**)<sup>62b,c</sup> (240 mg, 2.00 mmol, 1.0 equiv.) in anhydrous DCM  
43  
44 (10.0 mL). The ice-bath is removed, and the reaction mixture is allowed to stir at rt for 1 h.  
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46  
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48  
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51  
52 The reaction mixture is concentrated to dryness, and the residue is dissolved in THF  
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54 (10.0 mL). The solution is cooled to 0 °C, before a freshly prepared solution of  
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56  
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3  
4 4-trifluoromethylphenylmagnesium halide<sup>63</sup> (0.5 M in THF; 4.20 mL, 2.10 mmol,  
5  
6  
7 1.05 equiv.) is added dropwise. The reaction mixture is allowed to warm to rt overnight  
8  
9  
10 and treated with saturated aqueous NH<sub>4</sub>Cl (20 mL). The aqueous phase is extracted with  
11  
12  
13 EtOAc (3 x 30 mL), and the combined organic phases are dried over Na<sub>2</sub>SO<sub>4</sub> and  
14  
15  
16 concentrated. The residue is repeatedly purified by preparative RP-HPLC (Waters  
17  
18  
19 SunFire™ C<sub>18</sub>, gradient of acetonitrile in water, 0.1% TFA) and flash chromatography on  
20  
21  
22 silica gel (gradient of MeOH in DCM; 2% – 5%) to give 172 mg (35%) of the title compound  
23  
24  
25 as a colorless solid. R<sub>f</sub> (DCM:MeOH, 10:1) = 0.80. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz): δ =  
26  
27  
28 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.  
29  
30  
31  
32  
33  
34  
35 <sup>13</sup>C NMR (DMSO-d<sub>6</sub>, 101 MHz) δ = 140.1 (br d, *J* = 83 Hz), 131.3 – 131.6 (m), 131.0 (d,  
36  
37  
38 *J* = 10 Hz), 124.9 – 125.5 (m), 123.8 (q, *J* = 273 Hz), 28.8 (d, *J* = 68 Hz), 24.5 (d,  
39  
40  
41 *J* = 8 Hz) ppm. <sup>31</sup>P NMR (DMSO-d<sub>6</sub>, 162 MHz): δ = 57.7 ppm. IR (ATR): 2966, 1322,  
42  
43  
44 1177, 1163, 1125, 1104, 1060, 1010, 842, 718, 707 cm<sup>-1</sup>. HRMS (ESI<sup>+</sup>) calculated for  
45  
46  
47 C<sub>11</sub>H<sub>13</sub>F<sub>3</sub>OP [M+H]<sup>+</sup> m/z 249.0651, found 249.0650.  
48  
49

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51  
52 **1-[4-(Trifluoromethyl)phenyl]-1λ<sup>5</sup>-phosphan-1-one (22c)**. Oxalyl chloride (169 μL,  
53  
54  
55 2.00 mmol, 2.0 equiv.) is added dropwise at 0 °C to a solution of 1-hydroxy-1λ<sup>5</sup>-  
56  
57  
58  
59  
60

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3 phosphinan-1-one (**46c**)<sup>62c</sup> (134 mg, 1.00 mmol, 1.0 equiv.) in anhydrous DCM (5.00 mL).  
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6

7 The ice-bath is removed, and the reaction mixture is allowed to stir at rt for 1 h. The  
8  
9

10 reaction mixture is concentrated to dryness, and the residue is dissolved in THF  
11  
12

13 (5.00 mL). The solution is cooled to 0 °C, before a freshly prepared solution of  
14  
15

16 4-trifluoromethylphenylmagnesium halide<sup>63</sup> (1.0 M in THF; 1.20 mL, 1.20 mmol,  
17  
18

19 1.2 equiv.) is added dropwise. The reaction mixture is allowed to warm to rt overnight and  
20  
21

22 treated with of saturated aqueous NH<sub>4</sub>Cl (20 mL). The aqueous phase is extracted with  
23  
24

25 EtOAc (3 x 30 mL), and the combined organic phases are dried over Na<sub>2</sub>SO<sub>4</sub> and  
26  
27

28 concentrated. The residue is repeatedly purified by preparative RP-HPLC (Waters  
29  
30

31 SunFire™ C<sub>18</sub>, gradient of acetonitrile in water, 0.1% TFA) and flash chromatography on  
32  
33

34 silica gel (gradient of MeOH in DCM; 0% – 7% MeOH) to give 82.5 mg (32%) of the title  
35  
36

37 compound as a colorless solid. R<sub>f</sub> (DCM:MeOH, 10:1) = 0.55. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  
38  
39

40 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)  
41  
42

43 ppm. <sup>13</sup>C NMR (CDCl<sub>3</sub>, 101 MHz) δ = 137.7 (br d, *J* = 91 Hz), 133.6 (br d, *J* = 35 Hz),  
44  
45

46 130.6 (d, *J* = 9 Hz), 125.2 – 125.7 (m), 123.5 (q, *J* = 273 Hz), 28.3 (d, *J* = 65 Hz), 26.6 (d,  
47  
48

49 *J* = 7 Hz), 21.9 (d, *J* = 6 Hz) ppm. <sup>31</sup>P NMR (CDCl<sub>3</sub>, 162 MHz): δ = 32.0 ppm. IR (ATR):  
50  
51

2934, 1324, 1168, 1157, 1126, 1061, 1017, 937, 850, 813, 804, 713, 691, 681 cm<sup>-1</sup>.

HRMS (ESI<sup>+</sup>) calculated for C<sub>12</sub>H<sub>15</sub>F<sub>3</sub>OP [M+H]<sup>+</sup> m/z 263.0807, found 263.0811.

**4-[4-(Trifluoromethyl)phenyl]-1,4λ<sup>5</sup>-oxaphosphan-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<sup>5</sup>-oxaphosphan-4-one (**46d**)<sup>62b</sup> (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<sup>63</sup> (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<sub>4</sub>Cl (40 mL). The aqueous phase is extracted with EtOAc (3 x 20 mL) and the combined organic phases are dried over Na<sub>2</sub>SO<sub>4</sub> 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<sub>18</sub>, gradient of acetonitrile in water, 0.1% TFA) to give 64.1 mg (24%) of the title compound as a colorless solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ = 7.89 – 7.96 (m, 2H), 7.77 – 7.82 (m,

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4 2H), 4.10 – 4.27 (m, 4H), 2.22 – 2.33 (m, 2H), 2.01 – 2.13 (m, 2H) ppm.  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ,  
5  
6  
7 101 MHz)  $\delta$  = 136.5 (br d,  $J$  = 95 Hz), 133.2 – 134.6 (m), 130.8 (d,  $J$  = 9 Hz), 125.6 –  
8  
9  
10 126.0 (m), 123.4 (q,  $J$  = 273 Hz), 64.6 (d,  $J$  = 8 Hz), 29.6 (d,  $J$  = 65 Hz) ppm.  $^{31}\text{P}$  NMR  
11  
12  
13 ( $\text{CDCl}_3$ , 162 MHz):  $\delta$  = 25.1 ppm. IR (ATR): 2861, 1329, 1318, 1199, 1166, 1159, 1156,  
14  
15  
16 1126, 1104, 1085, 1062, 1017, 809, 720  $\text{cm}^{-1}$ . HRMS (ESI $^+$ ) calculated for  $\text{C}_{11}\text{H}_{13}\text{F}_3\text{O}_2\text{P}$   
17  
18  
19  
20  
21  $[\text{M}+\text{H}]^+$   $m/z$  265.0600, found 265.0605.  
22  
23

24 **4-[4-(Trifluoromethyl)phenyl]-1,4 $\lambda^5$ -azaphosphan-4-one (22e)**. A suspension of 1-  
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benzyl-4-[4-(trifluoromethyl)phenyl]-1,4 $\lambda^5$ -azaphosphan-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  $\text{H}_2$  (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<sup>TM</sup> Phenyl, gradient of acetonitrile in water, 0.1%  $\text{NH}_4\text{OH}$ ) to give 136 mg  
(65%) of the title compound as a colorless solid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  = 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.  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 101 MHz)  $\delta$  = 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,

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2  
3  $J = 65$  Hz) ppm.  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ , 162 MHz):  $\delta = 28.7$  ppm. IR (ATR): 3274, 1399, 1323,  
4  
5  
6  
7 1156, 1140, 1104, 1060, 1013, 947, 808, 717  $\text{cm}^{-1}$ . HRMS (ESI<sup>+</sup>) calculated for  
8  
9  
10  $\text{C}_{11}\text{H}_{14}\text{F}_3\text{NOP}$  [M+H]<sup>+</sup>  $m/z$  264.0760, found 264.0765.

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13  
14 **1-Methyl-4-[4-(trifluoromethyl)phenyl]-1,4 $\lambda^5$ -azaphosphinan-4-one (22f)**. 4-(Trifluoro-  
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16  
17 methyl)phenyl iodide (272 mg, 1.00 mmol, 1.0 equiv.) is added to a solution of  $\text{Pd}_2(\text{dba})_3$   
18  
19  
20 (11.4 mg, 12.5  $\mu\text{mol}$ , 2.5 mol%), Xantphos (14.5 mg, 25.0  $\mu\text{mol}$ , 5.0 mol%), and  
21  
22  
23 1-methyl-1,4 $\lambda^5$ -azaphosphinan-4-one (**47b**) (9.9 mg, 600  $\mu\text{mol}$ , 1.2 equiv.) in DIPEA  
24  
25  
26  
27 (128  $\mu\text{L}$ , 750  $\mu\text{mol}$ , 1.5 equiv.) and DMF (2.00 mL). The reaction mixture is sealed in a  
28  
29  
30  
31 microwave vial and heated at 80 °C for 3 d. The reaction mixture is filtered and directly  
32  
33  
34 purified by preparative RP-HPLC (Waters XBridge<sup>TM</sup> C<sub>18</sub>, gradient of acetonitrile in water,  
35  
36  
37 0.1%  $\text{NH}_4\text{OH}$ ) to give 78.0 mg (56%) of the title compound as light-yellow oil.  $^1\text{H}$  NMR  
38  
39  
40  
41 (DMSO- $d_6$ , 400 MHz):  $\delta = 8.00 - 8.09$  (m, 2H), 7.87 – 7.93 (m, 2H), 2.65 – 2.83 (m, 4H),  
42  
43  
44 2.23 – 2.34 (m, 5H), 1.89 – 2.02 (m, 2H) ppm.  $^{13}\text{C}$  NMR (DMSO- $d_6$ , 101 MHz)  $\delta = 138.1$   
45  
46  
47  
48 (br d,  $J = 91$  Hz), 131.4 – 132.2 (m), 131.3 (d,  $J = 10$  Hz), 125.2 – 125.8 (m), 123.7 (q,  
49  
50  
51  
52  $J = 272$  Hz), 51.0 (d,  $J = 7$  Hz), 45.7, 27.1 (d,  $J = 66$  Hz) ppm.  $^{31}\text{P}$  NMR (DMSO- $d_6$ , 162  
53  
54  
55  
56 MHz):  $\delta = 26.1$  ppm. IR (ATR): 2790, 1322, 1254, 1170, 1156, 1128, 1105, 1062, 1013,  
57  
58  
59  
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922, 812, 721, 605  $\text{cm}^{-1}$ . HRMS (ESI<sup>+</sup>) calculated for  $\text{C}_{12}\text{H}_{16}\text{F}_3\text{NOP}$   $[\text{M}+\text{H}]^+$   $m/z$  278.0916, found 278.0922.

**1-Isopropyl-4-[4-(trifluoromethyl)phenyl]-1,4 $\lambda^5$ -azaphosphinan-4-one (22g).**

4-(Trifluoromethyl)phenyl iodide (272 mg, 1.00 mmol, 1.0 equiv.) is added to a solution of  $\text{Pd}_2(\text{dba})_3$  (11.4 mg, 12.5  $\mu\text{mol}$ , 2.5 mol%), Xantphos (14.5 mg, 25.0  $\mu\text{mol}$ , 5.0 mol%), and 1-isopropyl-1,4 $\lambda^5$ -azaphosphinan-4-one (**47c**) (79.9 mg, 600  $\mu\text{mol}$ , 1.2 equiv.) in DIPEA (128  $\mu\text{L}$ , 750  $\mu\text{mol}$ , 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<sup>TM</sup> C<sub>18</sub>, gradient of acetonitrile in water, 0.1%  $\text{NH}_4\text{OH}$ ) to give 72.0 mg (47%) of the title compound as a colorless solid. <sup>1</sup>H NMR (DMSO- $d_6$ , 400 MHz):  $\delta$  = 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. <sup>13</sup>C NMR (DMSO- $d_6$ , 101 MHz)  $\delta$  = 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. <sup>31</sup>P NMR (DMSO- $d_6$ , 162 MHz):  $\delta$  = 28.3 ppm. IR (ATR): 2968, 2814, 1330, 1318, 1257,

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4 1205, 1160, 1127, 1104, 1062, 1015, 922, 816, 720, 699  $\text{cm}^{-1}$ . HRMS (ESI<sup>+</sup>) calculated  
5  
6  
7 for  $\text{C}_{14}\text{H}_{20}\text{F}_3\text{NOP}$   $[\text{M}+\text{H}]^+$   $m/z$  306.1229, found 306.1234.  
8  
9

10 **Methyl(4-(trifluoromethyl)phenyl)phosphinic acid (23a).** 4-(Trifluoromethyl)phenyl  
11  
12 iodide (136 mg, 500  $\mu\text{mol}$ , 1.0 equiv.), ethyl methylphosphinate (64.8 mg, 600  $\mu\text{mol}$ ,  
13  
14 1.2 equiv.) and DIPEA (111  $\mu\text{L}$ , 650  $\mu\text{mol}$ , 1.3 equiv.) is added to a solution of  $\text{Pd}(\text{OAc})_2$   
15  
16 (2.25 mg, 10.0  $\mu\text{mol}$ , 2.0 mol%) and Xantphos (6.36 mg, 11.0  $\mu\text{mol}$ , 2.2 mol%) in DMF  
17  
18 (1.80 mL) and DME (200  $\mu\text{L}$ ). The reaction mixture is sealed in a microwave vial and  
19  
20 heated at 115  $^\circ\text{C}$  overnight. The reaction mixture is acidified with TFA and purified by  
21  
22 preparative RP-HPLC (Waters XBridge<sup>TM</sup> Phenyl, gradient of acetonitrile in water, 0.1%  
23  
24 TFA) to give 47.0 mg (42%) of the title compound as a colorless solid.  $^1\text{H}$  NMR (DMSO-  
25  
26  $\text{d}_6$ , 400 MHz):  $\delta$  = 7.95 (br dd,  $J$  = 11.0, 8.3 Hz, 2H), 7.82 – 7.90 (m, 2H), 1.56 (d,  
27  
28  $J$  = 14.6 Hz, 3H) ppm.  $^{13}\text{C}$  NMR (DMSO- $\text{d}_6$ , 101 MHz)  $\delta$  = 140.3 (br d,  $J$  = 124 Hz), 131.5  
29  
30 (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,  
31  
32  $J$  = 100 Hz) ppm.  $^{31}\text{P}$  NMR (DMSO- $\text{d}_6$ , 162 MHz):  $\delta$  = 32.7 ppm. IR (ATR): 2156, 1688,  
33  
34  
35 1399, 1322, 1306, 1161, 1123, 1104, 1061, 1021, 968, 885, 836, 763  $\text{cm}^{-1}$ . HRMS (ESI<sup>+</sup>)  
36  
37 calculated for  $\text{C}_8\text{H}_9\text{F}_3\text{O}_2\text{P}$   $[\text{M}+\text{H}]^+$   $m/z$  225.0287, found 225.0293.  
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4 **Ethyl methyl[4-(trifluoromethyl)phenyl]phosphinate (23b)**. A mixture of 4-(trifluoro-  
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6 methyl)phenyl iodide (272 mg, 1.0 mmol, 1.0 equiv.), ethyl methylphosphinate (216 mg,  
7  
8 2.0 mmol, 2.0 equiv.), *N,N*-diisopropylamine (226  $\mu$ L, 1.3 mmol, 1.3 equiv.) and  
9  
10 XantphosPd G3 (95 mg, 0.10 mmol, 10 mol%) in toluene (4 mL) is stirred at 100 °C for  
11  
12 2 h. The mixture is allowed to cool to rt, and Palladium scavenger SiliaMetS-DMT  
13  
14 (Dimercaptotriazine, R79030B) (200 mg) is added, and stirring is continued for 15 min.  
15  
16  
17 The reaction mixture is filtered, and the filtrate is concentrated under reduced pressure.  
18  
19  
20 The residue is repeatedly purified by preparative RP-HPLC (Waters XBridge™ C<sub>18</sub>,  
21  
22 gradient of acetonitrile in water, 0.15% NH<sub>4</sub>OH) and flash chromatography on silica gel  
23  
24 (gradient of EtOAc in cyclohexane: 10% – 90% EtOAc) to give 95 mg (37%) of the title  
25  
26  
27 compound as colorless oil. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz):  $\delta$  = 7.99 (dd, *J* = 11.4, 8.3 Hz,  
28  
29 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* =  
30  
31 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. <sup>13</sup>C NMR  
32  
33 (DMSO-d<sub>6</sub>, 101 MHz)  $\delta$  = 137.1 (d, *J* = 123.5 Hz), 131.8 (d, *J* = 10.3 Hz), 131.7-132.0  
34  
35 (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,  
36  
37 *J* = 6.0 Hz), 14.7 (d, *J* = 101.1 Hz) ppm. <sup>31</sup>P NMR (DMSO-d<sub>6</sub>, 162 MHz):  $\delta$  = 39.8 ppm.  
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4       **[4-(Trifluoromethyl)phenyl]phosphonic acid (24a)**. Bromotrimethylsilane (7.16 mL,  
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6  
7 54.2 mmol, 3.0 equiv.) is added slowly at 0 °C to a solution of diethyl [4-(trifluoro-  
8  
9  
10 methyl)phenyl]phosphonate (**24e**) (5.10 g, 18.1 mmol, 1.0 equiv.) in MeCN (100 mL), and  
11  
12  
13 the reaction mixture is allowed to warm to rt overnight. Water (50 mL) is added, and the  
14  
15  
16 mixture is concentrated to dryness. The residue is purified by preparative RP-HPLC  
17  
18  
19 (Waters SunFire™ C<sub>18</sub>, gradient of acetonitrile in water, 0.1% TFA) to give 3.49 g (85%)  
20  
21  
22 of the title compound as a colorless solid. The spectral data is in accordance with literature  
23  
24  
25 reports.<sup>82</sup>  
26  
27  
28  
29  
30

