

Article

**Identification of the privileged position in the imidazo[1,2-a]pyridine ring of phosphonocarboxylates for development of Rab geranylgeranyl transferase (RGGT) inhibitors**

Aleksandra Ka#mierczak, Damian Kusy, Sanna P. Niinivehmas, Joanna Gmach, #ukasz Joachimiak, Olli T Pentikäinen, Edyta Gendaszewska-Darmach, and Katarzyna M. Blazewska

*J. Med. Chem.*, **Just Accepted Manuscript** • DOI: 10.1021/acs.jmedchem.7b00811 • Publication Date (Web): 27 Sep 2017

Downloaded from <http://pubs.acs.org> on September 28, 2017

**Just Accepted**

“Just Accepted” manuscripts have been peer-reviewed and accepted for publication. They are posted online prior to technical editing, formatting for publication and author proofing. The American Chemical Society provides “Just Accepted” as a free service to the research community to expedite the dissemination of scientific material as soon as possible after acceptance. “Just Accepted” manuscripts appear in full in PDF format accompanied by an HTML abstract. “Just Accepted” manuscripts have been fully peer reviewed, but should not be considered the official version of record. They are accessible to all readers and citable by the Digital Object Identifier (DOI®). “Just Accepted” is an optional service offered to authors. Therefore, the “Just Accepted” Web site may not include all articles that will be published in the journal. After a manuscript is technically edited and formatted, it will be removed from the “Just Accepted” Web site and published as an ASAP article. Note that technical editing may introduce minor changes to the manuscript text and/or graphics which could affect content, and all legal disclaimers and ethical guidelines that apply to the journal pertain. ACS cannot be held responsible for errors or consequences arising from the use of information contained in these “Just Accepted” manuscripts.

***Identification of the privileged position in the imidazo[1,2-a]pyridine ring of phosphonocarboxylates for development of Rab geranylgeranyl transferase (RGGT) inhibitors***

Aleksandra Kaźmierczak,<sup>b#</sup> Damian Kusy,<sup>a#</sup> Sanna P. Niinivehmas,<sup>c</sup> Joanna Gmach,<sup>a</sup> Łukasz Joachimiak,<sup>a</sup> Olli T. Pentikäinen,<sup>c,d</sup> Edyta Gendaszewska-Darmach,<sup>b</sup> Katarzyna M. Błazewska<sup>a\*</sup>

<sup>a</sup>*Institute of Organic Chemistry, Faculty of Chemistry, Lodz University of Technology, Żeromskiego Str. 116, 90-924 Łódź, Poland.*

<sup>b</sup>*Institute of Technical Biochemistry, Faculty of Biotechnology and Food Sciences, Lodz University of Technology, Stefanowskiego Str. 4/10, 90-924 Łódź, Poland.*

<sup>c</sup>*University of Jyväskylä, Department of Biological and Environmental Science & Nanoscience Center, P.O.Box 35, FI-40014 University of Jyväskylä, Finland.*

<sup>d</sup>*University of Turku, Institute of Biomedicine, FI-20520 Turku, Finland*

**ABSTRACT**

Members of the Rab GTPase family are master regulators of vesicle trafficking. When disregulated, they are associated with a number of pathological states. The inhibition of RGGT, an enzyme responsible for post-translational geranylgeranylation of Rab GTPases represents one way to control the activity of these proteins. Since the number of molecules modulating RGGT is limited, we combined molecular modeling with biological assays to ascertain how modifications of phosphonocarboxylates, the first reported RGGT inhibitors, rationally improve understanding of their structure-activity relationship. We have identified the privileged position in the core scaffold of the imidazo[1,2-a]pyridine ring, which can be modified without compromising compounds' potency. Thus modified compounds are micromolar inhibitors of Rab11A prenylation, simultaneously being inactive against Rap1A/Rap1B

1  
2  
3 modification, with the ability to inhibit proliferation of the HeLa cancer cell line.  
4  
5 These findings were rationalized by molecular docking, which recognized interaction  
6  
7 of phosphonic and carboxylic groups as decisive in phosphonocarboxylate  
8  
9 localization in the RGGT binding site.  
10  
11

## 12 INTRODUCTION

13  
14 Rab GTPases constitute the most abundant class among the Ras superfamily of small  
15  
16 GTP-binding proteins. They are considered master regulators of vesicle trafficking  
17  
18 and their secretion to the extracellular matrix. Rab geranylgeranyl transferase (RGGT,  
19  
20 Rab GGTase, GGT-II) is responsible for post-translational geranylgeranylation of  
21  
22 Rab GTPases (Fig. 1). Attachment of lipophilic prenyl group(s) is crucial for their  
23  
24 correct subcellular membrane localization and functioning. Most Rab GTPases  
25  
26 undergo double prenylation catalyzed by RGGT, with the formation of a thioether  
27  
28 bond between two C-terminal cysteines and 20-carbon isoprenoid chains, derived  
29  
30 from geranylgeranyl pyrophosphate (GGPP).  
31  
32

33  
34 The abnormal activities of RGGT and some Rab proteins have been identified in a  
35  
36 number of diseases, including neurodegenerative and infectious disorders<sup>1-3</sup> as well as  
37  
38 in several cancer types, in some cases being connected with increased tumor  
39  
40 aggression.<sup>4-6</sup> Specifically, members of the Rab11 family (Rab11A, Rab11B,  
41  
42 Rab25/Rab11C) along with their effectors exert an important role in development of  
43  
44 cancers of multiple lineages, including pancreas, skin, breast, colon, endometrial,  
45  
46 lung, ovarian, renal, prostate and bladder.<sup>1, 7</sup>  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

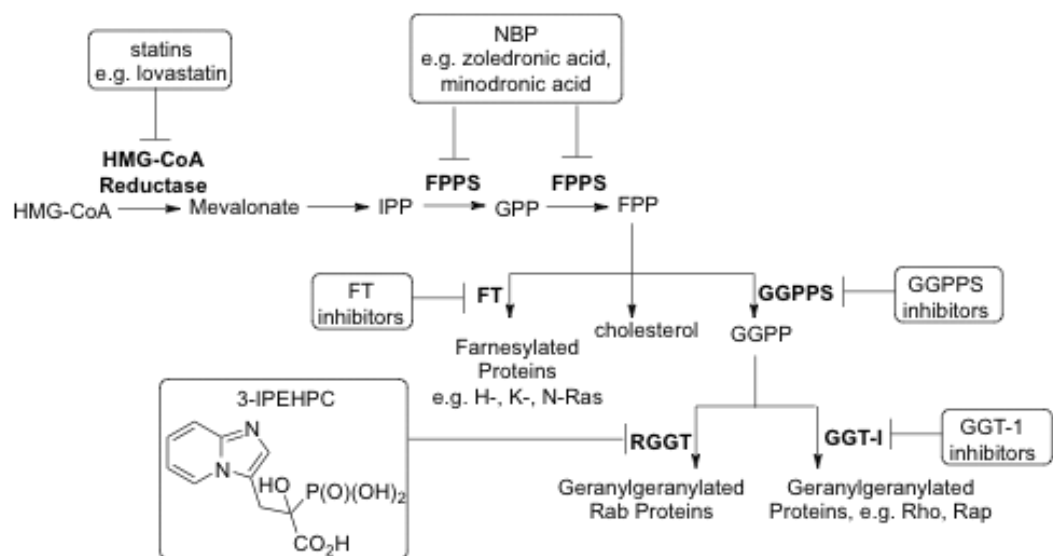


Figure 1. The isoprenoid biosynthesis pathway. NBP: nitrogen-containing bisphosphonates; FPPS: farnesyl pyrophosphate synthase; GGPPS: geranylgeranyl pyrophosphate synthase; FT: farnesyl transferase; GGT-1: geranylgeranyl transferase 1; FPP: farnesyl pyrophosphate; GPP: geranyl pyrophosphate; GGPP: geranylgeranyl pyrophosphate; RGGT: Rab geranylgeranyl transferase.

It has been also reported that disruption of prenylation by inhibition of more upstream enzymes of isoprenoid pathway, e.g. farnesyl pyrophosphate synthase, FPPS (by nitrogen-containing bisphosphonates (NBPs)), can reduce proliferation of malignant cells. Even though the molecular target of NBPs is farnesyl pyrophosphate synthase, their molecular mechanism of action might be related to downstream depletion of geranylgeranyl pyrophosphate, a substrate for geranylgeranyl transferases (Fig. 1).<sup>8-10</sup> Additionally, the unexpectedly low cytotoxicity of farnesyl transferase (FT) inhibitors, which should disrupt prenylation of the oncogenic K-Ras GTPase, is associated with alternative prenylation of this protein by geranylgeranyl transferases.<sup>10-12</sup> The combined therapy using both, farnesyl transferase and geranylgeranyl transferase inhibitors, may overcome this surrogate prenylation.<sup>10, 11</sup>

Therefore, identification of specific inhibitors of RGGT and their application as tools to study RGGT and Rab-connected processes may open new avenues for therapeutic intervention and advances in understanding of Rab proteins prenylation.

The  $\alpha$ -phosphonocarboxylate (PC), 3-PEHPC<sup>13</sup> derived from risedronate, bisphosphonate anti-osteoporotic drug, was the first identified inhibitor of RGGT, which showed moderate but selective activity. Up to now, several other classes of RGGT inhibitors have been reported,<sup>14-18</sup> with the most active analogs being developed from a tetrahydrobenzodiazepine core.<sup>16</sup> None of them were studied with respect to inhibition of first or second geranylgeranylation process, except for phosphonocarboxylates, which were reported to prohibit the introduction of the second geranylgeranyl group to Rabs, therefore selectively affecting Rabs, which require double prenylation.<sup>19</sup>

Further studies led to the identification of the more potent RGGT phosphonocarboxylate inhibitors. We found that other analogs of heterocyclic bisphosphonates show greater activity against RGGT than originally reported 3-PEHPC,<sup>20-22</sup> while those derived from aminoalkyl BP are inactive.<sup>22</sup> Oxidation of nitrogen in the pyridine ring of 3-PEHPC to *N*-oxide, did not improve activity against RGGT.<sup>23</sup> We demonstrated that the most active derivatives of currently known phosphonocarboxylates contain imidazo[1,2-*a*]pyridine (3-IPEHPC and its analogs)<sup>20, 21</sup> or the imidazole ring<sup>22</sup> in their structure.

Thus, here we describe the synthesis of an extended set of phosphonocarboxylate inhibitors (Fig. 2), varying in lipophilicity, size and geometry of substituent in order to probe their affinity towards RGGT. We investigated analogs of 3-IPEHPC with the diversely substituted imidazo[1,2-*a*]pyridine ring (**1a-1c**, **1e-1r**, **2a**, **2b**, **2d**, **2h**) as well as analogs with a modified phosphonic acid moiety, in the form of

hydroxy(phenyl)phosphoryl or ethyl(hydroxy)phosphoryl residues (**1s-t**, **2s-t**). We have also synthesized compounds potentially resembling GGPP, one of the RGGT substrate (**1u**, **1w**, **1y**, **2z**),<sup>24</sup> where a prenyl chain was mimicked with a polyphenyl moiety. Since it is suggested that PCs interact with the enzyme cavity storing the geranylgeranyl residue after first prenylation,<sup>15</sup> we hypothesized that such prenyl-mimicking moiety could inhibit RGGT by interacting with this lipophilic pocket.

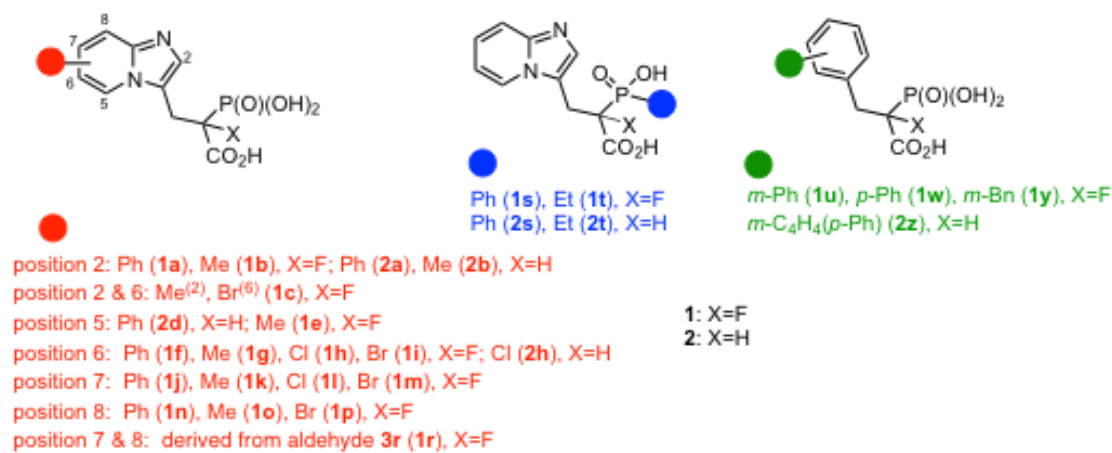


Figure 2. Structures of studied compounds.

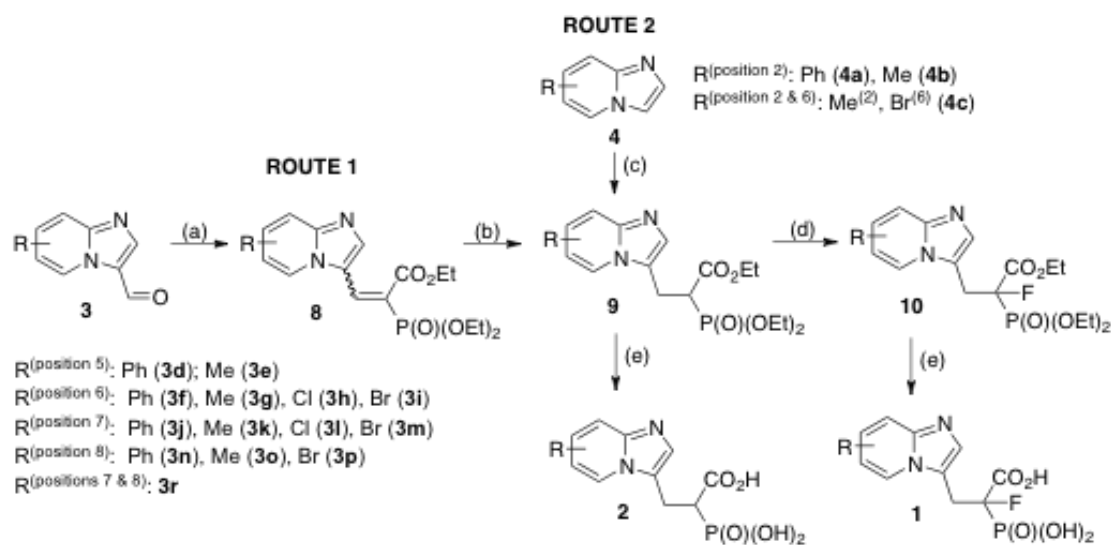
We examined the potency of thus synthesized compounds by investigating their effect on RGGT-driven geranylgeranylation of Rab11A, one of the most characterized molecule among all Rab proteins, along with nonselective prenylation of Rap1A/Rap1B, a strict substrate of GGTase-1.

## RESULTS AND DISCUSSION

### Synthesis of novel phosphonocarboxylate analogs

We applied synthetically robust approach, in which the functionalized phosphonocarboxylate scaffold was built through condensation of an aldehyde **3** and triethyl phosphonoacetate **5** or diethyl phosphinoacetate **6** (Scheme 1, route 1).<sup>25</sup> That

way we obviated the formation of the doubly substituted analog and necessity of preparing the alkylating entity, as was needed for the previously used low-yielding strategy.<sup>21</sup> While this new approach worked well for most studied analogs, it turned out troublesome for derivatives of 2-substituted imidazo[1,2-a]pyridines (Fig. 2, compounds **1a-c**), because preparation of corresponding starting aldehydes required low-yielding and tedious formylation, e.g. through Vilsmeier-Haack reaction.<sup>20</sup> Therefore, instead of using aldehydes **3** as the starting materials, we synthesized 2-substituted imidazo[1,2-a]pyridine analogs **4** and subjected them to Friedel-Crafts alkylation with ethyl 2-(diethoxyphosphoryl)acrylate **7** (Scheme 1, route 2), according to procedure applied for 2-phenylindolizine.<sup>26</sup> Unfortunately, none of these strategies worked for imidazo[1,2-a]pyridine analogs substituted with halogen atom in the position 5, therefore only representatives with alkyl and aryl substituent in this location were obtained.



*Scheme 1. Two strategies used for the synthesis of phosphonocarboxylates, presented on the example of 3-IPEHPC analogs. Reagents and conditions: (a) Triethyl phosphonoacetate,  $\text{TiCl}_4$ , TEA, DCM,  $-20^\circ\text{C}$  to rt; (b)  $\text{NaBH}_4$ ,  $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ , MeOH, -*

40 °C; (c) **7**, 1,4-dioxane, AlCl<sub>3</sub> (cat), reflux; (d) NFSI, BuLi, THF, -70 °C/ 20 minutes, -20 °C/ 1 h; (e) 12 M HCl, reflux.

Route 1 required synthesis of imidazo[1,2-a]pyridine-3-carbaldehydes **3** (Fig. 3a). For their synthesis, appropriate 2-aminopyridine analogs were used in the reaction with bromomalonaldehyde.<sup>27</sup> Apart from commercially available halogen and methyl substituted 2-aminopyridine, phenyl substituted analogs had to be first synthesized either from halogen-containing 2-aminopyridines or from the corresponding halogen-substituted aldehydes **3**, in the Suzuki-Miyaura coupling with phenylboronic acid.<sup>28</sup> Polyphenyl aldehydes **3u**, **3w**, **3y**, **3z** (Fig. 3), were synthesized according to literature procedures (see SI for experimental details).<sup>29, 30</sup>

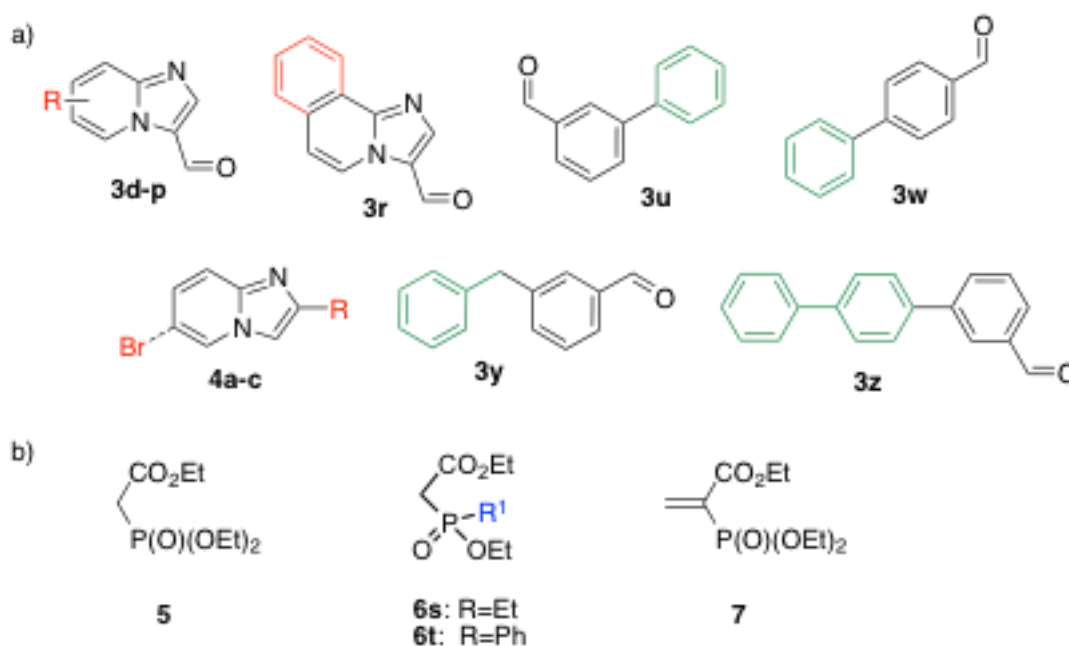


Figure 3. Starting materials for the synthesis of target compounds, representing a) heterocycle and aromatic part; b) phosphonoacetate and phosphinoacetate derivatives.



Thus obtained aldehydes **3** were subjected to  $\text{TiCl}_4$ -mediated condensation with phosphonoacetate **5** or phosphinoacetate **6**, in the presence of TEA (Scheme 1), following the procedure applied previously by Tanabe for condensation of triethyl phosphonoacetate and benzaldehyde.<sup>31</sup> The products **8** in the form of a *E/Z* mixture were obtained with yields in the range 40-84%.<sup>32</sup>

Compounds **8** were subjected to hydrogenation catalyzed by Pd-C. However, that reaction was accompanied by partial reduction of the pyridine ring, as was observed previously for 2-(imidazo[1,2-*a*]pyridin-2-yl)acetates.<sup>33</sup> Therefore, the reduction was carried out with  $\text{NaBH}_4$  and  $\text{NiCl}_2$  hydrate instead, to obtain products **9** with yields 59-98%.<sup>34</sup> While non-halogen containing analogs **8** could be reduced using conditions of 15 min at  $-20\text{ }^\circ\text{C}$ , reduction of halogen-containing derivatives required shorter time (8 min) and lower temperature ( $-40\text{ }^\circ\text{C}$ ), due to their propensity towards halogen-carbon bond cleavage (up to 30% of dehalogenated product was detected if such precaution was not undertaken). As we proved for selected examples, condensation and reduction steps can be run subsequently, without purification of an intermediate vinyl analog **8**, giving comparable yields to procedure involving its purification.

Thus obtained analogs **9** were subjected to fluorination using *N*-fluorobenzenesulfonimide (NFSI) and butyl lithium, according to procedure previously applied for fluorination of bisphosphonates.<sup>35</sup> Fluorinated products **10** were obtained with 41-98% yields (Scheme 1). The last step involved hydrolysis of desoxy **9** and fluoro **10** esters under acidic conditions. Final products were obtained with 55-99% yields<sup>36</sup> upon precipitation. The same procedure was applied in the synthesis of phosphinoacetate analogs **1s-t** and **2s-t**.

For the synthesis of analogs with the imidazo[1,2-*a*]pyridine ring substituted in the position 2, compounds **4** (obtained by condensation of suitable 2-aminopyridine and

chloroacetone or bromoacetophenone) were subject to Friedel-Crafts alkylation, leading to esters **9** with 55-63% yields (Scheme 1, route 2). This approach seem advantageous compared with route 1, the advantages being: (a) starting materials **4** are obtained in yields >70%, while synthesis of appropriate aldehydes **3** requires low yielding formylation; (b) substrates can be directly transformed to product **9**, thereby eliminating one reaction step; (c) avoidance of dehalogenation upon reduction, see (b). However, we found it applicable only to analogs of imidazo[1,2-a]pyridines, in which the position 2 is occupied by substituent. In such cases, selective alkylation takes place only on carbon 3, the position of imidazo[1,2-a]pyridine most activated.<sup>37</sup>  
<sup>38</sup> Thus obtained products of alkylation **9** were subjected to fluorination (72-95% yield) and hydrolysis (53-89% yield), according to the same protocol as the one described above.

In order to study the role of chirality in interaction between RGGT and  $\alpha$ -fluorinated phosphonocarboxylate analogs, we carried out the resolution of enantiomers on the example of compound **1i**. We used previously developed HPLC method,<sup>20</sup> utilizing weak anion exchange chiral column introduced by Lindner et al.<sup>39</sup>

All synthesized fluorine-containing compounds **1** were screened for their biological activity, using cell-based assays. Based on previous studies,<sup>21</sup> we predicted that desoxy analogs **2** should be less potent, therefore representatives of such were screened only in selected cases. In the case of **2d**, a fluoro analog was not obtained, leaving the 5-methyl substituted compound **1e** as the sole fluorinated representative of this position.

#### ***The cytotoxic efficacy of phosphonocarboxylates against HeLa cancer cell line***

Inhibition of prenyltransferases or enzymes in the mevalonate pathway may be associated with decreased cell viability.<sup>13, 40, 41</sup> Therefore, the newly synthesized

phosphonocarboxylate analogs were initially evaluated for their antiproliferative activity against the human epithelial adenocarcinoma cell line (HeLa), using previously described 3-IPEHPC<sup>20, 22</sup> as a reference. Taking into account that activities of tested compounds could be attenuated or modulated by serum proteins,<sup>42</sup> influence of FBS-containing and FBS-free media was also investigated (Table 1).

All analogs of 3-IPEHPC, in which a hydroxyl group on the branching carbon atom between the phosphonic and carboxylic groups (C- $\alpha$ ) was exchanged for a hydrogen atom (**2a**, **2b**, **2d**, **2h**), had no effect on the number of viable HeLa cells up to maximum concentration tested (2 mM) in both serum-containing or serum-free medium. The same effect was observed also for 2-(alkyl/aryl(hydroxy)phosphoryl)-propanoic acid analogs (**1s-t**, **2s-t**).

Introduction of a phenyl (**1a**, **1n**), a methyl (**1b**, **1o**) or a bromine (**1p**) substituent into the position 2 or 8 of the imidazo[1,2-a]pyridine ring of fluoro analogs did not show any effect on HeLa cell proliferation either. Substitution at the 7 (**1j-m**) or 5 (**1e**) position in turn had negligible or no effect when cells were cultured in complete medium, but in most cases significantly increased cytotoxic effect when applied under serum-free condition.

Remaining fluoro analogs modified at the 6 position of the imidazo[1,2-a]pyridine ring (**1f-i**) demonstrated cytotoxic effect under both medium conditions, being the most potent molecules, with IC<sub>50</sub> values ranging from 68  $\mu$ M to 323  $\mu$ M in fasting medium and from 267  $\mu$ M to 521  $\mu$ M in FBS-containing medium. They showed similar or even stronger effect when compared to the reference compound, 3-IPEHPC. It is noteworthy that introduction of an additional methyl substituent in the 2 position of compound **1i** (**1c**) led to significant limitation of antiproliferative activity against HeLa cells (IC<sub>50</sub> = 1952  $\mu$ M in complete medium).

Exchanging a heterocycle with biphenyl or benzylphenyl moieties resulted in no or weak cytotoxic effect in DMEM supplemented with FBS (**1u**, **1w**, **1y**), while the desoxy analog containing a triphenyl residue (**2z**) turned out to be very potent. The IC<sub>50</sub> values in fasting medium were in the range of 318 - 930  $\mu$ M for compounds **1u**, **1w**, **1y**, and the most active appeared to be **2z** with IC<sub>50</sub> below 25  $\mu$ M.

*Functionalization of the imidazo[1,2-a]pyridine ring in the position 6 increases potency of 3-IPEHPC analogs against Rab prenylation.*

All synthesized fluorine-containing compounds **1** and selected representatives of desoxy analogs **2** were screened for their ability to inhibit RGGT and GGT-1 in intact cells, which also allowed assessing their cellular availability. As previously,<sup>22</sup> the assays were based on determination of the unprenylated forms of Rab11A and Rap1A/Rap1B, which are modified with geranylgeranyl groups by RGGT and GGT-1, respectively. We reasoned that independent effect observed either for Rab11A or Rap1A/Rap1B would indicate selective inhibition of RGGT or GGT-1, while comparable effect for both proteins would indicate that mevalonate pathway enzymes, e.g. GGPPS or FPPS, might be affected, since they are providing prenyl pyrophosphate substrate for both transferases (Fig. 1).

Our choice of the method for activity assessment was dictated by the fact that most assays on isolated RGGT utilize diversely labeled, non-commercially available GGPP analogs, often requiring multi-step synthesis, and being labile due to the presence of pyrophosphate moiety. The differences in IC<sub>50</sub> values obtained in different *in vitro* assays<sup>16</sup> suggest that they may measure different modes of inhibition, none of them being adjusted to inhibitors of second geranylgeranylation, such as phosphonocarboxylates. For such inhibitors using labeled GGPP may lead to

ambiguous readout, since both, the properly doubly geranylgeranylated as well as mono geranylgeranylated intermediate will be functionalized with a visualizing handle. Therefore, we studied the activity of compounds through fractionation of cellular lysates and immunochemical detection of mis-prenylated Rab11A present in cytosol.

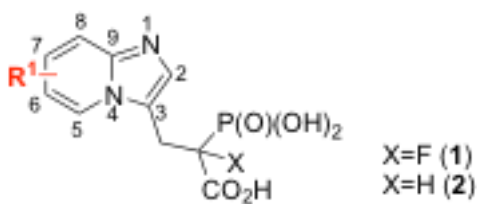
The inhibitory activity of the set of investigated compounds **1-2** was initially tested at 100  $\mu$ M concentration under serum-free conditions and the Rab11A enrichment in the cytosol fraction was examined with Western Blot analysis (Table 1). Treatment with the series of GGPP mimetics (**1u**, **1w**, **1y**, **2z**) and with desoxy analogs of 3-IPEHPC (**2a**, **2b**, **2d**, **2h**) did not deplete Rab11A from membrane fractions of HeLa cells. Among five analogs modified at the 2 or 8 position of the imidazo[1,2-a]pyridine ring, only two, compounds **1a** and **1o**, have shown an effect on Rab11A prenylation. 7-Substituted fluoro analogs (**1j-m**) did not inhibit prenylation of Rab11A, but they did show ability to reduce HeLa cells viability in serum-free medium. The 5-substituted fluoro analog, compound **1e**, has shown inhibition of Rab11A prenylation at 100  $\mu$ M and significant reduction of HeLa cell viability, but only in serum-free medium.

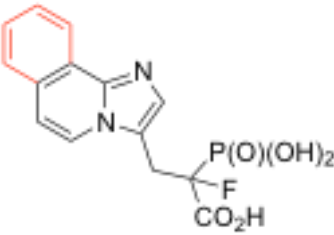
The set of phosphinic acid derivatives (**1s-t**, **2s-t**) also weakly inhibited Rab11A prenylation at 100  $\mu$ M, despite their non-cytotoxic character.

Interestingly, all the fluoro analogs containing substituent at the position 6 of the imidazo[1,2-a]pyridine ring (**1f-i**), enriched Rab11A protein level in cytosolic fraction, which correlates well with their ability to reduce HeLa cell viability. As an example of a desoxy analog, compound **2h** was also tested and it had no effect on both, HeLa cells viability and Rab11A potency. It supports the previously observed trend<sup>21, 43</sup> that fluorinated analogs are more active than their desoxy counterparts.

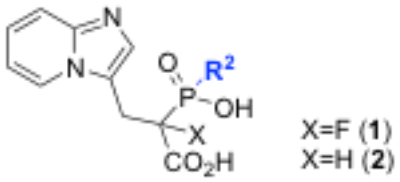
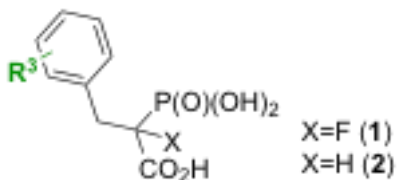
1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

Table 1. Effects of synthesized PC analogs on HeLa cell viability in serum-supplemented and serum-free medium<sup>a</sup>, and Rab11A prenylation tested at a concentration of 100  $\mu\text{M}$ <sup>b</sup>.

Entr	Compoun	R <sup>1</sup> / R <sup>2</sup> / R <sup>3</sup> (see structure) <sup>c</sup>	Reduction of HeLa cell viability (IC <sub>50</sub> / $\mu\text{M}$ ) <sup>d</sup>		Inhibition of Rab11A prenylation at concentratio n of 100 $\mu\text{M}$
			in medium supplemente d with 10% FBS	in serum- free mediu m	
					
1.	3-  IPEHPC <sup>c</sup>	H	585	167	+
2.	1a <sup>e</sup>	2-Ph	no effect	no effect	+
3.	1b	2-Me	no effect	no effect	-
4.	1c <sup>e</sup>	2-Me-6-Br	1952	879	-
5.	1e <sup>e</sup>	5-Me	1487	224	+

6.	1f <sup>e</sup>	6-Ph	510	68	+
7.	1g <sup>e</sup>	6-Me	358	222	+
8.	1h <sup>e</sup>	6-Cl	521	323	+
9.	1i <sup>e</sup>	6-Br	504	156	+
10.	1i-E1 <sup>f</sup>	6-Br	NE	NE	-
11.	1i-E2 <sup>f</sup>	6-Br	267	130	+
12.	1j <sup>e</sup>	7-Ph	1579	186	-
13.	1k	7-Me	no effect	1147	-
14.	1l	7-Cl	no effect	351	-
15.	1m	7-Br	no effect	634	-
16.	1n	8-Ph	no effect	no effect	-
17.	1o <sup>e</sup>	8-Me	no effect	no effect	+
18.	1p	8-Br	no effect	no effect	-
19.	1r <sup>e</sup>		747	122	-
20.	2a		2-Ph	no effect	-

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

21.	<b>2b</b>	2-Me	no effect	no effect	-
22.	<b>2d</b>	5-Ph	no effect	no effect	-
23.	<b>2h</b>	6-Cl	no effect	no effect	-
<div></div>					
24.	<b>1s<sup>g</sup></b>	Ph	no effect	no effect	+
25.	<b>1t<sup>g</sup></b>	Et	no effect	no effect	+
26.	<b>2s</b>	Ph	no effect	no effect	+
27.	<b>2t</b>	Et	no effect	no effect	+
<div></div>					
28.	<b>1u</b>	<i>m</i> -Ph	no effect	930	-
29.	<b>1w</b>	<i>p</i> -Ph	no effect	318	-
30.	<b>1y</b>	<i>m</i> -Bn	no effect	427	-
31.	<b>2z</b>	<i>m</i> -C <sub>6</sub> H <sub>4</sub> ( <i>p</i> -Ph)	778	<25	-



<sup>a</sup>HeLa cells were treated with the compounds for 72 h and then viable cell number was assayed. Represented data were calculated from the means of eight tested concentrations from at least 3 independent experiments.

<sup>b</sup>HeLa cells were treated for 48 h with 100  $\mu$ M concentration of the compounds, then lysed and separated into cytosolic and membrane-rich fractions and Western blotted for Rab11A and  $\beta$ -actin in cytosolic fractions. Data shown in the table, from at least 3 independent experiments, indicates for which compounds higher bands intensity compared to control (untreated cells) was observed.

<sup>c</sup> For analogs modified in the imidazo[1,2-a]pyridine ring, the position of modification is given according to the numbering of heterocycle.

<sup>d</sup> “no effect” stands for lack of response in cells treated with up to 2 mM concentration of inhibitor.

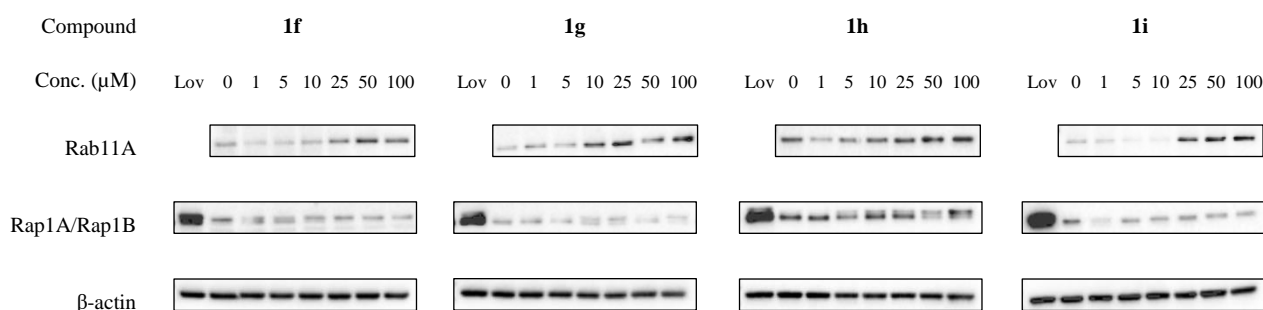
<sup>e</sup> Compounds in bold were evaluated to inhibit Rab11A and Rap1A/Rap1B prenylation in wide concentration range.

<sup>f</sup> The enantiomers of **1i** are distinguished as E1 and E2, based on their retention times during chiral HPLC separation. The enantiomer with the shorter retention time is labeled as E1, and the one with the longer retention time, as E2.

<sup>g</sup> Compounds demonstrated insignificant activity to inhibit Rab11A prenylation (based on densitometry analysis), which was the reason why they have not been tested in wide concentration range.

Thirteen compounds (3-IPEHPC, **1a**, **1c**, **1e-j**, **1o**, **1r**, **2s-t**) were selected for full panel 6 doses assay to determine the lowest effective dose inhibition of Rab11A prenylation based on their antiproliferative activity (IC<sub>50</sub> values) and the initial Western Blot screening at a single concentration of 100  $\mu$ M (see last column in Table 1). Selected compounds were assessed for their ability to inhibit Rab11A and Rap1A/Rap1B prenylation by RGGT and GGTase 1, respectively.

## A



B

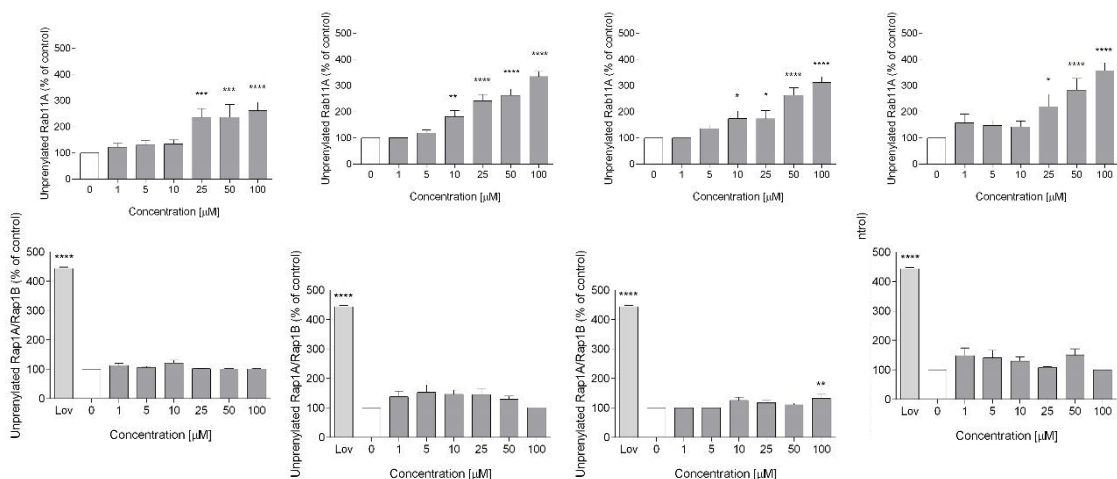


Figure 4. Effect of 6-substituted analogs of 3-IPEHPC (**1f-i**) on Rab11A and Rap1A/Rap1B prenylation in HeLa cells. Cells were treated for 48 h with the indicated concentrations of PCs ( $\mu\text{M}$ ) and 10  $\mu\text{M}$  lovastatin (Lov) acting as a positive control in serum-free medium. Subsequently cells were lysed and fractionated into cytosolic and membrane-rich fractions. Cytosolic fractions containing unprenylated proteins were western blotted for Rab11A, Rap1A/Rap1B and  $\beta$ -actin (A) and the immunoblot bands were quantified by densitometry analysis, normalized to  $\beta$ -actin, and displayed as a percentage of controls (B). Data represented mean  $\pm$  SEM from at least three independent experiments,  $*p \leq 0.05$ ,  $**p \leq 0.01$ ,  $***p \leq 0.001$  and  $****p \leq 0.0001$ .

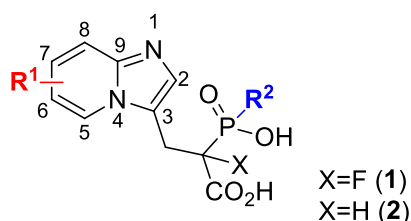
Since compounds **1j** and **1r** did not show any effect on Rab11A prenylation inhibition, their significant potency to reduce HeLa cell viability (Table 1) should be associated with different mechanism of action.

Compounds that showed no influence on HeLa cell viability (**1a**, **1o**, **2s-t**) were proven to be weak inhibitors of Rab11A prenylation. They demonstrated similar effect in the case of Rap1A/Rap1B prenylation, except for **1a**, which turned out to be inactive even at 100  $\mu\text{M}$  concentration. **1e** was another weak inhibitor, with equal LEDs obtained for both Rab11A and Rap1A/Rap1B prenylation. Such results suggest that those PCs may inhibit an enzyme of the mevalonate pathway such as GGPPS or FPPS (Fig. 1), responsible for synthesis of geranylgeranyl pyrophosphate, a substrate necessary for prenylation mediated by RGGT or GGTase 1. It cannot be excluded though that these compounds inhibit both, RGGT and GGT-1, at similar concentrations.

The  $\alpha$ -fluorine analogs of 3-IPEHPC with the imidazo[1,2-a]pyridine ring substituted in the position 6 were the most potent inhibitors of Rab11A prenylation as measured by LED (10  $\mu$ M for **1g**, **1h**; 25  $\mu$ M for **1f**, **1i**; Table 2). At the same time Rap1A/Rap1B prenylation was not affected (LED > 100  $\mu$ M), except for **1h** (LED = 100  $\mu$ M). Our data suggest that they are even stronger selective RGGT inhibitors than a reference ( $\pm$ )-3-IPEHPC (LED for inhibition of Rab11A = 25  $\mu$ M<sup>22</sup> or 50  $\mu$ M in our research model). Densitometry analysis confirmed their efficacy, showing at least 2.5-fold enrichment of unprenylated Rab11A in the cytosol fraction of treated cells compared to untreated control (Table 2). Compound **1c** combining structural features characteristics for **1i** (bromine in the position 6) and **1b** (methyl in the position 2) did not inhibit Rab11A and Rap1A/Rap1B prenylation up to 100  $\mu$ M. It confirmed that C6 substitution of the imidazo[1,2-a]pyridine ring is the key and privileged position among all analogs tested within this study, and simultaneous modification at other positions reduces compound' activity.

Similarly to the trend observed in viability assay (Table 1, **1i-E2**: IC<sub>50</sub> is 267  $\mu$ M in full medium and 130  $\mu$ M in serum-free medium; no effect for **1i-E1**), out of two enantiomers of **1i**, only one had the desired biological activity as measured by LED, confirming previous findings that chirality plays a pivotal role in interaction between phosponocarboxylates and RGGT.<sup>20</sup>

Table 2. Effects of selected PC analogs on Rab11A and Rap1A/Rap1B prenylation<sup>a</sup> in HeLa cells.



				Densitometry analyses of the quantity of Rab11A in cytosolic fractions after treatment with 100 μM concentrations of compounds (% of control ± SD) <sup>b</sup>		
Compound	R <sup>1</sup>	R <sup>2</sup>	Inhibition of Rab11A prenylation (LED/μM)			Inhibition of Rap1A/Rap1B prenylation (LED/μM)
1. 3-IPEHPC <sup>c</sup>	H	OH	50	258 ± 109	100	
2. 1a	2-Ph	OH	100	181 ± 81	no effect	
3. 1c	2-Me-6-Br	OH	no effect	129 ± 38	no effect	
4. 1e	5-Me	OH	100	155 ± 56	100	
5. 1f	6-Ph	OH	25	262 ± 102	no effect	
6. 1g	6-Me	OH	10	335 ± 69	no effect	
7. 1h	6-Cl	OH	10	312 ± 87	100	
8. 1i	6-Br	OH	25	357 ± 121	no effect	
9. 1i-E2	6-Br	OH	10	1539 ± 1143	no effect	
10. 1k	7-Me	OH	no effect	118 ± 20	not determined	
11. 1o	8-Me	OH	100	180 ± 70	100	

12.	2s	H	Ph	50	133 ± 36	100
13.	2t	H	Et	100	143 ± 42	50

<sup>a</sup> LED = lowest effective dose. No effect = LED is not included in concentration up to 100 μM.

<sup>b</sup> Densitometry analysis was performed with ImageLab™ Software (Bio-Rad) and relative unprenylated protein band intensity was normalized to β-actin and quantified with respect to controls (untreated cells).

<sup>c</sup> Inhibition of Rab11A prenylation (LED) by (S)-3-IPEHPC was determined to be 25 μM.

### ***Fractionation of prenylated and non-prenylated proteins prior to Western Blot***

Triton X-114 is the nonionic mild detergent, commonly used to extract membrane proteins from biological samples. It rarely denatures membrane proteins and allows phase separation above its clouding point (about 22°C). It was previously used for cell lysis and separation of hydrophobic prenylated proteins from their more polar counterparts.<sup>22, 44</sup> However, separation into hydrophilic and hydrophobic phases by Triton X-114 extraction is not highly effective and may be substantially improved. Our experience shows that the procedure based on the use of Triton X-114 is very tedious, partly due to inefficient lysis of cells and temperature dependent partitioning, both factors lowering protein yields and leading to contamination of cytosolic fraction with membrane proteins. While this method should leave no doubt when applied to proteins which are monoprenylated, e.g. by GGT-1 or FT,<sup>44</sup> in case of RGGT, which is an enzyme capable of mono- as well as double geranylgeranylation, the partition between detergent-rich and aqueous phase may raise the question about localization of not completely prenylated Rab GTPases. Similar problem may arise when using activity assays, based on attachment to Rabs an isoprenoid analogs functionalized either with a bioorthogonal, affinity or fluorescent handle. While this method is efficient for protein identification, it can give ambiguous read-out for inhibitors of

second prenylation, since both, the proper product of double geranylgeranylation as well as the mono geranylgeranylated intermediate will be tagged and therefore provide positive signal.

Therefore, knowing that previously studied phosphonocarboxylates are inhibitors of second geranylgeranylation,<sup>19, 22</sup> and based on our previous studies,<sup>22</sup> where we have shown that disruption of prenylation by phosphonocarboxylates leads to mislocalization of Rab proteins into cytosol, instead of Triton X-114 we applied commercial kit, dedicated to the enrichment of integral membrane proteins and membrane-associated proteins from cultured mammalian cells and eliminates the hassle of phase separation based on hydrophobicity. Here it was used for the first time for fractionation of prenylated proteins and it turned out highly reproducible and efficient for this type of studies.

### ***Molecular docking***

Since the crystal structure of phosphonocarboxylate-RGGT complex is not available, we elaborated the model of their interactions using molecular docking and new biological data. We determined that interactions of the acidic residues, phosphonic and carboxylic groups, guide the location of the novel inhibitors in the RGGT binding area. The suggested binding mode differs slightly from our previous study,<sup>21</sup> but depends now more on interactions that ensure that compounds are well stabilized into the binding site. As these novel compounds are smaller and chemically distinct from inhibitors of other classes that have been co-crystallized with RGGT,<sup>15-18</sup> the binding mode likely differs. In our induce fit docking simulations the phosphonic group of the novel RGGT inhibitors coordinates to zinc ion (Fig. 5). In addition, docking suggests that the phosphonic group could form a hydrogen bond with D238B. Furthermore,

several amino acids, K235B, D238B, Y241B and K105A, are in hydrogen bonding distance of the carboxylic acid group of the novel inhibitors (Fig. 5).

All the active compounds (**1f**, **1g**, **1h** and **1i**) are suggested to have similar binding mode (Fig. 5). Their substituents in the position 6 (Ph, Me, Cl, Br, respectively) face W244B indole side chain yielding to favorable packing. H190B and Y107A are in hydrogen bonding distance of N in the position 1 of the imidazo[1,2-a]pyridine ring. However, when Me is added to the position 2 (compound **1c**) this substitution prevents K105A from forming a hydrogen bond to the carboxylic acid, affecting disruptively the binding efficiency (Fig. 5; Table 2).

As far as chirality is concerned, we observed that one of the enantiomers of the active compound (**1i**) is mainly responsible for racemate activity towards RGGT. Based on previous studies when higher potency towards RGGT was detected for (*S*)-3-IPEHPC isomer,<sup>20</sup> we tentatively extended this stereochemical preference to fluorine analogs. Such preference for (*S*)-isomer might come from fluorine interaction with C240B and/or W244B, while in (*R*)-isomer there is no interaction with fluorine (see Figure S294). Having two acceptors around, donor adjusts itself to both, which might be responsible for stronger interaction than either one alone.

The methyl group present in other positions of the imidazo[1,2-a]pyridine ring, 5, 7 or 8 (compounds **1e**, **1k** and **1o**, respectively) cause a slight shift in the binding mode compared to e.g. the pose of compound **1g** when they pursue hydrophobic interactions with W52B, R144B, G192B, Y195B, W244B and F289B. Due to that shift, Y107A cannot form hydrogen bond with N in the position 1 of the imidazo[1,2-a]pyridine ring and thus some binding potential is lost.

The presence of a phenyl group in the position 2 of compound **1a** strongly influences the binding mode, making it very different from other analogs. It changes the

interactions formed with the carboxylic acid and the phosphonic group of the inhibitor. Still, the same amino acids, H190B, K235B, D238B, and Y241B, remain in hydrogen bonding distance. W244B and F289B form a flat hydrophobic layer for hydrophobic packing of both the imidazo[1,2-a]pyridine ring and the phenyl group. However, hydrogen bonding with N in the position 1 in the imidazo[1,2-a]pyridine ring is lost and with that also binding potential.

Based on docking simulations, inhibitor **2s** binds in principle similarly as e.g. compound **1c** or **1g** (Fig. 5) but phenyl group in the phosphinate shifts the binding pose so that aromatic carbocycle forms  $\pi$ - $\pi$  stacking interaction with F289B. With this interaction some binding potential is gained. However, simultaneously H190B or Y107A have difficulties to reach to hydrogen bonding distance of N in the position 1 of the imidazo[1,2-a]pyridine ring and thus some potential is likely lost. Basically, compound **2t** binds similarly as compound **2s**. But because **2t** has smaller, hydrophobic substitution in the phosphinate part, the shift in the binding mode towards F289B is larger and then H190B and Y107A have even bigger difficulties to reach N in the position 1 in the imidazo[1,2-a]pyridine ring to form the hydrogen bond.



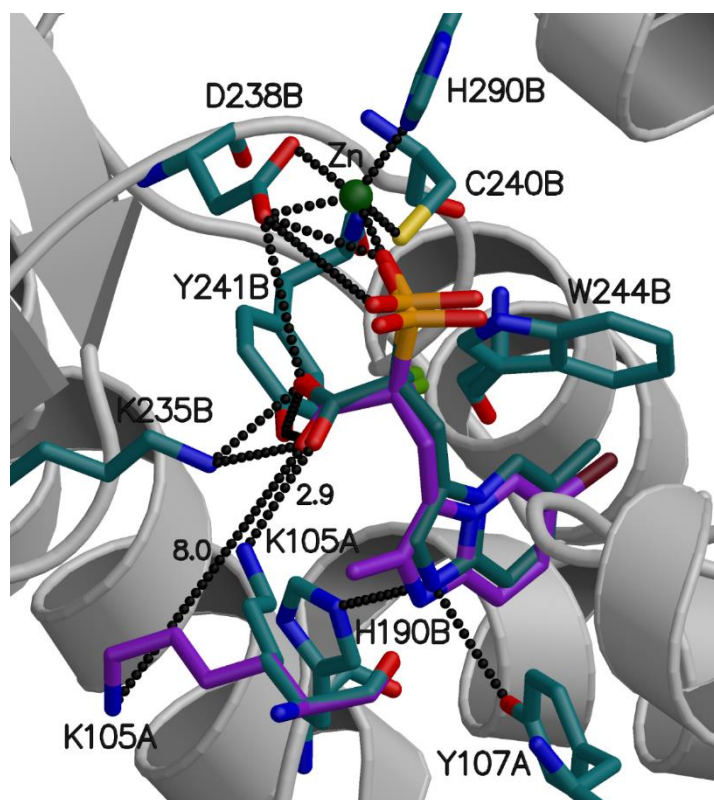


Figure 5. An example of the binding interactions of the novel RGGT inhibitors suggested by docking simulations. The phosphonic and the carboxylic acid groups guide the novel RGGT inhibitors to the close proximity of the catalytic zinc ion and several amino acids with hydrogen bonding ability (K235B, D238B, Y241B and K105A). In the binding of compound **1c** (purple) and compound **1g** (turquoise) K105A has a crucial role. When methyl group is added to the position 2 (compound **1c**) this substitution prevents K105A from forming a hydrogen bond to the carboxylic acid weakening the binding (Table 2). The black dashed lines indicate interactions between the inhibitor and the protein. Used atom colors: C in compounds **1c** and **1g** are in purple and in turquoise, respectively. O=red, N=blue, P=orange, S=yellow, F=bright green, Zn=dark green, Br=burgundy.

## Conclusions

We have elaborated convenient protocols for the synthesis of novel  $\alpha$ -fluoro and  $\alpha$ -desoxy phosphonocarboxylates functionalized with heterocycle or polyphenyl moieties. We have identified four phosphonocarboxylates (**1f**, **1g**, **1h**, **1i**) among them, which inhibit prenylation of Rab11A and show reduction of human HeLa cancer cell line viability. Three compounds have shown selectivity towards RGGT and no inhibition of geranylgeranylation of Rap1A/Rap1B protein up to 100  $\mu$ M concentration. All active compounds bear a substituent in the same location of the core scaffold, carbon C-6 of the imidazo[1,2-a]pyridine ring. Therefore, it was designated as the leading position for future modifications. Such choice is supported by molecular docking studies, which identified the coordination of phosphonic group to zinc cation, stabilized by several amino acid residues being in the hydrogen bonding distance to phosphonic and carboxylic groups as well as nitrogen atom in the position 1 of imidazo[1,2-a]pyridine ring, as the guiding interaction in the complex.

We evaluated compounds' potency by immunochemical detection of not completely prenylated Rab11A proteins, taking into consideration the possible ambiguity of their separation from fully digeranylgeranylated proteins. For the first time here we applied the commercially available kit for fractionation of membrane from cytosolic proteins, which in our hands exceeded previously used for this application Triton X-114, in terms of efficiency of lysis and reproducibility.

Phosphonocarboxylates as inhibitors of second prenylation mediated by RGGT, mostly affect digeranylgeranylated and not monogeranylgeranylated Rab proteins. Since it is still difficult to determine how specific prenylated proteins mediate different pathological processes, e.g. cancer cell growth and survival, such selectivity should be advantageous. Considering that inhibition of RGGT affects over 60

1  
2  
3 proteins, such broadness of targets pose a threat of high toxicity. It remains to be  
4  
5 determined if inhibition only of the second prenylation can lead to some salvage  
6  
7 effect on cell well-being and not be so deleterious to healthy cells.  
8  
9

10 The works on development of new analogs as more potent inhibitors of RGGT and  
11  
12 tools for studying Rab GTPase-associated processes combined with the studies on  
13  
14 elaboration of the efficient asymmetric synthesis of phosphonocarboxylates and  
15  
16 confirmation of the preferred stereochemistry for interaction with RGGT are in  
17  
18 progress now.  
19  
20

## 21 22 **Experimental Section**

### 23 24 *General*

25  
26  
27 *Synthesis.* All reagents were purchased from commercial sources and used as  
28  
29 obtained, unless specified otherwise. Thin-layer chromatography was performed  
30  
31 using silica gel 60 with F254 indicator on alumina plates. Compounds were purified  
32  
33 using Flash chromatography and 40-63  $\mu\text{m}$  silica gel. Solvent ratios for the purification  
34  
35 of compounds by flash chromatography are reported as volume ratios (v/v).  
36  
37 Preparative HPLC for purification of compounds **1s**, **1t** was performed using Gilson  
38  
39 Prep equipped with UV-VIS-156 detector and semipreparative column Kromasil 100-  
40  
41 5-C18 (5  $\mu\text{m}$ , 10 x 250 mm). Enantiomers of **1i** were separated using Chiralpak QN-  
42  
43 AX column (Chiral Technologies Europe; 0.46 cm x 15 cm), according to the method  
44  
45 previously described for 3-IPEHPC.<sup>20</sup> Each enantiomer was re-purified using the  
46  
47 same chiral column. Column was eluted isocratically (1 mL/min) with 0.7 M TEAAc  
48  
49 containing 75% MeOH at pH 5.8. The optical purity of enantiomers was evaluated  
50  
51 based on HPLC analysis using Chiralpak QN-AX column. The enantiomer with the  
52  
53 shorter retention time, 4.9 minute, has been labeled as E1, while the one with the  
54  
55 longer retention time, 5.7 minute, as E2.  
56  
57  
58  
59  
60

NMR spectra were measured at 250.13 or 700 MHz for  $^1\text{H}$  NMR, 62.90 or 170 MHz for  $^{13}\text{C}$  NMR, 283 or 101.30 MHz for  $^{31}\text{P}$  NMR on Bruker Avance DPX 250 and Bruker Avance II Plus 700 spectrometers, respectively. Chemical shifts ( $\delta$ ) are reported in parts per million (ppm) relative to: internal residual  $\text{CHCl}_3$  in  $\text{CDCl}_3$  ( $\delta$  7.26  $^1\text{H}$  NMR) or  $\text{CDCl}_3$  signal in  $^{13}\text{C}$  NMR ( $\delta$  77.16); internal residual HDO in  $\text{D}_2\text{O}$  ( $\delta$  4.79  $^1\text{H}$  NMR) or external 85%  $\text{H}_3\text{PO}_4$  ( $\delta$  0 ppm  $^{31}\text{P}$  NMR).  $^{31}\text{P}$  NMR and  $^{13}\text{C}$  NMR spectra were proton-decoupled. Coupling constants ( $J$ ) are quoted in Hz. The assignment of the signals in  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR was supported by two-dimensional experiments (COSY, HMQC, HMBC, DEPT135). In case of compounds obtained as diastereomeric mixtures, the ratio of diastereomers was determined based on  $^{31}\text{P}$  NMR and (if possible) sufficiently separated signals in  $^1\text{H}$  NMR. For compounds **8** the description of  $^1\text{H}$  and  $^{13}\text{C}$  NMR shows only major (at least 80%) isomer, (*Z*)-**8**, unless stated otherwise. For compounds **9s-t** and **10s-t**, chemical shifts in  $^1\text{H}$  and  $^{13}\text{C}$  NMR are enlisted for both diastereoisomers, if sufficiently separated, without distinguishing isomers. The purity of biologically tested compounds was evaluated by elemental analysis. All target compounds are >95% pure.

*Biological studies.* PrestoBlue<sup>®</sup> Cell Viability Reagent, Mem-PER<sup>™</sup> Plus Membrane Protein Extraction Kit, and all reagents for cell culture were purchased from Life Technologies (Carlsbad, CA, USA). Mem-PER<sup>™</sup> Plus Membrane Protein Extraction Kit was used for cell lysis and separation of cytosolic and membrane-rich fractions. Bradford Protein Assay and Clarity<sup>™</sup> Western ECL Substrate were obtained from Bio-Rad (Hercules, CA, USA). Protease inhibitor cocktail and lovastatin were purchased from Sigma (Saint Louis, MO, USA). Primary antibodies against Rab11A and Rap1A/Rap1B were obtained from Abcam (Cambridge, UK) and primary

antibodies against  $\beta$ -actin along with secondary HRP-linked antibodies were purchased from Cell Signaling Technology (Beverly, MA, USA).

*HeLa cell culture.* The cervical epithelial carcinoma HeLa cell line was purchased from the American Type Cell Collection (ATCC). Cells were cultured in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal bovine serum (FBS) containing 100 IU/ml penicillin and 100  $\mu$ g/ml streptomycin. Cells were incubated at 37°C in a humidified atmosphere of 95% air and 5% CO<sub>2</sub>.

For biological studies, PCs were dissolved in PBS at stock concentrations or 10 mM, and the pH adjusted to about 7. Compounds were stored at 4 °C or -20 °C (for longer storage) prior to use.

*Molecular docking.* Compounds were drawn with Maestro 2016.2 (Schrödinger Release 2016-2: Maestro, Schrödinger, LLC, New York, NY, 2016). Both (/all) stereoisomers were drawn for 11 compounds selected for molecular docking (compounds in Table 2: **1a**, **1c**, **1e**, **1f**, **1g**, **1h**, **1i**, **1k**, **1o**, **2s**, **2t**). First traditional molecular docking with Glide was tested. Protein structure for docking, (PDB ID 4GTS)<sup>16</sup>, was downloaded from the Protein Data Bank<sup>45</sup> and prepared with Protein Preparation Wizard. In docking, protein was held rigid except hydroxyl and thiol groups were allowed to rotate. In ligand binding larger conformational changes in the protein structure, according to the induced fit concept, are possible. In addition, the binding area of RGGT is spacious and the sensitivity of traditional molecular docking is not high enough. To better model the binding interactions of novel RGGT inhibitors induced fit docking (IFD) in Maestro 2016.2 was performed. In IFD side chains of amino acids in the defined distance from the ligand are allowed to move freely and thus subtleties of the interactions between the ligand and the protein can be considered more accurately than with traditional molecular docking. In IFD procedure

center of the docking box was set to catalytic zinc ion coordinate since zinc ion is considered important in binding. After the Glide molecular docking part of the IFD procedure 20 poses were accepted for Prime refinement. Protein amino acid residues were refined in 5 Å radius of the docking poses. OPLS3 force field<sup>46</sup> was used in the IFD procedure. In the end ten complexes were saved for the visual examination.

*General procedure for hydrolysis. Synthesis of compounds 1 and 2.* Compound **9/10** (0.50 mmol) was dissolved in 12 M HCl (5.5 mL). After 4-5 h of reflux the mixture was evaporated to dryness. The products were obtained as solids with 56-99% yields, upon precipitation (using water or petroleum/diethyl ether) or by sole removal of solvents.

*2-Fluoro-3-(2-phenylimidazo[1,2-a]pyridin-3-yl)-2-phosphonopropanoic acid (1a).*

Yield: 53%, scale: 0.093 g. **Elemental analysis:** C<sub>16</sub>H<sub>14</sub>FN<sub>2</sub>O<sub>5</sub>P (H<sub>2</sub>O)<sub>1.35</sub>, (C<sub>2</sub>H<sub>5</sub>OH)<sub>0.55</sub>, Calculated: C: 49.62, H: 4.87; N: 6.77, Found: C: 49.66; H: 4.88; N: 6.82, **<sup>1</sup>H NMR** (700 MHz, D<sub>2</sub>O pH 7) δ: 3.88 (ddd, <sup>2</sup>J<sub>HH</sub> = 16.0, <sup>3</sup>J<sub>PH</sub> = 8.7, <sup>3</sup>J<sub>FH</sub> = 4.4, CH<sub>2</sub>CPF, 1H), 4.17 (ddd, <sup>3</sup>J<sub>FH</sub> = 37.3, <sup>2</sup>J<sub>HH</sub> = 16.0, <sup>3</sup>J<sub>PH</sub> = 1.3, CH<sub>2</sub>CPF, 1H), 7.02 (td, <sup>3</sup>J<sub>HH</sub> = 6.9, <sup>4</sup>J<sub>HH</sub> = 1.1, CH<sub>Ar(6)</sub>, 1H), 7.41 (ddd, <sup>3</sup>J<sub>HH</sub> = 9.0, <sup>3</sup>J<sub>HH</sub> = 6.9, <sup>4</sup>J<sub>HH</sub> = 1.2, CH<sub>Ar(7)</sub>, 1H), 7.50 (tt, <sup>3</sup>J<sub>HH</sub> = 7.9, <sup>4</sup>J<sub>HH</sub> = 1.2, CH<sub>Ar</sub>, 1H), 7.58 (m, CH<sub>Ar(8)</sub>, CH<sub>Ph</sub>, 3H), 7.85 (dd, <sup>3</sup>J<sub>HH</sub> = 8.2, <sup>4</sup>J<sub>HH</sub> = 1.2, CH<sub>Ph</sub>, 2H), 8.63 (bd, <sup>3</sup>J<sub>HH</sub> = 6.9, CH<sub>Ar(5)</sub>, 1H), **<sup>31</sup>P NMR** (283 MHz, D<sub>2</sub>O pH 7) δ: 10.39 (d, <sup>2</sup>J<sub>PF</sub> = 71.9), **<sup>13</sup>C NMR** (176 MHz, D<sub>2</sub>O): 28.7 (bd, <sup>2</sup>J<sub>FC</sub> = 22.0, CH<sub>2</sub>CPF, 1C), 99.7 (dd, <sup>1</sup>J<sub>FC</sub> = 192.1, <sup>1</sup>J<sub>PC</sub> = 140.0, CH<sub>2</sub>CPF, 1C), 112.4 (s, CH<sub>Ar(6)</sub>, 1C), 115.1 (s, CH<sub>Ar(8)</sub>, 1C), 117.9 (dd, <sup>3</sup>J<sub>PC</sub> = 12.7, <sup>3</sup>J<sub>FC</sub> = 3.2, C<sub>Ar(3)</sub>, 1C), 126.3 (s, CH<sub>Ar(7)</sub>, 1C), 126.5 (d, <sup>5</sup>J<sub>PC</sub> = 5.8, CH<sub>Ar(5)</sub>, 1C), 128.0 (s, CH<sub>Ph</sub>, 1C), 128.6 (s, CH<sub>Ph</sub>, 2C), 128.9 (s, CH<sub>Ph</sub>, 2C), 134.2 (s, CH<sub>Ph</sub>, 1C), 142.8 (s, C<sub>Ar(2)</sub>, 1C), 145.1 (s, C<sub>Ar(9)</sub>, 1C), 176.3 (dd, <sup>2</sup>J<sub>PC</sub> = 21.5, <sup>2</sup>J<sub>FC</sub> = 3.3, CO<sub>2</sub>, 1C).

2-Fluoro-3-(2-methylimidazo[1,2-a]pyridin-3-yl)-2-phosphonopropanoic acid (**1b**).

Yield: 78%, scale: 0.093 g. **Elemental analysis:** C<sub>11</sub>H<sub>12</sub>FN<sub>2</sub>O<sub>5</sub>P (H<sub>2</sub>O)<sub>2</sub>, Calculated:

C: 39.06, H: 4.77; N: 8.28, Found: C: 38.70; H: 4.75; N: 8.11, **<sup>1</sup>H NMR** (700 MHz, D<sub>2</sub>O pH 7) δ: 2.44 (s, CH<sub>3</sub>, 3H), 3.65 (ddd, <sup>2</sup>J<sub>HH</sub> = 16.0, <sup>3</sup>J<sub>PH</sub> = 7.8, <sup>3</sup>J<sub>FH</sub> = 5.3, CH<sub>2</sub>CPF, 1H), 3.96 (dd, <sup>3</sup>J<sub>FH</sub> = 39.9, <sup>2</sup>J<sub>HH</sub> = 16.0, <sup>3</sup>J<sub>FH</sub> = 1.4, CH<sub>2</sub>CPF, 1H), 7.12 (td, <sup>3</sup>J<sub>HH</sub> = 6.9, <sup>4</sup>J<sub>HH</sub> = 1.3, CH<sub>Ar(6)</sub>, 1H), 7.50-7.56 (m, CH<sub>Ar(8,7)</sub>, 2H), 8.54 (d, <sup>3</sup>J<sub>HH</sub> = 6.9, CH<sub>Ar(5)</sub>, 1H), **<sup>31</sup>P NMR** (283 MHz, D<sub>2</sub>O pH 7) δ: 10.51 (d, <sup>2</sup>J<sub>PF</sub> = 71.6), **<sup>13</sup>C NMR** (176 MHz, D<sub>2</sub>O) δ: 11.3 (s, CH<sub>3</sub>, 1C), 28.7 (d, <sup>2</sup>J<sub>FC</sub> = 21.1, <sup>2</sup>J<sub>PC</sub> = 2.8, CH<sub>2</sub>CPF, 1C), 100.0 (dd, <sup>1</sup>J<sub>FC</sub> = 190.9, <sup>1</sup>J<sub>PC</sub> = 140.4, CH<sub>2</sub>CPF, 1C), 113.0 (s, CH<sub>Ar(8)</sub>, 1C), 113.6 (s, CH<sub>Ar(6)</sub>, 1C), 118.1 (d, <sup>3</sup>J<sub>PC</sub> = 13.4, <sup>3</sup>J<sub>FC</sub> = 2.4, C<sub>Ar(3)</sub>, 1C), 126.2 (s, CH<sub>Ar(5)</sub>, <sup>5</sup>J<sub>PC</sub> = 6.0, 1C), 128.2 (s, CH<sub>Ar(7)</sub>, 1C), 136.9 (s, C<sub>Ar(2)</sub>, 1C), 142.3 (s, C<sub>Ar(9)</sub>, 1C), 176.3 (dd, <sup>2</sup>J<sub>PC</sub> = 21.1, <sup>2</sup>J<sub>FC</sub> = 3.3, CO<sub>2</sub>, 1C).

3-(6-Bromo-2-methylimidazo[1,2-a]pyridin-3-yl)-2-fluoro-2-phosphonopropanoic

acid (**1c**). Yield: 73%, scale: 0.156 g. **Elemental analysis:** C<sub>11</sub>H<sub>11</sub>BrFN<sub>2</sub>O<sub>5</sub>P

(H<sub>2</sub>O)<sub>1.75</sub>, Calculated: C: 32.02, H: 3.54; N: 6.79, Found: C: 32.17; H: 3.7; N: 6.72. **<sup>1</sup>H**

**NMR** (700 MHz, D<sub>2</sub>O pH 7) δ: 2.40 (s, CH<sub>3</sub>, 3H), 3.59 (ddd, <sup>2</sup>J<sub>HH</sub> = 15.9, <sup>3</sup>J<sub>PH</sub> = 7.5,

<sup>3</sup>J<sub>FH</sub> = 5.3, CH<sub>2</sub>CPF, 1H), 3.93 (dd, <sup>3</sup>J<sub>FH</sub> = 40.7, <sup>2</sup>J<sub>HH</sub> = 15.9, CH<sub>2</sub>CPF, 1H), 7.39 (s,

CH<sub>Ar(8,7)</sub>, 1H), 8.70 (bs, CH<sub>Ar(5)</sub>, 1H), **<sup>31</sup>P NMR** (283 MHz, D<sub>2</sub>O pH 7) δ: 10.65 (d, <sup>2</sup>J<sub>PF</sub>

= 72.1), **<sup>13</sup>C NMR** (176 MHz, D<sub>2</sub>O): 12.5 (s, 1C), 28.7 (d, <sup>2</sup>J<sub>FC</sub> = 21.1, CH<sub>2</sub>CPF, 1C),

100.4 (dd, <sup>1</sup>J<sub>FC</sub> = 190.7, <sup>1</sup>J<sub>PC</sub> = 139.2, CH<sub>2</sub>CPF, 1C), 106.2 (s, CH<sub>Ar(6)</sub>, 1C), 115.2 (s,

CH<sub>Ar(8)</sub>, 1C), 118.2 (d, <sup>3</sup>J<sub>PC</sub> = 12.1, C<sub>Ar(3)</sub>, 1C), 125.8 (s, CH<sub>Ar(5)</sub>, 1C), 128.3 (s,

CH<sub>Ar(7)</sub>, 1C), 141.5 (s, C<sub>Ar(2)</sub>, 1C), 143.1 (s, C<sub>Ar(9)</sub>, 1C), 176.5 (bd, <sup>2</sup>J<sub>PC</sub> = 19.6, CO<sub>2</sub>,

1C).

2-Fluoro-3-(5-methylimidazo[1,2-a]pyridin-3-yl)-2-phosphonopropanoic acid (**1e**).

Yield: 56%, scale: 0.1 g; crystalized from H<sub>2</sub>O; **<sup>1</sup>H NMR** (700 MHz, D<sub>2</sub>O pH 7) δ:

3.04 (s, C<sub>Ar(5)</sub>, CH<sub>3</sub>, 3H), 4.24–4.09 (m, CH<sub>2</sub>CFP, 2H), 6.98 (d, <sup>3</sup>J<sub>HH</sub> = 6.9, CH<sub>Ar(6)</sub>, 1H), 7.49 (dd, <sup>3</sup>J<sub>HH</sub> = 8.8, 6.9, CH<sub>Ar(7)</sub>, 1H), 7.55 (d, <sup>3</sup>J<sub>HH</sub> = 8.8, CH<sub>Ar(8)</sub>, 1H), 7.63 (s, CH<sub>Ar(2)</sub>, 1H); <sup>13</sup>C NMR (700 MHz, D<sub>2</sub>O pH 7) δ: 20.9 (s, CH<sub>3</sub>, 1C), 31.6 (d, <sup>2</sup>J<sub>FC</sub> = 18.5, CH<sub>2</sub>CFP, 1C), 99.9 (dd, <sup>1</sup>J<sub>FC</sub> = 192.5, <sup>1</sup>J<sub>PC</sub> = 140.1, CFP, 1C), 112.1 (s, CH<sub>Ar(8)</sub>, 1C), 116.4 (s, CH<sub>Ar(6)</sub>, 1C), 124.4 (d, <sup>3</sup>J<sub>PC</sub> = 15.9, C<sub>Ar(3)</sub>, 1C), 126.6 (s, CH<sub>Ar(2)</sub>, 1C), 129.7 (s, CH<sub>Ar(7)</sub>, 1C), 139.8 (s, C<sub>Ar(5)</sub>, 1C), 144.6 (s, CH<sub>Ar(9)</sub>, 1C), 176.2 (d, <sup>2</sup>J<sub>FC</sub> = 21.1, CO<sub>2</sub>, 1C); <sup>31</sup>P NMR (283 MHz, D<sub>2</sub>O pH 7) δ: 10.81 (d, <sup>2</sup>J<sub>PF</sub> = 72.2)

*2-Fluoro-3-(6-phenylimidazo[1,2-a]pyridin-3-yl)-2-phosphonopropanoic acid (1f).*

Yield: 88%, scale: 0.06 g. **Elemental analysis:** C<sub>16</sub>H<sub>14</sub>FN<sub>2</sub>O<sub>5</sub>P (H<sub>2</sub>O)<sub>2</sub>, Calculated: C: 48.01, H: 4.53; N: 7.00, Found: C: 47.86; H: 4.60; N: 6.99. <sup>1</sup>H NMR (700 MHz, D<sub>2</sub>O pH 8) δ: 3.55–3.73 (m, CH<sub>2</sub>CPF, 1H), 3.98 (ddd, <sup>3</sup>J<sub>FH</sub> = 42.1, <sup>2</sup>J<sub>HH</sub> = 16.1, <sup>3</sup>J<sub>PH</sub> = 1.4, CH<sub>2</sub>CPF, 1H), 7.48–7.52 (m, CH<sub>Ar(2)</sub>, CH<sub>Ph</sub>, 2H), 7.57–7.61 (m, CH<sub>Ph</sub>, 2H), 7.64 (dd, <sup>3</sup>J<sub>HH</sub> = 9.3, <sup>5</sup>J<sub>HH</sub> = 0.6, CH<sub>Ar(8)</sub>, 1H), 7.68 (dd, <sup>3</sup>J<sub>HH</sub> = 9.3, <sup>4</sup>J<sub>HH</sub> = 1.7, CH<sub>Ar(7)</sub>, 1H), 7.81 (dd, <sup>3</sup>J<sub>HH</sub> = 8.2, <sup>4</sup>J<sub>HH</sub> = 1.0, CH<sub>Ph</sub>, 2H), 8.73 (bs, CH<sub>Ar(5)</sub>, 1H), <sup>31</sup>P NMR (283 MHz, D<sub>2</sub>O pH 8) δ: 10.26 (d, <sup>2</sup>J<sub>PF</sub> = 70.4), <sup>13</sup>C NMR (176 MHz, D<sub>2</sub>O): 29.2 (d, <sup>2</sup>J<sub>FC</sub> = 23.3, CH<sub>2</sub>CPF, 1C), 100.9 (dd, <sup>1</sup>J<sub>FC</sub> = 190.5, <sup>1</sup>J<sub>PC</sub> = 137.8, CH<sub>2</sub>CPF, 1C), 115.7 (s, CH<sub>Ar(8)</sub>, 1C), 122.5 (d, <sup>3</sup>J<sub>PC</sub> = 15.3, C<sub>Ar(3)</sub>, 1C), 122.7 (bs, CH<sub>Ar(5)</sub>, 1C), 125.8 (s, CH<sub>Ar(6)</sub>, 1C), 126.2 (s, CH<sub>Ar(7)</sub>, 1C), 127.1 (s, CH<sub>Ph</sub>, 2C), 127.9 (s, CH<sub>Ph</sub>, 1C), 129.2 (s, CH<sub>Ph</sub>, 2C), 131.5 (s, C<sub>Ar(2)</sub>, 1C), 137.2 (s, C<sub>Ph</sub>, 1C), 144.9 (s, C<sub>Ar(9)</sub>, 1C), 176.7 (dd, <sup>2</sup>J<sub>PC</sub> = 20.0, <sup>2</sup>J<sub>FC</sub> = 3.3, CO<sub>2</sub>, 1C).

*2-Fluoro-3-(6-methylimidazo[1,2-a]pyridin-3-yl)-2-phosphonopropanoic acid (1g).*

Yield: 64%, crystalized H<sub>2</sub>O. **Elemental analysis:** C<sub>11</sub>H<sub>12</sub>FN<sub>2</sub>O<sub>5</sub>P Calculated: C: 43.72; H: 4.00; N: 9.27. Found: C: 43.46; H: 4.08; N: 9.05. <sup>1</sup>H NMR (700 MHz, D<sub>2</sub>O pH 7) δ: 2.46 (s, CH<sub>3</sub>, 3H), 3.68 (dt, <sup>2</sup>J<sub>HH</sub> = 15.9, <sup>3</sup>J<sub>FH</sub> = 6.9, CHHCFFP, 1H), 3.95 (ddd, <sup>3</sup>J<sub>FH</sub> = 40.0, <sup>2</sup>J<sub>HH</sub> = 16.1, <sup>3</sup>J<sub>PH</sub> = 2.1, CHHCFFP, 1 H), 7.60 (s, CH<sub>Ar(2)</sub>, 1H), 7.63–7.66



(m,  $\text{CH}_{\text{Ar}(7)}$ ,  $\text{CH}_{\text{Ar}(8)}$ , 2H), 8.50 (s,  $\text{CH}_{\text{Ar}(5)}$ , 1H);  $^{13}\text{C}$  NMR (176 MHz,  $\text{D}_2\text{O}$  pH 7)  $\delta$ : 17.4 (s,  $\text{CH}_3$ , 1C), 29.0 (d,  $^2J_{\text{FC}} = 20.6$ ,  $\text{CH}_2\text{CFP}$ , 1C), 99.9 (dd,  $^1J_{\text{FC}} = 191.4$ ,  $^1J_{\text{PC}} = 141.0$ ,  $\text{CH}_2\text{CFP}$ , 1C), 112.1 (s,  $\text{CH}_{\text{Ar}(8)}$ , 1C), 122.6 (d,  $^3J_{\text{PC}} = 14.8$ ,  $\text{C}_{\text{Ar}(3)}$ , 1C), 123.0 (s,  $\text{CH}_{\text{Ar}(2)}$ , 1C), 124.3 (s,  $\text{CH}_{\text{Ar}(5)}$ , 1C), 126.4 (s,  $\text{C}_{\text{Ar}(6)}$ , 1C), 134.2 (s,  $\text{CH}_{\text{Ar}(7)}$ , 1C), 140.2 (s,  $\text{C}_{\text{Ar}(9)}$ , 1C), 175.8 (d,  $^2J_{\text{FC}} = 19.9$ ,  $\text{CO}_2\text{H}$ , 1C);  $^{31}\text{P}$  NMR (283 MHz,  $\text{D}_2\text{O}$  pH 7)  $\delta$ : 10.04 (d,  $^2J_{\text{PF}} = 71.7$ ); **HRMS**  $m/z$  Calculated: 303.0475 ( $\text{M} + \text{H}$ ) $^+$ , Found: 303.0547 ( $\text{M} + \text{H}$ ) $^+$ .

*3-(6-Chloroimidazo[1,2-a]pyridin-3-yl)-2-fluoro-2-phosphonopropanoic acid (1h).*

Yield: 55%, scale: 0.09 g. **Elemental analysis:**  $\text{C}_{10}\text{H}_9\text{ClFN}_2\text{O}_5\text{P} (\text{H}_2\text{O})_{0.3}$ , Calculated: C: 36.62, H: 2.95; N: 8.54, Found: C: 36.88; H: 2.96; N: 8.27.  $^1\text{H}$  NMR (250 MHz,  $\text{D}_2\text{O}$  pH 8)  $\delta$ : 3.60 (dt,  $^2J_{\text{HH}} = 15.9$ ,  $^3J_{\text{PH}} = 15.9$ ,  $^3J_{\text{FH}} = 6.6$ ,  $\text{CH}_2\text{CPF}$ , 1H), 3.90 (ddd,  $^3J_{\text{FH}} = 41.9$ ,  $^2J_{\text{HH}} = 15.9$ ,  $^3J_{\text{PH}} = 1.5$ ,  $\text{CH}_2\text{CPF}$ , 1H), 7.35 (d,  $^3J_{\text{HH}} = 9.5$ ,  $^4J_{\text{HH}} = 2.0$ ,  $\text{CH}_{\text{Ar}(7)}$ , 1H), 7.48 (s,  $\text{CH}_{\text{Ar}(2)}$ , 1H), 7.53 (d,  $^3J_{\text{HH}} = 9.5$ ,  $^4J_{\text{HH}} = 0.6$ ,  $\text{CH}_{\text{Ar}(8)}$ , 1H), 8.64 (bs,  $\text{CH}_{\text{Ar}(5)}$ , 1H),  $^{31}\text{P}$  NMR (283 MHz,  $\text{D}_2\text{O}$  pH 8)  $\delta$ : 10.15 (d,  $^2J_{\text{PF}} = 70.1$ ),  $^{13}\text{C}$  NMR (176 MHz,  $\text{D}_2\text{O}$ ): 29.00-29.3 (m,  $\text{CH}_2\text{CPF}$ , 1C), 100.9 (dd,  $^1J_{\text{FC}} = 190.1$ ,  $^1J_{\text{PC}} = 137.9$ ,  $\text{CH}_2\text{CPF}$ , 1C), 116.3 (s,  $\text{CH}_{\text{Ar}(8)}$ , 1C), 120.3 (s,  $\text{CH}_{\text{Ar}(6)}$ , 1C), 122.6 (d,  $^3J_{\text{PC}} = 12.2$ ,  $\text{C}_{\text{Ar}(3)}$ , 1C), 123.5 (d,  $^5J_{\text{PC}} = 6.6$ ,  $\text{CH}_{\text{Ar}(5)}$ , 1C), 126.5 (s,  $\text{CH}_{\text{Ar}(7)}$ , 1C), 131.9 (d,  $^5J_{\text{PC}} = 5.2$ ,  $\text{C}_{\text{Ar}(2)}$ , 1C), 144.0 (s,  $\text{C}_{\text{Ar}(9)}$ , 1C), 176.5 (dd,  $^2J_{\text{PC}} = 20.8$ ,  $^2J_{\text{FC}} = 3.5$ ,  $\text{CO}_2$ , 1C).