31       **Methoxy[4-(trifluoromethyl)phenyl]phosphinic acid (24b)**. According to a procedure  
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33  
34 reported in the literature,<sup>67</sup> 4-bromobenzotrifluoride (280 μL, 2.00 mmol, 1.0 equiv.) and  
35  
36  
37 dimethyl phosphite (222 μL, 2.40 mmol, 1.2 equiv.) is added to a suspension of Pd(OAc)<sub>2</sub>  
38  
39  
40 (8.98 mg, 40.0 μmol, 2 mol%), dppf (44.4 mg, 80.0 μmol 4 mol%), KOAc (19.6 mg,  
41  
42  
43 200 μmol, 10 mol%) and DIPEA (453 μL, 2.60 mmol, 1.3 equiv.) in THF (10.0 mL). The  
44  
45  
46 reaction mixture is sealed in a microwave vial and heated at 75 °C overnight. The reaction  
47  
48  
49 mixture is filtered over a plug of celite and concentrated. The residue is purified by  
50  
51  
52 preparative RP-HPLC (Waters XBridge™ C<sub>18</sub>, gradient of acetonitrile in water, 0.1% TFA)  
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4 to give 330 mg (69%) of the title compound as a light-yellow oil.  $^1\text{H}$  NMR (DMSO- $d_6$ , 400  
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6  
7 MHz):  $\delta$  = 7.84 – 7.92 (m, 4H), 3.55 ppm (s, 3H) ppm.  $^{13}\text{C}$  NMR (DMSO- $d_6$ , 101 MHz)  $\delta$   
8  
9  
10 = 135.6 (br d,  $J$  = 181 Hz), 131.9 (d,  $J$  = 10 Hz), 130.8 – 131.8 (m), 125.2 (br dd,  $J$  = 14,  
11  
12  
13 4 Hz), 123.9 (q,  $J$  = 273 Hz), 51.9 (d,  $J$  = 5 Hz) ppm.  $^{31}\text{P}$  NMR (DMSO- $d_6$ , 162 MHz):  $\delta$  =  
14  
15  
16 13.7 ppm. IR (ATR): 1400, 1321, 1167, 1124, 1106, 1061, 1040, 1017, 981, 837, 807,  
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18  
19  
20  
21 774, 705  $\text{cm}^{-1}$ . HRMS (ESI $^+$ ) calculated for  $\text{C}_8\text{H}_9\text{F}_3\text{O}_3\text{P}$   $[\text{M}+\text{H}]^+$   $m/z$  241.0236, found  
22  
23  
24 241.0234.  
25  
26  
27

28 **Ethoxy[4-(trifluoromethyl)phenyl]phosphinic acid (24c)**. Aqueous NaOH (4 M, 2.5 mL,  
29  
30  
31 10.0 mmol, 20.0 equiv.) is added to a solution of diethyl  
32  
33  
34 [4-(trifluoromethyl)phenyl]phosphonate (**24e**, 141 mg, 500  $\mu\text{mol}$ , 1.0 equiv.) in EtOH  
35  
36  
37 (2.50 mL), and the reaction mixture is stirred at rt for 5 d. Aqueous HCl (1 M, 20 mL) is  
38  
39  
40  
41 added, and the aqueous phase is extracted with DCM (4 x 15 mL). The combined organic  
42  
43  
44  
45 phases are dried over  $\text{MgSO}_4$  and concentrated. The residue is purified by RP-HPLC  
46  
47  
48 (Waters XBridge $^{\text{TM}}$  C $_{18}$ , gradient of acetonitrile in water, 0.1% TFA) to give 95.0 mg (75%)  
49  
50  
51  
52 of the title compound as a colorless solid.  $^1\text{H}$  NMR (DMSO- $d_6$ , 400 MHz):  $\delta$  = 7.83 – 7.94  
53  
54  
55 (m, 4H), 3.91 (dq,  $J$  = 8.1, 7.1 Hz, 2H), 1.18 (t,  $J$  = 7.0 Hz, 3H) ppm.  $^{13}\text{C}$  NMR (DMSO- $d_6$ ,  
56  
57  
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59  
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3 101 MHz)  $\delta$  = 136.3 (br d,  $J$  = 181 Hz), 131.8 (d,  $J$  = 10 Hz), 131.2 – 131.7 (m), 124.9 –  
4  
5  
6  
7 125.5 (m), 121.1 (q,  $J$  = 273 Hz), 61.0 (d,  $J$  = 5 Hz), 16.2 (d,  $J$  = 6 Hz) ppm.  $^{31}\text{P}$  NMR  
8  
9  
10 (DMSO- $d_6$ , 162 MHz):  $\delta$  = 12.3 ppm. IR (ATR): 2501, 2228, 1399, 1320, 1216, 1162,  
11  
12  
13 1125, 1107, 1063, 1040, 1007, 967, 836, 805, 708  $\text{cm}^{-1}$ . HRMS (ESI $^+$ ) calculated for  
14  
15  
16  
17  $\text{C}_9\text{H}_{11}\text{F}_3\text{O}_3\text{P}$  [M+H] $^+$   $m/z$  255.0392, found 255.0390.  
18  
19  
20

21 **Dimethyl [4-(trifluoromethyl)phenyl]phosphonate (24d)**. The reaction was performed  
22  
23 following a literature report.<sup>53</sup> Copper(I) oxide (14.3 mg, 100  $\mu\text{mol}$ , 5.0 mol%) and  
24  
25 1,10-phenanthroline (36.0 mg, 200  $\mu\text{mol}$ , 10 mol%) is added to a solution of 4-(trifluoro-  
26  
27 methyl)phenylboronic acid (380 mg, 2.00 mmol, 1.0 equiv.), dimethyl phosphite  
28  
29 (242 mg, 2.20 mmol, 1.1 equiv.) and DIPEA (511  $\mu\text{L}$ , 3.00 mmol, 1.5 equiv.) in MeCN  
30  
31 (5.00 mL), and the reaction mixture is stirred open to air for 3 d. The reaction mixture is  
32  
33 diluted with saturated aqueous  $\text{NaHCO}_3$  (50 mL) and EtOAc (40 mL). The organic phase  
34  
35 is dried over  $\text{MgSO}_4$  and concentrated. The residue is purified by flash chromatography  
36  
37 on silica gel (gradient of EtOAc in cyclohexane; 10% – 50% EtOAc) to give 180 mg (35%)  
38  
39 of the title compound as a colorless oil. The spectral data is in accordance with literature  
40  
41 reports.<sup>45</sup>  
42  
43  
44  
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4 **Diethyl [4-(trifluoromethyl)phenyl]phosphonate (24e)**. The reaction was performed  
5  
6  
7 using an adopted literature report.<sup>67</sup> 4-Bromobenzotrifluoride (4.50 mL, 20.0 mmol,  
8  
9  
10 1.0 equiv.) and diethyl phosphite (3.31 mL, 24.0 mmol, 1.2 equiv.) is added to a  
11  
12  
13 suspension of Pd(OAc)<sub>2</sub> (89.8 mg, 400 μmol, 2.0 mol%), dppf (444 mg, 800 μmol  
14  
15  
16 4.0 mol%), KOAc (196 mg, 2.00 mmol, 10 mol%) and DIPEA (4.42 mL, 3.00 mmol,  
17  
18  
19 1.3 equiv.) in THF (100 mL), and the reaction mixture is refluxed overnight. The mixture  
20  
21  
22 is filtered over a plug of celite and concentrated. The residue is dissolved in water  
23  
24  
25 (100 mL) and brine (100 mL), and the aqueous phase is extracted with EtOAc  
26  
27  
28 (3 x 100 mL). The combined organic phases are dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated.  
29  
30  
31  
32  
33  
34  
35 The residue is purified by preparative RP-HPLC (Waters SunFire™ C<sub>18</sub>, gradient of  
36  
37  
38 acetonitrile in water, 0.1% TFA) to give 5.10 g (90%) of the title compound as colorless  
39  
40  
41  
42 oil. The spectral data is in accordance with literature reports.<sup>53</sup>  
43  
44

45 **Diisopropyl [4-(trifluoromethyl)phenyl]phosphonate (24f)**. The reaction was performed  
46  
47  
48 using an adopted literature report.<sup>42c</sup> Pd(OAc)<sub>2</sub> (4.49 mg, 20.0 μmol, 2.0 mol%) and dppf  
49  
50  
51 (12.2 mg, 22.0 μmol 2.2 mol%) is added to a solution of 4-(trifluoromethyl)phenyl iodide  
52  
53  
54 (147 μL, 1.0 mmol, 1.0 equiv.), diisopropyl phosphite (199 mg, 1.20 mmol, 1.2 equiv.)  
55  
56  
57  
58  
59  
60

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3 and DIPEA (226  $\mu$ L, 1.30 mmol, 1.3 equiv.) in DMF (9.00 mL) and DME (1.00 mL). The  
4  
5  
6  
7 reaction mixture is sealed in a microwave vial and heated at 115  $^{\circ}$ C overnight. The  
8  
9  
10 reaction mixture is diluted with EtOAc (30 mL) and the organic phase is extracted with  
11  
12  
13  
14 water (2 x 20 mL) and brine (20 mL), dried over  $\text{Na}_2\text{SO}_4$  and concentrated. The residue  
15  
16  
17 is purified by flash chromatography on silica gel (gradient of EtOAc in cyclohexane; 0% –  
18  
19  
20 3% EtOAc) to give 230 mg (74%) of the title compound as a yellow oil. The spectral data  
21  
22  
23  
24 is in accordance with literature reports.<sup>42c</sup>

25  
26  
27  
28 **2-Hydroxyethoxy(4-(trifluoromethyl)phenyl)phosphinic acid (24g).** A solution of  
29  
30  
31 [4-(trifluoromethyl)phenyl]phosphonic dichloride (**49**) (263 mg, 1.00 mmol, 1.0 equiv.) in  
32  
33  
34 THF (3.00 mL) is added dropwise at 0  $^{\circ}$ C to a solution of ethylene glycol (55.9  $\mu$ L,  
35  
36  
37 1.05 mmol, 1.05 equiv.) and  $\text{Et}_3\text{N}$  (278  $\mu$ L, 2.00 mmol, 2.0 equiv.) in THF (20.0 mL), and  
38  
39  
40  
41 the reaction mixture is allowed to warm to rt overnight. The reaction mixture is filtered  
42  
43  
44  
45 over a plug of celite, and the filter cake is rinsed with EtOAc (20 mL). The combined  
46  
47  
48  
49 filtrates are concentrated and purified by flash chromatography on silica gel (gradient of  
50  
51  
52 MeOH in DCM; 0% – 15% MeOH) to give 51.0 mg (20%) of the title compound as  
53  
54  
55  
56 colorless oil.  $R_f$  (DCM:MeOH, 20:1) = 0.10.  $^1\text{H}$  NMR (DMSO- $d_6$ , 400 MHz):  $\delta$  = 7.88 –  
57  
58  
59  
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4 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,  
5  
6  
7 2H) ppm.  $^{13}\text{C}$  NMR (DMSO- $d_6$ , 101 MHz)  $\delta = 136.0$  (br d,  $J = 182$  Hz), 131.9 (d,  
8  
9  
10  $J = 10$  Hz), 131.2 – 131.8 (m), 124.8 – 125.4 (m), 123.8 (q,  $J = 273$  Hz), 66.6 (d,  $J = 6$  Hz),  
11  
12  
13 60.3 (d,  $J = 7$  Hz) ppm.  $^{31}\text{P}$  NMR (DMSO- $d_6$ , 162 MHz):  $\delta = 12.8$  ppm. IR (ATR): 3284,  
14  
15  
16 1653, 1400, 1322, 1168, 1125, 1062, 1017, 987, 951, 837, 706  $\text{cm}^{-1}$ . HRMS (ESI $^+$ )  
17  
18  
19  
20  
21 calculated for  $\text{C}_9\text{H}_{11}\text{F}_3\text{O}_4\text{P}$   $[\text{M}+\text{H}]^+$   $m/z$  271.0342, found 271.0343.  
22  
23

24 **2-[4-(Trifluoromethyl)phenyl]-1,3,2 $\lambda^5$ -dioxaphosphinan-2-one (25b)**. A solution of  
25  
26  
27 [4-(trifluoromethyl)phenyl]phosphonic dichloride (**49**) (263 mg, 1.00 mmol, 1.0 equiv.) in  
28  
29  
30 THF (3.00 mL) is added dropwise at 0 °C to a solution of 1,3-propanediol (79.9 mg,  
31  
32  
33 1.05 mmol, 1.05 equiv.) and  $\text{Et}_3\text{N}$  (278  $\mu\text{L}$ , 2.00 mmol, 2.0 equiv.) in THF (20.0 mL), and  
34  
35  
36  
37 the reaction mixture is allowed to warm to rt overnight. The reaction mixture is filtered  
38  
39  
40  
41 over a plug of celite and the filter cake is rinsed with EtOAc (20 mL). The combined  
42  
43  
44  
45 filtrates are concentrated and repeatedly purified by flash chromatography on silica gel  
46  
47  
48  
49 (gradient of MeOH in DCM; 0% – 5% MeOH and gradient of EtOAc in cyclohexane; 50%  
50  
51  
52 – 100% EtOAc) to give 130 mg (49%) of the title compound as colorless oil.  $R_f$   
53  
54  
55  
56 (DCM:MeOH, 20:1) = 0.45.  $^1\text{H}$  NMR (DMSO- $d_6$ , 400 MHz):  $\delta = 7.90$  – 7.98 (m, 4H), 4.45  
57  
58  
59  
60

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3 – 4.56 (m, 2H), 4.21 – 4.31 (m, 2H), 2.09 – 2.21 (m, 1H), 1.88 – 1.98 (m, 1H) ppm. <sup>13</sup>C  
4  
5  
6  
7 NMR (DMSO-d<sub>6</sub>, 101 MHz) δ = 133.6, 132.0 (d, *J* = 11 Hz), 131.5 – 132.9 (m), 125.5 –  
8  
9  
10 126.2 (m), 123.6 (q, *J* = 273 Hz), 68.1 (d, *J* = 6 Hz), 25.8 (d, *J* = 8 Hz) ppm. <sup>31</sup>P NMR  
11  
12  
13 (DMSO-d<sub>6</sub>, 162 MHz): δ = 9.5 ppm. IR (ATR): 2901, 1400, 1321, 1125, 1049, 1018, 932,  
14  
15  
16 875, 808, 754, 708, 698 cm<sup>-1</sup>. HRMS (ESI<sup>+</sup>) calculated for C<sub>10</sub>H<sub>11</sub>F<sub>3</sub>O<sub>3</sub>P [M+H]<sup>+</sup> *m/z*  
17  
18 267.0392, found 267.0392.  
19  
20  
21  
22  
23