*3-(6-Bromoimidazo[1,2-a]pyridin-3-yl)-2-fluoro-2-phosphonopropanoic acid (1i).*

Yield: 60%, scale: 0.056 g. **Elemental analysis:**  $\text{C}_{10}\text{H}_9\text{BrFN}_2\text{O}_5\text{P} (\text{H}_2\text{O})_{1.15}$ , Calculated: C: 30.97, H: 2.94; N: 7.22, Found: C: 31.25; H: 3.2; N: 7.05.  $^1\text{H}$  NMR (700 MHz,  $\text{D}_2\text{O}$  pH 7)  $\delta$ : 3.70 (m,  $\text{CH}_2\text{CPF}$ , 1H), 3.78 (ddd,  $^3J_{\text{FH}} = 38.9$ ,  $^2J_{\text{HH}} = 16.2$ ,  $^3J_{\text{PH}} = 3.20$ ,  $\text{CH}_2\text{CPF}$ , 1H), 7.73 (s,  $\text{CH}_{\text{Ar}(2)}$ , 1H), 7.74 (d,  $^3J_{\text{HH}} = 9.6$ ,  $\text{CH}_{\text{Ar}(7)}$ , 1H), 7.90 (bd,  $^3J_{\text{HH}} = 9.6$ ,  $\text{CH}_{\text{Ar}(8)}$ , 1H), 8.96 (bs,  $\text{CH}_{\text{Ar}(5)}$ , 1H),  $^{31}\text{P}$  NMR (283 MHz,  $\text{D}_2\text{O}$  pH 7)  $\delta$ : 10.14 (d,  $^2J_{\text{PF}} = 71.8$ ),  $^{13}\text{C}$  NMR (176 MHz,  $\text{D}_2\text{O}$ ): 28.3 (d,  $^2J_{\text{FC}} = 20.9$ ,  $\text{CH}_2\text{CPF}$ ,

1C), 98.3 (dd,  $^1J_{FC} = 192.8$ ,  $^1J_{PC} = 147.7$ ,  $\text{CH}_2\text{CPF}$ , 1C), 110.4 (s,  $\text{CH}_{\text{Ar}(6)}$ , 1C), 113.5 (s,  $\text{CH}_{\text{Ar}(8)}$ , 1C), 122.6 (d,  $^3J_{PC} = 15.4$ ,  $\text{C}_{\text{Ar}(3)}$ , 1C), 123.6 (s,  $\text{CH}_{\text{Ar}(5)}$ , 1C), 126.9 (s,  $\text{CH}_{\text{Ar}(7)}$ , 1C), 134.7 (s,  $\text{C}_{\text{Ar}(2)}$ , 1C), 139.7 (s,  $\text{C}_{\text{Ar}(9)}$ , 1C), 173.9 (d,  $^2J_{PC} = 20.1$ ,  $\text{CO}_2$ , 1C).

*2-Fluoro-3-(7-phenylimidazo[1,2-a]pyridin-3-yl)-2-phosphonopropanoic acid (1j).*

Yield: 64%, scale: 0.07 g.  $^1\text{H NMR}$  (700 MHz,  $\text{D}_2\text{O}$  pH 8)  $\delta$ : 3.55-3.73 (m,  $\text{CH}_2\text{CPF}$ , 1H), 3.97 (ddd,  $^3J_{\text{FH}} = 40.6$ ,  $^2J_{\text{HH}} = 16.2$ ,  $^3J_{\text{PH}} = 1.8$ ,  $\text{CH}_2\text{CPF}$ , 1H), 7.46 (dd,  $^3J_{\text{HH}} = 7.2$ ,  $^5J_{\text{HH}} = 1.7$ ,  $\text{CH}_{\text{Ar}(6)}$ , 1H), 7.48-7.56 (m,  $\text{CH}_{\text{Ph}}$ , 3H), 7.57 (s,  $\text{CH}_{\text{Ar}(2)}$ , 1H), 7.75 (dd,  $^3J_{\text{HH}} = 7.3$ ,  $\text{CH}_{\text{Ph}}$ , 1H), 7.80 (s,  $\text{CH}_{\text{Ar}(8)}$ , 1H), 8.56 (dd,  $^3J_{\text{HH}} = 7.2$ ,  $\text{CH}_{\text{Ar}(5)}$ , 2H),  $^{31}\text{P NMR}$  (283 MHz,  $\text{D}_2\text{O}$  pH 8)  $\delta$ : 10.66 (d,  $^2J_{\text{PF}} = 71.4$ ),  $^{13}\text{C NMR}$  (176 MHz,  $\text{D}_2\text{O}$ ): 28.9 (d,  $^2J_{\text{FC}} = 21.2$ ,  $^2J_{\text{PC}} = 2.2$ ,  $\text{CH}_2\text{CPF}$ , 1C), 100.0 (dd,  $^1J_{\text{FC}} = 191.3$ ,  $^1J_{\text{PC}} = 140.2$ ,  $\text{CH}_2\text{CPF}$ , 1C), 110.1 (s,  $\text{CH}_{\text{Ar}(8)}$ , 1C), 113.7 (s,  $\text{CH}_{\text{Ar}(6)}$ , 1C), 122.2 (d,  $^3J_{\text{PC}} = 14.2$ ,  $^3J_{\text{FC}} = 1.8$ ,  $\text{C}_{\text{Ar}(3)}$ , 1C), 126.06 (s,  $^5J_{\text{PC}} = 3.8$ ,  $\text{CH}_{\text{Ar}(5)}$ , 1C), 126.10 (s,  $\text{CH}_{\text{Ar}(2)}$ , 1C), 126.8 (s,  $\text{CH}_{\text{Ph}}$ , 2C), 128.9 (s,  $\text{CH}_{\text{Ph}}$ , 1C), 129.2 (s,  $\text{CH}_{\text{Ph}}$ , 2C), 136.8 (s,  $\text{CH}_{\text{Ph}}$ , 1C), 140.9 (s,  $\text{CH}_{\text{Ar}(7)}$ , 1C), 143.1 (s,  $\text{C}_{\text{Ar}(9)}$ , 1C), 175.8 (dd,  $^2J_{\text{PC}} = 20.8$ ,  $^2J_{\text{FC}} = 3.2$ ,  $\text{CO}_2$ , 1C).

*2-Fluoro-3-(7-methylimidazo[1,2-a]pyridin-3-yl)-2-phosphonopropanoic acid (1k).*

Yield: 82%, crystalized from  $\text{H}_2\text{O}$ .  $^1\text{H NMR}$  (700 MHz,  $\text{D}_2\text{O}$  pH 8)  $\delta$ : 2.43 (d,  $^4J_{\text{HH}} = 0.8$ ,  $\text{CH}_3$ , 3H), 3.60 (dt,  $^2J_{\text{HH}} = 16.0$ ,  $^3J_{\text{FH/PH}} = 6.6$ ,  $\text{CHHCFFP}$ , 1H), 3.89 (ddd,  $^3J_{\text{FH}} = 41.9$ ,  $^2J_{\text{HH}} = 16.0$ ,  $^3J_{\text{PH}} = 1.4$ ,  $\text{CHHCFFP}$ , 1 H), 6.89 (dd,  $^3J_{\text{HH}} = 7.1$ ,  $^4J_{\text{HH}} = 1.6$ ,  $\text{CH}_{\text{Ar}(6)}$ , 1H), 7.34-7.31 (m,  $\text{CH}_{\text{Ar}(8)}$ , 1H), 7.36 (s,  $\text{CH}_{\text{Ar}(7)}$ , 1H), 8.34 (d,  $^3J_{\text{HH}} = 7.1$ ,  $\text{CH}_{\text{Ar}(5)}$ , 1H);  $^{13}\text{C NMR}$  (176 MHz,  $\text{D}_2\text{O}$  pH 8)  $\delta$ : 20.5 (s,  $\text{CH}_3$ , 1C), 29.3 (d,  $^2J_{\text{FC}} = 21.4$ ,  $\text{CH}_2\text{CFP}$ , 1C), 101.1 (dd,  $^1J_{\text{FC}} = 190.2$ ,  $^1J_{\text{PC}} = 138.2$ ,  $\text{CH}_2\text{CFP}$ , 1C), 114.1 (s,  $\text{CH}_{\text{Ar}(8)}$ , 1C), 115.3 (s,  $\text{CH}_{\text{Ar}(6)}$ , 1C), 121.5 (d,  $^3J_{\text{PC}} = 14.1$ ,  $\text{C}_{\text{Ar}(3)}$ , 1C), 124.8 (d,  $^5J_{\text{FC}} = 4.5$ ,  $\text{CH}_{\text{Ar}(5)}$ , 1C), 130.5 (s,  $\text{CH}_{\text{Ar}(2)}$ , 1C), 137.5 (s,  $\text{C}_{\text{Ar}(7)}$ , 1C), 146.3 (s,  $\text{C}_{\text{Ar}(9)}$ , 1C), 176.9

(dd,  $^2J_{\text{FC}} = 20.7$ ,  $^2J_{\text{PC}} = 3.3$ ,  $\underline{\text{C}}\text{O}_2$ , 1C);  $^{13}\text{P}$  NMR (283 MHz,  $\text{D}_2\text{O}$  pH 8)  $\delta$ : 10.31 (d,  $^2J_{\text{PF}} = 70.6$ ).

*3-(7-Chloroimidazo[1,2-a]pyridin-3-yl)-2-fluoro-2-phosphonopropanoic acid (1l).*

Yield: 59%, scale: 0.073 g. **Elemental analysis:**  $\text{C}_{10}\text{H}_9\text{ClFN}_2\text{O}_5\text{P}$ , Calculated: C: 37.23, H: 2.81; N: 8.68, Found: C: 37.05; H: 3.05; N: 8.50.  $^1\text{H}$  NMR (250 MHz,  $\text{D}_2\text{O}$  pH 8)  $\delta$ : 3.38–3.62 (m,  $\underline{\text{CH}}_2\text{CPF}$ , 1H), 3.62–3.99 (m,  $\underline{\text{CH}}_2\text{CPF}$ , 1H), 6.97 (dd,  $^3J_{\text{HH}} = 7.5$ ,  $^4J_{\text{HH}} = 1.7$ ,  $\text{CH}_{\text{Ar}(6)}$ , 1H), 7.38 (s,  $\text{CH}_{\text{Ar}(2)}$ , 1H), 7.56 (d,  $^4J_{\text{HH}} = 1.7$ ,  $\text{CH}_{\text{Ar}(8)}$ , 1H), 8.37 (d,  $^3J_{\text{HH}} = 7.5$ ,  $\text{CH}_{\text{Ar}(5)}$ , 1H),  $^{31}\text{P}$  NMR (101 MHz,  $\text{D}_2\text{O}$  pH 8)  $\delta$ : 10.85 (d,  $^2J_{\text{PF}} = 70.3$ ).

*3-(7-Bromoimidazo[1,2-a]pyridin-3-yl)-2-fluoro-2-phosphonopropanoic acid (1m).*

Yield: 61%, scale: 0.08 g. **Elemental analysis:**  $\text{C}_{10}\text{H}_9\text{BrFN}_2\text{O}_5\text{P}$ , Calculated: C: 32.72, H: 2.47; N: 7.63, Found: C: 32.54; H: 2.67; N: 7.59.  $^1\text{H}$  NMR (250 MHz,  $\text{D}_2\text{O}$  pH 8)  $\delta$ : 3.61 (dt,  $^2J_{\text{HH}} = 16.0$ ,  $^3J_{\text{PH}} = 16.0$ ,  $^3J_{\text{FH}} = 6.6$ ,  $\underline{\text{CH}}_2\text{CPF}$ , 1H), 3.90 (ddd,  $^3J_{\text{FH}} = 41.8$ ,  $^2J_{\text{HH}} = 16.0$ ,  $^3J_{\text{PH}} = 1.4$ ,  $\underline{\text{CH}}_2\text{CPF}$ , 1H), 7.14 (dd,  $^3J_{\text{HH}} = 7.3$ ,  $^4J_{\text{HH}} = 1.9$ ,  $\text{CH}_{\text{Ar}(6)}$ , 1H), 7.44 (s,  $\text{CH}_{\text{Ar}(2)}$ , 1H), 7.81 (bs,  $\text{CH}_{\text{Ar}(8)}$ , 1H), 8.38 (d,  $^3J_{\text{HH}} = 7.3$ ,  $\text{CH}_{\text{Ar}(5)}$ , 1H),  $^{31}\text{P}$  NMR (283 MHz,  $\text{D}_2\text{O}$  pH 8)  $\delta$ : 10.14 (d,  $^2J_{\text{PF}} = 70.5$ ),  $^{13}\text{C}$  NMR (176 MHz,  $\text{D}_2\text{O}$ ): 29.1 (d,  $^2J_{\text{FC}} = 21.6$ ,  $\underline{\text{CH}}_2\text{CPF}$ , 1C), 100.8 (dd,  $^1J_{\text{FC}} = 190.4$ ,  $^1J_{\text{PC}} = 138.1$ ,  $\text{CH}_2\underline{\text{C}}\text{PF}$ , 1C), 116.0 (s,  $\text{CH}_{\text{Ar}(6)}$ , 1C), 118.0 (s,  $\text{CH}_{\text{Ar}(8)}$ , 1C), 119.0 (s,  $\text{CH}_{\text{Ar}(7)}$ , 1C), 122.4 (d,  $^3J_{\text{PC}} = 14.0$ ,  $\text{C}_{\text{Ar}(3)}$ , 1C), 126.0 (s,  $\text{CH}_{\text{Ar}(5)}$ , 1C), 131.5 (s,  $\text{C}_{\text{Ar}(2)}$ , 1C), 145.6 (s,  $\text{C}_{\text{Ar}(9)}$ , 1C), 176.5 (d,  $^2J_{\text{PC}} = 20.8$ ,  $^2J_{\text{FC}} = 3.3$ ,  $\underline{\text{C}}\text{O}_2$ , 1C).

*2-Fluoro-3-(8-phenylimidazo[1,2-a]pyridin-3-yl)-2-phosphonopropanoic acid (1n).*

Yield: 52%, scale: 0.08 g. **Elemental analysis:**  $\text{C}_{16}\text{H}_{14}\text{FN}_2\text{O}_5\text{P}$  ( $\text{H}_2\text{O}$ )<sub>1.65</sub>, Calculated: C: 48.78, H: 4.43; N: 7.11, Found: C: 48.58; H: 4.18; N: 7.05.  $^1\text{H}$  NMR (700 MHz,  $\text{D}_2\text{O}$  pH 8)  $\delta$ : 3.75 (m,  $\underline{\text{CH}}_2\text{CPF}$ , 1H), 4.01 (ddd,  $^3J_{\text{FH}} = 39.8$ ,  $^2J_{\text{HH}} = 16.0$ ,  $^3J_{\text{PH}} = 1.6$ ,  $\underline{\text{CH}}_2\text{CPF}$ , 1H), 7.37 (t,  $^3J_{\text{HH}} = 7.0$ ,  $\underline{\text{CH}}_{\text{Ar}(6)}$ , 1H), 7.59 (m,  $\underline{\text{CH}}_{\text{Ar}}$ , 3H), 7.64 (s,  $\text{CH}_{\text{Ar}(2)}$ ,

1H), 7.68 (d,  $^3J_{\text{HH}} = 7.0$ ,  $\underline{\text{CH}}_{\text{Ar}(7)}$ , 1H), 7.71 (d,  $^3J_{\text{HH}} = 7.2$ ,  $\text{CH}_{\text{Ph}}$ , 2H), 8.61 (d,  $^3J_{\text{HH}} = 7.0$ ,  $\text{CH}_{\text{Ar}(5)}$ , 1H),  $^{31}\text{P}$  NMR (283 MHz,  $\text{D}_2\text{O}$  pH 8)  $\delta$ : 10.11 (d,  $^2J_{\text{PF}} = 74.4$ ),  $^{13}\text{C}$  NMR (176 MHz,  $\text{D}_2\text{O}$ ): 28.8 (d,  $^2J_{\text{FC}} = 21.7$ ,  $\underline{\text{CH}}_2\text{CPF}$ , 1C), 99.1 (dd,  $^1J_{\text{FC}} = 192.5$ ,  $^1J_{\text{PC}} = 143.6$ ,  $\text{CH}_2\underline{\text{C}}\text{PF}$ , 1C), 115.4 (s,  $\text{CH}_{\text{Ar}(6)}$ , 1C), 122.8 (d,  $^3J_{\text{PC}} = 15.3$ ,  $\text{C}_{\text{Ar}(3)}$ , 1C), 125.0 (s,  $\text{C}_{\text{Ar}(2)}$ , 1C), 125.2 (d,  $^5J_{\text{PC}} = 4.4$ ,  $\text{CH}_{\text{Ar}(5)}$ , 1C), 127.5 (s,  $\text{CH}_{\text{Ar}(8)}$ , 1C), 128.6 (s,  $\text{CH}_{\text{Ph}}$ , 2C), 129.1 (s,  $\text{CH}_{\text{Ar}(7)}$ , 1C), 129.1 (s,  $\text{CH}_{\text{Ph}}$ , 2C), 129.3 (s,  $\text{CH}_{\text{Ph}}$ , 1C), 134.4 (s,  $\text{CH}_{\text{Ph}}$ , 1C), 141.0 (s,  $\text{C}_{\text{Ar}(9)}$ , 1C), 174.9 (bd,  $^2J_{\text{PC}} = 20.0$ ,  $\underline{\text{C}}\text{O}_2$ , 1C).

*2-Fluoro-3-(8-methylimidazo[1,2-a]pyridin-3-yl)-2-phosphonopropanoic acid (1o).*

Yield: 82%, crystalized from  $\text{H}_2\text{O}$ . **Elemental analysis:**  $\text{C}_{11}\text{H}_{12}\text{FN}_2\text{O}_5\text{P}$ , Calculated: C: 43.72, H: 4.00; N: 9.27, Found: C: 43.45; H: 4.06; N: 9.15.  $^1\text{H}$  NMR (700 MHz,  $\text{D}_2\text{O}$  pH 8)  $\delta$ : 2.56 (s,  $\underline{\text{CH}}_3$ , 3H), 3.67 (dt,  $^2J_{\text{HH}} = 16.0$ ,  $^3J_{\text{FH/PH}} = 6.8$ ,  $\underline{\text{CH}}\text{HCFP}$ , 1H), 3.84 (ddd,  $^3J_{\text{FH}} = 40.7$ ,  $^2J_{\text{HH}} = 16.2$ ,  $^3J_{\text{PH}} = 1.9$ ,  $\underline{\text{CH}}\text{HCFP}$ , 1 H), 7.16 (t,  $^3J_{\text{HH}} = 7.0$ ,  $\underline{\text{CH}}_{\text{Ar}(6)}$ , 1H), 7.44 (d,  $^3J_{\text{HH}} = 7.0$ ,  $\underline{\text{CH}}_{\text{Ar}(7)}$ , 1H), 7.59 (s,  $\underline{\text{CH}}_{\text{Ar}(2)}$ , 1H), 8.45 (d,  $^3J_{\text{HH}} = 6.9$ ,  $\underline{\text{CH}}_{\text{Ar}(5)}$ , 1H);  $^{13}\text{C}$  NMR (176 MHz,  $\text{D}_2\text{O}$  pH 8)  $\delta$ : 15.8 (s,  $\underline{\text{CH}}_3$ , 1C), 29.2 (d,  $^2J_{\text{FC}} = 18.3$ ,  $\underline{\text{CH}}_2\text{CFP}$ , 1C), 100.1 (dd,  $^1J_{\text{FC}} = 191.4$ ,  $^1J_{\text{CP}} = 140.3$ ,  $\text{CH}_2\underline{\text{C}}\text{FP}$ , 1C), 114.9 (s,  $\underline{\text{CH}}_{\text{Ar}(6)}$ , 1C), 123.0 (d,  $^3J_{\text{PC}} = 13.0$ ,  $\underline{\text{C}}_{\text{Ar}(3)}$ , 1C), 124.0 (d,  $^5J_{\text{FC}} = 4.3$ ,  $\underline{\text{CH}}_{\text{Ar}(5)}$ , 1C), 124.3 (s,  $\underline{\text{C}}_{\text{Ar}(8)}$ , 1C), 125.3 (s,  $\underline{\text{CH}}_{\text{Ar}(7)}$ , 1C), 128.5 (s,  $\underline{\text{CH}}_{\text{Ar}(2)}$ , 1C), 143.1 (s,  $\underline{\text{C}}_{\text{Ar}(9)}$ , 1C), 176.0 (dd,  $^2J_{\text{FC}} = 20.6$ ,  $^2J_{\text{PC}} = 3.1$ ,  $\underline{\text{C}}\text{O}_2$ , 1C);  $^{31}\text{P}$  NMR (283 MHz,  $\text{D}_2\text{O}$  pH 7)  $\delta$ : 11.00 (d,  $^2J_{\text{PF}} = 70.5$ ).

*3-(8-Bromoimidazo[1,2-a]pyridin-3-yl)-2-fluoro-2-phosphonopropanoic acid (1p).*

Yield: 79%, scale: 0.1 g. **Elemental analysis:**  $\text{C}_{10}\text{H}_9\text{BrFN}_2\text{O}_5\text{P}$  ( $\text{H}_2\text{O}$ )<sub>2</sub>, Calculated: C: 29.80, H: 3.25; N: 6.95, Found: C: 29.71; H: 3.26; N: 6.94.  $^1\text{H}$  NMR (250 MHz,  $\text{D}_2\text{O}$  pH 7)  $\delta$ : 3.62 – 3.73 (m,  $\underline{\text{CH}}_2\text{CPF}$ , 1H), 3.93 (ddd,  $^3J_{\text{FH}} = 40.1$ ,  $^2J_{\text{HH}} = 16.1$ ,  $^3J_{\text{PH}} = 2.70$ ,  $\underline{\text{CH}}_2\text{CPF}$ , 1H), 6.98 (m,  $\text{CH}_{\text{Ar}(6)}$ , 1H), 7.57 (s,  $\text{CH}_{\text{Ar}(2)}$ , 1H), 7.72 (m,  $\text{CH}_{\text{Ar}(7)}$ , 1H), 8.46 (dd,  $^3J_{\text{HH}} = 6.9$ ,  $^4J_{\text{HH}} = 0.9$ ,  $\text{CH}_{\text{Ar}(5)}$ , 1H),  $^{31}\text{P}$  NMR (283 MHz,  $\text{D}_2\text{O}$  pH 7)  $\delta$ : 10.50 (d,

$^2J_{\text{PF}} = 77.5$ ),  $^{13}\text{C}$  NMR (176 MHz,  $\text{D}_2\text{O}$ ): 28.8 (dd,  $^2J_{\text{FC}} = 21.4$ ,  $^2J_{\text{PC}} = 3.2$ ,  $\underline{\text{CH}_2\text{CPF}}$ , 1C), 98.8 (dd,  $^1J_{\text{FC}} = 192.1$ ,  $^1J_{\text{PC}} = 146.8$ ,  $\text{CH}_2\underline{\text{CPF}}$ , 1C), 108.6 (s,  $\text{CH}_{\text{Ar}(8)}$ , 1C), 113.5 (s,  $\text{CH}_{\text{Ar}(6)}$ , 1C), 123.0 (d,  $^3J_{\text{PC}} = 14.8$ ,  $\text{C}_{\text{Ar}(3)}$ , 1C), 125.0 (d,  $^5J_{\text{PC}} = 2.6$ ,  $\text{CH}_{\text{Ar}(5)}$ , 1C), 129.3 (s,  $\text{CH}_{\text{Ar}(7)}$ , 1C), 130.2 (s,  $\text{C}_{\text{Ar}(2)}$ , 1C), 142.7 (s,  $\text{C}_{\text{Ar}(9)}$ , 1C), 174.4 (dd,  $^2J_{\text{PC}} = 20.6$ ,  $^2J_{\text{FC}} = 3.4$ ,  $\underline{\text{CO}_2}$ , 1C).

*2-Fluoro-3-(imidazo[2,1-*a*]isoquinolin-3-yl)-2-phosphonopropanoic acid (1r)*. Yield: 35%, scale: 0.093 g.  $^1\text{H}$  NMR (700 MHz,  $\text{D}_2\text{O}$  pH 9)  $\delta$ : 3.66 (dt,  $^2J_{\text{HH}} = 16.0$ ,  $^3J_{\text{PH}} = 16.0$ ,  $^3J_{\text{FH}} = 6.6$ ,  $\underline{\text{CH}_2\text{CPF}}$ , 1H), 3.95 (dd,  $^3J_{\text{FH}} = 41.3$ ,  $^2J_{\text{HH}} = 16.0$ ,  $^3J_{\text{PH}} = 0.9$ ,  $\underline{\text{CH}_2\text{CPF}}$ , 1H), 7.29 (d,  $^3J_{\text{HH}} = 7.3$ ,  $\text{CH}_{\text{Ar}}$ , 1H), 7.42 (s,  $\text{CH}_{\text{Ar}}$ , 1H), 7.67-7.77 (m,  $\text{CH}_{\text{Ar}}$ , 2H), 7.89 (d,  $^3J_{\text{HH}} = 7.7$ ,  $\text{CH}_{\text{Ar}}$ , 1H), 8.26 (d,  $^3J_{\text{HH}} = 7.3$ ,  $\text{CH}_{\text{Ar}}$ , 1H), 8.42 (d,  $^3J_{\text{HH}} = 7.9$ ,  $\text{CH}_{\text{Ar}}$ , 1H).  $^{31}\text{P}$  NMR (283 MHz,  $\text{D}_2\text{O}$  pH 9)  $\delta$ : 10.33 (d,  $^2J_{\text{PF}} = 70.5$ ),  $^{13}\text{C}$  NMR (176 MHz,  $\text{D}_2\text{O}$ ): 29.1 (d,  $^2J_{\text{FC}} = 21.0$ ,  $\underline{\text{CH}_2\text{CPF}}$ , 1C), 100.7 (dd,  $^1J_{\text{FC}} = 190.5$ ,  $^1J_{\text{PC}} = 138.2$ ,  $\text{CH}_2\underline{\text{CPF}}$ , 1C), 112.8 (s,  $\text{CH}_{\text{Ar}}$ , 1C), 122.1 (s,  $\text{CH}_{\text{Ar}}$ , 1C), 122.4 (s,  $\text{CH}_{\text{Ar}}$ , 1C), 122.6 (s,  $\text{CH}_{\text{Ar}}$ , 1C), 124.1 (d,  $^3J_{\text{PC}} = 12.5$ ,  $\text{C}_{\text{Ar}}$ , 1C), 127.3 (s,  $\text{CH}_{\text{Ar}}$ , 1C), 128.2 (s,  $\text{CH}_{\text{Ar}}$ , 1C), 128.6 (s,  $\text{CH}_{\text{Ar}}$ , 1C), 128.8 (s,  $\text{CH}_{\text{Ar}}$ , 1C), 129.5 (s,  $\text{CH}_{\text{Ar}}$ , 1C), 142.9 (s,  $\text{CH}_{\text{Ar}}$ , 1C), 176.6 (dd,  $^2J_{\text{PC}} = 20.7$ ,  $^2J_{\text{FC}} = 3.2$ ,  $\underline{\text{CO}_2}$ , 1C).

*2-Fluoro-2-(hydroxy(phenyl)phosphoryl)-3-(imidazo[1,2-*a*]pyridin-3-yl)propanoic acid (1s)*. Yield: 68%, scale: 0.070 g. Purification by HPLC: the column was eluted at 5 ml/min using gradient of eluents A ( $\text{H}_2\text{O}$ ), B (acetonitrile), under the following conditions: isocratic elution from 0 to 5 min with A 100%, gradient from 5 to 15 min: 20% of B. **Elemental analysis:**  $\text{C}_{16}\text{H}_{14}\text{FN}_2\text{O}_4\text{P}$  ( $\text{H}_2\text{O}$ ) $_{1.75}$  ( $\text{CH}_3\text{CN}$ ) $_{0.05}$ , Calculated: C: 50.64, H: 4.66, N: 7.52; Found: C: 50.33, H: 4.50, N: 7.89.  $^{31}\text{P}$  NMR (283 MHz,  $\text{D}_2\text{O}$  pH 7):  $\delta$  23.11 (d,  $^2J_{\text{PF}} = 74.5$ ).  $^1\text{H}$  NMR (700 MHz,  $\text{D}_2\text{O}$  pH 7)  $\delta$  8.32 (dd,  $^3J_{\text{HH}} = 7.1$ ,  $^4J_{\text{HH}} = 1.4$ ,  $\underline{\text{CH}}_{\text{Ar}(5)}$ , 1H), 7.87 – 7.78 (m,  $\underline{\text{CH}}_{\text{Ph}}$ , 1H), 7.59 (td,  $^3J_{\text{HH}} = 7.5$ ,  $^4J_{\text{HH}} = 1.4$ ,  $\underline{\text{CH}}_{\text{Ph}}$ , 1H), 7.54 (d,  $^3J_{\text{HH}} = 9.0$ ,  $\underline{\text{CH}}_{\text{Ar}(8)}$ , 1H), 7.52 (td,  $^3J_{\text{HH}} = 7.7$ ,  $^3J_{\text{HH}} = 3.2$ ,  $\underline{\text{CH}}_{\text{Ph}}$ ,

2H), 7.42 (s,  $\text{CH}_{\text{Ar}(2)}$ , 1H), 7.37 (ddd,  $^3J_{\text{HH}} = 9.1$ ,  $^3J_{\text{HH}} = 6.7$ ,  $^4J_{\text{HH}} = 1.2$ ,  $\text{CH}_{\text{Ar}(7)}$ , 1H), 7.88 (td,  $^3J_{\text{HH}} = 6.9$ ,  $^4J_{\text{HH}} = 1.2$ ,  $\text{CH}_{\text{Ar}(6)}$ , 1H), 3.91 (ddd,  $^3J_{\text{FH}} = 39.8$ ,  $^3J_{\text{FH}} = 2.7$ ,  $^2J_{\text{HH}} = 16.0$ ,  $\text{PCCHH}$ , 1H), 3.70 (dt,  $^2J_{\text{HH}} = 15.5$ ,  $^3J_{\text{FH}} = 7.5$ ,  $\text{PCCHH}$ , 1H).  **$^{13}\text{C}$  NMR** (176 MHz,  $\text{D}_2\text{O}$  pH 1)  $\delta$  171.9 (dd,  $^2J_{\text{FC}} = 23.4$ ,  $^2J_{\text{PC}} = 4.1$ ,  $\text{CO}_2$ , 1C), 140.2 (s,  $\text{C}_{\text{Ar}(9)}$ , 1C), 133.8 (s,  $\text{CH}_{\text{Ar}(2)}$ , 1C), 132.7 (d,  $J_{\text{PC}} = 9.8$ ,  $\text{CH}_{\text{Ph}}$ , 2C), 131.3 (d,  $^1J_{\text{PC}} = 136.2$ ,  $\text{PC}_{\text{Ph}}$ , 1C), 128.5 (d,  $J_{\text{PC}} = 12.6$ ,  $\text{CH}_{\text{Ph}}$ , 2C), 126.8 (d,  $^4J_{\text{PC}} = 4.5$ ,  $\text{CH}_{\text{Ph}}$ , 1C), 132.5 (s,  $\text{CH}_{\text{Ar}}$ , 1C), 121.5 (s,  $\text{CH}_{\text{Ar}}$ , 1C), 121.4 (d,  $^3J_{\text{PC}} = 11.4$ ,  $\text{C}_{\text{Ar}(3)}$ , 1C), 117.2 (s,  $\text{CH}_{\text{Ar}}$ , 1C), 112.2 (s,  $\text{CH}_{\text{Ar}}$ , 1C), 99.0 (dd,  $^1J_{\text{FC}} = 197.3$ ,  $^1J_{\text{PC}} = 95.6$ ,  $\text{PCH}$ , 1C), 26.7 (d,  $^2J_{\text{FC}} = 19.6$ ,  $\text{PCFCH}_2$ , 1C).

*2-(Ethyl(hydroxy)phosphoryl)-2-fluoro-3-(imidazo[1,2-a]pyridin-3-yl)propanoic acid*

(**1t**). Yield: 70%. Purification by HPLC: the column was eluted at 5 ml/min using gradient of eluents A ( $\text{H}_2\text{O}$ ), B (acetonitrile): isocratic elution from 0 to 5 min with A 100%, gradient from 5 to 10 min: 100% of B. **Elemental analysis:**  $\text{C}_{12}\text{H}_{14}\text{FN}_2\text{O}_4\text{P}$  ( $\text{H}_2\text{O}$ )<sub>1.4</sub>, ( $\text{CH}_3\text{CN}$ )<sub>0.02</sub> Calculated: C: 44.32, H: 5.21, N: 8.67, Found: C: 44.25, H: 5.20, N: 8.80.  **$^{31}\text{P}$  NMR** (283 MHz,  $\text{D}_2\text{O}$  pH 1):  $\delta$  36.14 (d,  $^2J_{\text{PF}} = 62.2$ ).  **$^1\text{H}$  NMR** (700 MHz,  $\text{D}_2\text{O}$  pH 1)  $\delta$  8.73 (dd,  $^3J_{\text{HH}} = 6.9$ ,  $^4J_{\text{HH}} = 0.8$ ,  $\text{CH}_{\text{Ar}(5)}$ , 1H), 7.97 (ddd,  $^3J_{\text{HH}} = 9.0$ , 7.0,  $^4J_{\text{HH}} = 0.9$ ,  $\text{CH}_{\text{Ar}(7)}$ , 1H), 7.91 (dt,  $^3J_{\text{HH}} = 9.1$ ,  $\text{CH}_{\text{Ar}(8)}$ , 1H), 7.86 (s,  $\text{CH}_{\text{Ar}(2)}$ , 1H), 7.52 (td,  $^3J_{\text{HH}} = 7.0$ ,  $^4J_{\text{HH}} = 1.1$ ,  $\text{CH}_{\text{Ar}(6)}$ , 1H), 4.05 (ddd,  $^3J_{\text{FH}} = 39.3$ ,  $^3J_{\text{HH}} = 15.7$ ,  $^3J_{\text{PH}} = 2.5$ ,  $\text{PCCHCH}$ , 1H), 3.91–3.85 (m,  $\text{PCCHCH}$ , 1H), 1.88–1.72 (m,  $\text{PCH}_2$ , 2H), 1.16 (dt,  $^3J_{\text{PH}} = 17.8$ ,  $^3J_{\text{HH}} = 7.7$ ,  $\text{PCH}_2\text{CH}_3$ , 3H).  **$^{13}\text{C}$  NMR** (176 MHz,  $\text{D}_2\text{O}$  pH 1)  $\delta$  172.4 (dd,  $^2J_{\text{FC}} = 25.7$ ,  $^2J_{\text{PC}} = 2.8$ ,  $\text{CO}_2$ , 1C), 140.1 (s,  $\text{C}_{\text{Ar}(9)}$ , 1C), 133.6 (s,  $\text{CH}_{\text{Ar}(7)}$ , 1C), 126.7 (d,  $J = 3.9$ ,  $\text{CH}_{\text{Ar}(5)}$ , 1C), 121.5 (d,  $^3J_{\text{PC}} = 12.0$ ,  $\text{C}_{\text{Ar}(3)}$ , 1C), 121.1 (s,  $\text{CH}_{\text{Ar}(2)}$ , 1H), 117.0 (s,  $\text{CH}_{\text{Ar}(6)}$ , 1C), 112.0 (s,  $\text{CH}_{\text{Ar}(8)}$ , 1C), 98 ( $\text{PCF}$ , 1C), 26.2 (d,  $^2J_{\text{PC}} = 20.5$ ,  $\text{PCCH}_2$ , 1C), 19.8 (d,  $^1J_{\text{PC}} = 98.1$ ,  $\text{PCHCH}_2$ , 1C), 5.1 (d,  $^2J_{\text{PC}} = 6.1$ ,  $\text{CH}_3\text{CH}_2\text{P}$ , 1C).

3-([1,1'-Biphenyl]-3-yl)-2-fluoro-2-phosphonopropanoic acid (**1u**). Yield: 77%, scale: 0.5 mmol, crystalized from petroleum ether; **Elemental analysis**: C<sub>15</sub>H<sub>14</sub>FO<sub>5</sub>P (H<sub>2</sub>O)<sub>0.3</sub>, Calculated: C: 54.65, H: 4.46; Found: C:54.58; H:4.37; <sup>31</sup>P NMR (101 MHz, D<sub>2</sub>O pH 2): δ 9.20 (d, <sup>2</sup>J<sub>PF</sub> = 73.3). <sup>1</sup>H NMR (700 MHz, D<sub>2</sub>O pH 2) δ 3.52–3.66 (m, CH<sub>2</sub>CF, 2H), 7.36 (d, <sup>3</sup>J<sub>HH</sub> = 7.5, CH<sub>Ar</sub>, 1H), 7.47 (t, <sup>3</sup>J<sub>HH</sub> = 7.4, CH<sub>Ar</sub>, 1H), 7.50 (t, <sup>3</sup>J<sub>HH</sub> = 7.7, CH<sub>Ar</sub>, 1H), 7.56 (t, <sup>3</sup>J<sub>HH</sub> = 7.7, CH<sub>Ar</sub>, 2H), 7.61 – 7.65 (m, CH<sub>Ar</sub>, 2H), 7.72 (d, <sup>3</sup>J<sub>HH</sub> = 7.3, CH<sub>Ar</sub>, 2H). <sup>13</sup>C NMR (176 MHz, D<sub>2</sub>O pH 2) δ 172.2 (d, <sup>2</sup>J<sub>PF</sub> = 24.9, CO<sub>2</sub>, 1C), 140.7 and 140.4 (2s, C<sub>Ar</sub>, 2C), 135.2 (d, <sup>3</sup>J<sub>PC</sub> = 12.3, CCH<sub>2</sub>CP, 1C), 129.3 and 128.5 and 127.8 and 125.9 (4s, CH<sub>Ar</sub>, 4C), 129.1 (s, CH<sub>Ar</sub>, 3C), 127.0 (s, CH<sub>Ar</sub>, 2C), 97.0 (dd, <sup>1</sup>J<sub>FC</sub> = 191.3, <sup>1</sup>J<sub>PC</sub> = 147.0, PCF, 1C), 39.0 (d, <sup>2</sup>J<sub>PC</sub> = 19.5, PCCH<sub>2</sub>, 1C).

3-([1,1'-Biphenyl]-4-yl)-2-fluoro-2-phosphonopropanoic acid (**1w**). Yield: 66%, scale: 0.5 mmol, crystalized from petroleum ether; <sup>31</sup>P NMR (283MHz, D<sub>2</sub>O pH 2): δ 8.44 (d, <sup>2</sup>J<sub>PF</sub> = 74.7). <sup>1</sup>H NMR (700 MHz, D<sub>2</sub>O pH 2) δ 7.73 (s, CH<sub>Ar</sub>, 2H), 7.68 (s, CH<sub>Ar</sub>, 2H), 7.55 (bs, CH<sub>Ar</sub>, 2H), 7.46 (s, CH<sub>Ar</sub>, 3H), 3.48–3.67 (m, CH<sub>2</sub>CF, 2H). <sup>19</sup>F NMR (235 MHz, D<sub>2</sub>O, PhCF<sub>3</sub> in CDCl<sub>3</sub> used as reference δ -63.02) δ -176.11 (ddd, <sup>2</sup>J<sub>PF</sub> = 74.5, <sup>4</sup>J<sub>FH</sub> = 39.3, <sup>4</sup>J<sub>FH</sub> = 12.7). <sup>13</sup>C NMR (176 MHz, D<sub>2</sub>O pH 2) δ 172.4 (d, <sup>2</sup>J<sub>PF</sub> = 24.4, CO<sub>2</sub>, 1C), 140.2 and 139.5 (2s, C<sub>Ar</sub>, 2C), 133.9 (d, <sup>3</sup>J<sub>PC</sub> = 12.1, CCH<sub>2</sub>CP, 1C), 130.7 and 129.1 (2s, CH<sub>Ar</sub>, 4C), 127.7 (s, CH<sub>Ar</sub>, 1C), 126.9 (s, CH<sub>Ar</sub>, 4C), 97.1 (dd, <sup>1</sup>J<sub>FC</sub> = 191.5, <sup>1</sup>J<sub>PC</sub> = 147.5, PCF, 1C), 38.7 (d, <sup>2</sup>J<sub>PC</sub> = 19.9, PCCH<sub>2</sub>, 1C).

3-(3-Benzylphenyl)-2-fluoro-2-phosphonopropanoic acid (**1y**). Yield: 99%, scale: 0.5 mmol, no crystalization, only removal of solvents; **Elemental analysis**: C<sub>16</sub>H<sub>16</sub>FO<sub>5</sub>P (H<sub>2</sub>O)<sub>0.4</sub>, Calculated: C: 55.63, H: 4.9; Found: C: 55.68; H: 4.88; <sup>31</sup>P NMR (283 MHz, D<sub>2</sub>O pH 1): δ 9.40 (d, <sup>2</sup>J<sub>PF</sub> = 75.4). <sup>1</sup>H NMR (700 MHz, D<sub>2</sub>O pH 1) δ 3.31–3.56 (m, CH<sub>2</sub>CF, 2H), 4.01 (s, CH<sub>2</sub>C<sub>Ar</sub>, 2H), 7.09-7.40 (m, CH<sub>Ar</sub>, 9H). <sup>13</sup>C NMR (176

1  
2  
3 MHz, D<sub>2</sub>O pH 1)  $\delta$  172.2 (d,  $^2J_{\text{PF}} = 24.2$ ,  $\text{CO}_2$ , 1C), 141.9 and 141.8 (2s,  $\text{C}_{\text{Ar}}$ , 2C),  
4  
5 134.83(d,  $^3J_{\text{PC}} = 12.6$ ,  $\text{CCH}_2\text{CP}$ , 1C), 130.4 and 127.9 and 127.7 and 126.3 (4s,  $\text{CH}_{\text{Ar}}$ ,  
6  
7 4C), 128.80 and 128.76 (2s,  $\text{CH}_{\text{Ar}}$ , 5C), 97.0 (dd,  $^1J_{\text{FC}} = 191.7$ ,  $^1J_{\text{PC}} = 147.4$ ,  $\text{PCF}$ ,  
8  
9 1C), 41.0 (s,  $\text{C}_{\text{Ar}}\text{CH}_2\text{C}_{\text{Ar}}$ , 1C), 38.9 (d,  $^2J_{\text{PC}} = 20.0$ ,  $\text{PCCH}_2$ , 1C).