24 **5,5-Dimethyl-2-[4-(trifluoromethyl)phenyl]-1,3,2λ<sup>5</sup>-dioxaphosphan-2-one (25c).** A  
25  
26  
27  
28 solution of [4-(trifluoromethyl)phenyl]phosphonic dichloride (**49**) (263 mg, 1.00 mmol,  
29  
30  
31 1.0 equiv.) in THF (3.00 mL) is added dropwise to a solution of 2,2-dimethyl-1,3-  
32  
33  
34 propandiol (109 mg, 1.05 mmol, 1.05 equiv.) and Et<sub>3</sub>N (278 μL, 2.00 mmol, 2.0 equiv.) in  
35  
36  
37 THF (20.0 mL) at 0 °C, and the reaction mixture is allowed to warm to rt overnight. The  
38  
39  
40  
41  
42 reaction mixture is filtered over a plug of celite and the filter cake is rinsed with EtOAc  
43  
44  
45 (20 mL). The combined filtrates are concentrated, and the residue is purified by flash  
46  
47  
48 chromatography on silica gel (gradient of MeOH in DCM; 0% – 5% MeOH) to give 238 mg  
49  
50  
51 (81%) of the title compound as a colorless solid. R<sub>f</sub> (DCM:MeOH, 20:1) = 0.25. <sup>1</sup>H NMR  
52  
53  
54 (DMSO-d<sub>6</sub>, 400 MHz): δ = 7.91 – 7.99 (m, 4H), 4.15 (dd, *J* = 15.5, 11.2 Hz, 2H), 3.98 (dd,  
55  
56  
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4  $J = 11.2, 7.7$  Hz, 2H), 1.15 (s, 3H), 0.92 (s, 3H) ppm.  $^{13}\text{C}$  NMR (DMSO- $d_6$ , 101 MHz)  $\delta =$   
5  
6  
7 132.2 – 132.8 (m), 131.9 (d,  $J = 11$  Hz), 132.0 (br d,  $J = 182$  Hz), 125.5 – 126.2 (m), 123.6  
8  
9  
10 (q,  $J = 273$  Hz), 76.3 (d,  $J = 6$  Hz), 32.1 (d,  $J = 6$  Hz), 21.0, 20.0 ppm.  $^{31}\text{P}$  NMR (DMSO-  
11  
12  
13  $d_6$ , 162 MHz):  $\delta = 9.4$  ppm. IR (ATR): 2977, 1472, 1397, 1325, 1241, 1163, 1121, 1053,  
14  
15  
16  
17 1001, 961, 910, 826, 815, 710, 630  $\text{cm}^{-1}$ . HRMS (ESI $^+$ ) calculated for  $\text{C}_{12}\text{H}_{15}\text{F}_3\text{O}_3\text{P}$  [M+H] $^+$   
18  
19  
20  
21 m/z 295.0705, found 295.0707.  
22  
23

24 **2-[4-(Trifluoromethyl)phenyl]-1,3,6,2 $\lambda^5$ -dioxazaphosphocan-2-one hydrochloride (25d).**

25  
26  
27  
28 *Tert*-butyl 2-oxo-2-[4-(trifluoromethyl)phenyl]-1,3,6,2 $\lambda^5$ -dioxazaphosphocan-6-  
29  
30  
31 carboxylate (**50**) (39.5 mg, 100  $\mu\text{mol}$ , 1 equiv.) is dissolved in anhydrous HCl (4 M in  
32  
33  
34 1,4-dioxane; 0.200 mL), and the reaction mixture is stirred at rt for 1 h. The solution is  
35  
36  
37 concentrated to give 33.0 mg (quant.) of the title compound as a colorless solid.  $^1\text{H}$  NMR  
38  
39 (DMSO- $d_6$ , 400 MHz):  $\delta = 9.73$  (br s, 2H), 8.01 – 8.08 (m, 2H), 7.95 – 8.01 (m, 2H), 4.45  
40  
41  
42 – 4.55 (m, 2H), 4.29 – 4.42 (m, 2H), 3.38 – 3.52 (m, 4H) ppm.  $^{13}\text{C}$  NMR (DMSO- $d_6$ , 101  
43  
44  
45 MHz)  $\delta = 132.5$  – 133.1 (m), 132.0 (d,  $J = 10$  Hz), 131.2 (br d,  $J = 189$  Hz), 125.4 – 126.0  
46  
47  
48 (m), 123.5 (q,  $J = 273$  Hz), 62.8 (br d,  $J = 7$  Hz), 46.3 ppm.  $^{31}\text{P}$  NMR (DMSO- $d_6$ , 162  
49  
50  
51 MHz):  $\delta = 14.7$  ppm. IR (ATR): 2807, 1575, 1399, 1323, 1267, 1046, 1107, 1063, 1033,  
52  
53  
54  
55  
56  
57  
58  
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60

990, 923, 840, 817, 737, 703  $\text{cm}^{-1}$ . HRMS (ESI<sup>+</sup>) calculated for  $\text{C}_{11}\text{H}_{14}\text{F}_3\text{NO}_3\text{P}$  [M+H]<sup>+</sup> m/z 296.0658, found 296.0659.

**2-[4-(Trifluoromethyl)phenyl]-1,3,2λ<sup>5</sup>-oxazaphosphan-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<sub>3</sub>N (278  $\mu\text{L}$ , 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. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz):  $\delta$  = 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. <sup>13</sup>C NMR (DMSO-d<sub>6</sub>, 101 MHz)  $\delta$  = 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. <sup>31</sup>P NMR (DMSO-d<sub>6</sub>, 162 MHz):  $\delta$  = 14.2 ppm.

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4 IR (ATR): 3226, 1322, 1233, 1167, 1123, 1106, 1062, 1045, 1019, 982, 945, 871, 834,  
5  
6  
7 789, 758  $\text{cm}^{-1}$ . HRMS (ESI<sup>+</sup>) calculated for  $\text{C}_{10}\text{H}_{12}\text{F}_3\text{NO}_2\text{P}$   $[\text{M}+\text{H}]^+$   $m/z$  266.0552, found  
8  
9  
10 266.0551.  
11  
12

13  
14 **3-Methyl-2-[4-(trifluoromethyl)phenyl]-1,3,2 $\lambda^5$ -oxazaphosphinan-2-one (26b).** A  
15  
16  
17 solution of [4-(trifluoromethyl)phenyl]phosphonic dichloride (**49**) (263 mg, 1.00 mmol,  
18  
19  
20 1.0 equiv.) in THF (3.00 mL) is added dropwise to a solution of 3-methylamino-1-propanol  
21  
22  
23 (93.6 mg, 1.05 mmol, 1.05 equiv.) and  $\text{Et}_3\text{N}$  (278  $\mu\text{L}$ , 2.00 mmol, 2.0 equiv.) in THF  
24  
25  
26 (20.0 mL) at 0  $^\circ\text{C}$ , and the reaction mixture is allowed to warm to rt overnight. The reaction  
27  
28  
29  
30  
31 mixture is filtered over a plug of celite, and the filter cake is rinsed with EtOAc (20 mL).  
32  
33  
34  
35 The combined filtrates are concentrated and purified by flash chromatography on silica  
36  
37  
38 gel (gradient of MeOH in DCM+0.1%  $\text{Et}_3\text{N}$ ; 0% – 5% MeOH) to give 189 mg (68%) of the  
39  
40  
41 title compound as a colorless oil.  $R_f$  (DCM+0.1%  $\text{Et}_3\text{N}$ :MeOH, 20:1) = 0.48.  $^1\text{H}$  NMR  
42  
43  
44 (DMSO- $d_6$ , 400 MHz):  $\delta$  = 7.84 – 7.92 (m, 4H), 4.28 – 4.38 (m, 1H), 4.12 – 4.22 (m, 1H),  
45  
46  
47 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.  
48  
49  
50  
51  
52  $^{13}\text{C}$  NMR (DMSO- $d_6$ , 101 MHz)  $\delta$  = 136.5 (br d,  $J$  = 168 Hz), 132.0 (d,  $J$  = 10 Hz), 130.9  
53  
54  
55 – 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,  
56  
57  
58  
59  
60

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4  $J = 4$  Hz), 25.5 (d,  $J = 5$  Hz) ppm.  $^{31}\text{P}$  NMR (DMSO- $d_6$ , 162 MHz):  $\delta = 14.9$  ppm. IR  
5  
6  
7 (ATR): 2900, 1322, 1233, 1166, 1122, 1105, 1061, 1043, 1017, 975, 926, 875, 837, 793,  
8  
9  
10 783  $\text{cm}^{-1}$ . HRMS (ESI $^+$ ) calculated for  $\text{C}_{11}\text{H}_{14}\text{F}_3\text{NO}_2\text{P}$  [M+H] $^+$   $m/z$  280.0709, found  
11  
12  
13  
14 280.0718.  
15  
16

17 **1,3-Dimethyl-2-[4-(trifluoromethyl)phenyl]-1,3,2 $\lambda^5$ -diazaphospholan-2-one (27a).** A  
18  
19  
20  
21 solution of [4-(trifluoromethyl)phenyl]phosphonic dichloride (**49**) (263 mg, 1.00 mmol,  
22  
23  
24 1.0 equiv.) in THF (3.00 mL) is added dropwise to a solution of *N,N'*-  
25  
26  
27 dimethylethylenediamine (113  $\mu\text{L}$ , 1.05 mmol, 1.05 equiv.) and  $\text{Et}_3\text{N}$  (278  $\mu\text{L}$ , 2.00 mmol,  
28  
29  
30 2.0 equiv.) in THF (20.0 mL) at 0  $^\circ\text{C}$ , and the reaction mixture is allowed to warm to rt  
31  
32  
33  
34 overnight. The reaction mixture is filtered over a plug of celite, and the filter cake is rinsed  
35  
36  
37  
38 with EtOAc (20 mL). The combined filtrates are concentrated and purified by flash  
39  
40  
41 chromatography on silica gel (gradient of MeOH in DCM; 0% – 5% MeOH) to give 238 mg  
42  
43  
44 (86%) of the title compound as a colorless oil.  $R_f$  (DCM:MeOH, 20:1) = 0.39.  $^1\text{H}$  NMR  
45  
46  
47 (DMSO- $d_6$ , 400 MHz):  $\delta = 7.79 - 7.87$  (m, 4H), 3.26 – 3.30 (m, 2H), 3.18 – 3.25 (m, 2H),  
48  
49  
50 2.38 (d,  $J = 9.9$  Hz, 6H) ppm.  $^{13}\text{C}$  NMR (DMSO- $d_6$ , 101 MHz)  $\delta = 136.9$  (br d,  $J = 151$  Hz),  
51  
52  
53  
54 132.8 (d,  $J = 10$  Hz), 130.9 – 131.6 (m), 124.8 – 125.5 (m), 124.4 (q,  $J = 273$  Hz), 47.6 (d,  
55  
56  
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4  $J = 9$  Hz), 31.0 (d,  $J = 6$  Hz) ppm.  $^{31}\text{P}$  NMR (DMSO- $d_6$ , 162 MHz):  $\delta = 26.0$  ppm. IR (ATR):

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6  
7 1397, 1321, 1266, 1212, 1158, 1119, 1103, 1061, 1035, 1016, 941, 837, 727, 719  $\text{cm}^{-1}$ .

8  
9  
10 HRMS (ESI $^+$ ) calculated for  $\text{C}_{11}\text{H}_{15}\text{F}_3\text{N}_2\text{OP}$   $[\text{M}+\text{H}]^+$   $m/z$  279.0869, found 279.0874.

11  
12  
13  
14 **2-[4-(Trifluoromethyl)phenyl]-1,3,2 $\lambda^5$ -diazaphosphinan-2-one (27b).** A solution of  
15  
16  
17 [4-(trifluoromethyl)phenyl]phosphonic dichloride (**49**) (263 mg, 1.00 mmol, 1.0 equiv.) in  
18  
19  
20 THF (3.00 mL) is added dropwise to a solution of 1,3-propanediamine (77.8 mg,  
21  
22  
23 1.05 mmol, 1.05 equiv.) and  $\text{Et}_3\text{N}$  (278  $\mu\text{L}$ , 2.00 mmol, 2.0 equiv.) in THF (20.0 mL) at  
24  
25  
26 0  $^\circ\text{C}$ , and the reaction mixture is allowed to warm to rt overnight. The reaction mixture is  
27  
28  
29 filtered over a plug of celite, and the filter cake is rinsed with EtOAc (20 mL). The  
30  
31  
32 combined filtrates are concentrated and purified by flash chromatography on silica gel  
33  
34  
35 (gradient of MeOH in DCM+0.1%  $\text{Et}_3\text{N}$ ; 0% – 10% MeOH) to give 58.0 mg (22%) of the  
36  
37  
38 title compound as a colorless solid.  $R_f$  (DCM+0.1%  $\text{Et}_3\text{N}$ :MeOH, 20:1) = 0.27.  $^1\text{H}$  NMR  
39  
40  
41 (DMSO- $d_6$ , 400 MHz):  $\delta = 7.87 - 7.95$  (m, 2H), 7.79 – 7.84 (m, 2H), 4.84 – 4.92 (m, 2H),  
42  
43  
44 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.  
45  
46  
47  
48  
49  
50  
51  
52  $^{13}\text{C}$  NMR (DMSO- $d_6$ , 101 MHz)  $\delta = 141.7$  (br d,  $J = 143$  Hz), 131.2 (d,  $J = 10$  Hz), 129.4  
53  
54  
55 – 130.8 (m), 124.5 – 125.2 (m), 124.0 (q,  $J = 272$  Hz), 41.2 (d,  $J = 3$  Hz), 26.2 (d,  
56  
57  
58  
59  
60

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3  
4  $J = 6$  Hz) ppm.  $^{31}\text{P}$  NMR (DMSO- $d_6$ , 162 MHz):  $\delta = 13.5$  ppm. IR (ATR): 3181, 1395,  
5  
6  
7 1314, 1185, 1159, 1113, 1100, 1058, 1016, 998, 960, 868, 828, 797, 701  $\text{cm}^{-1}$ . HRMS  
8  
9  
10 (ESI $^+$ ) calculated for  $\text{C}_{10}\text{H}_{13}\text{F}_3\text{N}_2\text{OP}$   $[\text{M}+\text{H}_2\text{O}+\text{H}]^+$   $m/z$  283.0818, found 283.0818.

11  
12  
13  
14 **1,3-Dimethyl-2-[4-(trifluoromethyl)phenyl]-1,3,2 $\lambda^5$ -diazaphosphinan-2-one (27c).** A  
15  
16  
17 solution of [4-(trifluoromethyl)phenyl]phosphonic dichloride (**49**) (263 mg, 1.00 mmol,  
18  
19  
20 1.0 equiv.) in THF (3.00 mL) is added dropwise to a solution of *N,N'*-dimethyl-1,3-  
21  
22  
23 propanediamine (107 mg, 1.05 mmol, 1.05 equiv.) and  $\text{Et}_3\text{N}$  (278  $\mu\text{L}$ , 2.00 mmol,  
24  
25  
26 2.0 equiv.) in THF (20.0 mL) at 0  $^\circ\text{C}$ , and the reaction mixture is allowed to warm to rt  
27  
28  
29 overnight. The reaction mixture is filtered over a plug of celite, and the filter cake is rinsed  
30  
31  
32 with EtOAc (20 mL). The combined filtrates are concentrated and purified by flash  
33  
34  
35 chromatography on silica gel (gradient of MeOH in DCM; 0% – 5% MeOH) to give 207 mg  
36  
37  
38 (71%) of the title compound as a colorless oil.  $R_f$  (DCM+0.1%  $\text{Et}_3\text{N}$ :MeOH, 20:1) = 0.30.  
39  
40  
41  
42  $^1\text{H}$  NMR (DMSO- $d_6$ , 400 MHz):  $\delta = 7.79 - 7.88$  (m, 4H), 3.05 – 3.21 (m, 4H), 2.39 (d,  
43  
44  
45  $J = 10.0$  Hz, 6H), 1.97 – 2.09 (m, 1H), 1.83 – 1.93 (m, 1H) ppm.  $^{13}\text{C}$  NMR (DMSO- $d_6$ , 101  
46  
47  
48 MHz)  $\delta = 138.1$  (br d,  $J = 146$  Hz), 132.2 (d,  $J = 9$  Hz), 130.0 – 131.4 (m), 124.8 – 125.3  
49  
50  
51 (m), 123.9 (q,  $J = 272$  Hz), 49.8, 34.5 (d,  $J = 4$  Hz), 25.0 (d,  $J = 3$  Hz) ppm.  $^{31}\text{P}$  NMR  
52  
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3  
4 (DMSO-d<sub>6</sub>, 162 MHz):  $\delta$  = 16.1 ppm. IR (ATR): 2932, 1322, 1260, 1164, 1121, 1103,  
5  
6  
7 1059, 1017, 979, 874, 747, 711, 658 cm<sup>-1</sup>. HRMS (ESI<sup>+</sup>) calculated for C<sub>12</sub>H<sub>17</sub>F<sub>3</sub>N<sub>2</sub>OP  
8  
9  
10 [M+H]<sup>+</sup> m/z 293.1025, found 293.1025.