10  
11  
12 *3-(2-Phenylimidazo[1,2-a]pyridin-3-yl)-2-phosphonopropanoic acid (2a)*. Yield:  
13  
14 75%, scale: 0.075 g.  $^1\text{H NMR}$  (250 MHz, D<sub>2</sub>O pH 8)  $\delta$ : 2.83-3.03 (m, 1H), 3.31-3.47  
15  
16 (m, 1H), 3.67-3.89 (m, 1H), 7.01 (td,  $^3J_{\text{HH}} = 6.9$ ,  $^4J_{\text{HH}} = 1.2$ , 1H), 7.32 – 7.42 (m, 1H),  
17  
18 7.43-7.49 (m, 1H), 7.49 – 7.60 (m, 3H), 7.92 – 7.78 (m, 2H), 8.50 (dd,  $^3J_{\text{HH}} = 6.9$ ,  
19  
20  $^4J_{\text{HH}} = 1.1$ , 1H),  $^{31}\text{P NMR}$  (101 MHz, D<sub>2</sub>O pH 8)  $\delta$ : 15.98.

21  
22  
23 *3-(2-Methylimidazo[1,2-a]pyridin-3-yl)-2-phosphonopropanoic acid (2b)*. Yield:  
24  
25 43%, scale: 0.1 g.  $^1\text{H NMR}$  (250 MHz, D<sub>2</sub>O pH 8)  $\delta$ : 2.34 (s, 1H), 2.84 (ddd,  $^2J_{\text{PH}} =$   
26  
27 19.2,  $^3J_{\text{HH}} = 12.5$ ,  $^3J_{\text{HH}} = 2.5$ , 1H), 3.15 (ddd,  $^2J_{\text{HH}} = 15.4$ ,  $^3J_{\text{PH}} = 7.8$ ,  $^3J_{\text{HH}} = 2.5$ , 1H),  
28  
29 3.51 (ddd,  $^2J_{\text{HH}} = 15.4$ ,  $^3J_{\text{HH}} = 12.5$ ,  $^3J_{\text{PH}} = 4.7$ , 1H), 6.93 (td,  $^3J_{\text{HH}} = 6.8$ ,  $^4J_{\text{HH}} = 1.0$ ,  
30  
31 1H), 7.20 - 7.34 (m, 1H), 7.37 - 7.46 (m, 1H), 8.27 (bdd,  $^3J_{\text{HH}} = 6.8$ ,  $^4J_{\text{HH}} = 0.8$ , 1H),  
32  
33  $^{31}\text{P NMR}$  (101 MHz, D<sub>2</sub>O pH 8)  $\delta$ : 16.00.

34  
35  
36 *3-(6-Bromo-2-methylimidazo[1,2-a]pyridin-3-yl)-2-phosphonopropanoic acid (2c)*.  
37  
38 Yield: 89% yield, scale: 0.23 g.  $^1\text{H NMR}$  (250 MHz, D<sub>2</sub>O pH 7)  $\delta$ : 2.36 (s, 1H), 2.87  
39  
40 (ddd,  $^2J_{\text{PH}} = 19.4$ ,  $^3J_{\text{HH}} = 12.6$ ,  $^3J_{\text{HH}} = 2.6$ , 1H), 3.14 (ddd,  $^2J_{\text{HH}} = 15.4$ ,  $^3J_{\text{PH}} = 7.1$ ,  $^3J_{\text{HH}}$   
41  
42  $= 2.6$ , 1H), 3.52 (ddd,  $^2J_{\text{HH}} = 15.4$ ,  $^3J_{\text{HH}} = 12.6$ ,  $^3J_{\text{PH}} = 5.3$ , 1H), 7.26-7.40 (m, 2H),  
43  
44 8.48 - 8.62 (m, 1H),  $^{31}\text{P NMR}$  (101 MHz, D<sub>2</sub>O pH 7)  $\delta$ : 15.73 (s).

45  
46  
47 *3-(5-phenylimidazo[1,2-a]pyridin-3-yl)-2-phosphonopropanoic acid (2d)*: Yield:  
48  
49 76%, scale: 0.040 g.  $^1\text{H NMR}$  (250 MHz, D<sub>2</sub>O pH 8)  $\delta$ : 2.55 - 2.60 (m, 1H), 2.64 -  
50  
51 2.71 (m, 1H), 2.99 (ddd,  $^2J_{\text{HH}} = 22.2$ ,  $^3J_{\text{HH}} = 12.30$ ,  $^3J_{\text{PH}} = 2.60$ , 1H), 6.80 (d,  $^3J_{\text{HH}} =$   
52  
53 6.9,  $^4J_{\text{HH}} = 1.2$ , 1H), 7.38 (d,  $^3J_{\text{HH}} = 9.0$ ,  $^3J_{\text{HH}} = 6.29$ , 1H), 7.47 (s, 1H), 7.54 – 7.57 (m,  
54  
55  
56  
57  
58  
59  
60



1H), 7.58 (dd,  $^3J_{\text{HH}} = 9.0$ ,  $^4J_{\text{HH}} = 1.2$ , 1H) 7.59–7.64 (m, 3H), 7.48 – 7.68 (m, 1H),  $^{31}\text{P}$  NMR (101 MHz, D<sub>2</sub>O pH 8)  $\delta$ : 14.87.

*3-(5-Methylimidazo[1,2-a]pyridin-3-yl)-2-phosphonopropanoic acid (2e)*. Yield: 66%; scale: 0.23 g; crystalized from H<sub>2</sub>O. **Elemental analysis:** C<sub>11</sub>H<sub>13</sub>N<sub>2</sub>O<sub>5</sub>P (H<sub>2</sub>O)<sub>1.45</sub> Calculated: C: 42.57; H: 5.16; N: 9.03. Found: C: 42.60; H: 5.08; N: 9.11.  $^1\text{H}$  NMR (250 MHz, D<sub>2</sub>O)  $\delta$  3.01 (s, 3H), 3.15-4.01 (m, 3H), 7.12 (d,  $^3J_{\text{HH}} = 7.3$ , 1H), 7.58–7.75 (m, 3H).  $^{31}\text{P}$  NMR (250 MHz, D<sub>2</sub>O):  $\delta$  13.65.

*3-(6-Phenylimidazo[1,2-a]pyridin-3-yl)-2-phosphonopropanoic acid (2f)*. Yield: 97%, scale: 0.1 g;  $^1\text{H}$  NMR (250 MHz, D<sub>2</sub>O pH 8)  $\delta$ : 3.05 (ddd,  $^2J_{\text{PH}} = 15.7$ ,  $^3J_{\text{HH}} = 12.6$ ,  $^3J_{\text{HH}} = 2.6$ , 1H), 3.17–3.30 (m, 1H), 3.38 - 3.59 (m, 1H), 7.38 (s, 1H), 7.44-7.49 (m, 1H), 7.51-7.59 (m, 2H), 7.61-7.65 (m, 2H), 7.73-7.81 (m, 2H), 8.56 (bs, 1H),  $^{31}\text{P}$  NMR (101 MHz, D<sub>2</sub>O pH 8)  $\delta$ : 15.97.

*3-(6-Methylimidazo[1,2-a]pyridin-3-yl)-2-phosphonopropanoic acid (2g)*. Yield: 56%; scale: 0.24 g; crystalized from H<sub>2</sub>O. **Elemental analysis:** C<sub>11</sub>H<sub>13</sub>N<sub>2</sub>O<sub>5</sub>P (H<sub>2</sub>O)<sub>1.45</sub> Calculated: C: 42.57; H: 5.16; N: 9.03. Found: C: 42.43; H: 4.95; N: 8.96.  $^1\text{H}$  NMR (250 MHz, D<sub>2</sub>O)  $\delta$  2.43 (s, 3H), 3.27-3.65 (m, 3H); 7.64 (s, 1H), 7.70 (d,  $^3J_{\text{HH}} = 9.3$ , 1H), 7.76 (d,  $^3J_{\text{HH}} = 9.8$ , 1H), 8.40 (s, 1H).  $^{31}\text{P}$  NMR (250 MHz, D<sub>2</sub>O)  $\delta$ : 14.67.

*3-(6-Chloroimidazo[1,2-a]pyridin-3-yl)-2-phosphonopropanoic acid (2h)*. Yield: 77%, scale: 0.1 g.  $^1\text{H}$  NMR (250 MHz, D<sub>2</sub>O pH 8)  $\delta$ : 3.02 (ddd,  $^2J_{\text{PH}} = 20.5$ ,  $^3J_{\text{HH}} = 12.9$ ,  $^3J_{\text{HH}} = 2.5$ , 1H), 3.18 (ddd,  $^2J_{\text{HH}} = 15.9$ ,  $^3J_{\text{PH}} = 7.5$ ,  $^3J_{\text{HH}} = 2.5$ , 1H), 3.44 (ddd,  $^2J_{\text{HH}} = 15.9$ ,  $^3J_{\text{HH}} = 12.9$ ,  $^3J_{\text{PH}} = 5.0$ , 1H), 7.36 (dd,  $^3J_{\text{HH}} = 9.6$ ,  $^4J_{\text{HH}} = 1.9$ , 1H), 7.42 (s, 1H), 7.54 (dd,  $^3J_{\text{HH}} = 9.6$ ,  $^5J_{\text{HH}} = 0.8$ , 1H), 8.54 (dd,  $^4J_{\text{HH}} = 1.9$ ,  $^5J_{\text{HH}} = 0.8$ , 1H),  $^{31}\text{P}$  NMR (283 MHz, D<sub>2</sub>O pH 8)  $\delta$ : 15.18 (s),  $^{13}\text{C}$  NMR (176 MHz, D<sub>2</sub>O): 28.8 (bs, 1C),

49.8 (d,  $^1J_{\text{PC}} = 113.3$ , 1C), 116.4, 120.5, 122.7, 126.3 (d,  $^5J_{\text{PC}} = 4.6$ , 1C), 126.5 (d,  $^3J_{\text{PC}} = 19.6$ , 1C), 129.9 (d,  $^4J_{\text{PC}} = 7.0$ , 1C), 143.7, 180.3 (d,  $^2J_{\text{PC}} = 3.8$ , 1C).

*3-(6-Bromoimidazo[1,2-a]pyridin-3-yl)-2-phosphonopropanoic acid (2i)*. Yield: 32%, scale: 0.1 g. **Elemental analysis:**  $\text{C}_{10}\text{H}_{10}\text{BrN}_2\text{O}_5\text{P} (\text{H}_2\text{O})_{0.95}$ , Calculated: C: 32.80, H: 2.28; N: 7.65, Found: C: 32.78; H: 3.30; N: 7.64.  **$^1\text{H}$  NMR** (250 MHz,  $\text{D}_2\text{O}$  pH 7)  $\delta$ : 2.99 (ddd,  $^2J_{\text{PH}} = 20.4$ ,  $^3J_{\text{HH}} = 12.7$ ,  $^3J_{\text{HH}} = 2.5$ , 1H), 3.14 (ddd,  $^2J_{\text{HH}} = 16.0$ ,  $^3J_{\text{PH}} = 7.1$ ,  $^3J_{\text{HH}} = 2.5$ , 1H), 3.41 (ddd,  $^2J_{\text{HH}} = 16.0$ ,  $^3J_{\text{HH}} = 12.7$ ,  $^3J_{\text{PH}} = 4.8$ , 1H), 7.36 (s, 1H), 7.40-7.50 (m, 2H), 8.61 (bs, 1H),  **$^{31}\text{P}$  NMR** (101 MHz,  $\text{D}_2\text{O}$  pH 7)  $\delta$ : 15.81.

*3-(7-Phenylimidazo[1,2-a]pyridin-3-yl)-2-phosphonopropanoic acid (2j)*. Yield: 96%, scale: 0.053 g.  **$^1\text{H}$  NMR** (250 MHz,  $\text{D}_2\text{O}$  pH 8)  $\delta$ : 3.01 (ddd,  $^2J_{\text{PH}} = 20.4$ ,  $^3J_{\text{HH}} = 12.8$ ,  $^3J_{\text{HH}} = 2.5$ , 1H), 3.13-3.28 (m, 1H), 3.35-3.56 (m, 1H), 7.34 (dd,  $^3J_{\text{HH}} = 7.3$ ,  $^4J_{\text{HH}} = 1.8$ , 1H), 7.43-7.61 (m, 3H), 7.73-7.84 (m, 3H), 8.36 (bd,  $^3J_{\text{HH}} = 7.3$ , 1H).  **$^{31}\text{P}$  NMR** (101 MHz,  $\text{D}_2\text{O}$  pH 8)  $\delta$ : 16.05.

*3-(7-Methylimidazo[1,2-a]pyridin-3-yl)-2-phosphonopropanoic acid (2k)*. Yield: 45%, scale: 0.27 g. crystallized from  $\text{H}_2\text{O}$ . **Elemental analysis:**  $\text{C}_{11}\text{H}_{13}\text{N}_2\text{O}_5\text{P} (\text{H}_2\text{O})_{1.4}$  Calculated: C: 42.7; H: 5.15; N: 9.05. Found: C: 42.58; H: 4.96; N: 8.94.  **$^1\text{H}$  NMR** (250 MHz,  $\text{D}_2\text{O}$ )  $\delta$  2.41 (s, 3H); 2.85-3.67 (m, 3H), 6.89 (dd,  $^3J_{\text{HH}} = 7.1$ ,  $^4J_{\text{HH}} = 1.5$ , 1H); 7.27 (s, 1H); 7.31 (bs, 1H), 8.21 (d,  $^3J_{\text{HH}} = 7.0$ , 1H).  **$^{31}\text{P}$  NMR** (250 MHz,  $\text{D}_2\text{O}$ )  $\delta$  15.86.

*3-(7-Chloroimidazo[1,2-a]pyridin-3-yl)-2-phosphonopropanoic acid (2l)*. Yield: 77%, scale: 0.1 g. **Elemental analysis:**  $\text{C}_{10}\text{H}_{10}\text{ClN}_2\text{O}_5\text{Px} (\text{H}_2\text{O})_{0.35}$ , Calculated: C: 38.63, H: 3.47; N: 9.01, Found: C: 38.78; H: 3.62; N: 8.84.  **$^1\text{H}$  NMR** (250 MHz,  $\text{D}_2\text{O}$  pH 8)  $\delta$ : 2.97 (ddd,  $^2J_{\text{PH}} = 20.4$ ,  $^3J_{\text{HH}} = 12.7$ ,  $^3J_{\text{HH}} = 2.5$ , 1H), 3.15 (ddd,  $^2J_{\text{HH}} = 16.0$ ,  $^3J_{\text{PH}} = 7.8$ ,  $^3J_{\text{HH}} = 2.5$ , 1H), 3.41 (ddd,  $^2J_{\text{HH}} = 16.0$ ,  $^3J_{\text{HH}} = 12.7$ ,  $^3J_{\text{PH}} = 5.0$ , 1H), 7.02

(dd,  $^3J_{\text{HH}} = 7.3$ ,  $^4J_{\text{HH}} = 2.0$ , 1H), 7.34 (s, 1H), 7.59 (d,  $^4J_{\text{HH}} = 2.0$ , 1H), 8.28 (d,  $^3J_{\text{HH}} = 7.3$ , 1H),  $^{31}\text{P}$  NMR (101 MHz, D<sub>2</sub>O pH 8)  $\delta$ : 15.77.

*3-(8-Phenylimidazo[1,2-a]pyridin-3-yl)-2-phosphonopropanoic acid (2n)*. Yield: 75%, scale: 0.1 g. **Elemental analysis:** C<sub>16</sub>H<sub>15</sub>N<sub>2</sub>O<sub>5</sub>P (H<sub>2</sub>O)<sub>1.25</sub>, (HCl)<sub>1.15</sub> Calculated: C: 46.79, H: 4.58; N: 6.82, Found: C: 46.79; H: 4.62; N: 6.76.  $^1\text{H}$  NMR (250 MHz, D<sub>2</sub>O pH 8)  $\delta$ : 3.02 (ddd,  $^2J_{\text{PH}} = 20.4$ ,  $^3J_{\text{HH}} = 12.7$ ,  $^3J_{\text{HH}} = 2.5$ , 1H), 3.12–3.27 (m, 1H), 3.36–3.54 (m, 1H), 7.09 (t,  $^3J_{\text{HH}} = 6.9$ , 1H), 7.33 – 7.40 (m, 2H), 7.44–7.58 (m, 3H), 7.70–7.79 (m, 2H), 8.31 (bd,  $^3J_{\text{HH}} = 6.9$ , 1H),  $^{31}\text{P}$  NMR (63 MHz, D<sub>2</sub>O pH 8)  $\delta$ : 15.95.

*3-(8-Methylimidazo[1,2-a]pyridin-3-yl)-2-phosphonopropanoic acid (2o)*. Yield: 67%, scale: 0.22 g; crystalized from H<sub>2</sub>O. **Elemental analysis:** C<sub>11</sub>H<sub>13</sub>N<sub>2</sub>O<sub>5</sub>P (H<sub>2</sub>O)<sub>0.2</sub> Calculated: C: 45.91; H: 4.69; N: 9.73. Found: C: 45.97; H: 4.72; N: 9.81.  $^1\text{H}$  NMR (250 MHz, D<sub>2</sub>O, pH 8)  $\delta$  2.57 (s, 3H), 3.28–3.70 (m, 3H), 7.39 (t,  $^3J_{\text{HH}} = 7.0$ , 1H), 7.70 (d,  $^3J_{\text{HH}} = 7.4$ , 1H), 7.73 (s, 1H), 8.45 (d,  $^3J_{\text{HH}} = 6.9$ , 1H).  $^{31}\text{P}$  NMR (250 MHz, D<sub>2</sub>O pH 8)  $\delta$  14.40.

*3-(8-Bromoimidazo[1,2-a]pyridin-3-yl)-2-phosphonopropanoic acid (2p)*. Yield: 80%, scale: 0.14 g. **Elemental analysis:** C<sub>10</sub>H<sub>10</sub>BrN<sub>2</sub>O<sub>5</sub>P (H<sub>2</sub>O)<sub>1.85</sub>, Calculated: C: 31.41, H: 3.61; N: 7.33, Found: C: 31.31; H: 3.44; N: 7.28,  $^1\text{H}$  NMR (250 MHz, D<sub>2</sub>O pH 7)  $\delta$ : 3.01 (ddd,  $^2J_{\text{PH}} = 20.7$ ,  $^3J_{\text{HH}} = 12.9$ ,  $^3J_{\text{HH}} = 2.6$ , 1H), 3.12–3.29 (m, 1H), 3.36–3.53 (m, 1H), 6.94 (t,  $^3J_{\text{HH}} = 7.1$ , 1H), 7.42 (s, 1H), 7.65 (d,  $^3J_{\text{HH}} = 7.4$ , 1H), 8.36 (d,  $^3J_{\text{HH}} = 6.9$ , 1H),  $^{31}\text{P}$  NMR (101 MHz, D<sub>2</sub>O pH 7)  $\delta$ : 15.76.

*3-(Imidazo[2,1-a]isoquinolin-3-yl)-2-phosphonopropanoic acid (2r)*. Yield: 84%, scale: 0.065 g.  $^1\text{H}$  NMR (250 MHz, D<sub>2</sub>O pH 9)  $\delta$ : 3.01 (ddd,  $^2J_{\text{PH}} = 20.6$ ,  $^3J_{\text{HH}} = 12.80$ ,  $^3J_{\text{HH}} = 2.70$ , 1H), 3.14–3.29 (m, 1H), 3.37–3.56 (m, 1H), 7.23–7.35 (m, 2H), 7.62–7.73 (m, 2H), 7.82–7.91 (m, 1H), 8.13 (d,  $^3J_{\text{HH}} = 7.5$ , 1H), 8.32–8.45 (m, 1H),  $^{31}\text{P}$  NMR (101 MHz, D<sub>2</sub>O pH 9)  $\delta$ : 16.04.

2-(Hydroxy(phenyl)phosphoryl)-3-(imidazo[1,2-*a*]pyridin-3-yl)propanoic acid (**2s**).

Yield: 68%, scale: 0.065 g, crystalized from Et<sub>2</sub>O. **Elemental analysis:** C<sub>16</sub>H<sub>15</sub>N<sub>2</sub>O<sub>4</sub>P (H<sub>2</sub>O)<sub>1.3</sub> (HCl)<sub>0.9</sub>, Calculated: C: 49.72, H: 4.82, N: 7.25 Found: C: 49.75, H: 4.91, N: 7.16. **<sup>31</sup>P NMR** (283 MHz, D<sub>2</sub>O, pH 2): δ 25.28. **<sup>1</sup>H NMR** (700 MHz, D<sub>2</sub>O pH 2) δ 8.47–8.42 (m, 1H), 7.96–7.91 (m, 1H), 7.85–7.81 (m, 1H), 7.77–7.72 (m, 2H), 7.67 (s, 1H), 7.58 (t, <sup>3</sup>J<sub>HH</sub> = 7.5, 1H), 7.52 – 7.47 (m, 3H), 3.58 – 3.40 (m, 3H). **<sup>13</sup>C NMR** (176 MHz, D<sub>2</sub>O pH 2) δ 173.5 (d, <sup>2</sup>J<sub>PC</sub> = 3.8, 1C), 139.7 (s, 1C), 133.3 (s, 1C), 133.3 (d, <sup>1</sup>J<sub>PC</sub> = 133.6, 1C), 131.8 (d, <sup>4</sup>J<sub>PC</sub> = 2.1, 1C), 131.4 (d, J<sub>PC</sub> = 9.8, 2C), 128.4 (d, J<sub>PC</sub> = 12.5, 2C), 125.9 (s, 1C), 124.7 (d, <sup>3</sup>J<sub>PC</sub> = 13.6, 1C), 119.5 (s, 1C), 117.1 (s, 1C), 112.1 (s, 1C), 47.9 (d, <sup>1</sup>J<sub>PC</sub> = 76.6, 1C), 20.7.

2-(Ethyl(hydroxy)phosphoryl)-3-(imidazo[1,2-*a*]pyridin-3-yl)propanoic acid (**2t**).

Yield: 87%, scale: 0.10 g, crystalized from Et<sub>2</sub>O. **<sup>31</sup>P NMR**(101 MHz, D<sub>2</sub>O, pH 2): δ 42.07. **<sup>1</sup>H NMR** (250 MHz, D<sub>2</sub>O pH 2) δ 8.62 (d, <sup>3</sup>J<sub>HH</sub> = 7.0, 1H), 7.97–7.81 (m, 2H), 7.73 (s, 1H), 7.49 (td, <sup>3</sup>J<sub>HH</sub> = 6.8, <sup>4</sup>J<sub>HH</sub> = 1.6, 1H), 3.66–3.31 (m, 3H), 1.90–1.73 (m, 2H), 1.16 (dt, <sup>3</sup>J<sub>HH</sub> = 7.8, <sup>3</sup>J<sub>PH</sub> = 3.0, 3H). **<sup>13</sup>C NMR** (63 MHz, D<sub>2</sub>O) δ 171.8 (s, 1C), 138.0 (s, 1C), 131.5, 124.2, 117.4, 115.2, 110.3, 123.3 (d, <sup>3</sup>J<sub>PC</sub> = 15.4, 1C), 44.3 (d, <sup>1</sup>J<sub>PC</sub> = 69.7, 1C), 19.5 (d, <sup>1</sup>J<sub>PC</sub> = 97.7, 1C), 18.0 (s, 1C), 3.5 (d, <sup>2</sup>J<sub>PC</sub> = 5.8, 1C).

3-([1,1'-Biphenyl]-3-yl)-2-phosphonopropanoic acid (**2u**). Yield: 90%, scale: 0.5 mmol; pure compound isolated by removal of solvents; **Elemental analysis:** C<sub>15</sub>H<sub>15</sub>O<sub>5</sub>P (H<sub>2</sub>O)<sub>0.55</sub>, Calculated: C: 56.95, H: 5.13; Found: C:56.93; H:5.09; **<sup>31</sup>P NMR** (101 MHz, D<sub>2</sub>O pH 2): δ 18.76. **<sup>1</sup>H NMR** (250 MHz, D<sub>2</sub>O pH 2) δ 2.88-3.23 (m, 3H), 6.75-7.26 (m, 9H).

3-([1,1'-Biphenyl]-4-yl)-2-phosphonopropanoic acid (**2w**). Yield: 70%, scale: 0.5 mmol, crystalized from water; **<sup>31</sup>P NMR** (101 MHz, D<sub>2</sub>O pH 2): δ 15.74. **<sup>1</sup>H NMR**

(250 MHz, D<sub>2</sub>O pH 2)  $\delta$  3.08–3.31 (m, 3H), 7.34–7.47 (m, 3H), 7.47–7.58 (m, 2H), 7.60–7.75 (m, 4H),

*3-(3-benzylphenyl)-2-phosphonopropanoic acid (2y)*: Yield: 98%, scale: 0.5 mmol, crystalized from petroleum ether; **Elemental analysis**: C<sub>16</sub>H<sub>17</sub>O<sub>5</sub>P (H<sub>2</sub>O)<sub>0.05</sub>, Calculated: C: 59.90, H: 5.56; Found: C:59.83; H:5.37; <sup>31</sup>P NMR (101 MHz, D<sub>2</sub>O pH 2):  $\delta$  18.47. <sup>1</sup>H NMR (250 MHz, D<sub>2</sub>O pH 2)  $\delta$  2.93–3.29 (m, 3H), 3.69 (s, 2H), 6.79–6.91 (m, 1H), 6.96–7.18 (m, 8H).

*3-([1,1':4',1''-Terphenyl]-3-yl)-2-phosphonopropanoic acid (2z)*. Yield: 95%, crystalized from H<sub>2</sub>O. **Elemental analysis**: C<sub>21</sub>H<sub>19</sub>O<sub>5</sub>P (H<sub>2</sub>O)<sub>1.2</sub>, Calculated: C: 62.44, H: 5.34; Found: C: 62.28; H: 5.13; <sup>31</sup>P NMR (283 MHz, D<sub>2</sub>O, pH 7): 16.85. <sup>1</sup>H NMR (700 MHz, D<sub>2</sub>O pH 7)  $\delta$  7.87–7.81 (m, 4H), 7.79 (d, <sup>3</sup>J<sub>HH</sub> = 7.4, 2H), 7.72 (s, 1H), 7.57 (t, <sup>3</sup>J<sub>HH</sub> = 6.5, 3H), 7.48 (t, <sup>3</sup>J<sub>HH</sub> = 7.6, 2H), 7.40 (d, <sup>3</sup>J<sub>HH</sub> = 7.6, 1H), 3.28–3.13 (m, 2H), 2.99 (ddd, <sup>2</sup>J<sub>PH</sub> = 20.4, <sup>3</sup>J<sub>HH</sub> = 12.4, 2.9, 1H). <sup>13</sup>C NMR (176 MHz, D<sub>2</sub>O)  $\delta$  181.0 (d, <sup>2</sup>J<sub>PC</sub> = 3.0, 1C), 143.9 (d, <sup>3</sup>J<sub>PC</sub> = 16.6, 1C), 140.3, 140.1, 140.0, 139.7, 129.40, 129.30, 128.13, 127.99, 127.77, 127.64, 127.15, 127.06, 124.37 (13s, CH<sub>Ar</sub>, 17C), 54.3 (d, <sup>1</sup>J<sub>PC</sub> = 112.8, 1C), 35.5 (s, 1C).

*General procedure for the synthesis of compounds (8d-z)*. Reaction was carried out under argon atmosphere using oven-dried glassware. A 100 mL two-neck round-bottom flask was charged with **5** (1.79 g, 8.0 mmole, 1.2 equiv) dissolved in DCM (20 mL). The solution was cooled down below -30 °C (internal temperature control), TiCl<sub>4</sub> (0.877 mL, 8 mmole, 1.2 equiv) was slowly added *via* syringe, followed by Et<sub>3</sub>N (2.63 mL, 0.0187 mole, 2.8 equiv). The reaction mixture was stirred for 15 minutes at -30 °C. Then, solution of aldehyde **3** (6.67 mmole, 1 equiv) in DCM (20 mL) was dropwisely added for 15 minutes at the temperature below -30 °C. The

resulting mixture was stirred at room temperature for 16 h and then quenched with 25 mL of water and was made basic with saturated  $\text{Na}_2\text{CO}_3$  aqueous solution to  $\text{pH} > 9$ . The water layer was extracted with diethyl ether (5 x 25 mL). Organic layer was dried over anhydrous  $\text{Mg}_2\text{SO}_4$ , solvent was evaporated and the residue was subjected to column chromatography using as eluent DCM:Acetone (85:15) to give product as (Z)/(E) mixture in the form of orange oil. The same procedure was applied for the synthesis of compounds **8s-z**. In case of **8u-z** analogs the elimination reaction was not complete and up to 50% of hydroxy analogs remained, which were easily separated from the desired product. *Note: The crude product of condensation can be subjected to reduction without prior purification.*

*Ethyl 2-(diethoxyphosphoryl)-3-(5-phenylimidazo[1,2-a]pyridin-3-yl)acrylate (8d).*

Yield: 53 %, scale: 0.24 g, E/Z = 0.3:1, ( $\text{CH}_2\text{Cl}_2$ :acetone 85:15), (Z)-**8d**:  $^1\text{H}$  NMR (700 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.04 (t,  $^3J_{\text{HH}} = 7.10$ , 3H), 1.14 (t,  $^3J_{\text{HH}} = 6.9$ , 6H), 3.96-4.09 (m, 4H), 4.17 (q,  $^3J_{\text{HH}} = 7.1$ , 2H), 6.71 (dd,  $^3J_{\text{HH}} = 6.9$ ,  $^4J_{\text{HH}} = 1.2$ , 1H), 7.27 (dd,  $^3J_{\text{HH}} = 8.9$ ,  $^3J_{\text{HH}} = 6.9$ , 1H), 7.32 (d,  $^3J_{\text{PH}} (E) = 41.6$ , 1H), 7.34-7.41 (m, 5H), 7.56 (dd,  $^3J_{\text{HH}} = 8.9$ ,  $^4J_{\text{HH}} = 1.2$ , 1H), 8.34 (s, 1H),  $^{31}\text{P}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$ : 14.14;  $^{13}\text{C}$  NMR (176 MHz,  $\text{CDCl}_3$ )  $\delta$ : 14.0, 16.10 and 16.14 (2s, 2C), 60.8, 62.25, 62.29, 114.0 (d,  $^1J_{\text{PC}} = 192.3$ , 1C), 116.2, 117.2, 127.0, 128.1 (s, 2C), 129.1 (s, 2C), 129.7, 134.5, 141.1 (d,  $^1J_{\text{PC}} = 3.5$ , 1C), 142.6 (s, 1C), 149.1 (s, 1C), 165.4 (d,  $^2J_{\text{PC}} = 15.9$ , 1C).

*Ethyl 2-(diethoxyphosphoryl)-3-(5-methylimidazo[1,2-a]pyridin-3-yl)acrylate (8e).*

Yield: 60%. Scale: 9.4 mmol, 1.5 g. Ratio of isomers (E)/(Z) 1: 0.1 ( $\text{CHCl}_3$ :MeOH 50:1  $R_f$  0.28).  $^{31}\text{P}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$ : 15.98 (E) and 13.77 (Z).  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.15 (t,  $^3J_{\text{HH}} = 7.2$ , 3H), 1.22 (t,  $^3J_{\text{HH}} = 7.1$ , 6H), 2.76 (s, 3H), 4.11–3.92 (m, 4H), 4.16 (q,  $^3J_{\text{HH}} = 7.1$ , 2H), 6.58 (d,  $^3J_{\text{HH}} = 6.9$ , 1H), 7.08 (t,  $^3J_{\text{HH}} = 8.8$ , 7.0, 1H), 7.40 (d,  $^3J_{\text{HH}} = 8.9$ , 1H), 8.01 (s, 1H), 8.18 (d,  $^3J_{\text{PH}} = 23.5$ , 1H).  $^{13}\text{C}$  NMR

(63 MHz, CDCl<sub>3</sub>)  $\delta$  13.9, 16.1 (s,  $^3J_{PC}$  = 6.6, 2C), 22.1, 61.4, 62.4 (d,  $^2J_{PC}$  = 5.3, 2C), 115.8, 116.3, 116.9 (s,  $^1J_{PC}$  = 184.3, 1C), 121.9 (d,  $^3J_{PC}$  = 24.9, 1C), 127.0 (s, 1C), 137.3 (s, 1C), 137.3 (t,  $^2J_{PC}$  = 4.9, 1C), 140.2, 149.2, 165.9 (d,  $^2J_{PC}$  = 12.5, 1C).

*Ethyl 2-(diethoxyphosphoryl)-3-(6-phenylimidazo[1,2-a]pyridin-3-yl)acrylate (8f).*

Yield: 80%, scale: 0.5 g, (E)/(Z) 1:0.14, (CH<sub>2</sub>Cl<sub>2</sub>:acetone 85:15), **(E)-8f**:  $^1\text{H NMR}$  (700 MHz, CDCl<sub>3</sub>)  $\delta$ : 1.37 (t,  $^3J_{HH}$  = 7.00, 9H), 4.10-4.28 (m, 4H), 4.39 (q,  $^3J_{HH}$  = 7.2, 2H), 7.42-7.55 (m, 3H), 7.56-7.68 (m, 3H), 7.78 (m, 1H), 8.06 (d,  $^3J_{PH}$  (Z) = 23.8, 1H), 8.48 (s, 1H), 8.53 (s, 1H),  $^{31}\text{P NMR}$  (101 MHz, CDCl<sub>3</sub>)  $\delta$ : 17.17 (E) and 13.95 (Z).

*Ethyl 2-(diethoxyphosphoryl)-3-(6-methylimidazo[1,2-a]pyridin-3-yl)acrylate (8g).*

Yield: 60%; scale: 0.5 g. (E)/(Z) 1: 0.03 (DCM:Acetone 9:1 R<sub>f</sub> 0.19).  $^{31}\text{P NMR}$  (101 MHz, CDCl<sub>3</sub>)  $\delta$ : 17.67 (E) and 14.17 (Z).  $^1\text{H NMR}$  (250 MHz, CDCl<sub>3</sub>)  $\delta$ : 1.28 (t,  $^3J_{HH}$  = 7.1, 3H), 1.28 (td,  $^3J_{HH}$  = 7.1,  $^4J_{PH}$  = 0.7, 6H), 2.31 (s, 3H), 4.02-4.17 (m, 2H); 4.28 (q,  $^3J_{HH}$  = 7.1, 2H), 7.16 (dd,  $^3J_{HH}$  = 9.1,  $^4J_{HH}$  = 1.7, 1H), 7.51 (d,  $^3J_{HH}$  = 9.1,  $^4J_{HH}$  = 0.9, 1H), 7.92 (d,  $^3J_{PH}$  = 23.9, 1H), 8.08 (s, 1H), 8.43 (s, 1H).

*Ethyl 3-(6-chloroimidazo[1,2-a]pyridin-3-yl)-2-(diethoxyphosphoryl)acrylate (8h).*

Yield: 57% yield, scale: 0.5 g, (E)/(Z) = 50/1, (CH<sub>2</sub>Cl<sub>2</sub>:acetone 85:15);  $^{31}\text{P NMR}$  (283 MHz, CDCl<sub>3</sub>)  $\delta$ : 15.71 (E) and 12.41 (Z).  $^1\text{H NMR}$  (700 MHz, CDCl<sub>3</sub>)  $\delta$ : 1.36 (t,  $^3J_{HH}$  = 7.10, 3H), 1.37 (t,  $^3J_{HH}$  = 7.1, 6H), 4.10-4.28 (m, 4H), 4.37 (q,  $^3J_{HH}$  = 7.2, 2H), 7.35 (dd,  $^3J_{HH}$  = 9.4,  $^4J_{HH}$  = 1.8, 1H), 7.66 (dd,  $^3J_{HH}$  = 9.4,  $^5J_{HH}$  = 0.7, 1H), 7.90 (d,  $^3J_{PH}$  (Z) = 23.7, 1H), 8.38 (d,  $^4J_{HH}$  = 1.8, 1H), 8.49 (s, 1H),  $^{13}\text{C NMR}$  (176 MHz, CDCl<sub>3</sub>)  $\delta$ : 14.1, 16.32, 16.36, 61.7, 62.77, 62.80, 117.3 (d,  $^1J_{PC}$  = 184.3, 1C), 118.8, 120.8 (d,  $^3J_{PC}$  = 24.5, 1C), 122.1, 122.8, 128.5, 133.2 (d,  $^2J_{PC}$  = 9.9, 1C), 141.6 (s, 1C), 146.1 (s, 1C), 165.6 (d,  $^2J_{PC}$  = 11.6, 1C).

*Ethyl 3-(6-bromoimidazo[1,2-a]pyridin-3-yl)-2-(diethoxyphosphoryl)acrylate (8i).*

Yield: 52%, scale: 0.34 g, (*E*)/(*Z*) 50/1,  $R_{f(E)}$  0.36, (CH<sub>2</sub>Cl<sub>2</sub>:acetone 85:15), (*E*)-**8i**:

**<sup>31</sup>P NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$ : 16.52 (*E*) and 13.27 (*Z*), **<sup>1</sup>H NMR** (700 MHz, CDCl<sub>3</sub>)  $\delta$ : 1.35 (t,  $^3J_{HH} = 7.10$ , 3H), 1.36 (t,  $^3J_{HH} = 7.1$ , 6H), 4.12 - 4.25 (m, 4H), 4.36 (q,  $^3J_{HH} = 7.1$ , 2H), 7.43 (dd,  $^3J_{HH} = 9.4$ ,  $^4J_{HH} = 1.7$ , 1H), 7.59 (d,  $^3J_{HH} = 9.4$ , 1H), 7.90 (d,  $^3J_{PH} (Z) = 23.8$ , 1H), 8.45 (s, 1H), 8.52 (d,  $^4J_{HH} = 1.7$ , 1H), **<sup>13</sup>C NMR** (176 MHz, CDCl<sub>3</sub>)  $\delta$ : 14.2, 16.42, 16.44, 61.8, 62.87, 62.90, 109.4, 117.5 (d,  $^1J_{PC} = 184.3$ , 1C), 119.1, 120.8 (d,  $^3J_{PC} = 24.2$ , 1C), 124.3, 130.8, 133.3 (d,  $^2J_{PC} = 10.1$ , 1C), 141.5, 146.3, 165.7 (d,  $^2J_{PC} = 11.7$ , 1C).

*Ethyl 2-(diethoxyphosphoryl)-3-(7-phenylimidazo[1,2-a]pyridin-3-yl)acrylate (8j).*

Yield: 52%, scale: 0.5 g, *E/Z* 100/0, (CH<sub>2</sub>Cl<sub>2</sub>:acetone 85:15), (*E*)-**8h**: **<sup>31</sup>P NMR** (101

MHz, CDCl<sub>3</sub>)  $\delta$ : 16.61, **<sup>1</sup>H NMR** (700 MHz, CDCl<sub>3</sub>)  $\delta$ : 1.38 (t,  $^3J_{HH} = 7.00$ , 9H), 4.10 - 4.26 (m, 4H), 4.39 (q,  $^3J_{HH} = 7.00$ , 2H), 7.32 (dd,  $^3J_{HH} = 7.1$ ,  $^4J_{HH} = 1.7$ , 1H), 7.45 (t,  $^3J_{HH} = 7.4$ , 1H), 7.51 (t,  $^3J_{HH} = 7.5$ , 2H), 7.69 (t,  $^3J_{HH} = 7.5$ , 2H), 7.92 (s, 1H), 8.03 (d,  $^3J_{PH} (Z) = 23.8$ , 1H), 8.40 (d,  $^3J_{HH} = 7.1$ , 1H), 8.61 (s, 1H), **<sup>13</sup>C NMR** (176 MHz, CDCl<sub>3</sub>)  $\delta$ : 14.1, 16.28, 16.32, 61.4, 62.5, 62.6, 113.9, 115.0, 115.1 (d,  $^1J_{PC} = 185.5$ , 1C), 120.3 (d,  $^3J_{PC} = 24.0$ ), 123.7, 126.8 (s, 2C), 128.9, 129.2 (s, CH<sub>Ph</sub>, 2C), 133.9 (d,  $^2J_{PC} = 10.2$ , 1C), 137.6, 140.5, 142.6, 148.4, 165.7 (d,  $^2J_{PC} = 12.0$ , 1C).

*Ethyl 2-(diethoxyphosphoryl)-3-(7-methylimidazo[1,2-a]pyridin-3-yl)acrylate (8k).*

Yield: 47%, scale: 0.64 g. (*E*)/(*Z*) 1: 0.02 (DCM:acetone 9:1  $R_f$  0.21). **<sup>31</sup>P NMR**

(101MHz, CDCl<sub>3</sub>):  $\delta$  17.39 (*E*) and 13.84 (*Z*). **<sup>1</sup>H NMR** (250 MHz, CDCl<sub>3</sub>)  $\delta$ : 8.51 (s, 1H), 8.22 (d,  $^3J_{HH}=7.1$ , 1H), 7.95 (d,  $^3J_{PH} = 23.8$ , 1H), 7.42 (d,  $^4J_{HH} = 0.7$ , 1H), 6.82 (dd,  $^3J_{HH} = 7.0$ ,  $^4J_{HH} = 1.6$ , 1H), 4.32 (q,  $^3J_{HH} = 7.1$ , 3H), 4.22 - 4.03 (m, 6H), 2.41 (s, 3H), 1.31 (t,  $^3J_{HH} = 7.1$ , 9H). **<sup>13</sup>C NMR** (63 MHz, CDCl<sub>3</sub>)  $\delta$  165.5 (d,  $^2J_{FC}=12.6$ , 1C), 148.2 (s, 1C), 141.9 and 140.0 (2s, 2C), 134.2 (d,  $^2J_{PC}= 10.3$ , 1C), 119.9 (d,  $^3J_{PC} =$



23.7, 1C), 116.7 and 116.7 (2s, 2C), 113.5 (d,  $^1J_{PC}$  = 186.2, 1C), 62.3 (d,  $^2J_{PC}$  = 5.3, 2C), 61.1, 21.0, 16.1 (d,  $^3J_{PC}$  = 6.7, 2C), 13.9.

*Ethyl 3-(7-chloroimidazo[1,2-a]pyridin-3-yl)-2-(diethoxyphosphoryl)acrylate (8l).*

Yield: 67%, scale 1 g, (E)/(Z) 5/1,  $R_f(E)$  0.36,  $R_f(Z)$  0.21, (CH<sub>2</sub>Cl<sub>2</sub>:acetone 85:15),

**(E)-8l -  $^1H$  NMR** (250 MHz, CDCl<sub>3</sub>)  $\delta$ : 1.36 (t,  $^3J_{HH}$  = 7.10, 3H), 1.37 (t,  $^3J_{HH}$  = 7.1, 3H), 1.37 (t,  $^3J_{HH}$  = 7.1, 3H), 4.10-4.25 (m, 4H), 4.37 (q,  $^3J_{HH}$  = 7.1, 2H), 7.01 (dd,  $^3J_{HH}$  = 7.3,  $^4J_{HH}$  = 2.1, 1H), 7.71 (bd,  $^4J_{HH}$  = 2.1, 1H), 7.92 (d,  $^3J_{PH}$  (Z) = 23.7, 1H), 1H), 8.28 (d,  $^3J_{HH}$  = 7.3, 1H), 8.51 (s, 1H).  **$^{31}P$  NMR** (101 MHz, CDCl<sub>3</sub>): 16.70 (E) and 13.43 (Z),  **$^{13}C$  NMR** (63 MHz, CDCl<sub>3</sub>)  $\delta$ : 14.1, 16.2, 16.3, 61.6, 62.6, 62.7, 115.7, 116.8 (d,  $^1J_{PC}$  = 184.6, 1C), 117.4, 120.6 (d,  $^3J_{PC}$  = 24.2, 1C), 124.1, 133.3 (d,  $^2J_{PC}$  = 10.1, 1C), 134.1, 141.9, 147.6, 165.5 (d,  $^2J_{PC}$  = 12.3, 1C).

*Ethyl 3-(7-bromoimidazo[1,2-a]pyridin-3-yl)-2-(diethoxyphosphoryl)acrylate (8m).*

Yield: 68%, scale: 0.2 g, (E)/(Z) = 10/1,  $R_f(E)$  0.33,  $R_f(Z)$  0.27, (CH<sub>2</sub>Cl<sub>2</sub>:acetone 85:15), **(E)-8l:  $^{31}P$  NMR** (283 MHz, CDCl<sub>3</sub>)  $\delta$ : 16.68 (E) and 13.43 (Z),  **$^1H$  NMR** (700 MHz, CDCl<sub>3</sub>)  $\delta$ : 1.34 (t,  $^3J_{HH}$  = 7.1, 3H), 1.35 (t,  $^3J_{HH}$  = 7.1, 6H), 4.09-4.23 (m, 4H), 4.35 (q,  $^3J_{HH}$  = 7.1, 2H), 7.11 (dd,  $^3J_{HH}$  = 7.3,  $^4J_{HH}$  = 1.9, 1H), 7.88 (d,  $^4J_{HH}$  = 1.9, 1H), 7.91 (d,  $^3J_{PH}$  (Z) = 23.8, 1H), 1H), 8.25 (d,  $^3J_{HH}$  = 7.3, 1H), 8.47 (s, 1H).  **$^{13}C$  NMR** (176 MHz, CDCl<sub>3</sub>)  $\delta$ : 14.2, 16.39, 16.43, 61.8, 62.87, 62.88, 116.9 (d,  $^1J_{PC}$  = 184.7, 1C), 118.2, 120.8 (d,  $^3J_{PC}$  = 24.1), 120.9, 121.8, 124.3, 133.4 (d,  $^2J_{PC}$  = 10.1, 1C), 141.9, 148.0, 165.7 (d,  $^2J_{PC}$  = 12.3, 1C).

*Ethyl 2-(diethoxyphosphoryl)-3-(8-phenylimidazo[1,2-a]pyridin-3-yl)acrylate (8n).*

Yield: 78% yield, scale: 0.3 g, (E)/(Z) 25/1, (CH<sub>2</sub>Cl<sub>2</sub>:acetone 85:15), **(E)-8h:  $^{31}P$  NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$ : 17.01 (E) and 13.86 (Z),  **$^1H$  NMR** (250 MHz, CDCl<sub>3</sub>)  $\delta$ : 1.35 (t,  $^3J_{HH}$  = 7.10, 3H), 1.37 (t,  $^3J_{HH}$  = 7.1, 6H), 4.09 - 4.27 (m, 4H), 4.36 (q,  $^3J_{HH}$  = 7.1, 2H), 7.11 (t,  $^3J_{HH}$  = 6.8, 1H), 7.40-7.56 (m, 4H), 7.87-7.94 (m, 2H), 8.00 (d,  $^3J_{PH}$

(Z) = 24.1, 1H), 8.35 (bd,  $^3J_{\text{HH}} = 6.8$ , 1H), 8.50 (s, 1H),  $^{13}\text{C}$  NMR (63 MHz,  $\text{CDCl}_3$ )  $\delta$ : 14.1, 16.2, 16.3, 61.5, 62.6, 62.7, 114.4, 116.1 (d,  $^1J_{\text{PC}} = 185.2$ , 1C), 120.7 (d,  $^3J_{\text{PC}} = 24.2$ , 1C), 122.6, 125.9, 128.56, 128.57, 129.0 (s, 2C), 131.4, 133.6 (d,  $^2J_{\text{PC}} = 9.9$ , 1C), 135.6, 140.9, 146.5, 165.7 (d,  $^2J_{\text{PC}} = 12.0$ , 1C).

*Ethyl 2-(diethoxyphosphoryl)-3-(8-methylimidazo[1,2-a]pyridin-3-yl)acrylate (8o).*

Yield: 70%. scale: 1 g. (E)/(Z) 1: 0.03 (DCM:Acetone 9:1  $R_f$  0.09).  $^{31}\text{P}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$ : 16.84 (E) and 13.63 (Z).  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ )  $\delta$  1.32 (t,  $^3J_{\text{HH}} = 7.1$ , 9H), 2.59 (s, 3H), 3.93-4.23 (m, 4H), 4.32 (q,  $^3J_{\text{HH}} = 7.12$ , 2H), 6.89 (t,  $^3J_{\text{HH}} = 6.9$ , 1H), 7.14 (d,  $^3J_{\text{HH}} = 7.0$ , 1H), 7.92 (d,  $^3J_{\text{PH}} = 23.8$ , 1H), 8.18 (d,  $^3J_{\text{HH}} = 6.9$ , 1H), 8.44 (s, 1H).

*Ethyl 3-(8-bromoimidazo[1,2-a]pyridin-3-yl)-2-(diethoxyphosphoryl)acrylate (8p).*

Yield: 48%, scale: 0.7 g, (E)/(Z) 5/1,  $R_f(\text{E})$  0.37,  $R_f(\text{Z})$  0.23, ( $\text{CH}_2\text{Cl}_2$ :acetone 85:15), (E)-8p:  $^{31}\text{P}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$ : 15.98 (E) and 12.92 (Z),  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.36 (t,  $^3J_{\text{HH}} = 7.2$ , 3H), 1.37 (t,  $^3J_{\text{HH}} = 7.1$ , 3H), 1.38 (t,  $^3J_{\text{HH}} = 7.1$ , 3H), 4.11-4.27 (m, 4H), 4.37 (q,  $^3J_{\text{HH}} = 7.1$ , 2H), 6.91 (t,  $^3J_{\text{HH}} = 7.2$ , 1H), 7.64 (dd,  $^3J_{\text{HH}} = 7.4$ ,  $^4J_{\text{HH}} = 0.9$ , 1H), 7.89 (d,  $^3J_{\text{PH}}(\text{Z}) = 23.7$ , 1H), 8.33 (bd,  $^3J_{\text{HH}} = 6.6$ , 1H), 8.46 (s, 1C).  $^{13}\text{C}$  NMR (63 MHz,  $\text{CDCl}_3$ )  $\delta$ : 14.0, 16.2, 16.3, 61.7, 62.7, 62.8, 112.5, 114.2, 118.0 (d,  $^1J_{\text{PC}} = 184.1$ , 1C), 121.8 (d,  $^3J_{\text{PC}} = 24.3$ , 1C), 123.1, 129.5, 133.0 (d,  $^2J_{\text{PC}} = 9.9$ , 1C), 140.5, 145.4, 165.4 (d,  $^2J_{\text{PC}} = 11.8$ , 1C).

*Ethyl 2-(diethoxyphosphoryl)-3-(imidazo[2,1-a]isoquinolin-3-yl)acrylate (8r).* Yield:

43%, scale: 0.4 g, (E)/(Z) 1:0.15, ( $\text{CH}_2\text{Cl}_2$ :acetone 85:15), (E)-8r:  $^1\text{H}$  NMR (700 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.37 (m, 9H), 4.13-4.24 (m, 4H), 4.38 (q,  $^3J_{\text{HH}} = 7.2$ , 2H), 7.23 (d,  $^3J_{\text{HH}} = 7.3$ , 1H), 7.64 (bt,  $^3J_{\text{HH}} = 8.0$ , 1H), 7.67 (bt,  $^3J_{\text{HH}} = 7.5$ , 1H), 7.76 (bd,  $^3J_{\text{HH}} = 7.5$ , 1H), 7.96 (d,  $^3J_{\text{PH}}(\text{Z}) = 23.8$ , 1H), 8.10 (d,  $^3J_{\text{HH}} = 7.4$ , 1H), 8.40, 8.66 (bd,  $^3J_{\text{HH}} = 8.00$ , 1H),  $^{31}\text{P}$  NMR (283 MHz,  $\text{CDCl}_3$ )  $\delta$ : 16.72 (E) and 13.61 (Z),  $^{13}\text{C}$  NMR (176

1  
2  
3 MHz, CDCl<sub>3</sub>) δ: 14.2, 16.4, 16.5, 61.8, 62.79, 62.82, 114.7, 117.5 (d, <sup>1</sup>J<sub>PC</sub> = 184.5,  
4 1C), 120.4, 122.2 (d, <sup>3</sup>J<sub>PC</sub> = 24.2, C) 123.6, 124.1, 127.1, 128.9, 129.6, 130.3, 133.7  
5  
6 (d, <sup>2</sup>J<sub>PC</sub> = 9.8, 1C), 139.0, 145.8, 165.9 (d, <sup>2</sup>J<sub>PC</sub> = 12.0, 1C).  
7  
8

9  
10 *Ethyl 2-(ethoxy(phenyl)phosphoryl)-3-(imidazo[1,2-a]pyridin-3-yl)acrylate (8s).*  
11

12 Yield: 71%; scale: 1 g. (*E*)/(*Z*) 1:0.06 (CH<sub>2</sub>Cl<sub>2</sub>:acetone 8:2, R<sub>f</sub> 0.25). <sup>31</sup>P NMR (283  
13 MHz, CDCl<sub>3</sub>): 29.45 (*E*) and 29.90 (*Z*); <sup>1</sup>H NMR (700 MHz, CDCl<sub>3</sub>) (*E*)-**8s**: δ 8.57  
14 (s, 1H), 8.41 (d, <sup>3</sup>J<sub>HH</sub> = 7.1, 1H), 8.19 (d, <sup>3</sup>J<sub>PH</sub> = 20.6, 1H), 7.85 – 7.78 (m, 2H), 7.65  
15 (bd, <sup>3</sup>J<sub>HH</sub> = 8.9, 1H), 7.46 (m, 1H), 7.41 – 7.37 (m, 2H), 7.34 (ddd, <sup>3</sup>J<sub>HH</sub> = 8.9, 6.8,  
16 <sup>4</sup>J<sub>HH</sub> = 1.1, 1H), 6.98 (td, <sup>3</sup>J<sub>HH</sub> = 6.8, <sup>4</sup>J<sub>HH</sub> = 1.1, 1H), 4.22 – 4.02 (m, 4H), 1.36 (t,  
17 <sup>3</sup>J<sub>HH</sub> = 7.0, 3H), 1.10 (t, <sup>3</sup>J<sub>HH</sub> = 7.2, 3H). <sup>13</sup>C NMR (176 MHz, CDCl<sub>3</sub>) δ 165.7 (d,  
18 <sup>2</sup>J<sub>PC</sub> = 12.8, 1C), 148.0, 142.1, 134.0 (d, <sup>2</sup>J<sub>PC</sub> = 9.1, 1C), 132.1 (d, <sup>4</sup>J<sub>PC</sub> = 3.3, 1C),  
19 131.7 (d, J<sub>PC</sub> = 10.2, 2C), 131.3 (d, <sup>1</sup>J<sub>PC</sub> = 148.8, 1C), 128.2 (d, J<sub>PC</sub> = 13.9, 2C), 127.6  
20 124.0, 120.8 (d, <sup>3</sup>J<sub>PC</sub> = 19.3, 1C), 118.4, 117.9 (d, <sup>1</sup>J<sub>PC</sub> = 127.7, 1C), 114.3, 61.4 (d,  
21 <sup>2</sup>J<sub>PC</sub> = 6.1, 1C), 61.2, 16.5 (d, <sup>3</sup>J<sub>PC</sub> = 6.5, 1C), 13.9.  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35

36 *Ethyl 2-(ethoxy(ethyl)phosphoryl)-3-(imidazo[1,2-a]pyridin-3-yl)acrylate (8t).* Yield:  
37 77%; scale: 0.6 g; solvent used in reaction – THF, (*E*)/(*Z*) 1:0.11 (CH<sub>2</sub>Cl<sub>2</sub>:acetone  
38 85:15 R<sub>f</sub> 0.23). <sup>31</sup>P NMR (283 MHz, CDCl<sub>3</sub>): δ 45.96 (*E*) and 44.70 (*Z*). <sup>1</sup>H NMR  
39 (700 MHz, CDCl<sub>3</sub>) δ 8.54 (s, 1H), 8.45 (dd, <sup>3</sup>J<sub>HH</sub> = 6.5, <sup>4</sup>J<sub>HH</sub> = 3.1, 1H), 8.01 (d, <sup>3</sup>J<sub>PH</sub>  
40 = 19.4, 1H), 7.66 (dd, <sup>3</sup>J<sub>HH</sub> = 8.9, <sup>4</sup>J<sub>HH</sub> = 1.0, 1H), 7.38 – 7.33 (m, 1H), 6.98 (td, <sup>3</sup>J<sub>HH</sub>  
41 = 6.8, <sup>4</sup>J<sub>HH</sub> = 1.0, 1H), 4.36 – 4.28 (m, 2H), 4.09–3.88 (m, 2H), 2.08 – 1.92 (m, 2H),  
42 1.32 (t, <sup>3</sup>J<sub>HH</sub> = 7.2, 3H), 1.26 (t, <sup>3</sup>J<sub>HH</sub> = 7.0, 3H), 1.15 (dt, <sup>3</sup>J<sub>PH</sub> = 20.2, <sup>3</sup>J<sub>HH</sub> = 7.7, 3H).  
43 <sup>13</sup>C NMR (176 MHz, CDCl<sub>3</sub>) δ 166.2 (d, <sup>2</sup>J<sub>PC</sub> = 13.4, 1C), 148.0, 141.6, 134.7 (d, <sup>2</sup>J<sub>PC</sub>  
44 = 8.4, 1C), 127.6, 124.2, 120.8 (d, <sup>3</sup>J<sub>PC</sub> = 18.1, 1C), 118.4, 116.9 (d, <sup>1</sup>J<sub>PC</sub> = 115.2, 1C),  
45 114.3, 61.4, 60.8 (d, <sup>2</sup>J<sub>PC</sub> = 6.9, 1C), 21.9 (d, <sup>1</sup>J<sub>PC</sub> = 107.3, 1C), 16.4 (d, <sup>3</sup>J<sub>PC</sub> = 6.5,  
46 1C), 14.2, 5.7 (d, <sup>2</sup>J<sub>PC</sub> = 4.2, 1C).  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

*Ethyl 3-([1,1'-biphenyl]-3-yl)-2-(diethoxyphosphoryl)acrylate (8u)*. Yield: 67% (98% purity, 2% mol aldehyde from  $^1\text{H}$  NMR); scale: 0.5 g; (*E*)/(*Z*) 1:0.04,  $R_f(E)$  = 0.66,  $R_f(Z)$  = 0.57 ( $\text{CHCl}_3$ :acetone 10:1),  $^{31}\text{P}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  14.97 (*E*) and 14.25 (*Z*).  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.22 (t,  $^3J_{\text{HH}}$  = 7.1, 3H), 1.38 (dt,  $^3J_{\text{HH}}$  = 7.1,  $^4J_{\text{HP}}$  = 0.6, 6H), 4.12 – 4.24 (m, 4H), 4.28 (q,  $^3J_{\text{HH}}$  = 7.2, 2H), 7.32 – 7.50 (m, 5H), 7.50 – 7.66 (m, 4H), 7.72 [(*E*) d,  $^3J_{\text{PH}}(E)$  = 24.2, 1H], 8.24 [(*Z*) d,  $^3J_{\text{PH}}(Z)$  = 43.3, 1H].  $^{13}\text{C}$  NMR (63 MHz,  $\text{CDCl}_3$ )  $\delta$  13.7, 16.1 (d,  $^3J_{\text{PC}}$  = 6.7, 2C), 61.6, 62.6 (d,  $^2J_{\text{PC}}$  = 5.0, 2C), 124.8 (d,  $^1J_{\text{PC}}$  = 178.7, 1C), 126.8 (s, 2C), 128.7 (s, 2C), 127.6, 127.7, 127.8, 128.89, 128.92, 134.1 (d,  $^3J_{\text{CP}}$  = 20.2, 1C), 140.0, 141.5, 147.8 (d,  $^3J_{\text{PC}}$  = 6.5, 1C), 166.3 (d,  $^2J_{\text{PC}}$  = 12.5, 1C).

*Ethyl 3-([1,1'-biphenyl]-4-yl)-2-(diethoxyphosphoryl)acrylate (8w)*. Yield: 44%; scale: 1.27 g; purity 95% (5% mol aldehyde based on  $^1\text{H}$  NMR). (*E*)/(*Z*) 1:0.1 [ $R_f(E)$  = 0.55,  $R_f(Z)$  = 0.46 ( $\text{CHCl}_3$ :acetone 10:1)],  $^{31}\text{P}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  14.84 (*E*), 12.43 (*Z*).  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.28 (t,  $^3J_{\text{HH}}$  = 7.1, 3H), 1.38 (dt,  $^3J_{\text{HH}}$  = 7.1,  $^4J_{\text{PH}}$  = 0.6, 6H), 4.14–4.27 (m, 4H), 4.31 (q,  $^3J_{\text{HH}}$  = 7.2, 2H), 7.33–7.54 (m, 5H), 7.55 – 7.65 (m, 4H), 7.67 [(*E*): d,  $^3J_{\text{PH}}(E)$  = 24.1, 1H], 8.21 [(*Z*): d,  $^3J_{\text{PH}}(Z)$  = 43.5, 1H].  $^{13}\text{C}$  NMR (63 MHz,  $\text{CDCl}_3$ ):  $\delta$  13.8, 16.2 (d,  $^3J_{\text{CP}}$  = 6.6, 2C), 61.6, 62.6 (d,  $^2J_{\text{PC}}$  = 5.1, 2C), 124.1 (d,  $^1J_{\text{CP}}$  = 178.8, 1C), 127.9, 126.9, 127.1, 128.8, 129.76, 132.40 (d,  $^3J_{\text{PC}}$  = 20.3, 1C), 139.80, 143.08, 147.5 (d,  $^3J_{\text{PC}}$  = 6.4, 1C), 166.4 (d,  $^2J_{\text{PC}}$  = 12.6, 1C).

*Ethyl 3-(3-benzylphenyl)-2-(diethoxyphosphoryl)acrylate (8y)*. Yield: 84%; scale: 0.82 g; (*E*)/(*Z*) 1:0.04 ( $R_f(E)$  0.65,  $R_f(Z)$  0.53 ( $\text{CHCl}_3$ :acetone 10:1),  $^{31}\text{P}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  14.48 (*E*) and 12.00 (*Z*).  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ )  $\delta$  1.17 (t,  $^3J_{\text{HH}}$  = 7.1, 3H), 1.34 (dt,  $^3J_{\text{HH}}$  = 7.1,  $^4J_{\text{PH}}$  = 0.6, 6H), 3.94 (s, 2H), 4.06 – 4.23 (m, 6H), 7.10–7.32 (m, 9H), 7.58 [(*E*) d,  $^3J_{\text{PH}}(E)$  = 24.2, 1H], 8.13 [(*Z*) d,  $^3J_{\text{PH}}(Z)$  = 43.9, 1H].

**<sup>13</sup>C NMR** (63 MHz, CDCl<sub>3</sub>) δ 13.8, 16.2 (d, <sup>3</sup>J<sub>PC</sub> = 6.7, 2C), 41.7, 61.6, 62.7 (d, <sup>2</sup>J<sub>PC</sub> = 5.1, 2C), 124.4 (d, <sup>1</sup>J<sub>PC</sub> = 178.6, 1C), 126.3, 127.1, 128.8, 128.6, 128.9, 129.6, 131.1 (7s, 9C), 133.8 (d, <sup>3</sup>J<sub>PC</sub> = 20.1, 1C), 140.3, 141.7, (2s, 2C), 148.0 (d, <sup>3</sup>J<sub>PC</sub> = 6.3, 1C), 166.4 (d, <sup>2</sup>J<sub>PC</sub> = 12.6, 1C).

*Ethyl 3-([1,1':4',1''-terphenyl]-3-yl)-2-(diethoxyphosphoryl)acrylate (8z)*. Yield: 71%; scale: 0.86 g; (*E*)/(*Z*) 1:0.01 (*R*<sub>f</sub>(*E*) = 0.24 (CHCl<sub>3</sub>:acetone 10:1), **<sup>31</sup>P NMR** (283 MHz, CDCl<sub>3</sub>) δ 14.39 (*E*) and 12.23 (*Z*). **<sup>1</sup>H NMR** (700 MHz, CDCl<sub>3</sub>) δ 7.75 (d, <sup>3</sup>J<sub>PH</sub> = 24.1, 1H), 7.72 (s, 1H), 7.68 – 7.61 (m, 7H), 7.47 – 7.41 (m, 4H), 7.35 (dt, <sup>3</sup>J<sub>HH</sub> = 7.4, 1.0, 1H), 4.30 (q, <sup>3</sup>J<sub>HH</sub> = 7.1, 2H), 4.27 – 4.17 (m, 4H), 1.39 (t, <sup>3</sup>J<sub>HH</sub> = 7.1, 6H), 1.23 (t, <sup>3</sup>J<sub>HH</sub> = 7.2, 3H). **<sup>13</sup>C NMR** (176 MHz, CDCl<sub>3</sub>) δ 166.4 (d, <sup>2</sup>J<sub>PC</sub> = 12.4 Hz, 1C), 148.0 (d, <sup>3</sup>J<sub>PC</sub> = 6.3, 1C), 141.1, 140.5, 140.4, 139.0, 134.2 (d, <sup>3</sup>J<sub>PC</sub> = 20.0, 1C), 129.2, 128.9, 128.8, 127.9, 127.8, 127.6, 127.5, 127.3, 127.0 (9s, 13C), 125.0 (d, <sup>1</sup>J<sub>PC</sub> = 178.3, 1C), 62.8 (d, <sup>2</sup>J<sub>PC</sub> = 5.1, 2C), 61.7, 16.2 (d, <sup>3</sup>J<sub>PC</sub> = 6.5, 2C), 13.9.

#### *General procedure for the synthesis of compounds 9*

*Route 1 (9d-z)*. A 50 mL two-neck round-bottom flask was charged with **8** (1.83 mmol, 1 equiv), NiCl<sub>2</sub> × 6 H<sub>2</sub>O (0.52 g, 2.2 mmol, 1.2 equiv) and dissolved in methanol (10 mL). Flask was submerged in a dry ice/acetone cooling bath (−40 °C) and then NaBH<sub>4</sub> (0.083 g, 2.2 mmol, 1.2 equiv) was added. The mixture was stirred at (−40°C, internal control) for 8 min then quenched with 4 mL of NH<sub>4</sub>Cl. Solution was made basic with saturated Na<sub>2</sub>CO<sub>3</sub> solution to pH>9. The water layer was extracted with dichloromethane (4 x 10 ml). Organic layer was dried over anhydrous MgSO<sub>4</sub> solvent was evaporated and residue was subjected to column chromatography using DCM: acetone (100:20) system as eluent to give product as orange oil. *Note: For compounds not containing aromatic ring substituted with halogen atom less stringent conditions (−20 °C, 15 minutes) could be applied.*

*Ethyl 2-(diethoxyphosphoryl)-3-(5-phenylimidazo[1,2-a]pyridin-3-yl)propanoate*

(**9d**). Yield: 63%, scale: 0.1 g,  $R_f$  0.1 ( $\text{CH}_2\text{Cl}_2$ :acetone 85:15),  $^1\text{H NMR}$  (700 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.14 (t,  $^3J_{\text{HH}} = 7.10$ , 3H), 1.17 (t,  $^3J_{\text{HH}} = 7.10$ , 3H), 1.23 (t,  $^3J_{\text{HH}} = 7.10$ , 3H), 2.71 (ddd,  $^2J_{\text{HH}} = 16.1$ ,  $^3J_{\text{PH}} = 9.0$ ,  $^3J_{\text{HH}} = 3.8$ , 1H), 2.85 (ddd,  $^2J_{\text{HH}} = 16.1$ ,  $^3J_{\text{HH}} = 11.7$ ,  $^3J_{\text{PH}} = 9.2$ , 1H), 3.08 (ddd,  $^2J_{\text{PH}} = 22.8$ ,  $^3J_{\text{HH}} = 11.7$ ,  $^3J_{\text{HH}} = 3.8$ , 1H), 3.79-3.93 (m, 2H), 3.95-4.08 (m, 4H), 6.62 (dd,  $^3J_{\text{HH}} = 6.8$ ,  $^4J_{\text{HH}} = 1.2$ , 1H), 7.16 (dd,  $^3J_{\text{HH}} = 9.0$ ,  $^3J_{\text{HH}} = 6.8$ , 1H), 7.37 (s, 1H), 7.43-7.45 (m, 1H), 7.47-7.53 (m, 4H), 7.59 (dd,  $^3J_{\text{HH}} = 9.0$ ,  $^4J_{\text{HH}} = 1.2$ , 1H),  $^{31}\text{P NMR}$  (283 MHz,  $\text{CDCl}_3$ ): 20.88,  $^{13}\text{C NMR}$  (176 MHz,  $\text{CDCl}_3$ ): 14.1, 16.39 (d,  $^3J_{\text{PC}} = 6.0$ , 1C), 16.41 (d,  $^3J_{\text{PC}} = 5.5$ , 1C), 25.5 (d,  $^2J_{\text{PC}} = 1.7$ , 1C), 44.7 (d,  $^1J_{\text{PC}} = 131.0$ , 1C), 61.7, 62.8 (d,  $^2J_{\text{PC}} = 6.7$ , 1C), 63.0 (d,  $^2J_{\text{PC}} = 6.3$ , 1C), 115.2, 117.4, 123.0 (d,  $^3J_{\text{PC}} = 20.3$ , 1C), 123.7, 128.35, 128.29, 129.5, 129.6, 129.8, 133.0, 135.1, 138.8, 147.5, 168.4 (d,  $^2J_{\text{PC}} = 5.0$ , 1C).

*Ethyl 2-(diethoxyphosphoryl)-3-(5-methylimidazo[1,2-a]pyridin-3-yl)propanoate*

(**9e**). Yield: 64%, scale 1.1 g ( $\text{CHCl}_3$ :MeOH 40:1  $R_f$  0.22).  $^1\text{H NMR}$  (250 MHz,  $\text{CDCl}_3$ )  $\delta$  1.21 (t,  $^3J_{\text{HH}} = 7.17$ , 3H), 1.34 (t,  $^3J_{\text{HH}} = 7.1$ , 6H), 2.88 (s, 3H), 3.38 (ddd,  $^2J_{\text{PH}} = 22.6$ ,  $^3J_{\text{HH}} = 11.6$ , 3.1, 1H), 3.64-3.99 (m, 2H), 4.09 - 4.24 (m, 6H), 6.49 (bd,  $^3J_{\text{HH}} = 6.8$ , 1H), 7.01 (t,  $^3J_{\text{HH}} = 6.75$ , 1H), 7.34 (s, 1H), 7.43 (d,  $^3J_{\text{HH}} = 9.1$ , 1H).  $^{31}\text{P NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  21.08. **HRMS**  $m/z$  found 369.1583, calculated  $(\text{M}+\text{H})^+$  369.1508.

*Ethyl 2-(diethoxyphosphoryl)-3-(6-phenylimidazo[1,2-a]pyridin-3-yl)propanoate* (**9f**).

Yield: 73%, scale: 0.2 g,  $R_f$  0.1 ( $\text{CH}_2\text{Cl}_2$ :acetone 85:15),  $^1\text{H NMR}$  (700 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.20 (t,  $^3J_{\text{HH}} = 7.20$ , 3H), 1.36 (t,  $^3J_{\text{HH}} = 7.10$ , 3H), 3.31-3.51 (m, 2H), 3.58-3.77 (m, 1H), 4.10-4.29 (m, 6H), 7.38-7.54 (m, 5H), 7.57-7.64 (m, 2H), 7.67 (dd,  $^3J_{\text{HH}} = 9.4$ ,  $^4J_{\text{HH}} = 0.7$ , 1H), 8.18-8.21 (m, 1H),  $^{31}\text{P NMR}$  (283 MHz,  $\text{CDCl}_3$ ): 21.73. **HRMS**:  $m/z$  Calculated: 431.1730 ( $\text{M} + \text{H})^+$ , Found: 431.1739 ( $\text{M} + \text{H})^+$ .

*Ethyl 2-(diethoxyphosphoryl)-3-(6-methylimidazo[1,2-a]pyridin-3-yl)propanoate* (**9g**). Yield: 77%, scale 3.3 mmol, (CHCl<sub>3</sub>:MeOH 40:1 R<sub>f</sub> 0.12). **<sup>1</sup>H NMR** (250 MHz, CDCl<sub>3</sub>) δ 1.17 (t, <sup>3</sup>J<sub>HH</sub> = 7.1, 3H), 1.38 (m, 6H); 2.32 (s, 3H), 3.73-3.22 (m, 3H); 4.01-4.30 (m, 6H); 6.99 (dd, <sup>3</sup>J<sub>HH</sub> = 9.2, <sup>3</sup>J<sub>HH</sub> = 1.6, 1H); 7.35 (s, 1H); 7.46 (d, <sup>3</sup>J<sub>HH</sub> = 9.1, 1H); 7.75 (s, 1H). **<sup>31</sup>P NMR** (101 MHz, CDCl<sub>3</sub>) δ 21.82. **HRMS** m/z found 369.1583, calculated (M+H)<sup>+</sup> 369.1508.

*Ethyl 3-(6-chloroimidazo[1,2-a]pyridin-3-yl)-2-(diethoxyphosphoryl)propanoate* (**9h**). Yield: 87% yield, scale: 0.4 g, (CH<sub>2</sub>Cl<sub>2</sub>:acetone 85:15), **<sup>1</sup>H NMR** (700 MHz, CDCl<sub>3</sub>) δ: 1.15 (t, <sup>3</sup>J<sub>HH</sub> = 7.10, 3H), 1.31 (t, <sup>3</sup>J<sub>HH</sub> = 7.10, 6H), 3.22 - 3.34 (m, 2H), 3.48-3.58 (m, 1H), 4.02 - 4.21 (m, 6H), 7.08 (dd, <sup>3</sup>J<sub>HH</sub> = 9.6, <sup>4</sup>J<sub>HH</sub> = 1.9, 1H), 7.39 (s, 1H), 7.48 (bt, <sup>3</sup>J<sub>HH</sub> = 9.6, 1H), 8.05 (s, <sup>4</sup>J<sub>HH</sub> = 1.9, <sup>5</sup>J<sub>HH</sub> = 0.7, 1H), **<sup>31</sup>P NMR** (283 MHz, CDCl<sub>3</sub>) δ: 20.91. **<sup>13</sup>C NMR** (176 MHz, CDCl<sub>3</sub>) δ: 14.0, 16.37 (d, <sup>3</sup>J<sub>PC</sub> = 6.1, 1C), 16.40 (d, <sup>3</sup>J<sub>PC</sub> = 5.9, 1C), 21.5 (d, <sup>2</sup>J<sub>PC</sub> = 3.7, 1C), 44.3 (d, <sup>1</sup>J<sub>PC</sub> = 129.9, 1C), 62.0, 63.2 (d, <sup>2</sup>J<sub>PC</sub> = 6.9, 1C), 63.3 (d, <sup>2</sup>J<sub>PC</sub> = 6.5, 1C), 118.3, 120.8, 121.2, 121.8 (d, <sup>3</sup>J<sub>PC</sub> = 18.3, 1C), 125.3, 132.6, 144.0, 168.1 (d, <sup>2</sup>J<sub>PC</sub> = 5.1, 1C). **HRMS**: m/z Calculated: 389,1028 (M + H)<sup>+</sup>, Found: 389.1039 (M + H)<sup>+</sup>.

*Ethyl 3-(6-bromoimidazo[1,2-a]pyridin-3-yl)-2-(diethoxyphosphoryl)propanoate* (**9i**). Yield: 75 %, scale (0.32 g), R<sub>f</sub> 0.08, (CH<sub>2</sub>Cl<sub>2</sub>:acetone 85:15), **<sup>1</sup>H NMR** (700 MHz, CDCl<sub>3</sub>) δ: 1.18 (t, <sup>3</sup>J<sub>HH</sub> = 7.10, 3H), 1.34 (t, <sup>3</sup>J<sub>HH</sub> = 7.10, 6H), 3.21 - 3.41 (m, 2H), 3.45-3.64 (m, 1H), 4.03-4.28 (m, 6H), 7.20 (dd, <sup>3</sup>J<sub>HH</sub> = 9.5, <sup>4</sup>J<sub>HH</sub> = 1.8, 1H), 7.40 (s, 1H), 7.46 (d, <sup>3</sup>J<sub>HH</sub> = 9.5, <sup>5</sup>J<sub>HH</sub> = 0.8, 1H), 8.16 (d, <sup>4</sup>J<sub>HH</sub> = 1.8, <sup>5</sup>J<sub>HH</sub> = 0.8, 1H), **<sup>31</sup>P NMR** (283 MHz, CDCl<sub>3</sub>): 21.40.

*Ethyl 2-(diethoxyphosphoryl)-3-(7-phenylimidazo[1,2-a]pyridin-3-yl)propanoate* (**9j**). Yield: 82 % yield, scale: 0.2 g, R<sub>f</sub> 0.09 (CH<sub>2</sub>Cl<sub>2</sub>:acetone 85:15), **<sup>1</sup>H NMR** (700 MHz, CDCl<sub>3</sub>) δ: 1.20 (t, <sup>3</sup>J<sub>HH</sub> = 7.10, 3H), 1.36 (t, <sup>3</sup>J<sub>HH</sub> = 7.10, 3H), 1.37 (t, <sup>3</sup>J<sub>HH</sub> = 7.10,

3H), 3.24-3.50 (m, 2H), 3.64 (ddd,  $^2J_{\text{HH}} = 16.4$ ,  $^3J_{\text{HH}} = 11.7$ ,  $^3J_{\text{PH}} = 6.9$ , 1H), 4.06-4.35 (m, 6H), 7.15 (dd,  $^3J_{\text{HH}} = 7.2$ ,  $^4J_{\text{HH}} = 1.8$ , 1H), 7.34-7.42 (m, 1H), 7.42-7.52 (m, 3H), 7.61-7.70 (m, 2H), 7.80 (dd,  $^4J_{\text{HH}} = 1.8$ ,  $^5J_{\text{HH}} = 0.8$ , 1H), 8.09 (dd,  $^3J_{\text{HH}} = 7.2$ ,  $^5J_{\text{HH}} = 0.8$ , 1H),  **$^{31}\text{P}$  NMR** (283 MHz,  $\text{CDCl}_3$ ): 21.22.  **$^{13}\text{C}$  NMR** (176 MHz,  $\text{CDCl}_3$ ): 14.1, 16.49 (d,  $^3J_{\text{PC}} = 7.7$ , 1C), 16.52 (d,  $^3J_{\text{PC}} = 7.7$ , 1C), 21.7 (d,  $^2J_{\text{PC}} = 3.5$ , 1C), 44.6 (d,  $^1J_{\text{PC}} = 129.3$ , 1C), 62.0, 63.2 (d,  $^2J_{\text{PC}} = 6.8$ , 1C), 63.3 (d,  $^2J_{\text{PC}} = 6.5$ , 1C), 112.5, 114.8, 121.0 (d,  $^3J_{\text{PC}} = 18.3$ , 1C), 123.1, 126.9 (s, 2C), 128.3, 129.2 (s, 2C), 132.5, 137.1, 138.8, 146.2, 168.4 (d,  $^2J_{\text{PC}} = 5.0$ , 1C).

*Ethyl 2-(diethoxyphosphoryl)-3-(7-methylimidazo[1,2-a]pyridin-3-yl)propanoate* (**9k**). Yield: 92%; scale: 0.27 mmol; (no purification by column chromatography needed).  **$^1\text{H}$  NMR** (250 MHz,  $\text{CDCl}_3$ )  $\delta$  1.18 (t,  $^3J_{\text{HH}} = 7.1$ , 3H), 1.40-1.30 (m, 6H), 2.39 (s, 3H), 3.19 - 3.69 (m, 3H), 4.01 - 4.30 (m, 6H), 6.68 (d,  $^3J_{\text{HH}} = 7.0$ ,  $\text{CH}_{\text{Ar}(6)}$ , 1H), 7.34 (s, 2H), 7.91 (d,  $^3J_{\text{HH}} = 7.0$ , 1H).  **$^{13}\text{C}$  NMR** (176 MHz,  $\text{CDCl}_3$ )  $\delta$  168.1 (d,  $^2J_{\text{FC}} = 5.0$ , 1C), 145.9, 134.6, 131.0, 122.2, 120.2 (d,  $^3J_{\text{PC}} = 17.7$ , 1C), 116.0, 114.9, 63.1 (d,  $^2J_{\text{PC}} = 6.3$ , 1C), 63.0 (d,  $^2J_{\text{PC}} = 6.7$ , 1C), 61.7, 44.3 (d,  $^1J_{\text{PC}} = 129.5$ , 1C), 21.4 (d,  $^2J_{\text{PC}} = 2.8$ , 1C), 21.0, 16.22 (d,  $^3J_{\text{PC}} = 6.6$ , 1C) 16.18 (d,  $^3J_{\text{PC}} = 6.7$ , 1C), 13.8.  **$^{31}\text{P}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  21.66. **HRMS**  $m/z$  found 369.1582, calculated  $(\text{M}+\text{H})^+$  369.1508.

*Ethyl 3-(7-chloroimidazo[1,2-a]pyridin-3-yl)-2-(diethoxyphosphoryl)propanoate* (**9l**). Yield: 59%, scale: 0.4 g,  $R_f$  0.09, ( $\text{CH}_2\text{Cl}_2$ :acetone 85:15).  **$^1\text{H}$  NMR** (250 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.15 (t,  $^3J_{\text{HH}} = 7.10$ , 3H), 1.31 (t,  $^3J_{\text{HH}} = 7.10$ , 3H), 1.31 (t,  $^3J_{\text{HH}} = 7.10$ , 3H), 3.19 - 3.42 (m, 2H), 3.47-3.63 (m, 1H), 4.03-4.26 (m, 6H), 6.79 (dd,  $^3J_{\text{HH}} = 7.3$ ,  $^4J_{\text{HH}} = 2.1$ , 1H), 7.37 (s, 1H), 7.54 (d,  $^4J_{\text{HH}} = 2.1$ ,  $^5J_{\text{HH}} = 0.8$ , 1H), 7.95 (d,  $^3J_{\text{HH}} = 7.3$ ,  $^5J_{\text{HH}} = 0.8$ , 1H).  **$^{31}\text{P}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$ : 21.30.  **$^{13}\text{C}$  NMR** (63 MHz,  $\text{CDCl}_3$ )  $\delta$ : 14.0, 16.40 (d,  $^3J_{\text{PC}} = 5.7$ , 1C), 16.41 (d,  $^3J_{\text{PC}} = 5.7$ , 1C), 21.5 (d,  $^2J_{\text{PC}} = 3.3$  1C),



44.5 (d,  $^1J_{PC} = 129.4$ , 1C), 62.0, 63.2 (d,  $^2J_{PC} = 6.3$ , 1C), 63.3 (d,  $^2J_{PC} = 6.3$ , 1C), 114.0, 116.8, 121.6 (d,  $^3J_{PC} = 18.3$ , 1C), 123.6, 130.5, 132.6, 145.4, 168.2 (d,  $^2J_{PC} = 5.1$ , 1C).