11  
12  
13  
14 **4-(Diethylphosphoryl)pyridine (28a)**. A solution of Pd<sub>2</sub>(dba)<sub>3</sub> (45.7 mg, 50.0  $\mu$ mol,  
15  
16  
17 5 mol%) and Xantphos (57.9 mg, 100  $\mu$ mol, 10 mol%) in 1,4-dioxane (2.00 mL) is stirred  
18  
19  
20 at rt for 10 min and then added to a solution of 4-bromopyridine hydrochloride (194 mg,  
21  
22  
23 1.00 mmol, 1.0 equiv.), diethylphosphine oxide (106 mg, 1.00 mmol, 1.0 equiv.) and  
24  
25  
26  
27 DIPEA (383  $\mu$ L, 2.20 mmol, 2.2 equiv.) in 1,4-dioxane (4.00 mL). The reaction mixture is  
28  
29  
30 heated at 80 °C for 2 days, allowed to cool to room temperature and diluted with saturated  
31  
32  
33 aqueous NaHCO<sub>3</sub> solution. The mixture is extracted with dichloromethane (4 x 20 mL),  
34  
35  
36  
37 and the combined organic layers are dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under  
38  
39  
40 reduced pressure. The residue is purified by flash chromatography on silica gel (gradient  
41  
42  
43 of MeOH in DCM; 0% – 10% MeOH) to give 79.0 mg (43%) of the title compound as a  
44  
45  
46  
47 colorless solid. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz):  $\delta$  = 8.72 – 8.77 (m, 2H), 7.66 – 7.72 (m,  
48  
49  
50 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<sup>+</sup>)  
51  
52  
53  
54  
55  
56 [M+H]<sup>+</sup> m/z 184.19.

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2  
3 **Ethyl methyl(pyridin-4-yl)phosphinate (28b)**. Pd(OAc)<sub>2</sub> (4.49 mg, 20.0 μmol, 2.0 mol%)  
4  
5  
6  
7 and Xantphos (12.7 mg, 22.0 μmol, 2.2 mol%) is added to a solution of 4-bromopyridine  
8  
9  
10 hydrochloride (194 mg, 1.00 mmol, 1.0 equiv.), ethyl methylphosphinate (130 mg,  
11  
12  
13 1.20 mmol, 1.2 equiv.) and DIPEA (401 μL, 1.30 mmol, 2.3 equiv.) in toluene (1.60 mL)  
14  
15  
16 and DME (400 μL). The reaction mixture is sealed in a microwave vial and heated at  
17  
18 80 °C for 2 d. The reaction mixture is diluted with saturated aqueous NaHCO<sub>3</sub> (30 mL)  
19  
20  
21 and extracted with DCM (4 x 20 mL). The combined organic phases are dried over  
22  
23  
24 Na<sub>2</sub>SO<sub>4</sub> and concentrated. The residue is purified by flash chromatography on silica gel  
25  
26  
27  
28 (gradient of MeOH in DCM; 0% – 10% MeOH) to give 161 mg (87%) of the title compound  
29  
30  
31 as a yellow oil. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz): δ = 8.76 – 8.80 (m, 2H), 7.66 – 7.73 (m,  
32  
33  
34 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,  
35  
36  
37 *J* = 14.8 Hz, 3H), 1.20 (t, *J* = 7.0 Hz, 3H) ppm. <sup>13</sup>C NMR (DMSO-d<sub>6</sub>, 101 MHz) δ = 150.0  
38  
39  
40  
41 (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,  
42  
43  
44 *J* = 6 Hz), 14.4 (d, *J* = 101 Hz) ppm. <sup>31</sup>P NMR (DMSO-d<sub>6</sub>, 162 MHz): δ = 39.2 ppm. IR  
45  
46  
47  
48 (ATR): 3445, 2985, 1401, 1219, 1205, 1132, 1026, 956, 834, 785, 756 cm<sup>-1</sup>. HRMS (ESI<sup>+</sup>)  
49  
50  
51  
52 calculated for C<sub>8</sub>H<sub>13</sub>NO<sub>2</sub>P [M+H]<sup>+</sup> *m/z* 186.0678, found 186.0684.  
53  
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4 **Diethyl (pyridin-4-yl)phosphonate (28c)**. The reaction was performed according to a  
5  
6 literature report.<sup>67</sup> To a suspension of Pd(OAc)<sub>2</sub> (17.9 mg, 80.0 μmol, 2.0 mol%), dppf  
7  
8 (88.7 mg, 160 μmol 4.0 mol%), KOAc (39.3 mg, 400 μmol, 10 mol%) and DIPEA  
9  
10 (1.60 mL, 9.20 mmol, 2.3 equiv.) in THF (20.0 mL) is added 4-bromopyridine  
11  
12 hydrochloride (778 mg, 4.00 mmol, 1.0 equiv.) and diethyl phosphite (618 μL, 4.80 mmol,  
13  
14 1.2 equiv.). The reaction mixture is sealed in a microwave vial and heated at 70 °C for  
15  
16 24 h. The reaction mixture is filtered through a plug of celite, and the filtrate is  
17  
18 concentrated. The residue is purified by preparative RP-HPLC (Waters SunFire™ C<sub>18</sub>,  
19  
20 gradient of acetonitrile in water, 0.1% TFA), and the appropriate fractions are combined  
21  
22 and diluted with saturated aqueous NaHCO<sub>3</sub> (100 mL). The aqueous phase is extracted  
23  
24 with EtOAc (3 x 75 mL), and the combined organic phases are dried over Na<sub>2</sub>SO<sub>4</sub> and  
25  
26 concentrated to give 629 mg (73%) of the title compound as light-yellow oil. The spectral  
27  
28 data is in accordance with the literature.<sup>67</sup>

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49 **4-((4-Methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzoic acid**  
50  
51  
52 **trifluoroacetate salt (37a·TFA)**. LiOH (59.9 mg, 2.00 mmol, 10.0 equiv.) is added to a  
53  
54 solution of ethyl 4-((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-

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3  
4 yl)amino)phenyl)carbamoyl)benzoate trifluoroacetate salt (**37b**·TFA, 90.7 mg, 200  $\mu$ mol,  
5  
6  
7 1.0 equiv.) in a solvent mixture of THF/MeOH/H<sub>2</sub>O (*v:v:v*, 2:1:1; 4 mL), and the reaction  
8  
9  
10 mixture is stirred at rt overnight. Aqueous HCl (1M, 5 mL) is added, and the mixture is  
11  
12  
13 concentrated. The residue is dissolved in DMF, filtered and purified by preparative RP-  
14  
15  
16 HPLC (Waters SunFire™ C<sub>18</sub>, gradient of acetonitrile in water, 0.1% TFA) to give 84.0 mg  
17  
18 (80%) of the title compound as a yellow solid. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz):  $\delta$  = 10.36  
19  
20  
21 (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,  
22  
23  
24 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),  
25  
26  
27 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. <sup>13</sup>C  
28  
29  
30 NMR (DMSO-d<sub>6</sub>, 101 MHz)  $\delta$  = 166.7, 164.6, 161.0, 160.8, 159.6, 149.4, 146.4, 138.8,  
31  
32  
33 137.7, 136.9, 136.6, 133.2, 133.0, 130.1, 129.2, 127.8, 124.6, 117.2, 116.8, 107.7,  
34  
35  
36 17.6 ppm. IR (ATR): 1674, 1575, 1530, 1423, 1406, 1300, 1286, 1199, 1183, 1125, 796,  
37  
38  
39 719, 674, 654 cm<sup>-1</sup>. HRMS (ESI<sup>+</sup>) calculated for C<sub>24</sub>H<sub>20</sub>N<sub>5</sub>O<sub>3</sub> [M+H]<sup>+</sup> *m/z* 426.1561, found  
40  
41  
42 426.1558.  
43  
44  
45  
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48  
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51

52 **Ethyl 4-((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)carbamoyl)benzoate**  
53  
54  
55  
56 **trifluoroacetate salt (37b·TFA)**. HATU (384 mg, 1.00 mmol, 1.0 equiv.) is added to a  
57  
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60

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3  
4 solution of ethyl terephthalate (194 mg, 1.00 mmol, 1.0 equiv.) and DIPEA (518  $\mu$ L,  
5  
6  
7 3.00 mmol, 3.0 equiv.) in DMF (5.00 mL), and the reaction mixture is stirred at rt for  
8  
9  
10 10 min. Then 6-methyl-*N*-(4-(pyridin-3-yl)pyrimidin-2-yl)benzene-1,3-diamine (51)  
11  
12  
13 (277 mg, 1.00 mmol, 1.0 equiv.) is added, and the reaction mixture is heated at 50 °C for  
14  
15  
16  
17 1 h. The reaction mixture is acidified using TFA and directly purified by preparative RP-  
18  
19  
20 HPLC (Waters SunFire™ C<sub>18</sub>, gradient of acetonitrile in water, 0.1% TFA) to give 509 mg  
21  
22  
23 (90%) of the title compound as a yellow solid. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz):  $\delta$  = 10.39  
24  
25  
26 (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,  
27  
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*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. <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 101 MHz)  
 $\delta$  = 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<sup>-1</sup>. HRMS (ESI<sup>+</sup>) calculated for C<sub>26</sub>H<sub>24</sub>N<sub>5</sub>O<sub>3</sub> [M+H]<sup>+</sup> *m/z* 454.1874, found  
454.1873.

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2  
3 ***N'*-(4-Methyl-3-[[4-(pyridin-3-yl)pyrimidin-2-yl]amino}phenyl)benzene-1,4-**  
4  
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6  
7 **dicarboxamide trifluoroacetate salt (38a·TFA)**. HATU (384 mg, 1.00 mmol, 1.0 equiv.) is  
8  
9  
10 added to a solution of terephthalic acid monoamide (165 mg, 1.00 mmol, 1.0 equiv.) and  
11  
12  
13  
14 DIPEA (518  $\mu$ L, 3.00 mmol, 3.0 equiv.) in DMF (5.00 mL), and the reaction mixture is  
15  
16  
17 stirred at rt for 10 min. Then 6-methyl-*N'*-(4-(pyridin-3-yl)pyrimidin-2-yl)benzene-1,3-  
18  
19  
20 diamine (**51**) (277 mg, 1.00 mmol, 1.0 equiv.) is added, and the reaction mixture is heated  
21  
22  
23  
24 at 50 °C for 1 h. The reaction mixture is acidified using TFA and directly purified by  
25  
26  
27  
28 preparative RP-HPLC (Waters XBridge™ C<sub>18</sub>, gradient of acetonitrile in water, 0.1% TFA)  
29  
30  
31 to give 462 mg (86%) of the title compound as a yellow solid. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400  
32  
33  
34 MHz):  $\delta$  = 10.30 (s, 1H), 9.35 (dd,  $J$  = 2.2, 0.6 Hz, 1H), 9.04 (s, 1H), 8.79 (dd,  $J$  = 5.0,  
35  
36  
37 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,  
38  
39  
40  
41  $J$  = 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),  
42  
43  
44 7.44 – 7.54 (m, 3H), 7.23 (d,  $J$  = 8.5 Hz, 1H), 2.24 (s, 3H) ppm. <sup>13</sup>C NMR (DMSO-d<sub>6</sub>, 101  
45  
46  
47  
48 MHz)  $\delta$  = 167.1, 164.7, 161.0, 160.7, 159.6, 149.1, 146.1, 137.6, 137.3, 137.0, 136.7,  
49  
50  
51  
52 133.1, 130.1, 127.7, 127.5, 127.4, 124.7, 117.2, 116.8, 107.7, 17.6 ppm. IR (ATR): 3312,  
53  
54  
55  
56  
57  
58  
59  
60

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2  
3 1664, 1578, 1532, 1404, 1198, 1126, 801, 721, 670 cm<sup>-1</sup>. HRMS (ESI<sup>+</sup>) calculated for  
4  
5  
6  
7 C<sub>24</sub>H<sub>21</sub>N<sub>6</sub>O<sub>2</sub> [M+H]<sup>+</sup> m/z 425.1741, found 425.1726.  
8  
9

10 ***N*'-Methyl-*N*'-(4-methyl-3-{[4-(pyridin-3-yl)pyrimidin-2-yl]amino}phenyl)benzene-1,4-**  
11  
12 **dicarboxamide trifluoroacetate salt (38b-TFA).** HATU (384 mg, 1.00 mmol, 1.0 equiv.) is  
13  
14 added to a solution of *N*-methyl terephthalic acid monoamide (179 mg, 1.00 mmol,  
15  
16 1.0 equiv.) and DIPEA (518 μL, 3.00 mmol, 3.0 equiv.) in DMF (5.00 mL), and the  
17  
18 reaction mixture is stirred at rt for 10 min. Then 6-methyl-*N*'-(4-(pyridin-3-yl)pyrimidin-2-  
19  
20 yl)benzene-1,3-diamine (**51**) (277 mg, 1.00 mmol, 1.0 equiv.) is added, and the reaction  
21  
22 mixture is heated at 50 °C for 1 h. The reaction mixture is acidified using TFA and directly  
23  
24 purified by preparative RP-HPLC (Waters SunFire™ C<sub>18</sub>, gradient of acetonitrile in water,  
25  
26 0.1% TFA) to give 450 mg (81%) of the title compound as an orange solid. <sup>1</sup>H NMR  
27  
28 (DMSO-d<sub>6</sub>, 400 MHz): δ = 10.31 (s, 1H), 9.38 (d, *J* = 1.8 Hz, 1H), 9.07 (s, 1H), 8.82 (dd,  
29  
30 *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,  
31  
32 *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),  
33  
34 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,  
35  
36 *J* = 4.4 Hz, 3H), 2.24 (s, 3H) ppm. <sup>13</sup>C NMR (DMSO-d<sub>6</sub>, 101 MHz) δ = 165.9, 164.7, 161.0,  
37  
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3 160.4, 159.6, 148.4, 145.5, 137.7, 137.6, 137.1, 137.0, 136.9, 130.1, 127.7, 127.6, 127.0,  
4  
5  
6  
7 125.1, 117.2, 116.9, 107.7, 26.3, 17.6 ppm. IR (ATR): 3321, 1630, 1576, 1530, 1198,  
8  
9  
10 1185, 1135, 807, 720, 704, 671 cm<sup>-1</sup>. HRMS (ESI<sup>+</sup>) calculated for C<sub>25</sub>H<sub>23</sub>N<sub>6</sub>O<sub>2</sub> [M+H]<sup>+</sup> m/z  
11  
12  
13  
14 439.1877, found 439.1876.  
15  
16

17 ***N,N*-Dimethyl-*N*-(4-methyl-3-[[4-(pyridin-3-yl)pyrimidin-2-yl]amino]phenyl)benzene-**  
18  
19  
20 **1,4-dicarboxamide trifluoroacetate salt (38c·TFA).** HATU (384 mg, 1.00 mmol, 1.0 equiv.)  
21  
22 is added to a solution of *N,N*-dimethyl terephthalic acid monoamide (193 mg, 1.00 mmol,  
23  
24 1.0 equiv.) and DIPEA (518 μL, 3.00 mmol, 3.0 equiv.) in DMF (5.00 mL), and the  
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3 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,  
4  
5  
6 3H) ppm.  $^{13}\text{C}$  NMR (DMSO- $d_6$ , 101 MHz):  $\delta = 169.4, 164.8, 161.0, 160.6, 159.6, 149.0,$   
7  
8  
9  
10 146.0, 139.3, 137.6, 137.1, 137.0, 135.6, 133.2, 130.1, 127.7, 127.6, 126.8, 124.8, 117.2,  
11  
12  
13 116.8, 107.7, 34.7, 29.4, 17.6 ppm. IR (ATR): 1606, 1578, 1532, 1453, 1406, 1180, 1129,  
14  
15  
16  
17 837, 799, 720, 672  $\text{cm}^{-1}$ . HRMS (ESI $^+$ ) calculated for  $\text{C}_{26}\text{H}_{25}\text{N}_6\text{O}_2$  [M+H] $^+$   $m/z$  453.2034,  
18  
19  
20  
21 found 453.2034.  
22  
23

24 **4-Methanesulfinyl-*N*-(4-methyl-3-[[4-(pyridin-3-yl)pyrimidin-2-yl]amino}phenyl)-**  
25  
26  
27 **benzamide trifluoroacetate salt (39·TFA).** HATU (384 mg, 1.00 mmol, 1.0 equiv.) is added  
28  
29 to a solution of 4-methanesulfinylbenzoic acid (184 mg, 1.00 mmol, 1.0 equiv.) and  
30  
31  
32 to a solution of 4-methanesulfinylbenzoic acid (184 mg, 1.00 mmol, 1.0 equiv.) and  
33  
34  
35 DIPEA (518  $\mu\text{L}$ , 3.00 mmol, 3.0 equiv.) in DMF (5.00 mL), and the reaction mixture is  
36  
37  
38 stirred at rt for 10 min. Then 6-methyl-*N*-(4-(pyridin-3-yl)pyrimidin-2-yl)benzene-1,3-  
39  
40  
41 diamine (**51**) (277 mg, 1.00 mmol, 1.0 equiv.) is added, and the reaction mixture is heated  
42  
43  
44  
45 at 50  $^\circ\text{C}$  for 1 h. The reaction mixture is acidified using TFA and purified by preparative  
46  
47  
48 RP-HPLC (Waters SunFire $^{\text{TM}}$  C $_{18}$ , gradient of acetonitrile in water, 0.1% TFA) to give  
49  
50  
51  
52 512 mg (92%) of the title compound as an orange solid.  $^1\text{H}$  NMR (DMSO- $d_6$ , 400 MHz):  
53  
54  
55  
56  $\delta = 10.35$  (s, 1H), 9.36 (d,  $J = 1.6$  Hz, 1H), 9.05 (s, 1H), 8.80 (dd,  $J = 5.0, 1.5$  Hz, 1H),  
57  
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4 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),  
5  
6  
7 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),  
8  
9  
10 2.24 (s, 3H) ppm.  $^{13}\text{C}$  NMR (DMSO- $d_6$ , 101 MHz):  $\delta = 164.6, 161.0, 160.6, 159.6, 149.7,$   
11  
12  
13  
14 148.8, 145.8, 137.6, 137.3, 137.1, 136.9, 133.2, 130.1, 128.4, 127.8, 124.9, 123.6, 117.2,  
15  
16  
17 116.8, 107.7, 43.1, 17.6 ppm. IR (ATR): 1667, 1603, 1575, 1530, 1451, 1405, 1185, 1133,  
18  
19  
20  
21 843, 798, 720  $\text{cm}^{-1}$ . HRMS (ESI $^+$ ) calculated for  $\text{C}_{24}\text{H}_{22}\text{N}_5\text{O}_2\text{S}$   $[\text{M}+\text{H}]^+$   $m/z$  444.1489,  
22  
23  
24 found 444.1490.

25  
26  
27  
28 **4-Methanesulfonyl-*N*-(4-methyl-3-[[4-(pyridin-3-yl)pyrimidin-2-yl]amino}phenyl)-**  
29  
30  
31 **benzamide trifluoroacetate salt (40·TFA).** HATU (384 mg, 1.00 mmol, 1.0 equiv.) is added  
32  
33  
34 to a solution of 4-methanesulfonylbenzoic acid (200 mg, 1.00 mmol, 1.0 equiv.) and  
35  
36  
37 DIPEA (518  $\mu\text{L}$ , 3.00 mmol, 3.0 equiv.) in DMF (5.00 mL), and the reaction mixture is  
38  
39  
40  
41  
42 stirred at rt for 10 min. Then 6-methyl-*N*-(4-(pyridin-3-yl)pyrimidin-2-yl)benzene-1,3-  
43  
44  
45 diamine (**51**) (277 mg, 1.00 mmol, 1.0 equiv.) is added, and the reaction mixture is heated  
46  
47  
48  
49 at 50  $^\circ\text{C}$  for 1 h. The reaction mixture is acidified using TFA and purified by preparative  
50  
51  
52 RP-HPLC (Waters SunFire $^{\text{TM}}$  C $_{18}$ , gradient of acetonitrile in water, 0.1% TFA) to give  
53  
54  
55  
56 522 mg (91%) of the title compound as an orange solid. $^{73}$   $^1\text{H}$  NMR (DMSO- $d_6$ , 400 MHz):  
57  
58  
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3  $\delta = 10.45$  (s, 1H), 9.36 (d,  $J = 1.6$  Hz, 1H), 9.05 (s, 1H), 8.79 (dd,  $J = 5.0, 1.5$  Hz, 1H),  
4  
5  
6  
7 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  
9  
10 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),  
11  
12  
13 3.29 (s, 3H), 2.24 (s, 3H) ppm.  $^{13}\text{C}$  NMR (DMSO- $d_6$ , 101 MHz):  $\delta = 164.1, 161.0, 160.6,$   
14  
15  
16  
17 159.6, 149.0, 146.0, 143.0, 139.5, 137.7, 137.0, 136.7, 133.1, 130.2, 128.6, 127.9, 127.0,  
18  
19  
20  
21 124.8, 117.1, 116.8, 107.7, 43.3, 17.6 ppm. IR (ATR): 1668, 1575, 1529, 1452, 1295,  
22  
23  
24 1184, 1150, 799, 784, 720  $\text{cm}^{-1}$ . HRMS (ESI $^+$ ) calculated for  $\text{C}_{24}\text{H}_{22}\text{N}_5\text{O}_3\text{S}$  [M+H] $^+$  m/z  
25  
26  
27  
28 460.1438, found 460.1432.  
29  
30

31 **4-[Imino(methyl)oxo- $\lambda^6$ -sulfanyl]-*N*-(4-methyl-3-[[4-(pyridin-3-yl)pyrimidin-2-yl]amino]-**  
32  
33  
34 **phenyl)benzamide (41a). Step 1: Synthesis of 4-[imino(methyl)oxo- $\lambda^6$ -sulfanyl]benzoic**  
35  
36 **acid.** LiOH (239 mg, 10.0 mmol, 10.0 equiv.) is added to a solution of methyl 4-  
37  
38 [imino(methyl)oxo- $\lambda^6$ -sulfanyl]benzoate<sup>89</sup> (213 mg, 1.00 mmol, 1.0 equiv.)  
39  
40  
41 in THF/MeOH/H<sub>2</sub>O ( $\nu:\nu:\nu$ , 2:1:1; 4.00 mL), and the reaction mixture is stirred at rt  
42  
43  
44  
45 overnight. Aqueous HCl (1M, 35 mL) is added, and the aqueous phase is extracted with  
46  
47  
48  
49 EtOAc (10 x 30 mL). The combined organic phases are dried over Na<sub>2</sub>SO<sub>4</sub> and  
50  
51  
52 concentrated. The residue is purified by RP-HPLC (Waters XBridge<sup>TM</sup>-C<sub>18</sub>, gradient of  
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3 acetonitrile in water, 0.1% TFA) to give 299 mg of a crude reaction product which is used  
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6  
7 directly in the next reaction step.  
8  
9

10 **Step 2: Synthesis of 4-[imino(methyl)oxo- $\lambda^6$ -sulfanyl]-*N*-(4-methyl-3-{[4-(pyridin-3-**  
11 **yl)pyrimidin-2-yl]amino}phenyl)benzamide (41a).** HATU (576 mg, 1.50 mmol, 1.5 equiv.)  
12  
13  
14 is added to a solution of the crude 4-[imino(methyl)oxo- $\lambda^6$ -sulfanyl]benzoic acid (Step 1,  
15  
16  
17 assumption: 1.00 mmol), 6-methyl-*N*-(4-(pyridin-3-yl)pyrimidin-2-yl)benzene-1,3-  
18  
19  
20  
21 diamine (**51**) (333 mg, 1.20 mmol, 1.2 equiv.) and DIPEA (518  $\mu$ L, 3.00 mmol, 3.0 equiv.)  
22  
23  
24 in DMF (5.00 mL), and the reaction mixture is stirred at rt overnight. The reaction mixture  
25  
26  
27  
28 is acidified using TFA and repeatedly purified by preparative RP-HPLC (Waters  
29  
30  
31 XBridge<sup>TM</sup> C<sub>18</sub>, gradient of acetonitrile in water, 0.1% TFA; Waters XBridge<sup>TM</sup> C<sub>18</sub>,  
32  
33  
34 gradient of methanol in water, 0.1% NH<sub>4</sub>OH) to give 90.0 mg (20%) of the title compound  
35  
36  
37  
38 as light-yellow solid. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz):  $\delta$  = 10.39 (s, 1H), 9.28 (dd, *J* = 2.2,  
39  
40  
41 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  
42  
43  
44 (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,  
45  
46  
47 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,  
48  
49  
50  
51 *J* = 8.5 Hz, 1H), 4.37 (s, 1H), 3.12 (d, *J* = 0.6 Hz, 3H), 2.23 (s, 3H) ppm. <sup>13</sup>C NMR (DMSO-  
52  
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4 d<sub>6</sub>, 151 MHz) δ = 164.3, 161.6, 161.1, 159.4, 151.3, 148.1, 146.6, 138.5, 137.8, 136.8,  
5  
6  
7 134.4, 132.2, 130.1, 128.2, 127.9, 127.2, 123.7, 117.1, 116.7, 107.5, 45.5, 17.6 ppm. IR  
8  
9  
10 (ATR): 3230, 2987, 1668, 1585, 1559, 1524, 1415, 996, 813, 755, 708, 688, 650 cm<sup>-1</sup>.  
11  
12  
13  
14 HRMS (ESI<sup>+</sup>) calculated for C<sub>24</sub>H<sub>23</sub>N<sub>6</sub>O<sub>2</sub>S [M+H]<sup>+</sup> m/z 459.1598, found 459.1593.  
15  
16

17 **4-[Methyl(methylimino)oxo-λ<sup>6</sup>-sulfanyl]-N-(4-methyl-3-[[4-(pyridine-3-yl)pyrimidin-2-yl]-**  
18  
19  
20 **amino}phenyl)benzamide (41b). Step 1: Synthesis of 4-[methyl(methylimino)oxo-λ<sup>6</sup>-**  
21 **sulfanyl]benzoic acid.** A solution of methyl 4-[imino(methyl)oxo-λ<sup>6</sup>-sulfanyl]benzoate<sup>89</sup>  
22  
23  
24 (213 mg, 1.00 mmol, 1.0 equiv.) in aqueous formaldehyde solution (37%; 2.00 mL) and  
25  
26  
27 formic acid (8.00 mL) is refluxed for 36 h. The reaction mixture is cooled to rt and carefully  
28  
29  
30  
31 treated with saturated aqueous NaHCO<sub>3</sub> (40 mL) and solid NaHCO<sub>3</sub>. The basic aqueous  
32  
33  
34 phase is extracted with EtOAc (3 x 20 mL), and the combined organic phases are dried  
35  
36  
37 over MgSO<sub>4</sub> and concentrated. The residue is purified by RP-HPLC (Waters XBridge™  
38  
39  
40 C<sub>18</sub>, gradient of acetonitrile in water, 0.1% NH<sub>4</sub>OH) to give 135 mg (~60%, ~70% purity)  
41  
42  
43  
44 of a crude reaction product which is directly dissolved in aqueous HCl (4 M; 2.00 mL) and  
45  
46  
47 heated at 80 °C overnight. The reaction mixture is concentrated, and the residue is used  
48  
49  
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51  
52  
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55  
56 in the next step without further purification.  
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58  
59  
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4       **Step 2: Synthesis of 4-[methyl(methylimino)oxo- $\lambda^6$ -sulfanyl]-*N*-(4-methyl-3-[[4-**  
5  
6  
7 **(pyridine-3-yl)pyrimidin-2-yl]amino}phenyl)benzamide (41b).** HATU (346 mg, 900  $\mu$ mol,  
8  
9  
10 1.5 equiv.) is added to a solution of crude 4-[methyl(methylimino)oxo- $\lambda^6$ -sulfanyl]benzoic  
11  
12  
13  
14 acid (Step 1, approx. 600  $\mu$ mol, 1.0 equiv.), 6-methyl-*N*'-(4-(pyridin-3-yl)pyrimidin-2-  
15  
16  
17 yl)benzene-1,3-diamine (**51**) (200 mg, 720  $\mu$ mol, 1.2 equiv.) and DIPEA (311  $\mu$ L,  
18  
19  
20 1.80 mmol, 3.0 equiv.) in DMF (3.00 mL), and the reaction mixture is stirred at rt for 2 h.  
21  
22  
23  
24 The reaction mixture is acidified using TFA and repeatedly purified by preparative RP-  
25  
26  
27  
28 HPLC (Waters SunFire™ C<sub>18</sub>, gradient of acetonitrile in water, 0.1% TFA; Waters  
29  
30  
31 XBridge™ Phenyl, gradient of methanol in water, 0.1% NH<sub>4</sub>OH) to give 57.0 mg (20%) of  
32  
33  
34  
35 the title compound as light-yellow solid. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz):  $\delta$  = 10.42 (s, 1H),  
36  
37  
38 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,  
39  
40  
41  
42 *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,  
43  
44  
45  
46 *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,  
47  
48  
49 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),  
50  
51  
52 2.24 (s, 3H) ppm. <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 151 MHz):  $\delta$  = 164.4, 161.6, 161.1, 159.4, 151.3,  
53  
54  
55  
56 148.2, 141.7, 138.9, 137.8, 136.8, 134.4, 132.2, 130.1, 128.6, 128.3, 127.9, 123.7, 117.1,  
57  
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3 116.7, 107.5, 43.4, 29.1, 17.6 ppm. IR (ATR): 3414, 1674, 1578, 1518, 1479, 1423, 1395,  
4  
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6  
7 1239, 1146, 847, 799, 746, 702 cm<sup>-1</sup>. HRMS (ESI<sup>+</sup>) calculated for C<sub>25</sub>H<sub>25</sub>N<sub>6</sub>O<sub>2</sub>S [M+H]<sup>+</sup>  
8  
9  
10 m/z 473.1760, found 473.1750.