*Ethyl 3-(7-bromoimidazo[1,2-a]pyridin-3-yl)-2-(diethoxyphosphoryl)propanoate* (**9m**). Yield: 63%, scale: 0.24 g,  $R_f$  0.10, (CH<sub>2</sub>Cl<sub>2</sub>:acetone 85:15).  **$^1H$  NMR** (700 MHz, CDCl<sub>3</sub>)  $\delta$ : 1.19 (t,  $^3J_{HH} = 7.10$ , 3H), 1.35 (t,  $^3J_{HH} = 7.10$ , 3H), 1.35 (t,  $^3J_{HH} = 7.10$ , 3H), 3.27-3.39 (m, 2H), 3.54 - 3.62 (m, 1H), 4.08 - 4.24 (m, 6H), 6.95 (dd,  $^3J_{HH} = 7.2$ ,  $^4J_{HH} = 1.9$ , 1H), 7.40 (s, 1H), 7.78 (d,  $^4J_{HH} = 1.9$ , 1H), 7.93 (d,  $^3J_{HH} = 7.2$ , 1H).  **$^{31}P$  NMR** (283 MHz, CDCl<sub>3</sub>): 21.34,  **$^{13}C$  NMR** (176 MHz, CDCl<sub>3</sub>): 14.1, 16.5 (m, 2C), 21.6 (d,  $^2J_{PC} = 3.5$ , 1C), 44.6 (d,  $^1J_{PC} = 129.6$ , 1C), 62.1 (s, 1C), 63.3 (d,  $^2J_{PC} = 7.1$ , 1C), 63.4 (d,  $^2J_{PC} = 6.4$ , 1C), 116.4, 117.9, 120.3, 121.8 (d,  $^3J_{PC} = 18.0$ , 1C), 123.6, 132.6, 145.9, 168.3 (d,  $^2J_{PC} = 5.0$ , 1C), **HRMS**:  $m/z$  Calculated: 433.0522 (M + H)<sup>+</sup>, Found: 433.0529 (M + H)<sup>+</sup>.

*Ethyl 2-(diethoxyphosphoryl)-3-(8-phenylimidazo[1,2-a]pyridin-3-yl)propanoate* (**9n**). Yield: 98% yield, scale: 0.2 g,  $R_f$  0.16 (CH<sub>2</sub>Cl<sub>2</sub>:acetone 85:15),  **$^1H$  NMR** (700 MHz, CDCl<sub>3</sub>)  $\delta$ : 1.24 (t,  $^3J_{HH} = 7.10$ , 3H), 1.37 (t,  $^3J_{HH} = 7.10$ , 3H), 1.38 (t,  $^3J_{HH} = 7.10$ , 3H), 3.31-3.50 (m, 2H), 3.56-3.70 (m, 1H), 4.30-4.07 (m, 6H), 6.97 (t,  $^3J_{HH} = 6.9$ , 1H), 7.31 (dd,  $^3J_{HH} = 6.9$ ,  $^4J_{HH} = 1.1$ , 1H), 7.38-7.57 (m, 4H), 7.91-7.98 (m, 2H), 8.04 (dd,  $^3J_{HH} = 6.9$ ,  $^4J_{HH} = 1.1$ , 1H),  **$^{31}P$  NMR** (283 MHz, CDCl<sub>3</sub>): 21.60.

*Ethyl 2-(diethoxyphosphoryl)-3-(8-methylimidazo[1,2-a]pyridin-3-yl)propanoate* (**9o**). Yield: 95%, scale: 3.0 mmol, (purification by column chromatography not needed).  **$^1H$  NMR** (250 MHz, CDCl<sub>3</sub>)  $\delta$  1.20 (t,  $^3J_{HH} = 7.1$ , 3H), 1.29-1.42 (m, 6H), 2.59 (s, 3H), 3.15-3.73 (m, 3H), 4.03-4.32 (m, 6H), 6.77 (t,  $^3J_{HH} = 6.8$ , 1H), 6.97 (d,  $^3J_{HH} = 6.9$  Hz, 1H), 7.41 (s, 1H), 7.89 (d,  $^3J_{HH} = 6.9$ , 1H).  **$^{31}P$  NMR** (250 MHz, CDCl<sub>3</sub>)  $\delta$  21.33. **HRMS**  $m/z$  found 369.1585, theoretical (M+H)<sup>+</sup> 369.1508.

*Ethyl 3-(8-bromoimidazo[1,2-a]pyridin-3-yl)-2-(diethoxyphosphoryl)propanoate*

(**9p**). Yield: 36% (2 steps), scale: 0.19 g,  $R_f$  0.19, (CH<sub>2</sub>Cl<sub>2</sub>:acetone 85:15). **<sup>1</sup>H NMR** (250 MHz, CDCl<sub>3</sub>)  $\delta$ : 1.19 (t,  $^3J_{HH} = 7.10$ , 3H), 1.34 (t,  $^3J_{HH} = 7.10$ , 3H), 1.35 (t,  $^3J_{HH} = 7.10$ , 3H), 3.28 - 3.39 (m, 2H), 3.55 - 3.64 (m, 1H), 4.08 - 4.23 (m, 6H), 6.73 (t,  $^3J_{HH} = 7.0$ , 1H), 7.44 (d,  $^3J_{HH} = 7.0$ , 1H), 7.49 (s, 1H), 8.04 (d,  $^3J_{HH} = 7.0$ , 1H). **<sup>31</sup>P NMR**  $\delta$ : (250 MHz, CDCl<sub>3</sub>): 20.64; **<sup>13</sup>C NMR**  $\delta$ : (250 MHz, CDCl<sub>3</sub>): 14.1, 16.47 (d,  $^3J_{PC} = 6.1$ , 1C), 16.52 (d,  $^3J_{PC} = 6.1$ , 1C), 21.9 (d,  $^2J_{PC} = 3.3$ , 1C), 44.5 (d,  $^1J_{PC} = 129.5$ , 1C), 62.1, 63.3 (d,  $^2J_{PC} = 6.4$ , 1C), 63.4 (d,  $^2J_{PC} = 6.4$ , 1C), 112.3, 112.6, 122.7, 123.3 (d,  $^3J_{PC} = 18.2$ , 1C), 126.5 132.4, 143.6, 168.3 (d,  $^2J_{PC} = 5.1$ , 1C).

*Ethyl 2-(diethoxyphosphoryl)-3-(imidazo[2,1-a]isoquinolin-3-yl)propanoate* (**9r**).

Yield: 93%, scale: 0.2 g, (CH<sub>2</sub>Cl<sub>2</sub>:acetone 85:15). **<sup>1</sup>H NMR** (700 MHz, CDCl<sub>3</sub>)  $\delta$ : 1.19 (t,  $^3J_{HH} = 7.10$ , 3H), 1.33-1.42 (m, 6H), 3.31-3.45 (m, 2H), 3.56-3.69 (m, 1H), 4.09-4.18 (m, 2H), 4.19 - 4.24 (m, 4H), 7.10 (d,  $^3J_{HH} = 7.3$ , 1H), 7.38 (s, 1H), 7.56 (bt,  $^3J_{HH} = 7.5$ , 1H), 7.62 (bt,  $^3J_{HH} = 7.6$ , 1H), 7.70 (bd,  $^3J_{HH} = 7.9$ , 1H), 7.78 (d,  $^3J_{HH} = 7.3$ , 1H), 8.60 (d,  $^3J_{HH} = 8.0$ , 1H) **<sup>31</sup>P NMR** (101 MHz, CDCl<sub>3</sub>): 21.67, **<sup>13</sup>C NMR** (176 MHz, CDCl<sub>3</sub>): 14.1, 16.5 (d,  $^3J_{PC} = 6.1$ , 1C), 16.6 (d,  $^3J_{PC} = 6.1$ , 1C), 21.7 (d,  $^2J_{PC} = 3.6$ , 1C), 45.0 (d,  $^1J_{PC} = 129.3$ , 1C), 62.0, 63.3 (d,  $^2J_{PC} = 6.9$ , 1C), 63.4 (d,  $^2J_{PC} = 6.4$ , 1C), 113.3, 120.6, 123.3, 123.4 (d,  $^3J_{PC} = 18.0$ , 1C), 124.1, 127.0, 128.3, 128.4, 129.2, 129.4, 145.4, 168.4 (d,  $^2J_{PC} = 5.1$ , 1C).

*Ethyl 2-(ethoxy(phenyl)phosphoryl)-3-(imidazo[1,2-a]pyridin-3-yl)propanoate* (**9s**).

Yield: 68%, scale: 1.1 g, (CHCl<sub>3</sub>:MeOH 90:1  $R_f$  0.24) **<sup>31</sup>P NMR**: diastereoisomers 37.21 and 36.48 (ratio 1.2 : 1); **<sup>1</sup>H NMR** (700 MHz, CDCl<sub>3</sub>)  $\delta$  7.93 and 7.87 (2d,  $^3J_{HH} = 6.9$ , 1H), 7.79–7.69 (m, 2H), 7.57–7.40 (m, 4H), 7.32 and 7.29 (2s, 2H), 7.04-7.08 (m, 1H), 6.79–6.69 (m, 1H), 4.19–3.81 (m, 4H), 3.60–3.28 (m, 3H), 1.31 (t,  $^3J_{HH} = 7.0$ , 3H), 1.27 (t,  $^3J_{HH} = 7.0$ , 3H), 0.96 (t,  $^3J_{HH} = 7.1$ , 1H), 0.92 (t,  $^3J_{HH} = 7.1$ , 1H).

**<sup>13</sup>C NMR** (176 MHz, CDCl<sub>3</sub>) δ: [168.4 (s), 168.2 (d, <sup>2</sup>J<sub>PC</sub> = 4.1), 1C], [145.6 (s), 145.5 (s), 1C] [133.1 (d, <sup>4</sup>J<sub>PC</sub> = 2.5) 133.0 (d, <sup>4</sup>J<sub>PC</sub> = 2.3), 1C)], [132.4 (d, J<sub>PC</sub> = 9.9, 2C), 132.0 (d, J<sub>PC</sub> = 9.8, 2C)], [131.7, 131.6 (s, 1C)], [128.7 (d, J<sub>PC</sub> = 12.8, 2C), 128.6 (d, J<sub>PC</sub> = 12.9, 2C)], 128.0 (d, <sup>1</sup>J<sub>PC</sub> = 131.1, 1C), [123.7 (s, 1C), 123.6 (s, 1C)], [123.03 (s, 1C), 122.94 (s, 1C)], [121.0 (d, <sup>3</sup>J<sub>PC</sub> = 5.6, 1C), 120.9 (d, <sup>3</sup>J<sub>PC</sub> = 6.0, 1C)], 117.9 (s, 1C), [112.23 (s, 1C), 112.21 (s, 1C)], [62.0 (d, <sup>2</sup>J<sub>PC</sub> = 6.3, 1C), 61.9 (d, <sup>2</sup>J<sub>PC</sub> = 5.9, 1C)], [61.61 (s, 1C), 61.56 (s, 1C)], [47.8 (d, <sup>1</sup>J<sub>PC</sub> = 85.6, 1C), 47.5 (d, <sup>1</sup>J<sub>PC</sub> = 85.2, 1C)], [20.9 (s, 1C), 20.7 (s, 1C)], [16.5 (d, <sup>3</sup>J<sub>PC</sub> = 5.6, 1C), 16.4 (d, <sup>3</sup>J<sub>PC</sub> = 6.4, 1C)], [13.8 (s, 1C), 13.7 (s, 1C)]. **HRMS:** m/z Calculated: 387.1476 (M + H)<sup>+</sup>, Found: 387.1480 (M + H)<sup>+</sup>.

*Ethyl 2-(ethoxy(ethyl)phosphoryl)-3-(imidazo[1,2-a]pyridin-3-yl)propanoate (9t).*

Yield: 69%, scale: 0.75 g, (CHCl<sub>3</sub>:AcOEt 20:1 R<sub>f</sub> 0.20). **<sup>31</sup>P NMR** (101 MHz, CDCl<sub>3</sub>): diastereoisomers 51.70 and 50.86 (ratio 1.1 : 1). **<sup>1</sup>H NMR** (700 MHz, CDCl<sub>3</sub>) δ: 7.95 (bt, <sup>3</sup>J<sub>HH</sub> = 6.8, 1H), 7.45 (bd, <sup>3</sup>J<sub>HH</sub> = 8.9, 1H), 7.29 (bs, 1H), 7.03 (dd, <sup>3</sup>J<sub>HH</sub> = 14.6, 6.3), 1H), 6.71 (dd, <sup>3</sup>J<sub>HH</sub> = 6.9, 1H), 4.13 – 3.94 (m, 4H), 3.50–3.13 (m, 3H), 1.83–1.74 (m, 2H), [1.22 (t, <sup>3</sup>J<sub>HH</sub> = 7.0, 3H), 1.22 (t, <sup>3</sup>J<sub>HH</sub> = 7.1, 3H)], 1.14–1.09 (m, 3H), [1.08 (t, <sup>3</sup>J<sub>HH</sub> = 7.7, 3H), 1.06 (t, <sup>3</sup>J<sub>HH</sub> = 7.7, 3H)]. **<sup>13</sup>C NMR** (176 MHz, CDCl<sub>3</sub>) δ: [168.9 (s, 1C), 168.5 (d, <sup>2</sup>J<sub>PC</sub> = 2.5, 1C)], [145.5 (s, 1C), 145.4 (s, 1C)], 131.4 (s, 1C), [123.7 (s, 1C), 123.6 (s, 1C)], 122.9 (s, 1C), [121.3 (d, <sup>3</sup>J<sub>PC</sub> = 14.8, 1C), 120.9 (d, <sup>3</sup>J<sub>PC</sub> = 15.4, 1C)], [117.8 (s, 1C), 117.7 (s, 1C)], [112.3 (s, 1C), 112.2 (s, 1C)], 61.7–61.6 (m, 1C), 61.3–61.2 (m, 1C), 46.2 (d, <sup>1</sup>J<sub>PC</sub> = 71.8, 1C), 46.1 (d, <sup>1</sup>J<sub>PC</sub> = 71.8, 1C), [20.9 (bs, 1C), 19.7 (bs, 1C)], [21.1 (d, <sup>1</sup>J<sub>PC</sub> = 96.7, 1C), 19.4 (d, <sup>1</sup>J<sub>PC</sub> = 96.4, 1C)], [16.5 (d, <sup>3</sup>J<sub>PC</sub> = 6.0, 1C), 16.3 (d, <sup>3</sup>J<sub>PC</sub> = 6.1, 1C)], 13.8 (s, 1C), [5.4 (d, <sup>2</sup>J<sub>PC</sub> = 5.5, 1C), 5.1 (d, <sup>2</sup>J<sub>PC</sub> = 6.6, 1C)]. **HRMS** m/z Calculated: 339.1476 (M + H)<sup>+</sup>, Found: 339.1405 (M + H)<sup>+</sup>.

*Ethyl 3-([1,1'-biphenyl]-3-yl)-2-(diethoxyphosphoryl)propanoate (9u)*. Yield: 75%, scale: 1.10 g.  $R_f$  0,22 (Hexane:AcOEt 1:1);  $^{31}\text{P}$  NMR:  $\delta$  22.29.  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ )  $\delta$  1.11 (t,  $^3J_{\text{HH}} = 7.1$ , 3H), 1.35 and 1.36 (2dt,  $^3J_{\text{HH}} = 7.1$ ,  $^4J_{\text{HP}} = 0.5$ , 6H), 3.18–3.42 (m, 3H), 4.03 – 4.26 (m, 6H), 7.15–7.20 (m, 1H), 7.27–7.47 and 7.50–7.59 (2m, 8H).  $^{13}\text{C}$  NMR (63 MHz,  $\text{CDCl}_3$ )  $\delta$  13.9, 16.3 (d,  $^3J_{\text{PC}} = 5.9$ , 2C), 32.8 (d,  $^2J_{\text{PC}} = 4.2$ , 1C), 47.6 (d,  $^1J_{\text{PC}} = 129.1$ , 1C), 61.2, 62.7 and 62.8 (2d,  $^2J_{\text{PC}} = 7.5$ , 2C), 126.9, 128.6 (2s, 4C), 125.4, 126.9, 127.2, 127.3, 128.8, 138.9 (d,  $^3J_{\text{PC}} = 16.0$ , 1C), 140.8, 141.3 (2s, 2C), 168.4 (d,  $^2J_{\text{PC}} = 4.5$ ).

*Ethyl 3-([1,1'-biphenyl]-4-yl)-2-(diethoxyphosphoryl)propanoate (9w)*. Yield: 85%, scale: 1.09 g;  $R_f$  0,34 (Hexane:AcOEt 1:1);  $^{31}\text{P}$  NMR:  $\delta$  22.49.  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ )  $\delta$  1.16 (t,  $^3J_{\text{HH}} = 7.1$ , 3H), 1.36 (2dt,  $^3J_{\text{HH}} = 7.1$ ,  $^4J_{\text{PH}} = 0.5$ , 6H), 3.40–3.13 (m, 3H), 4.06 – 4.29 (m, 6H), 7.24–7.60 (m, 9H).  $^{13}\text{C}$  NMR (63 MHz,  $\text{CDCl}_3$ )  $\delta$ : 13.9, 16.3 (d,  $^3J_{\text{PC}} = 4.8$ , 2C), 32.4, 47.6 (d,  $^1J_{\text{PC}} = 128.8$ , 1C), 61.1, 62.7 and 62.8 (2d,  $^2J_{\text{PC}} = 7.5$ , 2C), 126.9, 127.1 (2s, 5C), 128.7, 129.0 (2s, 4C), 137.5 (d,  $^3J_{\text{PC}} = 16.0$ , 1C), 139.5 and 140.7 (2s, 2C), 168.4 (d,  $^2J_{\text{PC}} = 4.7$ , 1C).

*Ethyl 3-(3-benzylphenyl)-2-(diethoxyphosphoryl)propanoate (9y)*. Yield: 68%; scale: 0.76 g.  $R_f$  0.21 (Hexane:AcOEt 1:1);  $^{31}\text{P}$  NMR  $\delta$  21.81;  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ )  $\delta$  1.02 (t,  $^3J_{\text{HH}} = 7.1$ , 3H), 1.25 (t,  $^3J_{\text{HH}} = 7.1$ , 6H), 2.99–3.24 (m, 3H), 3.84 (s, 2H), 3.88–4.17 (m, 6H), 7.23 – 6.91 (m, 9H).  $^{13}\text{C}$  NMR (63 MHz,  $\text{CDCl}_3$ )  $\delta$  13.8, 16.2 (d,  $^3J_{\text{PC}} = 5.7$ , 2C), 32.6 (d,  $^2J_{\text{PC}} = 4.1$ , 1C), 41.7, 47.5 (d,  $^1J_{\text{PC}} = 129.0$ , 1C), 61.1, 62.6, 62.7 (2d,  $^2J_{\text{PC}} = 6.8$ , 2C), 128.2, 128.6 (2s, 4C), 125.9, 126.2, 127.2, 128.5, 129.0, 138.5 (d,  $^3J_{\text{PC}} = 16.1$ , 1C), 140.8, 141.2, 168.3 (d,  $^2J_{\text{PC}} = 4.5$ , 1C).

*Ethyl 3-([1,1':4',1''-terphenyl]-3-yl)-2-(diethoxyphosphoryl)propanoate (9z)*. Yield: 62%; scale: 2.17 g;  $R_f$  0.41 (Hexane:AcOEt 2:1).  $^{31}\text{P}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  22.61.  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ )  $\delta$  7.72–7.59 (m, 6H), 7.54–7.31 (m, 6H), 7.23–

7.17 (m, 1H), 4.27–4.04 (m, 6H), 3.44–3.18 (m, 3H), 1.36 (t,  $^3J_{\text{HH}} = 7.1$ , 3H), 1.37 (t,  $^3J_{\text{HH}} = 7.1$ , 3H), 1.14 (t,  $^3J_{\text{HH}} = 7.1$ , 3H).  $^{13}\text{C}$  NMR (63 MHz,  $\text{CDCl}_3$ )  $\delta$  168.4 (d,  $^2J_{\text{PC}} = 4.7$ , 1C), 140.8, 140.5, 140.1, 139.7, 139.1 (d,  $^3J_{\text{PC}} = 16.0$ , 1C), 129.0, 128.7, 127.6, 127.4, 127.34, 127.28, 126.9, 125.4 (8s, 13C), 62.9 (d,  $^2J_{\text{PC}} = 6.7$ , 1C), 62.7 (d,  $^2J_{\text{PC}} = 7.0$ , 1C), 61.3 (s, 1C), 47.6 (d,  $^1J_{\text{PC}} = 129.1$ , 1C), 32.8 (d,  $^2J_{\text{PC}} = 4.3$ , 1C), 16.4 (d,  $^3J_{\text{PC}} = 5.9$ , 1C), 16.3 (d,  $^3J_{\text{PC}} = 6.1$ , 1C), 14.0 (s, 1C). **HRMS**  $m/z$  Calculated: 489.1807 ( $\text{M} + \text{H}$ ) $^+$ , Found: 489.1807 ( $\text{M} + \text{H}$ ) $^+$ .

**Route 2 (9a-c).** Reaction was carried out under argon atmosphere using oven-dried glassware. A 50 mL round-bottom flask was charged with appropriate 2-substituted imidazo[1,2-a]pyridine **4** (0.474 mmol, 1 equiv.), ethyl 2-(diethoxyphosphoryl)acrylate (134 mg, 0.569 mmol, 1.2 equiv and dioxane 6 mL). The mixture was heated and stirred. Then  $\text{AlCl}_3$  (6.5 mg, 0.0474 mmol, 0.1 equiv) was added. The solution was stirred for 12 h at reflux. The crude mixture was evaporated under reduced pressure, dissolved in 5 ml of water and made basic with saturated  $\text{Na}_2\text{CO}_3$  solution to  $\text{pH} > 9$ . The water layer was extracted with chloroform (5 x 25 ml). Organic layer was dried over anhydrous  $\text{Mg}_2\text{SO}_4$ , evaporated and residue was subjected to flash chromatography using DCM: acetone in gradient as eluent 0  $\Rightarrow$  40 % of acetone in 40 minutes to give product as orange oil.

**Ethyl 2-(diethoxyphosphoryl)-3-(2-phenylimidazo[1,2-a]pyridin-3-yl)propanoate (9a).** Yield: 55% yield, scale 0.25 g, ( $\text{CH}_2\text{Cl}_2$ :acetone 85:15).  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ )  $\delta$ : 0.97 (t,  $^3J_{\text{HH}} = 7.10$ , 3H), 1.27 (t,  $^3J_{\text{HH}} = 7.10$ , 6H), 3.26 (ddd,  $^2J_{\text{PH}} = 22.1$ ,  $^3J_{\text{HH}} = 10.4$ ,  $^3J_{\text{HH}} = 3.8$ , 1H), 3.66 (ddd,  $^3J_{\text{HH}} = 15.8$ ,  $^3J_{\text{PH}} = 10.0$ ,  $^3J_{\text{HH}} = 3.8$ , 1H), 3.80–3.95 (m, 3H), 4.05–4.15 (m, 4H), 6.81 (t,  $^3J_{\text{HH}} = 6.8$ , 1H), 7.13–7.17 (m, 1H), 7.32 (t,  $^3J_{\text{HH}} = 7.4$ , 1H), 7.42 (t,  $^3J_{\text{HH}} = 7.7$ , 2H), 7.58 (d,  $^3J_{\text{HH}} = 9.0$ , 1H), 7.79 (d,  $^3J_{\text{HH}} = 7.2$ , 2H), 8.18 (d,  $^3J_{\text{HH}} = 6.8$ , 1H),  $^{31}\text{P}$  NMR (250 MHz,  $\text{CDCl}_3$ ): 20.97,  $^{13}\text{C}$  NMR (700

1  
2  
3 MHz, CDCl<sub>3</sub>): 13.8, 16.36 (d, <sup>3</sup>J<sub>PC</sub> = 5.8, 1C), 16.38 (d, <sup>3</sup>J<sub>PC</sub> = 5.8, 1C), 21.6 (bs, 1C),  
4  
5 44.3 (d, <sup>1</sup>J<sub>PC</sub> = 128.8, 1C), 61.9, 63.0 (d, <sup>2</sup>J<sub>PC</sub> = 6.8, 1C), 63.2 (d, <sup>2</sup>J<sub>PC</sub> = 6.4, 1C),  
6  
7 112.3, 117.0 (d, <sup>3</sup>J<sub>PC</sub> = 16.0, 1C), 117.5, 123.8, 124.3, 127.8, 128.2 (s, 2C), 128.6 (s,  
8  
9 2C), 134.4 (s, 1C), 143.2 (s, 1C), 144.8 (s, 1C), 168.5 (d, <sup>2</sup>J<sub>PC</sub> = 4.5, 1C).

10  
11  
12 *Ethyl 2-(diethoxyphosphoryl)-3-(2-methylimidazo[1,2-a]pyridin-3-yl)propanoate*  
13  
14 (**9b**). Yield: 63% yield, scale: 0.3 g, (CH<sub>2</sub>Cl<sub>2</sub>:acetone 85:15). <sup>1</sup>H NMR (700 MHz,  
15  
16 CDCl<sub>3</sub>) δ: 1.14 (t, <sup>3</sup>J<sub>HH</sub> = 7.10, 3H), 1.36 (m, 6H), 2.43 (s, 3H), 3.20 (m, 1H), 3.39 (m,  
17  
18 1H), 3.66 (m, 1H), 4.00-4.31 (m, 6H), 6.80 (td, <sup>3</sup>J<sub>HH</sub> = 6.8, <sup>4</sup>J<sub>HH</sub> = 1.2, 1H), 7.13 (ddd,  
19  
20 <sup>3</sup>J<sub>HH</sub> = 9.0, <sup>3</sup>J<sub>HH</sub> = 6.8, <sup>4</sup>J<sub>HH</sub> = 1.2, 1H), 7.50 (bd, <sup>3</sup>J<sub>HH</sub> = 9.0, 1H), 8.01 (bd, <sup>3</sup>J<sub>HH</sub> = 6.8,  
21  
22 1H), <sup>31</sup>P NMR (283 MHz, CDCl<sub>3</sub>): 21.43, <sup>13</sup>C NMR (176 MHz, CDCl<sub>3</sub>): 13.2, 13.8,  
23  
24 16.28 (d, <sup>3</sup>J<sub>PC</sub> = 6.0 1C), 16.33 (d, <sup>3</sup>J<sub>PC</sub> = 6.0, 1C), 20.8 (d, <sup>2</sup>J<sub>PC</sub> = 3.5, 1C), 44.0 (d,  
25  
26 <sup>1</sup>J<sub>PC</sub> = 128.5, 1C), 61.8 (s, 1C), 63.0 (d, <sup>2</sup>J<sub>PC</sub> = 6.8, 1C), 63.1 (d, <sup>2</sup>J<sub>PC</sub> = 6.2, 1C), 111.9  
27  
28 (s, 1C), 116.5 (d, <sup>3</sup>J<sub>PC</sub> = 15.0, 1C), 116.7, 122.9, 123.5, 141.0, 144.4, 168.3 (d, <sup>2</sup>J<sub>PC</sub> =  
29  
30 4.7, 1C).

31  
32  
33 *Ethyl 3-(6-bromo-2-methylimidazo[1,2-a]pyridin-3-yl)-2-(diethoxyphosphoryl)-*  
34  
35 *propanoate (9c)*. Yield: 60% yield, scale: 0.4 g, (CH<sub>2</sub>Cl<sub>2</sub>:acetone 85:15), <sup>1</sup>H NMR  
36  
37 (700 MHz, CDCl<sub>3</sub>) δ: 1.09 (t, <sup>3</sup>J<sub>HH</sub> = 7.10, 3H), 1.30 (t, <sup>3</sup>J<sub>HH</sub> = 7.10, 6H), 2.33 (s, 3H),  
38  
39 3.11 (ddd, <sup>2</sup>J<sub>PH</sub> = 22.7, <sup>3</sup>J<sub>HH</sub> = 10.5, <sup>3</sup>J<sub>HH</sub> = 3.5, 1H), 3.29 (ddd, <sup>2</sup>J<sub>HH</sub> = 15.8, <sup>3</sup>J<sub>PH</sub> =  
40  
41 10.2, <sup>3</sup>J<sub>HH</sub> = 3.5, 1H), 3.55 (ddd, <sup>2</sup>J<sub>HH</sub> = 15.8, <sup>3</sup>J<sub>HH</sub> = 10.5, <sup>3</sup>J<sub>PH</sub> = 7.9, 1H), 3.99-4.08  
42  
43 (m, 2H), 4.10 - 4.17 (m, 4H), 7.10 (dd, <sup>3</sup>J<sub>HH</sub> = 9.4, <sup>4</sup>J<sub>HH</sub> = 1.8, 1H), 7.31 (dd, <sup>3</sup>J<sub>HH</sub> =  
44  
45 9.4, <sup>4</sup>J<sub>HH</sub> = 0.6, 1H), 8.08 (d, <sup>4</sup>J<sub>HH</sub> = 1.1, 1H), <sup>31</sup>P NMR (283 MHz, CDCl<sub>3</sub>): 20.70,  
46  
47 <sup>13</sup>C NMR (176 MHz, CDCl<sub>3</sub>): 13.4, 13.9, 16.4 (m, 2C), 20.9 (d, <sup>2</sup>J<sub>PC</sub> = 4.0, 1C), 44.1  
48  
49 (d, <sup>1</sup>J<sub>PC</sub> = 128.7, 1C), 62.0, 63.1 (d, <sup>2</sup>J<sub>PC</sub> = 6.7, 1C), 63.2 (d, <sup>2</sup>J<sub>PC</sub> = 6.5, 1C), 106.6,  
50  
51 117.40 (d, <sup>3</sup>J<sub>PC</sub> = 15.7, 1C), 117.41, 123.2, 126.8, 142.1, 142.8, 168.3 (d, <sup>2</sup>J<sub>PC</sub> = 4.7,  
52  
53 1C).

*General procedure for fluorination. Synthesis of compounds 10.* Reaction was carried out under argon atmosphere using oven-dried glassware. A solution of the phosphonocarboxylate triester **9** (1 equiv, 1.01 mmol) in anhydrous THF (8 mL) was cooled to  $-78^{\circ}\text{C}$ , and n-BuLi (1.6 M in Hex, 1.5 equiv) was added via syringe. The solution was stirred for 10 min at  $-78^{\circ}\text{C}$ , allowed to warm up to  $0^{\circ}\text{C}$ , and stirred for 1 h, and then cooled back to  $-78^{\circ}\text{C}$ . Then, a solution of N-fluoro-N-(phenylsulfonyl)-benzenesulfonamide (1.2 equiv) in anhydrous THF (8 mL) was added dropwise via syringe. The reaction mixture was stirred at  $-78^{\circ}\text{C}$  for 10 min, warmed up to rt and stirred for additional 4.5 h. The reaction mixture was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$ , concentrated under vacuum. It was basified with solution of  $\text{Na}_2\text{CO}_3$ , up to pH 9, extracted with  $\text{CHCl}_3$  (3x). The organic layer was dried over anhydrous  $\text{MgSO}_4$ , concentrated to dryness under vacuum, and purified by column chromatography. The products were isolated as oils in 40 – 80 % yields.

*Ethyl 2-(diethoxyphosphoryl)-2-fluoro-3-(2-phenylimidazo[1,2-a]pyridin-3-yl)propanoate (10a).* Yield: 72%, scale: 0.15 g, ( $\text{CH}_2\text{Cl}_2$ :acetone 85:15),  $^1\text{H}$  NMR (250MHz,  $\text{CDCl}_3$ )  $\delta$ : 0.91 (t,  $^3J_{\text{HH}} = 7.10$ , 3H), 1.34 (t,  $^3J_{\text{HH}} = 7.10$ , 3H), 1.35 (t,  $^3J_{\text{HH}} = 7.10$ , 3H), 3.41-3.64 (m, 1H), 3.82-4.04 (m, 2H), 4.13 - 4.44 (m, 5H), 6.83 (dt,  $^3J_{\text{HH}} = 6.9$ ,  $^4J_{\text{HH}} = 1.2$ , 1H), 7.20 (ddd,  $^3J_{\text{HH}} = 9.0$ ,  $^3J_{\text{HH}} = 6.7$ ,  $^4J_{\text{HH}} = 1.2$ , 1H), 7.29-7.40 (m, 1H), 7.41-7.50 (m, 2H), 7.57-7.68 (m, 1H), 7.69-7.79 (m, 2H), 8.21 (bd,  $^3J_{\text{HH}} = 6.9$ , 1H),  $^{31}\text{P}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$ : 12.15 (d,  $^2J_{\text{PF}} = 83.3$ ). HRMS: m/z Calculated: 449,1636 ( $\text{M} + \text{H}^+$ ), Found: 449.1659 ( $\text{M} + \text{H}^+$ ).

*Ethyl 2-(diethoxyphosphoryl)-2-fluoro-3-(2-methylimidazo[1,2-a]pyridin-3-yl)propanoate (10b).* Yield: 72%, scale: 0.15 g, ( $\text{CH}_2\text{Cl}_2$ :acetone 85:15).  $^1\text{H}$  NMR (700 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.15 (t,  $^3J_{\text{HH}} = 7.10$ , 3H), 1.34 (t,  $^3J_{\text{HH}} = 7.15$ , 3H), 1.36 (t,  $^3J_{\text{HH}} = 7.15$ , 3H), 2.41 (s, 3H), 3.71 (ddd,  $^2J_{\text{HH}} = 16.3$ ,  $^3J_{\text{FH}} = 12.7$ ,  $^3J_{\text{PH}} = 6.9$ , 1H), 3.87

(ddd,  $^2J_{\text{HH}} = 16.3$ ,  $^3J_{\text{FH}} = 35.5$ ,  $^3J_{\text{PH}} = 6.5$ , 1H), 4.10-4.21 (m, 2H), 4.21-4.29 (m, 4H), 6.77 (t,  $^3J_{\text{HH}} = 6.8$ , 1H), 7.15 (m, 1H), 7.51 (t,  $^3J_{\text{HH}} = 9.0$ , 1H), 8.10 (d,  $^3J_{\text{HH}} = 6.6$ , 1H).  **$^{31}\text{P}$  NMR** (283 MHz,  $\text{CDCl}_3$ )  $\delta$ : 11.74 (d,  $^2J_{\text{PF}} = 82.7$ ),  **$^{13}\text{C}$  NMR** (176MHz,  $\text{CDCl}_3$ )  $\delta$ : 13.5, 13.9, 16.49 (d,  $^3J_{\text{PC}} = 5.3$ , 1C), 16.51 (d,  $^3J_{\text{PC}} = 5.4$ , 1C), 28.1 (d,  $^2J_{\text{FC}} = 20.4$ , 1C), 62.9, 64.6 (d,  $^2J_{\text{PC}} = 7.0$ , 1C), 64.9 (d,  $^2J_{\text{PC}} = 6.7$ , 1C), 96.4 (dd,  $^1J_{\text{FC}} = 200.2$ ,  $^1J_{\text{PC}} = 160.6$ , 1C), 112.0, 112.8 (d,  $^3J_{\text{PC}} = 12.6$ , 1C), 116.6 (s, 1C), 124.2 (d,  $^5J_{\text{FC}} = 6.2$ , 1C), 124.6, 142.6, 145.0, 166.7 (dd,  $^2J_{\text{FC}} = 22.4$ ,  $^2J_{\text{PC}} = 4.2$ , 1C).

*Ethyl-3-(6-bromo-2-methylimidazo[1,2-a]pyridin-3-yl)-2-(diethoxyphosphoryl)-2-fluoropropanoate (10c)*. Yield: 75%, scale: 0.2 g, ( $\text{CH}_2\text{Cl}_2$ :acetone 85:15).  **$^1\text{H}$  NMR** (700 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.18 (t,  $^3J_{\text{HH}} = 7.10$ , 3H), 1.36 (t,  $^3J_{\text{HH}} = 7.10$ , 6H), 2.38 (s, 3H), 3.56-3.98 (m, 2H), 4.07-4.38 (m, 6H), 7.17 (dd,  $^3J_{\text{HH}} = 9.5$ ,  $^4J_{\text{HH}} = 1.8$ , 1H), 7.36 (d,  $^3J_{\text{HH}} = 9.5$ , 1H), 8.20 (bs, 1H),  **$^{31}\text{P}$  NMR** (283 MHz,  $\text{CDCl}_3$ )  $\delta$ : 11.82 (d,  $^2J_{\text{PF}} = 82.0$ ),  **$^{13}\text{C}$  NMR** (176 MHz,  $\text{CDCl}_3$ )  $\delta$ : 13.6, 13.8, 16.36, 16.39, 28.0 (d,  $^2J_{\text{PC}} = 21.0$ , 1C), 62.9, 64.6 (d,  $^2J_{\text{PC}} = 7.0$ , 1C), 64.8 (d,  $^2J_{\text{PC}} = 7.0$ , 1C), 95.7 (dd,  $^1J_{\text{FC}} = 199.9$ ,  $^1J_{\text{PC}} = 160.7$ , 1C), 106.4, 113.3 (d,  $^3J_{\text{PC}} = 13.0$ , 1C), 117.2, 124.1 (d,  $^5J_{\text{FC}} = 6.5$ , 1C), 127.4, 143.5, 144.0, 166.5 (dd,  $^2J_{\text{FC}} = 22.6$ ,  $^2J_{\text{PC}} = 4.0$ , 1C).

*Ethyl 2-(diethoxyphosphoryl)-2-fluoro-3-(5-methylimidazo[1,2-a]pyridin-3-yl)propanoate (10e)*. Yield: 51%, scale: 0.30 g. ( $\text{CHCl}_3$ :MeOH (20:1) + TEA (0.2 %)).  **$^1\text{H}$  NMR** (250 MHz,  $\text{CDCl}_3$ )  $\delta$  1.20 (t,  $^3J_{\text{HH}} = 7.1$ , 3H), 1.37 (t,  $^3J_{\text{HH}} = 7.1$ , 3H), 1.38 (t,  $^3J_{\text{HH}} = 7.1$ , 3H), 2.85 (s, 3H), 4.16 - 4.35 (m, 8H), 6.52 (d,  $^3J_{\text{HH}} = 6.9$ , 1H), 7.05 (dd,  $^3J_{\text{HH}} = 8.5$ ,  $^3J_{\text{HH}} = 6.9$ , 1H), 7.46 (d,  $^3J_{\text{HH}} = 8.5$ , 1H), 7.47 (s, 1H);  **$^{13}\text{C}$  NMR** (63 MHz,  $\text{CDCl}_3$ )  $\delta$ : 14.0, 16.4 (d,  $^3J_{\text{PC}} = 5.5$ , 2C), 21.1, 30.4 (d,  $^2J_{\text{PC}} = 19.9$ , 1C), 62.8, 64.5 (d,  $^2J_{\text{PC}} = 7.0$ , 1C), 64.9 (d,  $^2J_{\text{PC}} = 6.4$ , 1C), 96.0 (dd,  $^1J_{\text{FC}} = 201.1$ ,  $^1J_{\text{PC}} = 158.5$ , 1C), 114.2, 116.2, 118.1 (d,  $^3J_{\text{PC}} = 14.6$ , 1C), 124.6, 135.0, 136.4, 148.0, 166.5 (dd,  $^2J_{\text{FC}} = 22.1$ ,  $^2J_{\text{PC}} = 3.5$  1C);  **$^{13}\text{P}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$ : 12.70 (d,  $^2J_{\text{PF}} = 83.6$ )



*Ethyl 2-(diethoxyphosphoryl)-2-fluoro-3-(6-phenylimidazo[1,2-a]pyridin-3-yl)propanoate (10f)*. Yield: 46%, scale: 0.1 g, (CH<sub>2</sub>Cl<sub>2</sub>:acetone 85:15). <sup>1</sup>H NMR (700 MHz, CDCl<sub>3</sub>) δ: 1.18 (t, <sup>3</sup>J<sub>HH</sub> = 7.10, 3H), 1.33 (t, <sup>3</sup>J<sub>HH</sub> = 7.10, 3H), 1.34 (t, <sup>3</sup>J<sub>HH</sub> = 7.10, 3H), 3.66-4.04 (m, 2H), 4.08-4.23 (m, 6H), 7.31-7.70 (m, 8H), 8.26 (bs, 1H), <sup>31</sup>P NMR (283 MHz, CDCl<sub>3</sub>) δ: 11.76 (d, <sup>2</sup>J<sub>PF</sub> = 81.9), <sup>13</sup>C NMR (176 MHz, CDCl<sub>3</sub>) δ: 14.0, 16.4 (bd, 1C), 16.5 (bd, 1C), 28.6 (d, <sup>2</sup>J<sub>FC</sub> = 18.8 1C), 62.8, 64.6 (d, <sup>2</sup>J<sub>PC</sub> = 7.0, 1C), 64.9 (d, <sup>2</sup>J<sub>PC</sub> = 6.6, 1C), 96.2 (dd, <sup>1</sup>J<sub>FC</sub> = 200.5, <sup>1</sup>J<sub>PC</sub> = 160.1, 1C), 117.2 (d, <sup>3</sup>J<sub>PC</sub> = 14.4, 1C), 117.6, 121.3 (s, <sup>5</sup>J<sub>PC</sub> = 4.9, 1C), 125.3, 127.0, 127.2 (s, 2C), 128.0 (s, 2C), 129.2 (s, 1C), 134.4 (s, 1C), 137.5 (s, 1C), 145.4 (s, 1C), 166.4 (dd, <sup>2</sup>J<sub>FC</sub> = 22.1, <sup>2</sup>J<sub>PC</sub> = 3.8, 1C).

*Ethyl 2-(diethoxyphosphoryl)-2-fluoro-3-(6-methylimidazo[1,2-a]pyridin-3-yl)propanoate (10g)*. Yield: 41%, scale: 0.3 g. (DCM:Aceton (7:3) + TEA (0.2 %)). <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ: 1.21 (t, <sup>3</sup>J<sub>HH</sub> = 7.1, 3H), 1.37 (t, <sup>3</sup>J<sub>HH</sub> = 7.3, 3H), 1.38 (t, <sup>3</sup>J<sub>HH</sub> = 7.1, 3H), 2.34 (s, 3H), 3.55-3.79 (m, 1H), 3.87 (ddd, <sup>3</sup>J<sub>FH</sub> = 37.4, <sup>2</sup>J<sub>HH</sub> = 16.2, <sup>3</sup>J<sub>PH</sub> = 5.8, 1H), 4.10-4.36 (m, 6H), 7.03 (d, <sup>3</sup>J<sub>HH</sub>=7.0, 1H), 7.44 (s, 1H), 7.49 (d, <sup>3</sup>J<sub>HH</sub>=7.2, 1H), 7.89 (s, 1H); <sup>13</sup>C NMR (250 MHz, CDCl<sub>3</sub>) δ: 14.3, 16.42, 16.44, 20.7, 29.0 (d, <sup>2</sup>J<sub>PC</sub>=20.3, 1C), 61.5, 63.6 (d, <sup>2</sup>J<sub>PC</sub>=7.4, 1C), 63.7 (d, <sup>2</sup>J<sub>PC</sub>=7.2, 1C), 102.2 (dd, <sup>1</sup>J<sub>FC</sub>=193.2, <sup>1</sup>J<sub>PC</sub>=137.1, 1C), 116.9, 122.3, 125.0, 126.4 (d, <sup>3</sup>J<sub>PC</sub>=14.9, 1C), 133.2, 139.0, 146.7, 171.3 (d, <sup>2</sup>J<sub>FC</sub>=22.1, 1C); <sup>31</sup>P NMR (250 MHz, CDCl<sub>3</sub>) δ: 12.39 (d, <sup>2</sup>J<sub>PF</sub>=82.6).

*Ethyl 3-(6-chloroimidazo[1,2-a]pyridin-3-yl)-2-(diethoxyphosphoryl)-2-fluoropropanoate (10h)*. Yield: 72%, scale: 0.12 g, (CH<sub>2</sub>Cl<sub>2</sub>:acetone 85:15), <sup>1</sup>H NMR (700 MHz, CDCl<sub>3</sub>) δ: 1.21 (t, <sup>3</sup>J<sub>HH</sub> = 7.10, 3H), 1.36 (t, <sup>3</sup>J<sub>HH</sub> = 7.10, 6H), 3.60-4.01 (m, 2H), 4.13-4.36 (m, 6H), 7.13 (dd, <sup>3</sup>J<sub>HH</sub> = 9.6, <sup>4</sup>J<sub>HH</sub> = 1.9, 1H), 7.49-7.56 (m, 2H), 8.15 (bs, 1H), <sup>31</sup>P NMR (283 MHz, CDCl<sub>3</sub>) δ: 11.59, (d, <sup>2</sup>J<sub>PF</sub> = 82.1), <sup>13</sup>C NMR (176

1  
2  
3 MHz, CDCl<sub>3</sub>)  $\delta$ : 14.0, 16.4, 16.5, 28.5 (d,  $^2J_{\text{FC}} = 20.8$ , 1C), 63.0, 64.7 (d,  $^2J_{\text{PC}} = 7.1$ ,  
4  
5 1C), 65.0 (d,  $^2J_{\text{PC}} = 6.7$ , 1C), 96.0 (dd,  $^1J_{\text{FC}}=199.5$ ,  $^1J_{\text{PC}}=160.3$ , 1C), 117.5 (d,  
6  
7  $^3J_{\text{PC}}=14.1$ , 1C), 118.5, 120.9, 122.0 (d,  $^5J_{\text{PC}} = 4.7$ , 1C), 125.8, 135.0, 144.5, 166.2 (d,  
8  
9  $^2J_{\text{FC}} = 18.9$ , 1C).

10  
11  
12 *Ethyl* 3-(6-bromoimidazo[1,2-*a*]pyridin-3-yl)-2-(diethoxyphosphoryl)-2-  
13  
14 fluoropropanoate (**10i**). Yield: 44%, scale: 0.2 g, R<sub>f</sub> 0.15 (CH<sub>2</sub>Cl<sub>2</sub>:acetone 85:15), **<sup>1</sup>H**  
15  
16 **NMR** (700 MHz, CDCl<sub>3</sub>)  $\delta$ : 1.23 (t,  $^3J_{\text{HH}} = 7.10$ , 3H), 1.38 (t,  $^3J_{\text{HH}} = 7.10$ , 6H), 3.71  
17  
18 (ddd,  $^2J_{\text{HH}} = 16.2$ ,  $^3J_{\text{FH}} = 12.4$ ,  $^3J_{\text{PH}} = 6.7$ , 1H), 3.87 (ddd,  $^3J_{\text{FH}} = 37.0$ ,  $^2J_{\text{HH}} = 16.2$ ,  
19  
20  $^3J_{\text{PH}} = 6.1$ , 1H), 4.23 (q,  $^3J_{\text{HH}} = 7.1$ , 2H), 4.25 - 4.33 (m, 4H), 7.24 (dd,  $^3J_{\text{HH}} = 9.5$ ,  
21  
22  $^4J_{\text{HH}} = 1.7$ , 1H), 7.49 (m, 2H), 8.26 (bs, 1H), **<sup>31</sup>P NMR** (283 MHz, CDCl<sub>3</sub>)  $\delta$ : 11.28  
23  
24 (d,  $^2J_{\text{PF}} = 83.2$ ), **<sup>13</sup>C NMR** (176 MHz, CDCl<sub>3</sub>)  $\delta$ : 14.1, 16.54 (d,  $^3J_{\text{PC}} = 5.9$ , 1C), 16.56  
25  
26 (d,  $^3J_{\text{PC}} = 5.9$ , 1C), 28.6 (d,  $^2J_{\text{FC}} = 20.5$ , 1C), 63.0, 64.7 (d,  $^2J_{\text{PC}} = 7.0$ , 1C), 65.1 (d,  
27  
28  $^2J_{\text{PC}} = 6.6$ , 1C), 95.7 (dd,  $^1J_{\text{FC}} = 199.5$ ,  $^1J_{\text{PC}} = 152.9$ , 1C), 107.5, 117.4 (d,  $^3J_{\text{PC}} = 15.2$ ,  
29  
30 1C), 118.6, 124.2 (d,  $^5J_{\text{FC}} = 4.9$ , 1C), 127.9, 135.0, 144.7, 166.3 (dd,  $^2J_{\text{FC}} = 22.0$ ,  $^2J_{\text{PC}}$   
31  
32 = 3.7, 1C), **HRMS**: m/z Calculated: 451.0428 (M + H)<sup>+</sup>, Found: 451.0443 (M + H)<sup>+</sup>.

33  
34  
35  
36  
37  
38  
39 *Ethyl* 2-(diethoxyphosphoryl)-2-fluoro-3-(7-phenylimidazo[1,2-*a*]pyridin-3-  
40  
41 yl)propanoate (**10j**). Yield: 66%, scale: 0.1 g, (CH<sub>2</sub>Cl<sub>2</sub>:acetone 85:15), **<sup>1</sup>H NMR** (700  
42  
43 MHz, CDCl<sub>3</sub>)  $\delta$ : 1.13 (t,  $^3J_{\text{HH}} = 7.10$ , 3H), 1.27-1.31 (m, 6H), 3.69 (ddd,  $^2J_{\text{HH}} = 16.3$ ,  
44  
45  $^3J_{\text{FH}} = 12.4$ ,  $^3J_{\text{PH}} = 6.7$ , 1H), 3.87 (ddd,  $^3J_{\text{FH}} = 37.3$ ,  $^2J_{\text{HH}} = 16.1$ ,  $^3J_{\text{PH}} = 5.9$ , 1H), 4.14  
46  
47 (q,  $^3J_{\text{HH}} = 7.1$ , 2H), 4.17- .24 (m, 4H), 7.07 (dd,  $^3J_{\text{HH}} = 7.2$ ,  $^4J_{\text{HH}} = 1.7$ , 1H), 7.28-7.33  
48  
49 (m, 1H), 7.38 (t,  $^3J_{\text{HH}} = 7.7$ , 2H), 7.44 (s, 1H), 7.56 (dd,  $^3J_{\text{HH}} = 8.3$ ,  $^4J_{\text{HH}} = 1.1$ , 2H),  
50  
51 7.72 (bs, 1H), 8.26 (d,  $^3J_{\text{HH}} = 7.1$ , 1H), **<sup>31</sup>P NMR** (283 MHz, CDCl<sub>3</sub>)  $\delta$ : 11.37 (d,  $^2J_{\text{PF}}$   
52  
53 = 82.3), **<sup>13</sup>C NMR** (176 MHz, CDCl<sub>3</sub>)  $\delta$ : 13.9, 16.29, 16.32, 28.3 (d,  $^2J_{\text{FC}} = 20.7$ , 1C),  
54  
55 62.7, 64.5 (d,  $^2J_{\text{PC}} = 6.8$ , 1C), 64.8 (d,  $^2J_{\text{PC}} = 6.6$ , 1C), 96.0 (dd,  $^1J_{\text{FC}} = 199.4$ ,  $^1J_{\text{PC}} =$   
56  
57 160.0, 1C), 112.3, 114.1, 116.5 (d,  $^3J_{\text{PC}} = 13.5$ , 1C), 123.8 (d,  $^5J_{\text{FC}} = 4.2$ , 1C), 126.7  
58  
59  
60

(s, 2C), 128.2, 129.0 (s, 2C), 134.2, 137.4, 138.3, 146.3, 166.1 (dd,  $^2J_{\text{FC}} = 22.5$ ,  $^2J_{\text{PC}} = 4.0$ , 1C).

*Ethyl 2-(diethoxyphosphoryl)-2-fluoro-3-(7-methylimidazo[1,2-a]pyridin-3-yl)propanoate (10k)*. Yield: 50%, scale: 0.30 g. DCM:MeOH (95:5) + TEA (0.2 %).  **$^1\text{H}$  NMR** (250 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.20 (t,  $^3J_{\text{HH}} = 7.1$ , 3H), 1.36 (t,  $^3J_{\text{HH}} = 7.1$ , 3H), 1.38 (t,  $^3J_{\text{HH}} = 7.0$ , 3H), 2.39 (s, 3H), 3.71 (ddd,  $^3J_{\text{FH}} = 13.2$ ,  $^2J_{\text{HH}} = 16.0$ ,  $^3J_{\text{PH}} = 6.2$ , 1H), 3.87 (ddd,  $^3J_{\text{FH}} = 36.8$ ,  $^2J_{\text{HH}} = 16.2$ ,  $^2J_{\text{PH}} = 5.8$ , 1 H), 4.16-4.33 (m, 6H), 6.66 (d,  $^3J_{\text{HH}} = 7.0$ , 1H), 7.34 (s, 1H), 7.41 (s, 1H), 8.0 (d,  $^3J_{\text{HH}} = 7.1$ , 1H);  **$^{13}\text{C}$  NMR** (250 MHz,  $\text{CDCl}_3$ )  $\delta$ : 14.2, 16.46, 16.47, 17.0, 28.7 (d,  $^2J_{\text{PC}} = 20.2$ , 1C), 62.3, 64.7 (d,  $^2J_{\text{PC}} = 6.8$ , 1C), 65.0 (d,  $^2J_{\text{PC}} = 7.1$ , 1C), 98.4 (dd,  $^1J_{\text{FC}} = 196.4$ ,  $^1J_{\text{PC}} = 149.8$ , 1C), 114.6, 115.4, 125.9 (d,  $^3J_{\text{PC}} = 15.7$ , 1C), 128.7, 131.6, 138.2, 146.3, 168.4 (d,  $^2J_{\text{FC}} = 21.0$ , 1C);  **$^{13}\text{P}$  NMR** (250 MHz,  $\text{CDCl}_3$ )  $\delta$ : 12.41 (d,  $^2J_{\text{PF}} = 82.3$ ).

*Ethyl 3-(7-chloroimidazo[1,2-a]pyridin-3-yl)-2-(diethoxyphosphoryl)-2-fluoropropanoate (10l)*. Yield: 78%, scale: 0.1 g,  $R_f$  0.14 ( $\text{CH}_2\text{Cl}_2$ :acetone 85:15),  **$^1\text{H}$  NMR** (700 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.16 (t,  $^3J_{\text{HH}} = 7.1$ , 3H), 1.30 (t,  $^3J_{\text{HH}} = 7.2$ , 3H), 1.31 (t,  $^3J_{\text{HH}} = 7.2$ , 3H), 3.67 (ddd,  $^2J_{\text{HH}} = 16.2$ ,  $^3J_{\text{FH}} = 12.6$ ,  $^3J_{\text{PH}} = 6.6$ , 1H), 3.82 (ddd,  $^2J_{\text{HH}} = 16.2$ ,  $^3J_{\text{FH}} = 39.9$ ,  $^3J_{\text{PH}} = 6.2$ , 1H), 4.08 - 4.29 (m, 6H), 6.77 (dd,  $^3J_{\text{HH}} = 7.3$ ,  $^4J_{\text{HH}} = 2.1$ , 1H), 7.42 (s, 1H), 7.53 (dd,  $^4J_{\text{HH}} = 2.0$ ,  $^5J_{\text{HH}} = 0.6$ , 1H), 8.01 (dd,  $^3J_{\text{HH}} = 7.3$ ,  $^5J_{\text{HH}} = 0.6$ , 1H),  **$^{31}\text{P}$  NMR** (283 MHz,  $\text{CDCl}_3$ )  $\delta$ : 11.69 (d,  $^2J_{\text{PF}} = 82.2$ ),  **$^{13}\text{C}$  NMR** (176 MHz,  $\text{CDCl}_3$ )  $\delta$ : 14.0, 16.4 (m, 2C), 28.4 (dd,  $^2J_{\text{FC}} = 20.4$ ,  $^2J_{\text{PC}} = 1.6$ , 1C), 62.9 (s, 1C), 64.6 (d,  $^2J_{\text{PC}} = 7.2$ , 1C), 64.9 (d,  $^2J_{\text{PC}} = 6.5$ , 1C), 96.1 (dd,  $^1J_{\text{FC}} = 199.6$ ,  $^1J_{\text{PC}} = 160.2$ , 1C), 114.0, 116.5, 117.2 (d,  $^3J_{\text{PC}} = 14.1$ , 1C), 124.4 (d,  $^5J_{\text{FC}} = 5.0$ , 1C), 131.0, 134.7, 145.8, 166.2 (dd,  $^2J_{\text{FC}} = 22.0$ ,  $^2J_{\text{PC}} = 3.8$ , 1C), **HRMS**:  $m/z$  Calculated: 407.0933 ( $\text{M} + \text{H}$ ) $^+$ , Found: 407.0932 ( $\text{M} + \text{H}$ ) $^+$ .

*Ethyl* 3-(7-bromoimidazo[1,2-*a*]pyridin-3-yl)-2-(diethoxyphosphoryl)-2-fluoropropanoate (**10m**). Yield: 76%, scale: 0.1 g, *R*<sub>f</sub> 0.17 (CH<sub>2</sub>Cl<sub>2</sub>:acetone 85:15), <sup>1</sup>H NMR (700 MHz, CDCl<sub>3</sub>) δ: 1.21 (t, <sup>3</sup>*J*<sub>HH</sub> = 7.10, 3H), 1.376 (t, <sup>3</sup>*J*<sub>HH</sub> = 7.10, 3H), 1.37 (t, <sup>3</sup>*J*<sub>HH</sub> = 7.10, 3H), 3.62-4.02 (m, 2H), 4.15-4.34 (m, 6H), 6.93 (dd, <sup>3</sup>*J*<sub>HH</sub> = 7.3, <sup>4</sup>*J*<sub>HH</sub> = 1.9, 1H), 7.47 (s, 1H), 7.77 (dd, <sup>4</sup>*J*<sub>HH</sub> = 1.9, <sup>5</sup>*J*<sub>HH</sub> = 0.7, 1H), 8.00 (dd, <sup>3</sup>*J*<sub>HH</sub> = 7.3, <sup>5</sup>*J*<sub>HH</sub> = 0.7, 1H), <sup>31</sup>P NMR (283 MHz, CDCl<sub>3</sub>) δ: 12.15 (d, <sup>2</sup>*J*<sub>PF</sub> = 82.2).

*Ethyl* 2-(diethoxyphosphoryl)-2-fluoro-3-(8-phenylimidazo[1,2-*a*]pyridin-3-yl)propanoate (**10n**). Yield: 98%, scale: 0.1 g, (CH<sub>2</sub>Cl<sub>2</sub>:acetone 85:15), <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ: 1.23 (t, <sup>3</sup>*J*<sub>HH</sub> = 7.10, 3H), 1.38 (t, <sup>3</sup>*J*<sub>HH</sub> = 7.10, 3H), 1.39 (t, <sup>3</sup>*J*<sub>HH</sub> = 7.10, 3H), 3.70-4.09 (m, 2H), 4.18-4.39 (m, 6H), 6.94 (t, <sup>3</sup>*J*<sub>HH</sub> = 6.9, 1H), 7.28-7.35 (m, 1H), 7.38-7.54 (m, 3H), 7.57 (s, 1H), 7.88-7.97 (m, 2H), 8.14 (bd, <sup>3</sup>*J*<sub>HH</sub> = 6.9, 1H), <sup>31</sup>P NMR (101 MHz, CDCl<sub>3</sub>) δ: 12.35 (d, <sup>2</sup>*J*<sub>PF</sub> = 82.7), HRMS: *m/z* Calculated: 449.1636 (M + H)<sup>+</sup>, Found: 449.1654 (M + H)<sup>+</sup>.

*Ethyl* 2-(diethoxyphosphoryl)-2-fluoro-3-(8-methylimidazo[1,2-*a*]pyridin-3-yl)propanoate (**10o**). Yield: 45%, scale: 0.3 g; DCM/acetone (85:15) + TEA (0.2 %). <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ: 1.19 (t, <sup>3</sup>*J*<sub>HH</sub> = 7.1, 3H), 1.35 (t, <sup>3</sup>*J*<sub>HH</sub> = 7.0, 3H), 1.36 (t, <sup>3</sup>*J*<sub>HH</sub> = 7.0, 3H), 2.56 (s, 3H), 4.01-3.55 (m, 1 H), 4.15-4.32 (m, 6H), 6.72 (t, <sup>3</sup>*J*<sub>HH</sub> = 6.9, 1H), 6.95 (d, <sup>3</sup>*J*<sub>HH</sub> = 6.8, 1H), 7.46 (s, 1H), 7.97 (d, <sup>3</sup>*J*<sub>HH</sub> = 6.8, 1H); <sup>13</sup>C NMR (63 MHz, CDCl<sub>3</sub>) δ: 14.1, 16.45, 16.54, 17.0, 28.6 (d, <sup>2</sup>*J*<sub>FC</sub>=20.3, <sup>2</sup>*J*<sub>PC</sub> = 2.0 1C), 62.9, 64.6 (d, <sup>2</sup>*J*<sub>PC</sub> = 7.0, 1C), 64.9 (d, <sup>2</sup>*J*<sub>PC</sub> = 6.8, 1C), 96.3 (bdd, <sup>1</sup>*J*<sub>FC</sub> = 199.3, <sup>1</sup>*J*<sub>PC</sub> = 159.7, 1C), 112.4, 117.1 (d, <sup>3</sup>*J*<sub>PC</sub> = 15.0, 1C), 121.8 (d, <sup>5</sup>*J*<sub>FC</sub> = 4.8, 1C), 123.1 (s, 1C), 127.6 (s, 1C), 133.4 (s, 1C), 146.6 (s, 1C), 166.4 (dd, <sup>2</sup>*J*<sub>FC</sub> = 22.5, <sup>2</sup>*J*<sub>PC</sub> = 4.1, 1C); <sup>31</sup>P NMR (101 MHz, CDCl<sub>3</sub>) δ: 12.51 (d, <sup>2</sup>*J*<sub>PF</sub> = 82.6).

*Ethyl* 3-(8-bromoimidazo[1,2-*a*]pyridin-3-yl)-2-(diethoxyphosphoryl)-2-fluoropropanoate (**10p**). Yield: 43% yield, scale: 0.13 g, *R*<sub>f</sub> 0.27 (CH<sub>2</sub>Cl<sub>2</sub>:acetone

85:15), **<sup>1</sup>H NMR** (700 MHz, CDCl<sub>3</sub>) δ: 1.24 (t, <sup>3</sup>J<sub>HH</sub> = 6.9, 3H), 1.37 (m, 6H), 3.71 (m, 1H), 3.90 (ddd, <sup>2</sup>J<sub>HH</sub> = 16.2, <sup>3</sup>J<sub>FH</sub> = 37.5, <sup>3</sup>J<sub>PH</sub> = 5.5, 1H), 4.14 - 4.34 (m, CH<sub>2</sub>O)<sub>2</sub>P, 6H), 6.73 (t, <sup>3</sup>J<sub>HH</sub> = 7.1, 1H), 7.46 (d, <sup>3</sup>J<sub>HH</sub> = 7.1, 1H), 7.57 (s, 1H), 8.13 (d, <sup>3</sup>J<sub>HH</sub> = 7.1, 1H), **<sup>31</sup>P NMR** (283 MHz, CDCl<sub>3</sub>) δ: 11.38 (d, <sup>2</sup>J<sub>PF</sub> = 82.3), **<sup>13</sup>C NMR** (176 MHz, CDCl<sub>3</sub>) δ: 14.0, 16.4 (m, 2C), 28.7 (dd, <sup>2</sup>J<sub>FC</sub> = 20.4, <sup>2</sup>J<sub>PC</sub> = 1.8, 1C), 62.9, 64.6 (d, <sup>2</sup>J<sub>PC</sub> = 6.6, 1C), 65.0 (d, <sup>2</sup>J<sub>PC</sub> = 7.2, 1C), 96.1 (d, <sup>1</sup>J<sub>FC</sub> = 199.8, <sup>1</sup>J<sub>PC</sub> = 160.0, 1C), 111.8, 112.5, 118.8 (d, <sup>3</sup>J<sub>PC</sub> = 14.3, 1C), 123.5 (d, <sup>5</sup>J<sub>FC</sub> = 5.0, 1C), 126.9 (s, 1C), 134.5, 144.0, 166.2 (dd, <sup>2</sup>J<sub>FC</sub> = 22.7, <sup>2</sup>J<sub>PC</sub> = 3.7, 1C), **HRMS**: m/z Calculated: 451.0428 (M + H)<sup>+</sup>, Found: 451.0443 (M + H)<sup>+</sup>.

*Ethyl 2-(diethoxyphosphoryl)-2-fluoro-3-(imidazo[2,1-a]isoquinolin-3-yl)propanoate (10r)*. Yield: 92%, scale: 0.1 g, (CH<sub>2</sub>Cl<sub>2</sub>:acetone 85:15), **<sup>1</sup>H NMR** (700 MHz, CDCl<sub>3</sub>) δ: 1.10-1.56 (m, 9H), 3.66-4.15 (m, 2H), 4.14-4.46 (m, 6H), 7.10 (d, <sup>3</sup>J<sub>HH</sub> = 7.4, 1H), 7.20-7.37 (m, 1H), 7.49 (s, 1H), 7.55-7.66 (m, 1H), 7.68-7.78 (m, 1H), 7.94 (d, <sup>3</sup>J<sub>HH</sub> = 7.4, 1H), 8.61 (d, <sup>3</sup>J<sub>HH</sub> = 7.6, 1H), **<sup>31</sup>P NMR** (283 MHz, CDCl<sub>3</sub>) δ: 12.38 (d, <sup>2</sup>J<sub>PF</sub> = 82.7), **<sup>13</sup>C NMR** (176 MHz, CDCl<sub>3</sub>) δ: 13.9, 16.2 (bd, 1C), 16.3 (bd, 1C), 28.2 (d, <sup>2</sup>J<sub>FC</sub> = 19.3, 1C), 62.7, 64.4 (d, <sup>2</sup>J<sub>PC</sub> = 7.1, 1C), 64.7 (d, <sup>2</sup>J<sub>PC</sub> = 6.7, 1C), 95.8 (dd, <sup>1</sup>J<sub>FC</sub> = 199.4, <sup>1</sup>J<sub>PC</sub> = 160.1, 1C), 113.0, 118.6 (d, <sup>3</sup>J<sub>PC</sub> = 14.5, 1C), 121.0 (d, <sup>5</sup>J<sub>PC</sub> = 4.6, 1C), 122.9, 123.3, 126.5, 127.9, 128.3, 129.1, 131.2, 143.4, 166.1 (dd, <sup>2</sup>J<sub>FC</sub> = 22.5, <sup>2</sup>J<sub>PC</sub> = 3.8, 1C), **HRMS**: m/z Calculated: 423.1480 (M + H)<sup>+</sup>, Found: 423.1493 (M + H)<sup>+</sup>.

*Ethyl 2-(ethoxy(phenyl)phosphoryl)-2-fluoro-3-(imidazo[1,2-a]pyridin-3-yl)propanoate (10s)*. Yield: 64%, scale: 0.15 g, (CHCl<sub>3</sub>:acetone 4:1). **<sup>31</sup>P NMR** (101 MHz, CDCl<sub>3</sub>): diastereoisomers 32.34 (d, <sup>2</sup>J<sub>PF</sub> = 78.8) and 30.24 (d, <sup>2</sup>J<sub>PF</sub> = 66.7); for one diastereoisomer **<sup>1</sup>H NMR** (250 MHz, CDCl<sub>3</sub>) δ 7.87 (dd, <sup>3</sup>J<sub>HH</sub> = 6.9, <sup>4</sup>J<sub>HH</sub> = 2.4, 1H), 7.75 - 7.68 (m, 2H), 7.59 - 7.50 (m, 1H), 7.46 (d, <sup>3</sup>J<sub>HH</sub> = 9.0, 1H), 7.44 - 7.39

(m, 2H), 7.37 (s, 1H), 7.06 (dd,  $^3J_{\text{HH}} = 9.0$ ,  $^3J_{\text{HH}} = 6.7$ , 1H), 6.68 (td,  $^3J_{\text{HH}} = 6.8$ ,  $^4J_{\text{HH}} = 1.1$ , 1H), 4.24 – 4.04 (m, 4H), 3.86 (ddd,  $^3J_{\text{FH}} = 36.6$ ,  $^2J_{\text{HH}} = 16.2$ ,  $^3J_{\text{PH}} = 6.4$ , 1H), 3.60 – 3.51 (m, 1H), 1.32 (t,  $^3J_{\text{HH}} = 7.0$ , 3H), 1.12 (t,  $^3J_{\text{HH}} = 7.1$ , 1H).  **$^{13}\text{C}$  NMR** (176 MHz,  $\text{CDCl}_3$ )  $\delta$  166.3 (d,  $^2J_{\text{FC}} = 22.9$ ,  $^2J_{\text{PC}} = 2.4$ , 1C), 145.8 (s, 1C), 133.9 (s, 1C), 133.6 (d,  $^4J_{\text{PC}} = 2.8$ , 1C), 133.1 (d,  $J_{\text{PC}} = 9.9$ , 2C), 128.6 (d,  $J_{\text{PC}} = 13.3$ , 2C), 125.6 (d,  $^1J_{\text{PC}} = 133.2$ , 1C), 124.1 (s, 1C), 123.8 (d,  $J = 4.8$ , 1C), 116.4 (d,  $^3J_{\text{PC}} = 12.8$ , 1C), 117.5 (s, 1C), 112.1 (s, 1C), 97.1 (d,  $^1J_{\text{FC}} = 203.2$ ,  $^1J_{\text{PC}} = 108.6$ , 1C), 62.9 – 62.8 (m, 1C), 62.6 (s, 1C), 27.9 – 27.7 (m, 1C), 16.5 (d,  $^3J_{\text{PC}} = 5.8$ , 1C), 14.0 (s, 1C).

*Ethyl 2-(ethoxy(ethyl)phosphoryl)-3-(imidazo[1,2-a]pyridin-3-yl)propanoate (10t).*

Yield: 71%, scale: 0.15 g. ( $\text{CHCl}_3$ :acetone 4:1).  **$^{31}\text{P}$  NMR** (101 MHz,  $\text{CDCl}_3$ ): diastereoisomers 46.42 (d,  $^2J_{\text{PF}} = 69.2$ ) and 47.79 (d,  $^2J_{\text{PF}} = 81.7$ );  **$^1\text{H}$  NMR** (700 MHz,  $\text{CDCl}_3$ )  $\delta$  8.10 – 8.04 (m, 1H), diastereoisomers 7.52 and 7.52 (2d,  $^3J_{\text{HH}} = 9.1$ , 1H), diastereoisomers 7.45 and 7.42 (2s, 1H), 7.14 – 7.07 (m, 1H), 6.79 – 6.74 (m, 1H), 4.30 – 4.05 (m, 4H), 3.86 – 3.59 (m, 3H), 1.91–1.79 (m, 2H), 1.32–1.29 (m, 3H), 1.22–1.10 (m, 6H).  **$^{13}\text{C}$  NMR** (176 MHz,  $\text{CDCl}_3$ )  $\delta$  [167.1 (dd,  $^2J_{\text{FC}} = 22.1$ ,  $^2J_{\text{PC}} = 5.7$ , 1C), 166.8 (dd,  $^2J_{\text{FC}} = 22.3$ ,  $^2J_{\text{PC}} = 3.8$ , 1C)], [146.14, 146.08 (2s, 1C)], [134.0 and 133.9 (2s, 1C)], [124.2 (s, 1C), 124.1 (s, 1C)], 123.9 (m, 1C), 117.8 (bs, 1C), 116.6 (d,  $^3J_{\text{PC}} = 11.6$ , 1C), 116.5 (d,  $^3J_{\text{PC}} = 12.2$ , 1C), [112.3 (s, 1C), 112.2 (s, 1C)], [98.2 (dd,  $^1J_{\text{FC}} = 203.4$ ,  $^1J_{\text{PC}} = 89.0$ , 1C), 97.8 (dd,  $^1J_{\text{FC}} = 200.6$ ,  $^1J_{\text{PC}} = 92.5$ , 1C)], 63.2 – 62.5 (m, 1C), [27.9 (dd,  $^3J_{\text{FC}} = 20.8$ ,  $^3J_{\text{PC}} = 4.0$ , 1C), 27.7 (dd,  $^3J_{\text{FC}} = 20.5$ ,  $^3J_{\text{PC}} = 3.6$ , 1C)], [19.03 (d,  $^1J_{\text{PC}} = 95.8$ , 1C), 18.97 (d,  $^1J_{\text{PC}} = 96.0$ , 1C)], [16.63 (d,  $^3J_{\text{PC}} = 6.0$ , 1C), 16.60 (d,  $^3J_{\text{PC}} = 6.0$ , 1C)], [13.95 (s, 1C), 13.92 (s, 1C)], [4.94 (d,  $^2J_{\text{PC}} = 6.5$ , 1C), 4.86 (d,  $^2J_{\text{PC}} = 7.0$ , 1C)].

*Ethyl 3-([1,1'-biphenyl]-3-yl)-2-(diethoxyphosphoryl)-2-fluoropropanoate (10u).*

Yield: 57%, scale: 0.3 g;  $R_f$  0.42 ( $\text{CH}_2\text{Cl}_2$ :AcOEt 20:1);  **$^{31}\text{P}$  NMR** (101 MHz,  $\text{CDCl}_3$ )

12.96 (d,  $^2J_{\text{PF}} = 83.0$ ).  **$^{19}\text{F}$  NMR** (235 MHz):  $\delta$  -178.38 (m,  $^2J_{\text{PF}} = 82.9$ ).  **$^1\text{H}$  NMR** (250 MHz,  $\text{CDCl}_3$ )  $\delta$  1.13 (t,  $^3J_{\text{HH}} = 7.1$ , 3H), 1.36 (t,  $^3J_{\text{HH}} = 7.1$ , 6H), 3.38–3.71 (m, 2H), 4.05–4.35 (m, 6H), 7.19–7.58 (m, 9H).  **$^{13}\text{C}$  NMR** (63 MHz,  $\text{CDCl}_3$ )  $\delta$  13.9, 16.4 (d,  $^3J_{\text{PC}} = 5.6$ , 2C), 39.3 (d,  $^3J_{\text{PC}} = 19.5$ , 1C), 62.3, 64.3 and 64.5 (2d,  $^2J_{\text{PC}} = 6.9$ , 2C), 95.7 (dd,  $^1J_{\text{FC}} = 200.0$ ,  $^1J_{\text{PC}} = 162.0$ , 1C), 126.2 (1s, 2C), 127.1 (1s, 2C), 127.3 (1s, 1C), 128.7 (1s,  $\underline{\text{CH}}_{\text{Ar}}$ , 3C), 129.2 (1s, 2C), 133.7 (d,  $^3J_{\text{PC}} = 13.0$ , 1C), 140.8, 141.2 (2s, 2C), 166.6 (d,  $^2J_{\text{PC}} = 4.5$ ,  $^2J_{\text{FC}} = 22.7$ , 1C). **HRMS**:  $m/z$  Calculated: 409.1509 ( $\text{M} + \text{H}$ )<sup>+</sup>, Found: 409.1589 ( $\text{M} + \text{H}$ )<sup>+</sup>.

*Ethyl 3-([1,1'-biphenyl]-4-yl)-2-(diethoxyphosphoryl)-2-fluoropropanoate* (**10w**).<sup>47</sup>

Yield: 80%, scale: 0.39 g,  $R_f$  0.27 ( $\text{CH}_2\text{Cl}_2$ :AcOEt 20:1);  **$^{31}\text{P}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  12.99 (d,  $^2J_{\text{PF}} = 83.00$ ).  **$^{19}\text{F}$  NMR** (235 MHz):  $\delta$  -178.51 (M part of ABMX spin system,  $^2J_{\text{PF}} = 83.03$ ).  **$^1\text{H}$  NMR** (250 MHz,  $\text{CDCl}_3$ )  $\delta$  1.18 (t,  $^3J_{\text{HH}} = 7.10$ , 3H), 1.37 (t,  $^3J_{\text{HH}} = 7.00$ , 6H), 3.49 and 3.54 (AB part of ABMX spin system,  $^2J_{\text{HH}} = -14.76$ ,  $^3J_{\text{PHa}} = 6.05$ ,  $^3J_{\text{PHb}} = 7.46$ ,  $^3J_{\text{FHb}} = 13.83$ ,  $^3J_{\text{FHa}} = 38.90$ , 2H), 4.12–4.36 (m, 6H), 7.27–7.59 (m, 9H).  **$^{13}\text{C}$  NMR** (63 MHz,  $\text{CDCl}_3$ )  $\delta$  14.0 (s, 1C), 16.4 (d,  $^3J_{\text{PC}} = 5.6$ , 2C), 38.9 (d,  $^2J_{\text{FC}} = 19.7$ , 1C), 62.3 (s, 1C), 64.3 and 64.6 (2d,  $^2J_{\text{PC}} = 6.95$ , 2C), 95.7 (dd,  $^1J_{\text{FC}} = 199.6$ ,  $^1J_{\text{PC}} = 161.8$ , 1C), 126.99 and 127.02 and 128.8 and 130.7 (2s, 8C), 127.3 (1s, 1C), 132.2 (d,  $^3J_{\text{PC}} = 13.1$ , 1C), 140.4 and 140.7 (2s, 2C), 166.6 (d,  $^2J_{\text{PC}} = 4.5$ ,  $^2J_{\text{FC}} = 22.8$ , 1C). **HRMS**  $m/z$  Calculated: 431.1400 ( $\text{M} + \text{Na}$ )<sup>+</sup>, Found: 431.1407 ( $\text{M} + \text{Na}$ )<sup>+</sup>.

*Ethyl 3-(3-benzylphenyl)-2-(diethoxyphosphoryl)-2-fluoropropanoate* (**10y**). Yield:

72%, scale: 0.55 g,  $R_f$  0.45 ( $\text{CH}_2\text{Cl}_2$ :AcOEt 20:1),  **$^{31}\text{P}$  NMR** (101 MHz,  $\text{CDCl}_3$ ) 13.05 (d,  $^2J_{\text{PF}} = 83.0$ ).  **$^{19}\text{F}$  NMR** (235 MHz):  $\delta$  -178.55 (m,  $^2J_{\text{PF}} = 83.1$ ).  **$^1\text{H}$  NMR** (250 MHz,  $\text{CDCl}_3$ )  $\delta$  1.10 (t,  $^3J_{\text{HH}} = 7.1$ , 3H), 1.35 (t,  $^3J_{\text{HH}} = 7.0$ , 6H), 3.27–3.60 (m, 2H), 3.92 (s, 2H), 3.98–4.13 (m, 2H), 4.14 – 4.32 (m, 4H), 7.31–7.03 (m, 9H).  **$^{13}\text{C}$**

**NMR** (63 MHz, CDCl<sub>3</sub>)  $\delta$  13.9, 16.4 (d,  $^3J_{PC}$  = 5.3, 2C), 39.1 (d,  $^3J_{PC}$  = 19.6, 1C), 41.8, 62.1, 64.2 and 64.4 (2d,  $^2J_{PC}$  = 6.8, 2C), 95.6 (dd,  $^1J_{FC}$  = 199.5,  $^1J_{PC}$  = 162.0, 1C), 128.1 (1s, 2C), 128.8 (1s, 2C), 128.4 (1s, 3C), 126.0, 130.8 (2s, 2C), 133.3 (d,  $^3J_{PC}$  = 13.2, 1C), 141.0 and 141.1 (2s, 2C), 166.4 (dd,  $^2J_{PC}$  = 4.5,  $^2J_{FC}$  = 23.0, 1C).  
**HRMS** m/z Calculated: 445.1556 (M + Na)<sup>+</sup>, Found: 445.1565 (M + Na)<sup>+</sup>.

#### *Determination of cytotoxicity*

HeLa cells were seeded into 96-well cell culture plates at a density of  $4 \times 10^3$  cells/well in 100  $\mu$ l of complete culture medium. On the following day, cells were washed with phosphate-buffered saline (PBS) and 100  $\mu$ l of fresh serum-containing or serum-free (fasting) medium was added. Subsequently HeLa cells were treated with PCs at eight concentrations and 72 h later PrestoBlue® Cell Viability Reagent was applied. Following 50 min incubation time at 37°C and 5% CO<sub>2</sub>, cell viability was determined by measuring the fluorescent signal (Ex/Em = 530/590 nm) on a Synergy 2 Microplate Reader (BioTek, Vermont, USA). The obtained fluorescence magnitudes were used to calculate cell viability expressed as a percent of the viability of the untreated control cells. The data expressed as the mean of at least 4 independent experiments were used to calculate the IC<sub>50</sub> parameter.

#### *Assessment of inhibition of Rab11 and Rap1A/Rap1B prenylation*

HeLa cells were seeded into 6-well cell culture plates at a density of  $4 \times 10^5$  cells/well in 3 ml of complete medium. On the following day, 1,5 ml of fresh serum-free medium was supplemented with PCs as well as lovastatin. After 48h of incubation, cell monolayers were rinsed with PBS and detached using trypsin-EDTA solution. The cytosolic and membrane-rich fractions, containing protease inhibitor cocktail, were isolated from cell pellets using Mem-PER™ Plus Membrane Protein Extraction Kit according to the manufacturers' instructions. The protein concentration in both



fractions was determined using Bradford Protein Assay. Equal amounts of protein (20  $\mu$ g) from cytosolic fractions were resolved by 12% SDS-PAGE gels and transferred on 0,2  $\mu$ m nitrocellulose membrane. Membranes were probed with  $\beta$ -actin, Rab11A or Rap1A/Rap1B antibodies and detected using the appropriate HRP-conjugated secondary antibody, followed by an ECL assay. Visualization of the chemiluminescent protein bands was performed using ChemiDoc™ MP Imaging System (Bio-Rad). Densitometry analysis was performed with ImageLab™ Software (Bio-Rad) and relative unprenylated protein band intensity was normalized to  $\beta$ -actin and quantified with respect to controls (untreated cells).

#### *Statistical analysis*

Unless stated otherwise, all the biological results are presented as means of 3-6 repeated experiments  $\pm$ SEM. Statistical differences between mean values of inhibitor treated and untreated samples were analyzed using one-way ANOVA followed by Dunnett's multiple comparisons test using GraphPad Prism (version 6.01 for Windows, GraphPad Software, La Jolla California USA, [www.graphpad.com](http://www.graphpad.com)). Confidence  $p$ -levels are indicated by asterisks, with \* denoting  $p \leq 0.05$ , \*\* denoting  $p \leq 0.01$ , \*\*\* denoting  $p \leq 0.001$ , and \*\*\*\* denoting  $p \leq 0.0001$ .

#### **Supporting Information**

Full experimental details, including spectra ( $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR,  $^{31}\text{P}$  NMR) of all compounds, data on separation of enantiomers, molecular formula strings and protein structures are provided. The cytotoxic efficacy on HeLa cell line of the studied compounds is also provided. This material is free of charge via the Internet at <http://pubs.acs.org>.

\* Corresponding author: [katarzyna.blazewska@p.lodz.pl](mailto:katarzyna.blazewska@p.lodz.pl)

# These authors contributed equally.

## Acknowledgements

The authors declare no competing financial interest.

This work was financially supported by the National Science Centre, Poland (2014/14/E/ST5/00491) and Ministry of Science and Higher Education, Poland (N N204 519839). The authors wish to acknowledge CSC –IT Center for Science, Finland, for generous computational resources (O.T.P.: jyy2516 and jyy2585). The authors thank Mr Jacek Reus, Ms Aleksandra Stańczyk, Ms Marta Krysztof for technical assistance. We thank Dr Marek Domin (Boston College) for HRMS of the esters **9** and **10**. We thank Prof. Edward Tate (Imperial College of London) for helpful discussions.

**Abbreviations Used:** RGGT, (Rab GGTase, GGT-2): Rab geranylgeranyl transferase; FPPS: farnesyl pyrophosphate synthase; GGPPS: geranylgeranyl pyrophosphate synthase; FT: farnesyl transferase; GGT-1: geranylgeranyl transferase 1; FPP: farnesyl pyrophosphate; GPP: geranyl pyrophosphate; GGPP: geranylgeranyl pyrophosphate; 3-IPEHPC: 3-(3-Pyridyl)-2-hydroxy-2-phosphonopropanoic acid; PC: phosphonocarboxylate; NBP: nitrogen-containing bisphosphonate.