11  
12  
13  
14 ***N*-(4-Methyl-3-[[4-(pyridine-3-yl)pyrimidin-2-yl]amino]phenyl)-4-sulfamoylbenzamide**  
15  
16  
17 **trifluoroacetate salt (42a·TFA)**. HATU (384 mg, 1.00 mmol, 1.0 equiv.) is added to a  
18  
19  
20  
21 solution of 4-sulfamoylbenzoic acid (201 mg, 1.00 mmol, 1.0 equiv.) and DIPEA (518 μL,  
22  
23  
24 3.00 mmol, 3.0 equiv.) in DMF (5.00 mL), and the reaction mixture is stirred at rt for  
25  
26  
27  
28 10 min. Then 6-methyl-*N*-(4-(pyridin-3-yl)pyrimidin-2-yl)benzene-1,3-diamine (**51**)  
29  
30  
31 (277 mg, 1.00 mmol, 1.0 equiv.) is added, and the reaction mixture is heated at 50 °C  
32  
33  
34  
35 overnight. The reaction mixture is acidified using TFA and purified by preparative RP-  
36  
37  
38 HPLC (Waters SunFire™ C<sub>18</sub>, gradient of acetonitrile in water, 0.1% TFA) to give 395 mg  
39  
40  
41 (69%) of the title compound as a yellow solid. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz): δ = 10.37  
42  
43  
44 (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  
45  
46  
47 (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  
48  
49  
50 (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),  
51  
52  
53 2.24 (s, 3H) ppm. <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 151 MHz): δ = 164.3, 161.0, 161.0, 159.5, 149.8,  
54  
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3 146.7, 146.4, 137.9, 137.7, 136.8, 136.2, 132.8, 130.1, 128.3, 127.8, 125.6, 124.4, 117.1,  
4  
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6  
7 116.8, 107.6, 17.6 ppm. IR (ATR): 3335, 1647, 1578, 1531, 1416, 1404, 1289, 1165,  
8  
9  
10 1157, 797, 610 cm<sup>-1</sup>. HRMS (ESI<sup>+</sup>) calculated for C<sub>23</sub>H<sub>21</sub>N<sub>6</sub>O<sub>3</sub> [M+H]<sup>+</sup> m/z 461.1390, found  
11  
12  
13  
14 461.1380.  
15  
16

17 ***N*-(4-Methyl-3-[[4-(pyridine-3-yl)pyrimidin-2-yl]amino]phenyl)-4-(methanesulfonyl)-**  
18  
19  
20 **benzamide trifluoroacetate salt (42b·TFA)**. HATU (384 mg, 1.00 mmol, 1.0 equiv.) is  
21  
22 added to a solution of 4-methanesulfonylbenzoic acid (215 mg, 1.00 mmol, 1.0 equiv.)  
23  
24 and DIPEA (518 μL, 3.00 mmol, 3.0 equiv.) in DMF (5.00 mL), and the reaction mixture  
25  
26  
27  
28 is stirred at rt for 10 min. Then 6-methyl-*N*-(4-(pyridin-3-yl)pyrimidin-2-yl)benzene-1,3-  
29  
30  
31  
32 diamine (**51**) (277 mg, 1.00 mmol, 1.0 equiv.) is added, and the reaction mixture is heated  
33  
34  
35  
36  
37  
38 at 50 °C overnight. The reaction mixture is acidified using TFA and purified by preparative  
39  
40  
41  
42 RP-HPLC (Waters SunFire™ C<sub>18</sub>, gradient of acetonitrile in water, 0.1% TFA) to give  
43  
44  
45 325 mg (55%) of the title compound as a yellow solid. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz): δ  
46  
47  
48 = 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),  
49  
50  
51  
52 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 –  
53  
54  
55  
56 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  
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4 (d,  $J = 8.5$  Hz, 1H), 2.45 (d,  $J = 4.9$  Hz, 3H), 2.24 (s, 3H) ppm.  $^{13}\text{C}$  NMR (DMSO- $d_6$ , 151  
5  
6  
7 MHz):  $\delta = 164.3, 161.0, 160.7, 159.6, 149.1, 146.1, 141.7, 138.5, 137.7, 136.9, 136.8,$   
8  
9  
10 133.1, 130.1, 128.5, 127.9, 126.7, 124.7, 117.1, 116.8, 107.7, 28.6, 17.6 ppm. IR (ATR):  
11  
12  
13 1671, 1575, 1531, 1451, 1199, 1161, 1133, 798, 721, 603  $\text{cm}^{-1}$ . HRMS (ESI $^+$ ) calculated  
14  
15  
16 for  $\text{C}_{24}\text{H}_{23}\text{N}_6\text{O}_3\text{S}$  [M+H] $^+$   $m/z$  475.1547, found 475.1541.  
17  
18  
19  
20

21 **4-(Dimethylsulfamoyl)-*N*-(4-methyl-3-[[4-(pyridine-3-yl)pyrimidin-2-yl]amino]phenyl)-**  
22  
23  
24 **benzamide (42c).** HATU (384 mg, 1.00 mmol, 1.0 equiv.) is added to a solution of  
25  
26  
27 4-dimethylsulfamoylbenzoic acid (229 mg, 1.00 mmol, 1.0 equiv.) and DIPEA (518  $\mu\text{L}$ ,  
28  
29  
30 3.00 mmol, 3.0 equiv.) in DMF (5.00 mL), and the reaction mixture is stirred at rt for  
31  
32  
33  
34 10 min. Then 6-methyl-*N*-(4-(pyridin-3-yl)pyrimidin-2-yl)benzene-1,3-diamine (**51**)  
35  
36  
37 (277 mg, 1.00 mmol, 1.0 equiv.) is added, and the reaction mixture is heated at 50  $^{\circ}\text{C}$   
38  
39  
40  
41 overnight. The reaction mixture is acidified using TFA and repeatedly purified by  
42  
43  
44 preparative RP-HPLC (Waters SunFire $^{\text{TM}}$  C $_{18}$ , gradient of acetonitrile in water, 0.1% TFA;  
45  
46  
47 Waters XBridge $^{\text{TM}}$  C $_{18}$ , gradient of acetonitrile in water, 0.1%  $\text{NH}_4\text{OH}$ ) to give 111 mg  
48  
49  
50  
51  
52 (23%) of the title compound as a colorless solid.  $^1\text{H}$  NMR (DMSO- $d_6$ , 400 MHz):  $\delta = 10.45$   
53  
54  
55  
56 (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  
57  
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4 (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),  
5  
6  
7 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),  
8  
9  
10 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.  $^{13}\text{C}$  NMR  
11  
12  
13 (DMSO- $d_6$ , 101 MHz)  $\delta = 164.1, 161.6, 161.1, 159.4, 151.3, 148.1, 139.0, 137.8, 137.2,$   
14  
15  
16  
17 136.7, 134.4, 132.2, 130.1, 128.6, 128.0, 127.5, 123.7, 117.2, 116.7, 107.5, 37.5,  
18  
19  
20  
21 17.6 ppm. IR (ATR): 1670, 1583, 1527, 1412, 1335, 1312, 1163, 1154, 753, 736, 704,  
22  
23  
24 601  $\text{cm}^{-1}$ . HRMS (ESI $^+$ ) calculated for  $\text{C}_{25}\text{H}_{25}\text{N}_6\text{O}_3\text{S}$   $[\text{M}+\text{H}]^+$   $m/z$  489.1703, found  
25  
26  
27  
28 489.1692.  
29  
30

31 **4-(Dimethylphosphoryl)-*N*-(4-methyl-3-[[4-(pyridin-3-yl)pyrimidin-2-yl]amino}phenyl)-**  
32  
33  
34 **benzamide trifluoroacetate salt (43-TFA).**<sup>74</sup> HATU (384 mg, 1.00 mmol, 1.0 equiv.) is  
35  
36 added to a solution of 4-(dimethylphosphoryl)benzoic acid<sup>90</sup> (164 mg, 830  $\mu\text{mol}$ ,  
37  
38 1.0 equiv.) and DIPEA (428  $\mu\text{L}$ , 3.00 mmol, 3.0 equiv.) in DMF (5.00 mL), and the  
39  
40  
41  
42 reaction mixture is stirred at rt for 10 min. Then 6-methyl-*N*-(4-(pyridin-3-yl)pyrimidin-2-  
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3 TFA) to give 522 mg (91%) of the title compound as an orange solid. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>,  
4  
5  
6  
7 400 MHz): δ = 10.33 (s, 1H), 9.38 – 9.42 (m, 1H), 9.09 (s, 1H), 8.80 – 8.88 (m, 2H), 8.59  
8  
9  
10 (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),  
11  
12  
13  
14 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,  
15  
16  
17 *J* = 8.5 Hz, 1H), 2.24 (s, 3H), 1.70 (d, *J* = 13.4 Hz, 6H) ppm. <sup>13</sup>C NMR (DMSO-d<sub>6</sub>, 101  
18  
19  
20  
21 MHz) δ = 164.8, 160.9, 160.2, 159.7, 147.8, 145.0, 139.2 (d, *J* = 93 Hz), 138.4, 137.5,  
22  
23  
24 136.9, 133.6, 130.1, 129.8 (d, *J* = 10 Hz), 127.8, 127.6 (d, *J* = 12 Hz), 125.3, 117.2,  
25  
26  
27 116.9, 107.8, 17.6, 17.6 (d, *J* = 71 Hz) ppm. <sup>31</sup>P NMR (DMSO-d<sub>6</sub>, 162 MHz): δ =  
28  
29  
30  
31 32.8 ppm. IR (ATR): 1662, 1576, 1528, 1189, 1139, 937, 836, 799, 752, 721, 706, 671  
32  
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34  
35 cm<sup>-1</sup>. HRMS (ESI<sup>+</sup>) calculated for C<sub>25</sub>H<sub>25</sub>N<sub>5</sub>O<sub>2</sub>P [M+H]<sup>+</sup> *m/z* 458.1740, found 458.1738.  
36  
37

38 **4-(Dimethylphosphoryl)-*N*-(4-methyl-3-[[4-(pyridin-3-yl)pyrimidin-2-yl]amino}phenyl)-**  
39  
40  
41 **benzamide (43)**. Concentrated aqueous NH<sub>4</sub>OH (2 drops) is added to a solution of  
42  
43  
44  
45 4-(dimethylphosphoryl)-*N*-(4-methyl-3-[[4-(pyridin-3-yl)pyrimidin-2-yl]amino}phenyl)-  
46  
47  
48 benzamide trifluoroacetate salt (**43-TFA**, 100 mg) in EtOH (5 mL), and the mixture is  
49  
50  
51 purified by preparative RP-HPLC (Waters XBridge<sup>TM</sup> C<sub>18</sub>, gradient of acetonitrile in water,  
52  
53  
54  
55 0.1% NH<sub>4</sub>OH) to give 64 mg (80%) of a colorless solid. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz): δ  
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3 = 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  
4  
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6  
7 (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  
9  
10 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,  $J = 8.2,$   
11  
12  
13 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,  
14  
15  
16  $J = 13.4$  Hz, 6H) ppm.  $^{13}\text{C}$  NMR (DMSO- $d_6$ , 101 MHz)  $\delta = 164.8, 161.6, 161.1, 159.4,$   
17  
18 151.3, 148.1, 139.2 (d,  $J = 93$  Hz), 137.8, 137.5 (d,  $J = 2$  Hz), 136.9, 134.4, 132.2, 130.0,  
19  
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21 129.8 (d,  $J = 10$  Hz), 127.8, 127.5 (d,  $J = 12$  Hz), 123.7, 117.1, 116.7, 107.5, 17.6, 17.6  
22  
23  
24 (d,  $J = 70$  Hz) ppm.  $^{31}\text{P}$  NMR (DMSO- $d_6$ , 162 MHz):  $\delta = 32.4$  ppm.  
25  
26  
27  
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30

31 **Ethyl methyl({4-[(4-methyl-3-[[4-(pyridin-3-yl)pyrimidin-2-yl]amino}phenyl]carbamoyl]-**  
32 **phenyl})phosphinate trifluoroacetate salt (44a·TFA) and methyl({4-[(4-methyl-3-[[4-**  
33 **(pyridin-3-yl)pyrimidin-2-yl]amino}phenyl]carbamoyl]phenyl})phosphinic acid trifluoro-**  
34 **acetate salt (44b·TFA). Step 1: Synthesis of methyl**  
35 **4-[ethoxy(methyl)phosphoryl]benzoate.**<sup>26</sup> Ethyl methylphosphinate (259 mg, 2.4 mmol,  
36  
37 1.2 equiv.), methyl 4-bromobenzoate (430 mg, 2.00 mmol, 1.0 equiv.) and DIPEA  
38  
39 (453  $\mu\text{L}$ , 650  $\mu\text{mol}$ , 1.3 equiv.) is added to a solution of Pd(OAc)<sub>2</sub> (8.98 mg, 40.0  $\mu\text{mol}$ ,  
40  
41 2.0 mol%) and Xantphos (25.5 mg, 44.0  $\mu\text{mol}$ , 2.2 mol%) in DMF (3.06 mL) and DME  
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(400  $\mu$ L), and the mixture is sealed in a microwave vial and heated at 110  $^{\circ}$ C for 5 h. The reaction mixture is acidified with TFA and purified by preparative RP-HPLC (Waters SunFire<sup>TM</sup> C<sub>18</sub>, gradient of acetonitrile in water, 0.1% TFA) to give 392 mg (81%) of the title compound as colorless oil. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz):  $\delta$  = 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. <sup>13</sup>C NMR (DMSO-d<sub>6</sub>, 101 MHz)  $\delta$  = 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. <sup>31</sup>P NMR (DMSO-d<sub>6</sub>, 162 MHz):  $\delta$  = 40.3 ppm. IR (ATR): 2988, 1724, 1276, 1193, 1158, 1102, 1030, 1018, 957, 884, 789, 761, 749, 696 cm<sup>-1</sup>. HRMS (ESI<sup>+</sup>) calculated for C<sub>11</sub>H<sub>16</sub>O<sub>4</sub>P [M+H]<sup>+</sup> 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.)

1  
2  
3 and THF/MeOH/H<sub>2</sub>O (v:v:v, 2:1:1; 20.0 mL), and the reaction mixture is stirred at rt for  
4  
5  
6  
7 30 min. Aqueous HCl (1 M, 25 mL) and brine (20 mL) is added, and the aqueous phase  
8  
9  
10 is extracted with EtOAc (10 x 25 mL). The combined organic layers are dried over MgSO<sub>4</sub>  
11  
12  
13 and concentrated under reduced pressure. The residue is dissolved in DMF (7.00 mL),  
14  
15  
16 and the mixture is treated with DIPEA (682 μL, 3.95 mmol, 3.0 equiv.). HATU (1.52 g,  
17  
18 3.95 mmol, 3.0 equiv.) is added in three equal portions (1.0 equiv. each) over a period of  
19  
20  
21 30 min. Then 6-methyl-*N*-(4-(pyridin-3-yl)pyrimidin-2-yl)benzene-1,3-diamine (51)  
22  
23  
24 (365 mg, 1.32 mmol, 1.0 equiv.) is added, and the reaction mixture is heated at 50 °C for  
25  
26  
27  
28 1 h. The reaction mixture is acidified using TFA and repeatedly purified by preparative  
29  
30  
31 RP-HPLC (Waters XBridge™ C<sub>18</sub>, gradient of acetonitrile in water, 0.1% TFA; Waters  
32  
33  
34 SunFire™ C<sub>18</sub>, gradient of acetonitrile in water, 0.1% TFA) to give 47.0 mg (6%) of the  
35  
36  
37 ethyl phosphinate **44a**·TFA and 130 mg (17%) of the corresponding phosphinic acid  
38  
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40  
41  
42  
43  
44  
45 **44b**·TFA both as yellow-orange solids.

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47  
48 Ethyl methyl({4-[(4-methyl-3-[(4-(pyridin-3-yl)pyrimidin-2-yl]amino)phenyl]carbamoyl]-  
49  
50  
51  
52 phenyl})phosphinate trifluoroacetate salt (**44a**·TFA). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz): δ =  
53  
54  
55 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  
56  
57  
58  
59  
60

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2  
3 (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 –  
4  
5  
6  
7 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  
8  
9  
10 (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,  
11  
12  
13  $J = 14.6$  Hz, 3H), 1.20 (t,  $J = 7.1$  Hz, 3H) ppm.  $^{13}\text{C}$  NMR (DMSO- $d_6$ , 101 MHz)  $\delta = 164.7,$   
14  
15  
16  
17 161.0, 160.7, 159.6, 149.3, 146.3, 138.3, 137.7, 136.9, 136.7, 135.3 (d,  $J = 123$  Hz),  
18  
19  
20  
21 133.0, 130.9 (d,  $J = 11$  Hz), 130.1, 127.8 (br s), 127.7 (br d,  $J = 12$  Hz), 124.7, 117.2,  
22  
23  
24 116.8, 107.7, 60.1 (d,  $J = 6$  Hz), 17.6, 16.3 (d,  $J = 6$  Hz), 14.9 (d,  $J = 101$  Hz) ppm.  $^{31}\text{P}$   
25  
26  
27  
28 NMR (DMSO- $d_6$ , 162 MHz):  $\delta = 40.5$  ppm. IR (ATR): 3273, 3090, 1667, 1573, 1530, 1452,  
29  
30  
31 1198, 1576, 1530, 1452, 1198, 1131, 1034, 797  $\text{cm}^{-1}$ . HRMS (ESI $^+$ ) calculated for  
32  
33  
34  
35  $\text{C}_{26}\text{H}_{27}\text{N}_5\text{O}_3\text{P}$  [M+H] $^+$   $m/z$  488.1846, found 488.1832.