## Literature

1. Kelly, E. E.; Horgan, C. P.; McCaffrey, M. W. Rab11 proteins in health and disease. *Biochem. Soc. Trans.* **2012**, *40*, 1360-1367.
2. Kelly, E. E.; Horgan, C. P.; Goud, B.; McCaffrey, M. W. The Rab family of proteins: 25 years on. *Biochem. Soc. Trans.* **2012**, *40*, 1337-1347.
3. Guichard, A.; Nizet, V.; Bier, E. RAB11-mediated trafficking in host-pathogen interactions. *Nat. Rev. Microbiol.* **2014**, *12*, 624-634.
4. Hendrix, A.; Maynard, D.; Pauwels, P.; Braems, G.; Denys, H.; Van den Broecke, R.; Lambert, J.; Van Belle, S.; Cocquyt, V.; Gespach, C.; Bracke, M.;

- Seabra, M. C.; Gahl, W. A.; De Wever, O.; Westbroek, W. Effect of the secretory small GTPase Rab27B on breast cancer growth, invasion, and metastasis. *J. Natl. Cancer Inst.* **2010**, *102*, 866-880.
5. Mitra, S.; Cheng, K. W.; Mills, G. B. Rab GTPases implicated in inherited and acquired disorders. *Semin. Cell Dev. Biol.* **2011**, *22*, 57-68.
6. Zhao, W.; Jamshidiha, M.; Lanyon-Hogg, T.; Recchi, C.; Cota, E.; Tate, E. W. Direct targeting of the Ras GTPase superfamily through structure-based design. *Curr. Top. Med. Chem.* **2017**, *17*, 16-29.
7. Bhuin, T.; Roy, J. K. Rab11 in disease progression. *Int. J. Mol. Cell. Med.* **2015**, *4*, 1-8.
8. Okamoto, S.; Jiang, Y.; Kawamura, K.; Shingyoji, M.; Tada, Y.; Sekine, I.; Takiguchi, Y.; Tatsumi, K.; Kobayashi, H.; Shimada, H.; Hiroshima, K.; Tagawa, M. Zoledronic acid induces apoptosis and S-phase arrest in mesothelioma through inhibiting Rab family proteins and topoisomerase II actions. *Cell Death Dis.* **2014**, *5*, e1517.
9. Ali, N.; Jurczyk, J.; Shay, G.; Tnimov, Z.; Alexandrov, K.; Munoz, M. A.; Skinner, O. P.; Pavlos, N. J.; Rogers, M. J. A highly sensitive prenylation assay reveals in vivo effects of bisphosphonate drug on the Rab prenylome of macrophages outside the skeleton. *Small GTPases* **2015**, *6*, 202-211.
10. Agabiti, S. S.; Liang, Y.; Wiemer, A. J. Molecular mechanisms linking geranylgeranyl diphosphate synthase to cell survival and proliferation. *Mol. Membr. Biol.* **2016**, *33*, 1-11.
11. Ochocki, J. D.; Distefano, M. D. Prenyltransferase inhibitors: treating human ailments from cancer to parasitic infections. *MedChemComm* **2013**, *4*, 476-492.

12. Lobell, R. B.; Omer, C. A.; Abrams, M. T.; Bhimnathwala, H. G.; Brucker, M. J.; Buser, C. A.; Davide, J. P.; DeSolms, S. J.; Dinsmore, C. J.; Ellis-Hutchings, M. S.; Kral, A. M.; Liu, D.; Lumma, W. C.; Machotka, S. V.; Rands, E.; Williams, T. M.; Graham, S. L.; Hartman, G. D.; Oliff, A. I.; Heimbrook, D. C.; Kohl, N. E. Evaluation of farnesyl:protein transferase and geranylgeranyl:protein transferase inhibitor combinations in preclinical models. *Cancer Res.* **2001**, *61*, 8758-8768.
13. Coxon, F. P.; Helfrich, M. H.; Larijani, B.; Muzylak, M.; Dunford, J. E.; Marshall, D.; McKinnon, A. D.; Nesbitt, S. A.; Horton, M. A.; Seabra, M. C.; Ebetino, F. H.; Rogers, M. J. Identification of a novel phosphonocarboxylate inhibitor of Rab geranylgeranyl transferase that specifically prevents Rab prenylation in osteoclasts and macrophages. *J. Biol. Chem.* **2001**, *276*, 48213-48222.
14. Watanabe, M.; Fiji, H. D. G.; Guo, L.; Chan, L.; Kinderman, S. S.; Slamon, D. J.; Kwon, O.; Tamanoi, F. Inhibitors of protein geranylgeranyltransferase I and Rab geranylgeranyltransferase identified from a library of allenolate-derived compounds. *J. Biol. Chem.* **2008**, *283*, 9571-9579.
15. Tan, K.-T.; Guiu-Rozas, E.; Bon, R. S.; Guo, Z.; Delon, C.; Wetzel, S.; Arndt, S.; Alexandrov, K.; Waldmann, H.; Goody, R. S.; Wu, Y.-W.; Blankenfeldt, W. Design, synthesis, and characterization of peptide-based Rab geranylgeranyl transferase inhibitors. *J. Med. Chem.* **2009**, *52*, 8025-8037.
16. Stigter, E. A.; Guo, Z.; Bon, R. S.; Wu, Y.-W.; Choidas, A.; Wolf, A.; Menninger, S.; Waldmann, H.; Blankenfeldt, W.; Goody, R. S. Development of selective, potent RabGGTase inhibitors. *J. Med. Chem.* **2012**, *55*, 8330-8340.
17. Bon, R. S.; Guo, Z.; Stigter, E. A.; Wetzel, S.; Menninger, S.; Wolf, A.; Choidas, A.; Alexandrov, K.; Blankenfeldt, W.; Goody, R. S.; Waldmann, H.

Structure-guided development of selective RabGGTase inhibitors. *Angew. Chem., Int. Ed.* **2011**, *50*, 4957-4961.

18. Deraeve, C.; Guo, Z.; Bon, R. S.; Blankenfeldt, W.; DiLucrezia, R.; Wolf, A.; Menninger, S.; Stigter, E. A.; Wetzel, S.; Choidas, A.; Alexandrov, K.; Waldmann, H.; Goody, R. S.; Wu, Y.-W. Psoromic acid is a selective and covalent Rab-prenylation inhibitor targeting autoinhibited RabGGTase. *J. Am. Chem. Soc.* **2012**, *134*, 7384-7391.

19. Baron, R. A.; Tavare, R.; Figueiredo, A. C.; Blazewska, K. M.; Kashemirov, B. A.; McKenna, C. E.; Ebetino, F. H.; Taylor, A.; Rogers, M. J.; Coxon, F. P.; Seabra, M. C. Phosphonocarboxylates inhibit the second geranylgeranyl addition by Rab geranylgeranyl transferase. *J. Biol. Chem.* **2009**, *284*, 6861-6868.

20. McKenna, C. E.; Kashemirov, B. A.; Blazewska, K. M.; Mallard-Favier, I.; Stewart, C. A.; Rojas, J.; Lundy, M. W.; Ebetino, F. H.; Baron, R. A.; Dunford, J. E.; Kirsten, M. L.; Seabra, M. C.; Bala, J. L.; Marma, M. S.; Rogers, M. J.; Coxon, F. P. Synthesis, chiral high performance liquid chromatographic resolution and enantiospecific activity of a potent new geranylgeranyl transferase inhibitor, 2-hydroxy-3-imidazo[1,2-a]pyridin-3-yl-2-phosphonopropionic acid. *J. Med. Chem.* **2010**, *53*, 3454-3464.

21. Błażewska, K. M.; Ni, F.; Haiges, R.; Kashemirov, B. A.; Coxon, F. P.; Stewart, C. A.; Baron, R.; Rogers, M. J.; Seabra, M. C.; Ebetino, F. H.; McKenna, C. E. Synthesis, stereochemistry and SAR of a series of minodronate analogues as RGGT inhibitors. *Eur. J. Med. Chem.* **2011**, *46*, 4820-4826.

22. Coxon, F. P.; Joachimiak, L.; Najumudeen, A. K.; Breen, G.; Gmach, J.; Oetken-Lindholm, C.; Way, R.; Dunford, J. E.; Abankwa, D.; Błażewska, K. M.

Synthesis and characterization of novel phosphonocarboxylate inhibitors of RGGT.  
*Eur. J. Med. Chem.* **2014**, *84*, 77-89.

23. Zhou, X.; Born, E. J.; Allen, C.; Holstein, S. A.; Wiemer, D. F. N-Oxide derivatives of 3-(3-pyridyl)-2-phosphonopropanoic acids as potential inhibitors of Rab geranylgeranylation. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 2331-2334.

24. Song, Y.; Lin, F.-Y.; Yin, F.; Hensler, M.; Rodrigues Poveda, C. A.; Mukkamala, D.; Cao, R.; Wang, H.; Morita, C. T.; Gonzalez Pacanowska, D.; Nizet, V.; Oldfield, E. Phosphonosulfonates are potent, selective inhibitors of dehydrosqualene synthase and staphyloxanthin biosynthesis in *Staphylococcus aureus*. *J. Med. Chem.* **2009**, *52*, 976-988.

25. The synthesis of phosphinic acid analogs (**1s**, **2s**, **1t**, **2t**) involved prior synthesis of phosphinates (**6s**, **6t**) from P(III) precursors (for details see supplementary information).

26. Matviiuk, T.; Mori, G.; Lherbet, C.; Rodriguez, F.; Pasca, M. R.; Gorichko, M.; Guidetti, B.; Voitenko, Z.; Baltas, M. Synthesis of 3-heteroaryl substituted pyrrolidine-2,5-diones via catalytic Michael reaction and evaluation of their inhibitory activity against InhA and *Mycobacterium tuberculosis*. *Eur. J. Med. Chem.* **2014**, *71*, 46-52.

27. Hayakawa, M.; Kaizawa, H.; Kawaguchi, K.-i.; Ishikawa, N.; Koizumi, T.; Ohishi, T.; Yamano, M.; Okada, M.; Ohta, M.; Tsukamoto, S.-i.; Raynaud, F. I.; Waterfield, M. D.; Parker, P.; Workman, P. Synthesis and biological evaluation of imidazo[1,2-a]pyridine derivatives as novel PI3 kinase p110 $\alpha$  inhibitors. *Bioorg. Med. Chem.* **2007**, *15*, 403-412.

28. Enguehard, C.; Hervet, M.; Thery, I.; Renou, J.-L.; Fauvelle, F.; Gueiffier, A. (Hetero)arylation of 6-halogenoimidazo[1,2-a]pyridines differently substituted at

C(2): influence of the 2-substituent on the Suzuki cross-coupling reaction. *Helv. Chim. Acta* **2001**, *84*, 3610-3615.

29. Sasaki, S.; Kitamura, S.; Negoro, N.; Suzuki, M.; Tsujihata, Y.; Suzuki, N.; Santou, T.; Kanzaki, N.; Harada, M.; Tanaka, Y.; Kobayashi, M.; Tada, N.; Funami, M.; Tanaka, T.; Yamamoto, Y.; Fukatsu, K.; Yasuma, T.; Momose, Y. Design, synthesis, and biological activity of potent and orally available G protein-coupled receptor 40 agonists. *J. Med. Chem.* **2011**, *54*, 1365-1378.

30. Maegawa, T.; Kitamura, Y.; Sako, S.; Udzu, T.; Sakurai, A.; Tanaka, A.; Kobayashi, Y.; Endo, K.; Bora, U.; Kurita, T.; Kozaki, A.; Monguchi, Y.; Sajiki, H. Heterogeneous Pd/C-catalyzed ligand-free, room-temperature Suzuki–Miyaura coupling reactions in aqueous media. *Chem. – Eur. J.* **2007**, *13*, 5937-5943.

31. Katayama, M.; Nagase, R.; Mitarai, K.; Misaki, T.; Tanabe, Y. Isolation of intermediary anti-aldol adducts of the Horner-Wadsworth-Emmons reaction utilizing direct titanium-aldol addition and Successive Bronsted acid promoted stereoselective elimination leading to (Z)- $\alpha,\beta$ -unsaturated esters. *Synlett* **2006**, *2006*, 129-132.

32. This strategy also worked for condensation of nicotinaldehyde with triethyl phosphonoacetate, showing applicability of this method also to pyridine analogs. Reduction of thus obtained compound leads to desoxy analog of the first RGGT inhibitor, compound 3-PEHPC.

33. Misra, A. P.; Raj, K.; Bhaduri, A. P. In search of imidazo[1,2-a]pyridine derivatives exhibiting resistance for catalytic hydrogenation. *Synth. Commun.* **1999**, *29*, 3227-3236.

34. In two out of twenty cases (**9k**, **9p**), yields were ~ 35%.

35. Lin, Y.-S.; Park, J.; De Schutter, J. W.; Huang, X. F.; Berghuis, A. M.; Sebag, M.; Tsantrizos, Y. S. Design and synthesis of active site inhibitors of the human

farnesyl pyrophosphate synthase: apoptosis and inhibition of ERK phosphorylation in multiple myeloma cells. *J. Med. Chem.* **2012**, 55, 3201-3215.

36. In four out of thirty three cases (**2k**, **2i**, **2d**, **1r**), yields were in the range 27-45%.

37. Paolini, J. P.; Robins, R. K. Aromaticity in heterocyclic systems. IV. Substitution reactions of imidazo [1,2-a]pyridine and related methyl derivatives. *J. Org. Chem.* **1965**, 30, 4085-4090.

38. Enguehard, C.; Renou, J.-L.; Collot, V.; Hervet, M.; Rault, S.; Gueiffier, A. Reactivity of 3-iodoimidazo[1,2-a]pyridines using a Suzuki-type cross-coupling reaction. *J. Org. Chem.* **2000**, 65, 6572-6575.

39. Laemmerhofer, M.; Lindner, W. Quinine and quinidine derivatives as chiral selectors. I. Brush type chiral stationary phases for high-performance liquid chromatography based on cinchonan carbamates and their application as chiral anion exchangers. *J. Chromatogr. A* **1996**, 741, 33-48.

40. Dudakovic, A.; Wiemer, A. J.; Lamb, K. M.; Vonnahme, L. A.; Dietz, S. E.; Hohl, R. J. Inhibition of geranylgeranyl diphosphate synthase induces apoptosis through multiple mechanisms and displays synergy with inhibition of other isoprenoid biosynthetic enzymes. *J. Pharmacol. Exp. Ther.* **2008**, 324, 1028-1036.

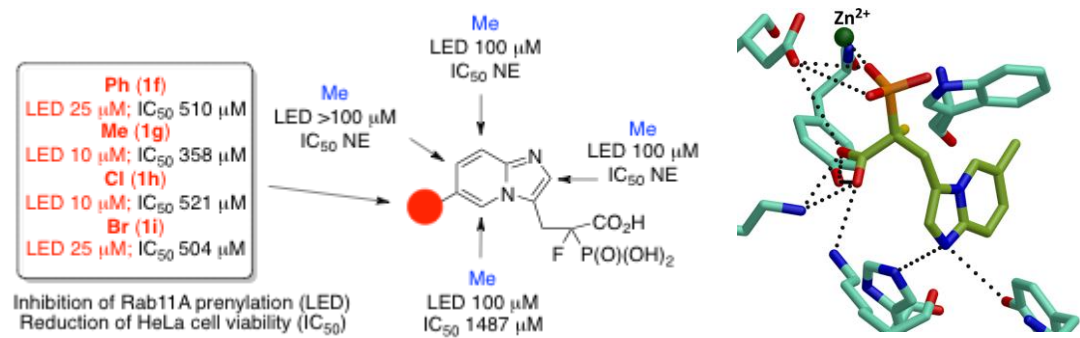
41. Wiemer, A. J.; Hohl, R. J.; Wiemer, D. F. The intermediate enzymes of isoprenoid metabolism as anticancer targets. *Anti-Cancer Agents Med. Chem.* **2009**, 9, 526-542.

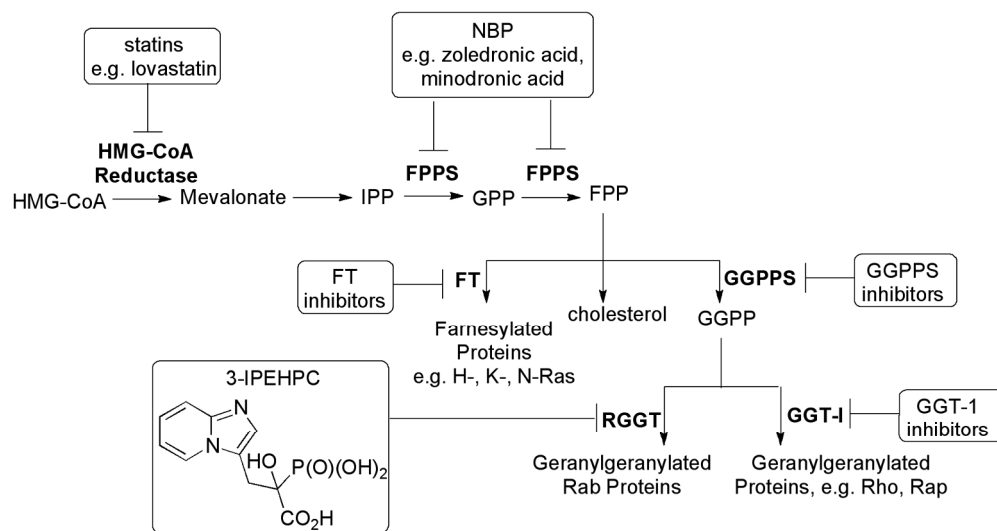
42. Ehrick, R. S.; Capaccio, M.; Puleo, D. A.; Bachas, L. G. Ligand-modified aminobisphosphonate for linking proteins to hydroxyapatite and bone surface. *Bioconjugate Chem.* **2008**, 19, 315-321.



- 1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60
43. Marma, M. S.; Xia, Z.; Stewart, C.; Coxon, F.; Dunford, J. E.; Baron, R.; Kashemirov, B. A.; Ebetino, F. H.; Triffitt, J. T.; Russell, R. G. G.; McKenna, C. E. Synthesis and biological evaluation of  $\alpha$ -halogenated bisphosphonate and phosphonocarboxylate analogues of risedronate. *J. Med. Chem.* **2007**, *50*, 5967-5975.
44. Palsuledesai, C. C.; Ochocki, J. D.; Markowski, T. W.; Distefano, M. D. A combination of metabolic labeling and 2D-DIGE analysis in response to a farnesyltransferase inhibitor facilitates the discovery of new prenylated proteins. *Mol. BioSyst.* **2014**, *10*, 1094-1103.
45. Berman, H. M.; Westbrook, J.; Feng, Z.; Gilliland, G.; Bhat, T. N.; Weissig, H.; Shindyalov, I. N.; Bourne, P. E. The Protein Data Bank. *Nucleic Acids Res.* **2000**, *28*, 235-242.
46. Harder, E.; Damm, W.; Maple, J.; Wu, C.; Reboul, M.; Xiang, J. Y.; Wang, L.; Lupyan, D.; Dahlgren, M. K.; Knight, J. L.; Kaus, J. W.; Cerutti, D. S.; Krilov, G.; Jorgensen, W. L.; Abel, R.; Friesner, R. A. OPLS3: a force field providing broad coverage of drug-like small molecules and proteins. *J. Chem. Theory Comput.* **2016**, *12*, 281-296.
47. Gmach, J.; Huben, K.; Blazewska, K. M.  $\alpha$ -Fluoro phosphonocarboxylates: the NMR analysis of the heteronuclear ABMX spin system. *Phosphorus, Sulfur Silicon Relat. Elem.* **2014**, *189*, 1216-1225.

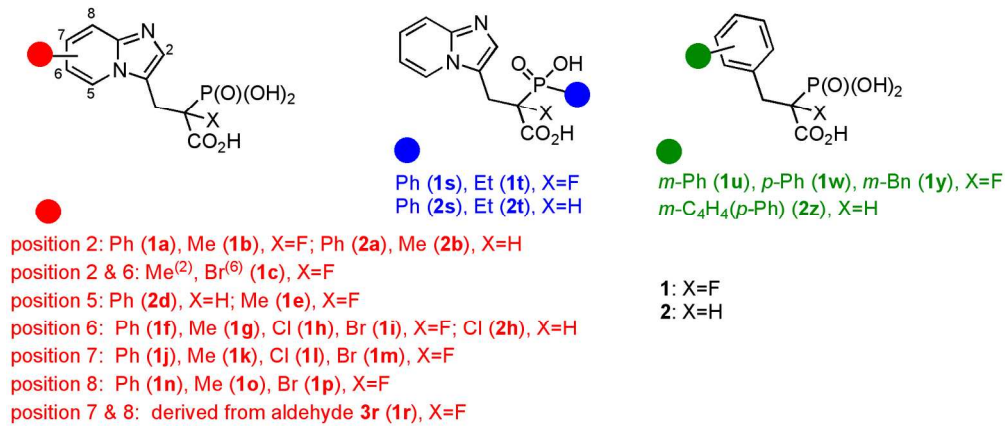
Table of Contents Graphic





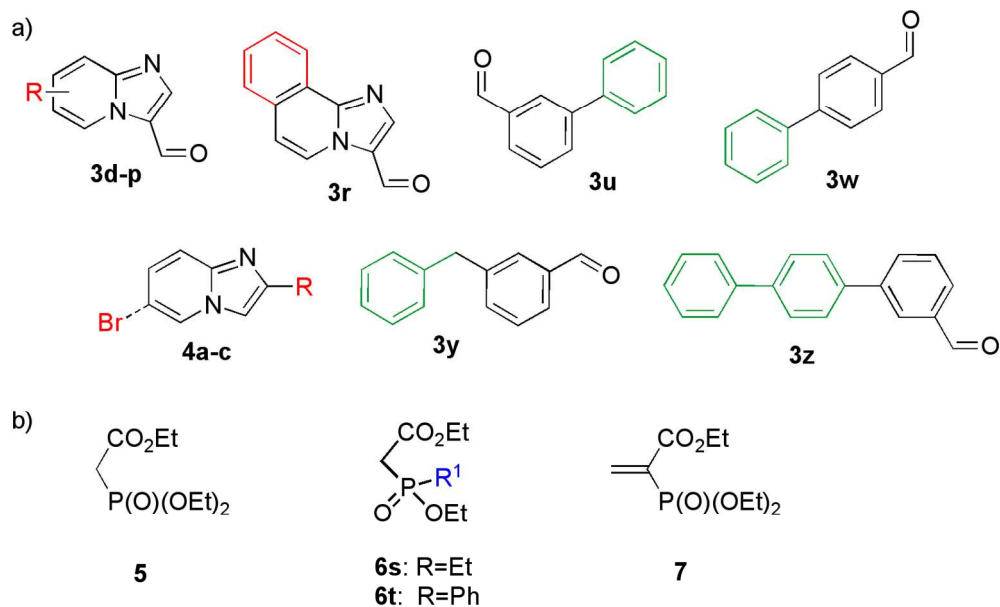
The isoprenoid biosynthesis pathway. NBP: nitrogen-containing bisphosphonates; FPPS: farnesyl pyrophosphate synthase; GGPPS: geranylgeranyl pyrophosphate synthase; FT: farnesyl transferase; GGT-1: geranylgeranyl transferase 1; FPP: farnesyl pyrophosphate; GPP: geranyl pyrophosphate; GGPP: geranylgeranyl pyrophosphate; RGGT: Rab geranylgeranyl transferase.

171x90mm (300 x 300 DPI)



Structures of studied compounds.

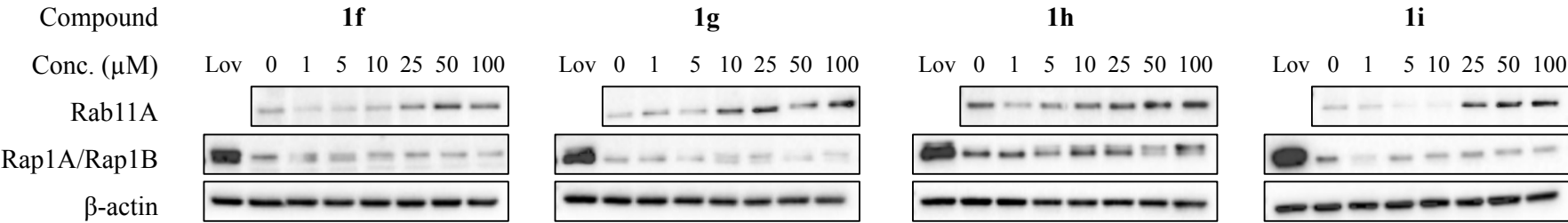
171x73mm (300 x 300 DPI)



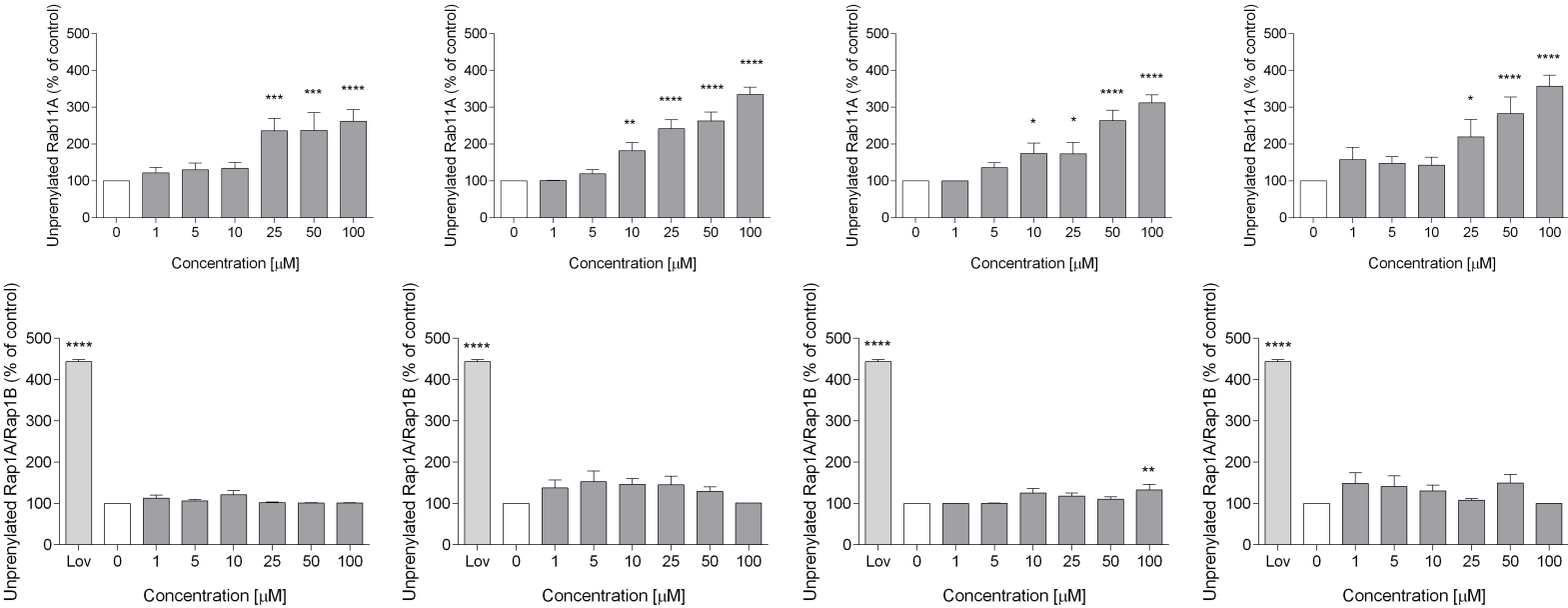
Starting materials for the synthesis of target compounds, representing a) heterocycle and aromatic part; b) phosphonoacetate and phosphinoacetate derivatives.

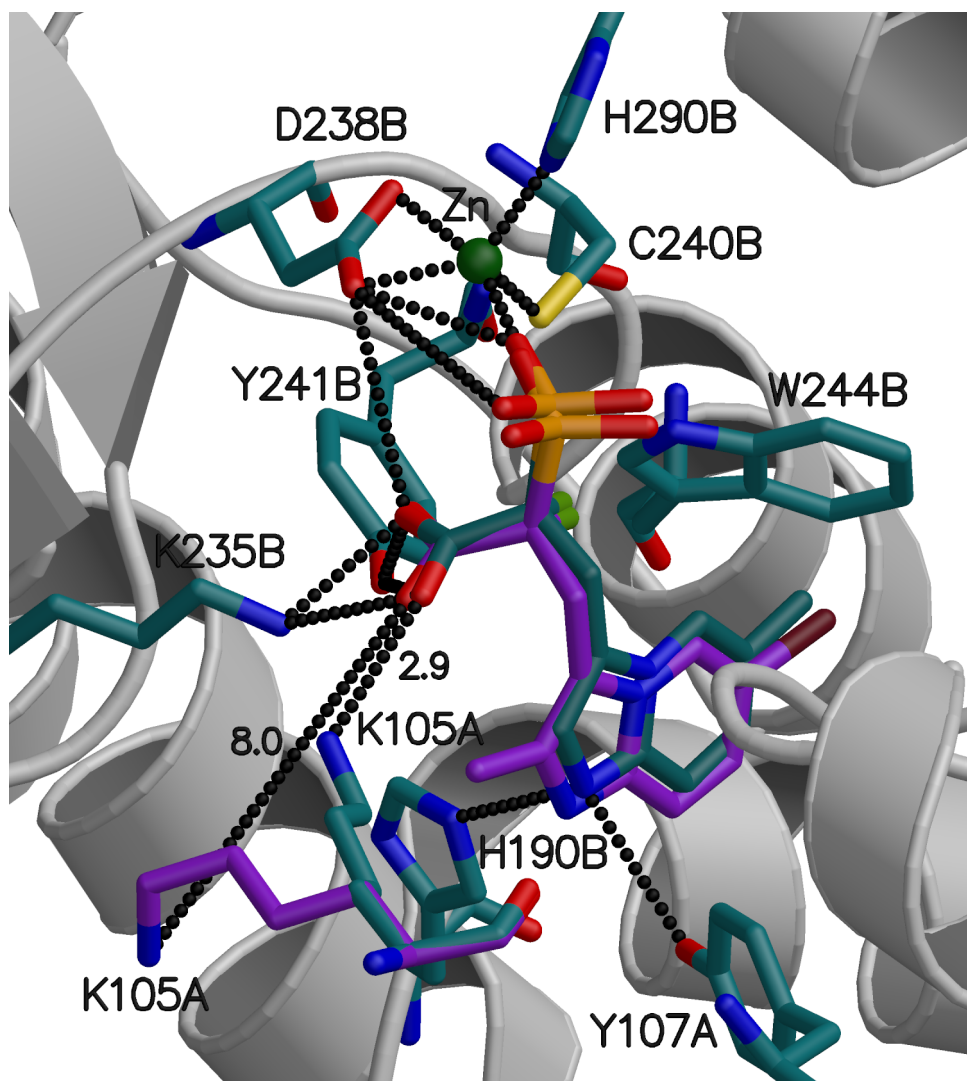
140x85mm (300 x 300 DPI)

**A**



**B**





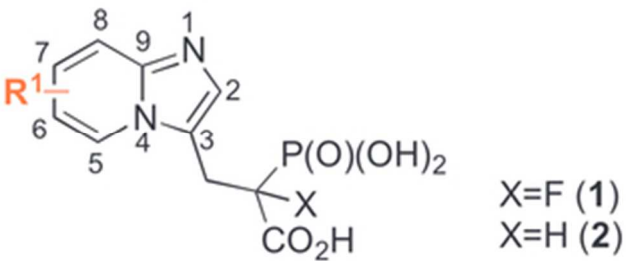


Table 1; row before entry 1

26x11mm (300 x 300 DPI)



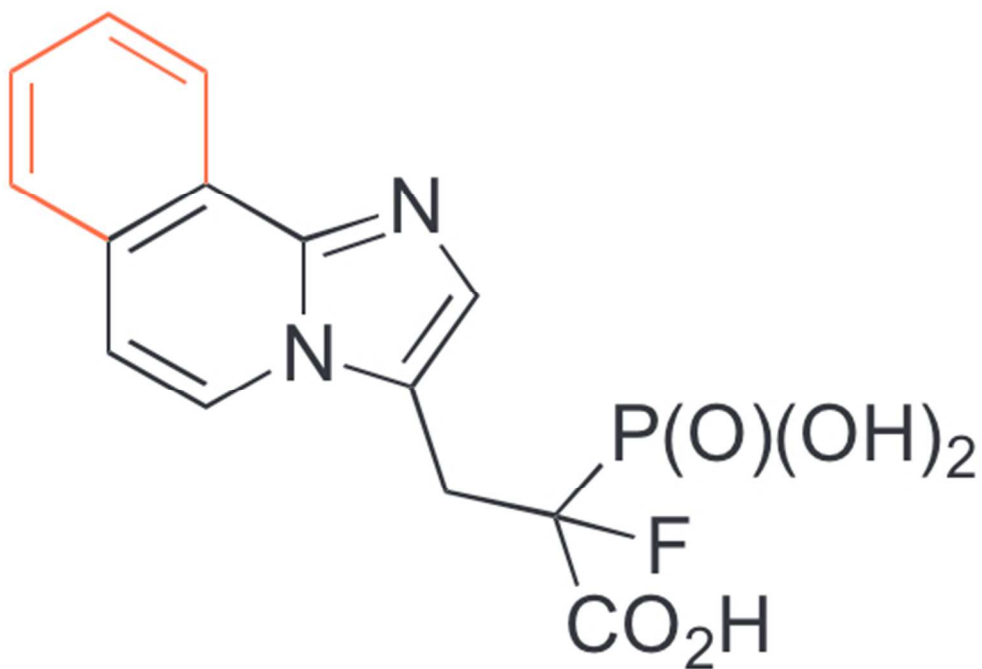


Table 1; entry 19

45x31mm (300 x 300 DPI)

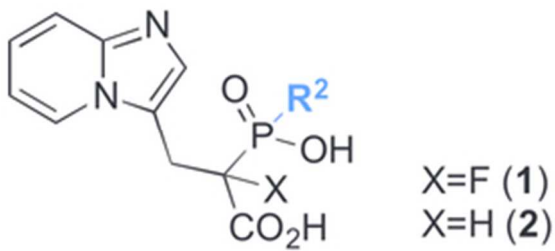


Table 1; row before entry 24

23x10mm (300 x 300 DPI)

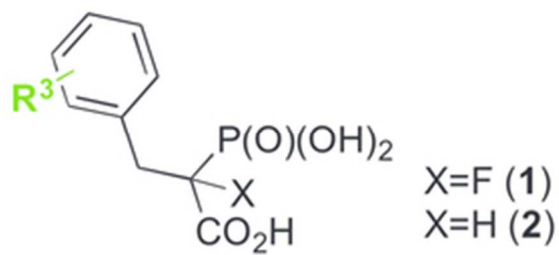


Table 1; row before entry 28

23x10mm (300 x 300 DPI)

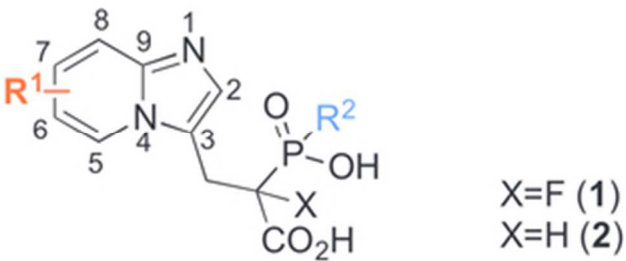
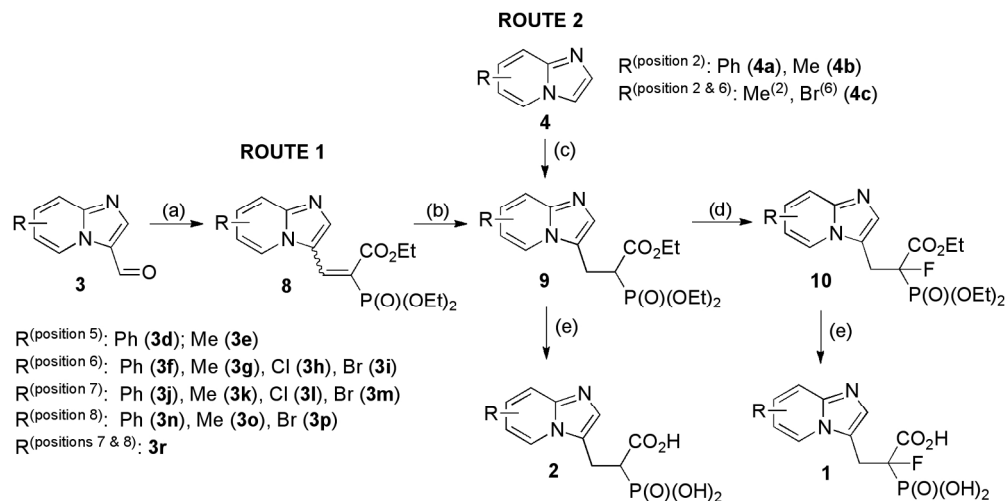


Table 2: at the top

26x11mm (300 x 300 DPI)



Two strategies used for the synthesis of phosphonocarboxylates, presented on the example of 3-IPEHPC analogs. Reagents and conditions: (a) Triethyl phosphonoacetate,  $\text{TiCl}_4$ , TEA, DCM, -20 °C to rt; (b)  $\text{NaBH}_4$ ,  $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ , MeOH, -40 °C; (c) **7**, 1,4-dioxane,  $\text{AlCl}_3$  (cat), reflux; (d) NFSI, BuLi, THF, -70 °C/ 20 minutes, -20 °C/ 1 h; (e) 12 M HCl, reflux.

177x88mm (300 x 300 DPI)

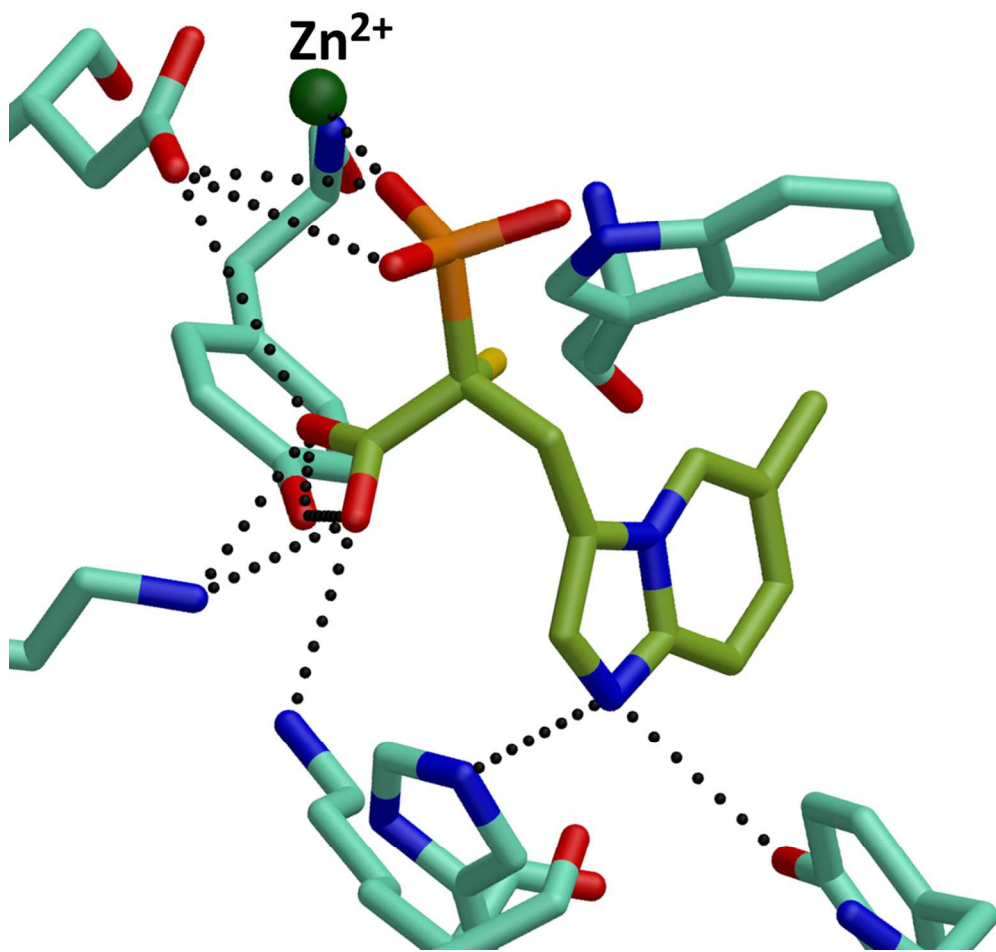
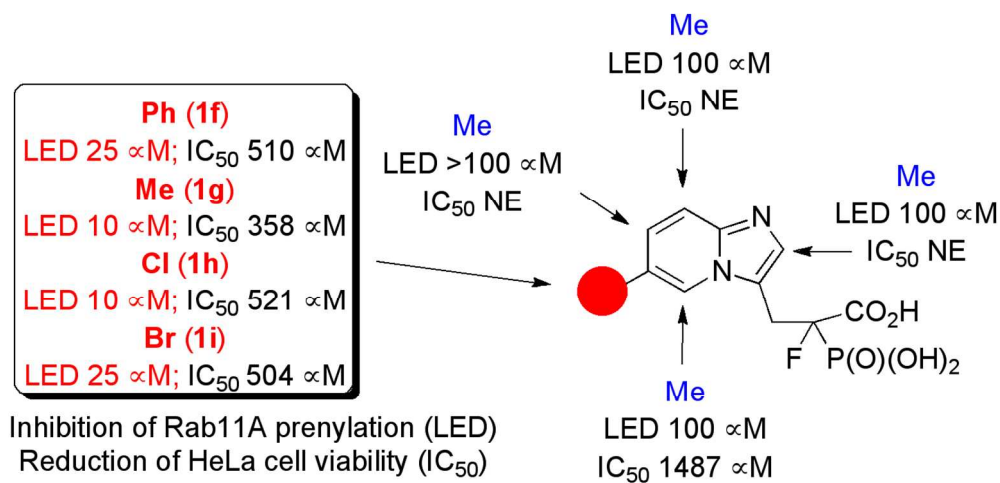


Table of contents graphic 2  
443x414mm (72 x 72 DPI)



122x60mm (300 x 300 DPI)