36  
37  
38 **Methyl({4-[(4-methyl-3-[[4-(pyridin-3-yl)pyrimidin-2-yl]amino}phenyl]carbamoyl]-**  
39  
40  
41 **phenyl})phosphinic acid trifluoroacetate salt (44b-TFA).**  $^1\text{H}$  NMR (DMSO- $d_6$ , 400 MHz):  $\delta$   
42  
43  
44  
45 = 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  
46  
47  
48 (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  
49  
50  
51 (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,  
52  
53  
54  
55  $J = 8.5$  Hz, 1H), 2.24 (s, 3H), 1.56 (d,  $J = 14.6$  Hz, 3H) ppm.  $^{13}\text{C}$  NMR (DMSO- $d_6$ , 101  
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60

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2  
3  
4 MHz)  $\delta$  = 164.8, 161.0, 160.6, 159.6, 149.0, 146.0, 138.6 (d,  $J$  = 125 Hz), 137.6, 137.5  
5  
6  
7 (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),  
8  
9  
10 124.8, 117.2, 116.8, 107.7, 17.6, 16.7 (d,  $J$  = 99 Hz) ppm.  $^{31}\text{P}$  NMR (DMSO- $d_6$ , 162 MHz):  
11  
12  
13  $\delta$  = 33.8 ppm. IR (ATR): 1665, 1602, 1575, 1528, 1451, 1182, 1132, 962, 877, 797, 719,  
14  
15  
16  
17 671, 608  $\text{cm}^{-1}$ . HRMS (ESI $^+$ ) calculated for  $\text{C}_{24}\text{H}_{23}\text{N}_5\text{O}_3\text{P}$  [M+H] $^+$   $m/z$  460.1533, found  
18  
19  
20  
21 460.1523.  
22  
23

24 **Methyl({4-[(4-methyl-3-[[4-(pyridin-3-yl)pyrimidin-2-yl]amino}phenyl]carbamoyl]-**  
25  
26  
27 **phenyl})phosphinic acid (44b)**. Aqueous NaOH (0.1 M, 0.140 mmol, 1 equiv.) is added to  
28  
29  
30  
31 a solution of methyl({4-[(4-methyl-3-[[4-(pyridin-3-yl)pyrimidin-2-  
32  
33  
34 yl]amino}phenyl]carbamoyl]phenyl})phosphinic acid trifluoroacetate salt (**44b-TFA**, 80.0  
35  
36  
37 mg, 0.140 mmol, 1 equiv.) in minimal amounts of EtOH, and the neutralized sample is  
38  
39  
40  
41 purified by flash chromatography on silica gel (gradient of MeOH in DCM; 10% – 50%  
42  
43  
44 MeOH, then isocratic DCM:MeOH:H $_2$ O, 1:1:0.1). Appropriate fractions are collected and  
45  
46  
47 concentrated. The residue is triturated with MTBE to give a quantitative yield of the title  
48  
49  
50  
51 compound as light-yellow solid.  $^1\text{H}$  NMR (DMSO- $d_6$ , 400 MHz):  $\delta$  = 10.30 (s, 1H), 9.26  
52  
53  
54 (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),  
55  
56  
57  
58  
59  
60

1  
2  
3 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  
4  
5  
6  
7 (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),  
8  
9  
10 7.18 (d,  $J = 8.5$  Hz, 1H), 2.22 (s, 3H), 1.22 (br d,  $J = 13.4$  Hz, 3H) ppm.  $^{13}\text{C}$  NMR (DMSO-  
11  
12  
13  $\text{d}_6$ , 101 MHz)  $\delta = 165.3, 161.6, 161.1, 159.4, 151.3, 148.1, 137.7, 137.1, 135.6, 134.4,$   
14  
15  
16  
17 132.2, 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  
19  
20  
21 18.9 (br d,  $J = 101$  Hz), 17.6 ppm.  $^{31}\text{P}$  NMR (DMSO- $\text{d}_6$ , 162 MHz):  $\delta = 21.8$  ppm.  
22  
23

24 **Diethyl {4-[(4-Methyl-3-[[4-(pyridin-3-yl)pyrimidin-2-yl]amino]phenyl)carbamoyl]-**  
25  
26  
27 **phenyl}phosphonate trifluoroacetate salt (45a·TFA).** HATU (384 mg, 1.00 mmol,  
28  
29 1.0 equiv.) is added to a solution of diethyl (4-carboxyphenyl)phosphonate (258 mg,  
30  
31 1.00 mmol, 1.0 equiv.) and DIPEA (519  $\mu\text{L}$ , 3.00 mmol, 3.0 equiv.) in DMF (5.00 mL), and  
32  
33  
34  
35 the reaction mixture is stirred at rt for 10 min. Then 6-methyl-*N*-(4-(pyridin-3-yl)pyrimidin-  
36  
37  
38 2-yl)benzene-1,3-diamine (**51**) (277 mg, 1.00 mmol, 1.0 equiv.) is added, and the reaction  
39  
40  
41  
42 mixture is heated at 50 °C overnight. The reaction mixture is acidified using TFA and  
43  
44  
45 purified by preparative RP-HPLC (Waters XBridge<sup>TM</sup> C<sub>18</sub>, gradient of acetonitrile in water,  
46  
47  
48 0.1% TFA) to give 522 mg (83%) of the title compound as a yellow solid.  $^1\text{H}$  NMR (DMSO-  
49  
50  
51  
52  $\text{d}_6$ , 400 MHz):  $\delta = 10.37$  (s, 1H), 9.33 (dd,  $J = 2.3, 0.8$  Hz, 1H), 9.02 (s, 1H), 8.76 (dd,  
53  
54  
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59  
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3  
4  $J = 5.0, 1.6$  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,  
5  
6  
7  $J = 2.0$  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,  
8  
9  
10 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  
11  
12  
13 (t,  $J = 7.1$  Hz, 6H) ppm.  $^{13}\text{C}$  NMR (DMSO- $d_6$ , 101 MHz)  $\delta = 164.6, 161.0, 160.9, 159.5,$   
14  
15  
16  
17 149.7, 146.6, 138.6 (d,  $J = 3$  Hz), 137.3 (d,  $J = 86$  Hz), 136.3, 132.9, 132.3, 131.3 (d,  
18  
19  
20  
21  $J = 10$  Hz), 130.5, 130.1, 127.8 (br s), 127.8 (br d,  $J = 15$  Hz), 124.5, 117.1, 116.8, 107.6,  
22  
23  
24 61.9 (d,  $J = 5$  Hz), 17.6, 16.1 (d,  $J = 6$  Hz) ppm.  $^{31}\text{P}$  NMR (DMSO- $d_6$ , 162 MHz):  $\delta =$   
25  
26  
27  
28 16.7 ppm. IR (ATR): 3293, 1575, 1529, 1453, 1243, 1178, 1134, 1046, 1019, 967, 959,  
29  
30  
31 798, 720  $\text{cm}^{-1}$ . HRMS (ESI $^+$ ) calculated for  $\text{C}_{27}\text{H}_{29}\text{N}_5\text{O}_3\text{P}$  [M+H] $^+$   $m/z$  518.1952, found  
32  
33  
34  
35 518.1956.

36  
37  
38 **Diethyl {4-[(4-methyl-3-[[4-(pyridin-3-yl)pyrimidin-2-yl]amino}phenyl)carbamoyl]-**  
39  
40  
41 **phenyl}phosphonate (45a)**. Concentrated aqueous  $\text{NH}_4\text{OH}$  solution (2 drops) is added to  
42  
43  
44  
45 a solution of diethyl {4-[(4-Methyl-3-[[4-(pyridin-3-yl)pyrimidin-2-  
46  
47  
48 yl]amino}phenyl)carbamoyl]phenyl}phosphonate trifluoroacetate salt (**45a**·TFA, 100 mg)  
49  
50  
51  
52 in EtOH (5 mL), and the mixture is purified by preparative RP-HPLC (Waters XBridge $^{\text{TM}}$   
53  
54  
55  
56  $\text{C}_{18}$ , gradient of acetonitrile in water, 0.1%  $\text{NH}_4\text{OH}$ ) to give 62 mg (76%) of a colorless  
57  
58  
59  
60

1  
2  
3 solid.  $^1\text{H}$  NMR (DMSO- $d_6$ , 400 MHz):  $\delta$  = 10.38 (s, 1H), 9.29 (d,  $J$  = 1.8 Hz, 1H), 8.97 (s,  
4  
5  
6 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,  
7  
8 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,  
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116.7, 107.5, 61.9 (d,  $J$  = 5 Hz), 17.6, 16.1 (d,  $J$  = 6 Hz) ppm.  $^{31}\text{P}$  NMR (DMSO- $d_6$ , 162 MHz):  $\delta$  = 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  $\mu\text{mol}$ , 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

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3  
4 purified by preparative RP-HPLC (Waters XBridge™ C<sub>18</sub>, gradient of acetonitrile in water,  
5  
6  
7 0.1% TFA) to give 28.0 mg (62%) of the title compound as a yellow-orange solid. <sup>1</sup>H NMR  
8  
9  
10 (DMSO-d<sub>6</sub>, 400 MHz): δ = 10.32 (s, 1H), 9.30 (d, *J* = 1.6 Hz, 1H), 8.99 (s, 1H), 8.72 (dd,  
11  
12  
13 *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,  
14  
15  
16 *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,  
17  
18  
19 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,  
20  
21  
22 1H), 3.88 – 3.96 (m, 3H), 2.23 (s, 3H), 1.20 ppm (t, *J* = 7.1 Hz, 3H) ppm. <sup>13</sup>C NMR  
23  
24  
25 (DMSO-d<sub>6</sub>, 101 MHz) δ = 164.8, 161.0, 161.0 (br s), 159.5, 149.8, 146.8, 137.8 (br d,  
26  
27  
28 *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,  
29  
30  
31 127.8, 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,  
32  
33  
34 16.2 (d, *J* = 6 Hz) ppm. <sup>31</sup>P NMR (DMSO-d<sub>6</sub>, 162 MHz): δ = 13.7 ppm. IR (ATR): 1635,  
35  
36  
37 1579, 1532, 1172, 1138, 1114, 1035, 1017, 952, 796, 757, 720, 695 cm<sup>-1</sup>. HRMS (ESI<sup>+</sup>)  
38  
39  
40  
41  
42 calculated for C<sub>25</sub>H<sub>25</sub>N<sub>5</sub>O<sub>4</sub>P [M+H]<sup>+</sup> *m/z* 490.1639, found 490.1632.  
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44  
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49 **Ethoxy{4-[(4-methyl-3-[[4-(pyridin-3-yl)pyrimidin-2-yl]amino}phenyl]carbamoyl]-**  
50  
51  
52 **phenyl}phosphinic acid (45b).** A solution of ethoxy{4-[(4-methyl-3-[[4-(pyridin-3-yl)-  
53  
54  
55 pyrimidin-2-yl]amino}phenyl]carbamoyl]phenyl}phosphinic acid trifluoroacetate salt  
56  
57  
58  
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60

1  
2  
3 (45a-TFA) (500 mg, 96.6  $\mu\text{mol}$ , 1.0 equiv.) in EtOH (10 mL) and aqueous NaOH (4 M,  
4  
5  
6  
7 9.67 mL) is stirred at 50 °C for 2 h. The mixture is cooled to room temperature, neutralized  
8  
9  
10 with 4 M aqueous HCl solution and purified by preparative RP-HPLC (Waters XBridge™  
11  
12  
13 C<sub>18</sub>, gradient of acetonitrile in water, 0.1% NH<sub>4</sub>OH) to give 240 mg of the title compound  
14  
15  
16  
17 as a 20:80 mixture of its free acid and its ammonium salt. The crude product is dissolved  
18  
19  
20 in acetonitrile and water at elevated temperature and freeze-dried to obtain 200 mg of the  
21  
22  
23  
24 title compound as a 61:39 mixture of its free acid and its ammonium salt. This material is  
25  
26  
27  
28 then triturated in aqueous HCl solution (0.1 N, 3.9 mL) overnight. The solids are collected  
29  
30  
31  
32 by filtration, washed with water and dried in vacuo to give 150 mg (31%) of the title  
33  
34  
35 compound as a yellowish solid. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz):  $\delta$  = 10.32 (s, 1H), 9.28 (d,  
36  
37  
38  $J$  = 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  
39  
40  
41 (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,  
42  
43  
44  
45  $J$  = 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,  
46  
47  
48 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  
49  
50  
51 (s, 3H), 1.19 ppm (t,  $J$  = 7.1 Hz, 3H) ppm. <sup>13</sup>C NMR (DMSO-d<sub>6</sub>, 101 MHz)  $\delta$  = 164.7,  
52  
53  
54  
55 161.6, 161.1 (br s), 159.4, 151.3, 148.1, 137.8 (br d,  $J$  = 3 Hz), 137.7 (d,  $J$  = 79 Hz),  
56  
57  
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4 136.9, 134.4, 134.4, 132.2, 130.9 (br d,  $J = 10$  Hz), 130.0, 127.8, 127.5 (br d,  $J = 14$  Hz),  
5  
6  
7 123.7 (br s), 117.2, 116.8, 107.5, 60.8 (d,  $J = 5$  Hz), 17.6, 16.2 (d,  $J = 6$  Hz) ppm.  $^{31}\text{P}$   
8  
9

10 NMR (DMSO- $d_6$ , 162 MHz):  $\delta = 13.6$  ppm.  
11  
12

13  
14 **{4-[(4-Methyl-3-[[4-(pyridin-3-yl)pyrimidin-2-yl]amino]phenyl)carbamoyl]phenyl}-**  
15

16  
17 **phosphonic acid (45c)**. Bromotrimethylsilane (380  $\mu\text{L}$ , 2.90 mmol, 6.04 equiv.) is added  
18  
19

20 to a suspension of diethyl {4-[(4-methyl-3-[[4-(pyridin-3-yl)pyrimidin-2-yl]amino]phenyl)-  
21  
22

23 carbamoyl]phenyl}phosphonate (**45a**·TFA) (250 mg, 0.48 mmol, 1.00 equiv.) in DCM (10  
24  
25

26 mL), and the reaction mixture is stirred at room temperature overnight. Another portion of  
27  
28

29 bromotrimethylsilane (380  $\mu\text{L}$ , 2.90 mmol, 6.04 equiv.) is added, and the mixture is stirred  
30  
31

32 for 8 h. Water is added, and the aqueous mixture is concentrated under reduced pressure.  
33  
34

35 The residue is dissolved in water and basified with aqueous  $\text{NH}_4\text{OH}$ . The precipitate is  
36  
37

38 collected by filtration, washed with  $\text{H}_2\text{O}$  and dried in vacuo to give 140 mg of the title  
39  
40

41 compound as its mono-ammonium salt. A portion of this material (115 mg, 0.24 mmol) is  
42  
43

44 triturated with aqueous hydrogen chloride solution (0.1 M, 2.4 mL), and the precipitate is  
45  
46

47 filtered, washed with water and dried in vacuo to obtain 95 mg (42%) of the title compound  
48  
49

50 as yellowish solid.  $^1\text{H}$  NMR (DMSO- $d_6$ , 400 MHz):  $\delta = 10.28$  (s, 1H), 9.28 (d,  $J = 1.7$  Hz,  
51  
52  
53  
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4 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,  
5  
6  
7  $J = 7.6, 1.8, 1.8$  Hz, 1H), 8.10 (s, 1H), 8.01 (dd,  $J = 8.1, 3.0$  Hz, 2H), 7.78-7.83 (m, 2H),  
8  
9  
10 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  
11  
12  
13 (br d,  $J = 8.2$  Hz, 1H), 2.23 (s, 3H) ppm.  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta = 164.8, 161.6,$   
14  
15  
16  
17 161.1, 159.4, 151.3, 148.1, 137.8, 137.3 (br d,  $J = 3$  Hz), 137.0 (br d,  $J = 86$  Hz), 136.9,  
18  
19  
20  
21 134.4, 132.2, 130.4 (br d,  $J = 10$  Hz), 130.0, 127.7, 127.2 (br d,  $J = 14$  Hz), 123.7, 117.2,  
22  
23  
24 116.7, 107.5, 17.6 ppm.  $^{31}\text{P}$  NMR (DMSO- $d_6$ , 162 MHz):  $\delta = 11.4$  ppm.

25  
26  
27  
28 **1-Methyl-1,4 $\lambda^5$ -azaphosphan-4-one (47b)**. The synthesis is performed according to  
29  
30  
31 an adopted literature protocol.<sup>65b</sup> LAH (1.0 M in THF; 16.9 mL, 16.9 mmol, 2.0 equiv.) is  
32  
33  
34 added dropwise at 0 °C to a solution of 4-ethoxy-1-methyl-1,4 $\lambda^5$ -azaphosphan-4-one<sup>65a</sup>  
35  
36  
37 (1.50 g, 8.45 mmol, 1.0 equiv.) in THF (50.0 mL), and the reaction mixture is stirred at  
38  
39  
40 0 °C for 45 min. Water (300  $\mu\text{L}$ ), aqueous NaOH (15%; 300  $\mu\text{L}$ ) and again water (900  $\mu\text{L}$ )  
41  
42  
43  
44 is added, and the slurry is stirred at rt for 1 h, filtered and concentrated. The residue is  
45  
46  
47  
48 repeatedly purified by flash chromatography on silica gel to give 500 mg (44%) of the title  
49  
50  
51  
52 compound as a pale-yellow semi-solid.  $R_f$  (EtOAc) = 0.30.  $^1\text{H}$  NMR (DMSO- $d_6$ , 400 MHz):  
53  
54  
55  
56  $\delta = 6.14 - 7.37$  (m, 1H), 2.74 - 2.93 (m, 2H), 2.31 - 2.44 (m, 2H), 2.15 - 2.24 (m, 3H),  
57  
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59  
60

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3 1.99 – 2.13 (m, 2H), 1.80 – 1.98 (m, 2H) ppm.  $^{13}\text{C}$  NMR (DMSO- $d_6$ , 101 MHz)  $\delta$  = 51.2  
4  
5  
6  
7 (d,  $J$  = 6 Hz), 45.3, 26.3 (d,  $J$  = 62 Hz) ppm.  $^{31}\text{P}$  NMR (DMSO- $d_6$ , 162 MHz):  $\delta$  =  
8  
9  
10 22.4 ppm. IR (ATR): 3399, 2945, 2797, 2338, 1665, 1258, 1158, 1109, 1018, 956, 921,  
11  
12  
13 765, 688  $\text{cm}^{-1}$ . HRMS (ESI $^+$ ) calculated for  $\text{C}_5\text{H}_{13}\text{NOP}$   $[\text{M}+\text{H}]^+$   $m/z$  134.0729, found  
14  
15  
16  
17 134.0728.  
18  
19  
20

21 **1-Isopropyl-1,4 $\lambda^5$ -azaphosphinan-4-one (47c)**. According to an adopted literature  
22  
23 protocol,<sup>65b</sup> a solution of  $\text{LiAlH}_4$  (1.0 M in THF; 19.5 mL, 19.5 mmol, 2.0 equiv.) is added  
24  
25 to a solution of 4-ethoxy-1-isopropyl-1,4 $\lambda^5$ -azaphosphinan-4-one (2.00 g, 9.75 mmol,  
26  
27 1.0 equiv.) in THF (100 mL) at 0 °C, and the mixture is stirred at 0 °C for 45 min. Water  
28  
29 (0.5 mL), aqueous sodium hydroxide (15%, 0.5 mL) and again water (1.5 mL) are added  
30  
31 to the reaction mixture, and the slurry is stirred at room temperature for 1 h. The mixture  
32  
33 is filtered, and the filtrate is concentrated under reduced pressure. The residue is purified  
34  
35 by flash chromatography on silica (gradient ethyl acetate/cyclohexane 4:1 to ethyl  
36  
37 acetate), appropriate fractions are concentrated and the obtained material is used without  
38  
39 further purification in the next step.  
40  
41  
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4 **1-Benzyl-4-[4-(trifluoromethyl)phenyl]-1,4λ<sup>5</sup>-azaphosphinan-4-one (48).** 4-(Trifluoro-  
5  
6  
7 methyl)phenyl iodide (272 mg, 1.00 mmol, 1.0 equiv.) is added to a solution of Pd<sub>2</sub>(dba)<sub>3</sub>  
8  
9  
10 (23.0 mg, 25.0 μmol, 2.5 mol%), Xantphos (29.0 mg, 50 μmol, 5.0 mol%), and 1-benzyl-  
11  
12  
13 1,4λ<sup>5</sup>-azaphosphinan-4-one (**47a**)<sup>65b</sup> (251 mg, 1.20 mmol, 1.2 equiv.) in DIPEA (255 μL,  
14  
15  
16 1.50 mmol, 1.5 equiv.) and DMF (4.00 mL). The reaction mixture is sealed in a microwave  
17  
18  
19 vial and heated at 110 °C overnight. The reaction mixture is diluted with saturated  
20  
21  
22 aqueous NaHCO<sub>3</sub> (20 mL) and the aqueous phase is extracted with EtOAc (3 x 20 mL).  
23  
24  
25  
26  
27  
28 The combined organic phases are dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated. The residue is  
29  
30  
31 purified by preparative RP-HPLC (Waters XBridge™ C<sub>18</sub>, gradient of acetonitrile in water,  
32  
33  
34 0.1% NH<sub>4</sub>OH) to give 283 mg (81%) of the title compound as light-yellow oil. <sup>1</sup>H NMR  
35  
36  
37 (DMSO-d<sub>6</sub>, 400 MHz): δ = 8.02 – 8.09 (m, 2H), 7.90 (dd, *J* = 8.4, 1.4 Hz, 2H), 7.31 – 7.38  
38  
39  
40 (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  
41  
42  
43 – 2.02 (m, 2H) ppm. MS (ESI<sup>+</sup>) calculated for C<sub>18</sub>H<sub>20</sub>F<sub>3</sub>NOP [M+H]<sup>+</sup> *m/z* 354.12, found  
44  
45  
46  
47  
48  
49 354.12.

50  
51  
52 **[4-(Trifluoromethyl)phenyl]phosphonic dichloride (49).** The reaction was performed  
53  
54  
55 using an adopted literature report.<sup>91</sup> Oxalyl chloride (1.59 g, 12.5 mmol, 2.5 equiv.) is  
56  
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4 added dropwise to a refluxing suspension of [4-(trifluoromethyl)phenyl]phosphonic acid  
5  
6  
7 **(24a)** (1.13 g, 5.00 mmol, 1.0 equiv.) in DCM (10.0 mL) and DMF (10.0  $\mu$ L), and the  
8  
9  
10 reaction mixture is heated at reflux for 1 h. The reaction mixture is concentrated, and the  
11  
12  
13  
14 yellow solid is used directly in the next step without further purification.  
15  
16

17 ***Tert*-butyl 2-oxo-2-[4-(trifluoromethyl)phenyl]-1,3,6,2 $\lambda$ <sup>5</sup>-dioxazaphosphocan-6-**  
18  
19  
20 **carboxyl-ate (50).** A solution of [4-(trifluoromethyl)phenyl]phosphonic dichloride **(49)**  
21  
22  
23  
24 (263 mg, 1.00 mmol, 1.0 equiv.) in THF (3.00 mL) is added dropwise to a solution of *tert*-  
25  
26  
27 butyl *N,N*-bis(2-hydroxyethyl)carbamate (216 mg, 1.05 mmol, 1.05 equiv.) and Et<sub>3</sub>N  
28  
29  
30 (278  $\mu$ L, 2.00 mmol, 2.0 equiv.) in THF (20.0 mL) at 0 °C, and the reaction mixture is  
31  
32  
33  
34 allowed to warm to rt overnight. The reaction mixture is filtered over a plug of celite and  
35  
36  
37  
38 the filter cake is rinsed with EtOAc (20 mL). The combined filtrates are concentrated and  
39  
40  
41  
42 purified by flash chromatography on silica gel (gradient of MeOH in DCM; 0% – 5%  
43  
44  
45 MeOH) to give 157 mg (40%) of the title compound as a colorless oil. R<sub>f</sub> (DCM:MeOH,  
46  
47  
48 20:1) = 0.25. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz):  $\delta$  = 7.86 – 7.98 (m, 4H), 4.52 – 4.63 (m, 2H),  
49  
50  
51 3.98 – 4.12 (m, 2H), 3.72 – 3.87 (m, 2H), 3.16 – 3.29 (m, 2H), 1.45 (s, 9H) ppm. <sup>13</sup>C NMR  
52  
53  
54 (DMSO-d<sub>6</sub>, 101 MHz)  $\delta$  = 154.1, 133.6 (br d, *J* = 199 Hz), 132.1 – 132.2 (m), 131.5 (d,  
55  
56  
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4  $J = 10$  Hz), 125.3 – 125.5 (m), 123.6 (q,  $J = 273$  Hz), 79.5, 65.9 (br d,  $J = 8$  Hz), 65.4 (br  
5  
6  
7 d,  $J = 7$  Hz) 50.4, 50.2, 28.0 ppm.  $^{31}\text{P}$  NMR (DMSO- $d_6$ , 162 MHz):  $\delta = 14.5$  ppm. IR  
8  
9  
10 (ATR): 1692, 1367, 1324, 1240, 1129, 1091, 1030, 1017, 903, 730, 702  $\text{cm}^{-1}$ . HRMS  
11  
12  
13  
14 (ESI $^+$ ) calculated for  $\text{C}_{16}\text{H}_{21}\text{F}_3\text{NNaO}_5\text{P}$   $[\text{M}+\text{Na}]^+$   $m/z$  418.1002, found 418.1003.  
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## 24 ASSOCIATED CONTENT

### 25 26 27 28 29 **Supporting Information.**

30  
31  
32  
33 Spectroscopic data for all new compounds, descriptions of the physicochemical and *in*  
34  
35  
36  
37 *vitro* assays, data for the biological activity of imatinib analogs in selected kinase assays  
38  
39  
40 as well as molecular formula strings can be found at <http://pubs.acs.org>.  
41  
42  
43

## 44 45 AUTHOR INFORMATION

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23 The manuscript was written through contributions of all authors. All authors have given  
24  
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26 approval to the final version of the manuscript.  
27  
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## 51 Notes

52  
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54  
55 The authors declare no competing financial interest.  
56  
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11  
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15  
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18  
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20  
21 discussions.  
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28 ABBREVIATIONS  
29

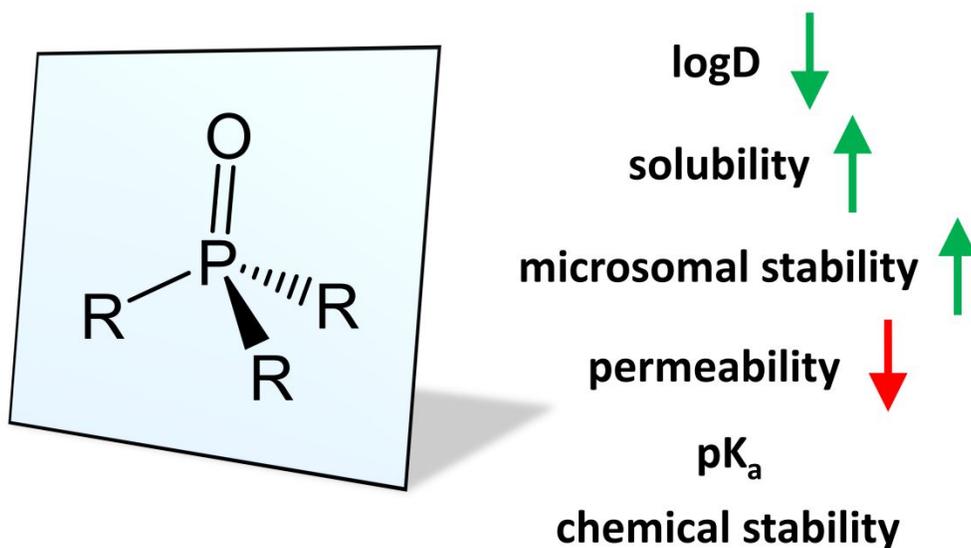
30 ABL1, Abelson murine leukemia viral oncogene homolog 1; ALK, anaplastic lymphoma  
31  
32  
33 kinase; CCR2, C-C chemokine receptor 2; dba, dibenzylideneacetone; DIPEA,  
34  
35  
36  
37 diisopropylethylamine; dppf, 1,1'-ferrocenediyl-bis(diphenylphosphine); EG, ethylene  
38  
39  
40  
41 glycol; ENaC, epithelial sodium channel; FG, functional group; HATU,  
42  
43  
44 *N*-[(dimethylamino)-1*H*-1,2,3-triazolo-[4,5-*b*]pyridin-1-ylmethylene]-*N*-  
45  
46  
47 methylmethanaminium hexafluorophosphate *N*-oxide; HDAC1, histone deacetylase 1;  
48  
49  
50  
51 HMDS, hexamethyldisilazane; HPLC, high-performance liquid chromatography; IUPAC,  
52  
53  
54  
55 International Union of Pure and Applied Chemistry, KIT, proto-oncogene c-KIT; LCK,  
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3 lymphocyte-specific protein tyrosine kinase; MetAP2, methionine aminopeptidase 2;  
4  
5  
6  
7 mTOR, mammalian target of Rapamycin; PDGFRb, platelet-derived growth factor  
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10 receptor beta; PR, progesterone receptor; SYK, spleen tyrosine kinase; TMS,  
11  
12  
13  
14 trimethylsilyl.  
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## 22 REFERENCES

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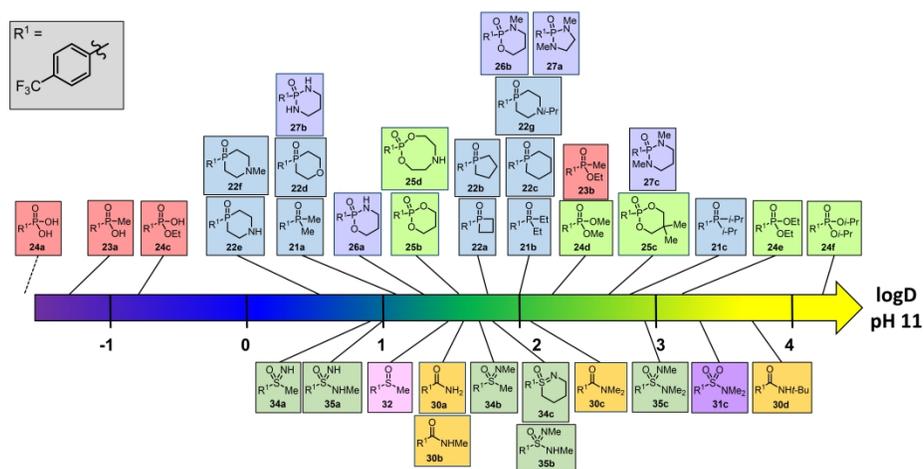


Figure 6: Graphical depiction of logD values of phosphorus-containing compounds and bioisosteres at pH 11.<sup>77</sup>

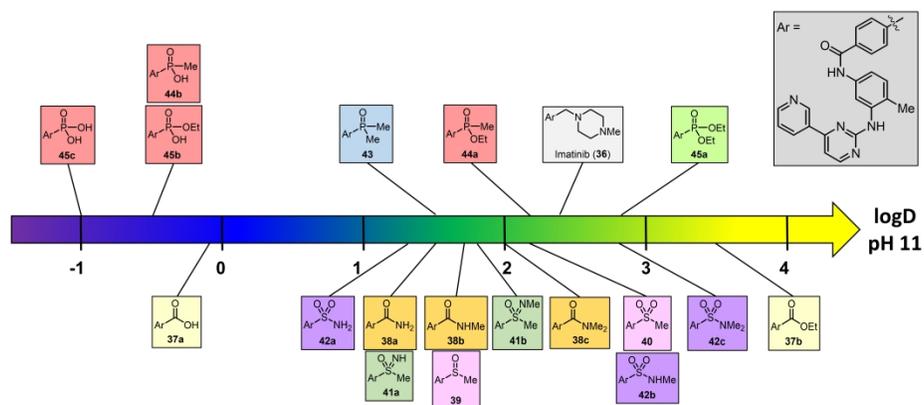
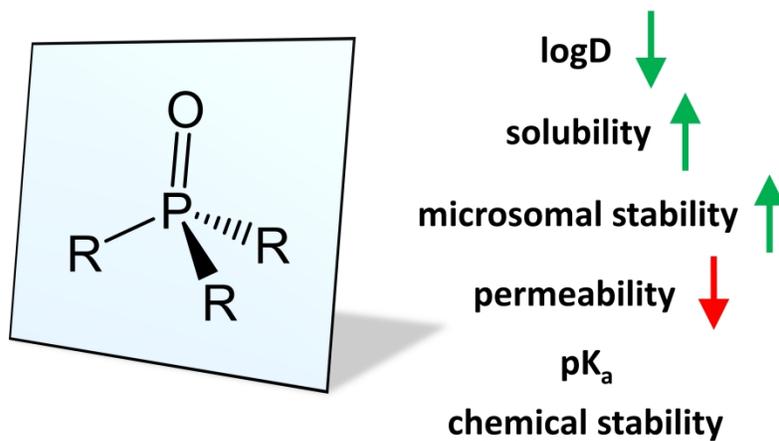


Figure 7: Graphical depiction of logD values of imatinib analogs at pH 11.



TOC graphic