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ORIGINAL PAPER

Bioactive amide and *α*-aminophosphonate inhibitors for methicillin-resistant *Staphylococcus aureus* (MRSA)

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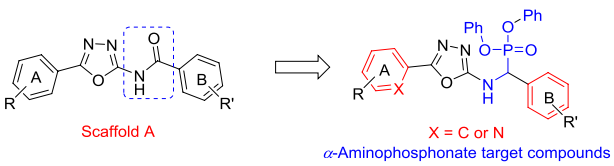
Abstract

Scaffolds of 2-acylamino-1,3,4-oxadiazole have been recently developed as transglycosylase inhibitors against MRSA. In the present study, structure–activity relationships of new derivatives of 2-acylamino-1,3,4-oxadiazole were explored with focus on the substitution of the aromatic rings. The in vitro antibacterial activity of these compounds against MRSA strain was evaluated using agar disc diffusion method. These inhibitors have an amide linker between 1,3,4-oxadiazole ring and the aromatic ring B. The role of this linker on the bioactivity of the compounds was also studied. The results showed promising series of 2-*α*-aminophosphonate-1,3,4-oxadiazole as inhibitors for MRSA strain. Both series revealed two structural features which appear to be essential for anti-MRSA activities, the first one is the incorporation of two electron-withdrawing groups at *meta*- and *para*- positions within aromatic ring B which contributed to a higher activity against MRSA strain. The second is the new *α*-aminophosphonate linker serving as bio-isosteric analogue of the corresponding amide linker and giving comparable results with the amide derivatives.

Graphical abstract



Keywords Phosphorus compounds · Drug research · Antibiotics · 1,3,4-oxadiazole · Amide coupling · *Staphylococcus aureus*

Introduction

Prevention of fatalities from antimicrobial resistance bacterial infections is one of current challenges in global health. It has been reported that methicillin-resistant *Staphylococcus aureus* (MRSA) is responsible for almost 50% of the 23,000 documented fatalities due to antibiotic-resistant infections in the United States [1]. The US Centers of Disease Control and Prevention (CDC) has identified the *S. aureus* strain as serious healthcare threat.

The *β*-lactamase-resistant antibiotic methicillin was discovered in 1959 and is still used as first-line treatment for *S. aureus* infections that show no response to classical penicillins. Two years later, the first case of MRSA was reported

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in England [2]. The *S. aureus* strain is resistant to many antibacterial drugs including macrolides [3], glycopeptides [4], oxazolidinones [5] and fluoroquinolones [4, 6–8]. There is currently a need to develop inhibitors to prevent the fatal infections from MRSA.

A high-throughput screening (HTS) study at The Genomics Research Center of Taiwan on a library of 2 million compounds was performed to evaluate the antimicrobial activity against MRSA including the inhibition of the transglycosylase enzyme. The results from this study showed the anti-MRSA activity of several compounds with minimal inhibitory concentration (MIC) values as low as 0.1 μg/cm^3 [9]. In this study, the oxadiazole derivatives (scaffold A, Fig. 1) have emerged as one of the top nine active scaffolds. We therefore selected these oxadiazole derivatives to study the substituent effects on the aromatic rings on the biological activity. To study the effect of the substitution on the aromatic rings on the biological activity, the 1,3,4-oxadiazoles and their derivatives have been shown to possess diverse and beneficial biological activities such as anti-inflammatory [10], antimicrobial [11–13], anticonvulsant [14], antiviral [15] and antimalarial effects [16].

Next, we considered incorporating α-aminophosphonate moiety in the oxadiazole derivatives. The α-aminophosphonate moiety was selected because compounds with α-aminophosphonate moiety have been shown to have intriguing biological activities. For example, compounds with α-aminophosphonate moiety are biologically active as antimicrobial [17, 18], antitumoral [19, 20] and antiviral agents [21] as possessing the ability to inhibit enzymes representing potential therapeutical targets [22, 23]. Another advantage for the α-aminophosphonate derivatives is their ability to serve as isosteric or bio-isosteric analogues of the corresponding amide and peptide counterparts (Fig. 1). The planar amide moiety can be replaced by the bulkier tetrahedral α-aminophosphonate group, obtaining a versatile and novel fragment that leads to unique physical properties such as pK_A values and aqueous solubility as well as the biological properties [24, 25].

The biological activities of α-aminophosphonate compound **2** bearing the 1,3,4-oxadiazole moiety have not been reported. Further evaluations of their biological activities on different strains of bacteria are currently needed. We report in the current study, α-aminophosphonate compounds with the 1,3,4-oxadiazole moiety that show bioactivity as antimicrobial agents.

This study aims at the optimization of the amide moiety of scaffold A to improve the anti-MRSA activity. This is accomplished by replacing the amide moiety of scaffold A with the tetrahedral α-aminophosphonate group, as well as varying the substitution at the B ring. This led to the synthesis of new target of inhibitor **2**. In addition, the phenyl ring of compound **1** (ring A) was replaced with the corresponding heterocyclic pyridine ring that has predictable effects on lipophilicity, polar surface area and hydrogen bonding capacity required to improve the water solubility [26].

Results and discussion

Chemistry

Different substitution patterns at the phenyl rings A and B of compound **1** have already been investigated within HTS study to identify the preliminary SAR. Based on these findings, our first endeavours were devoted at synthesizing novel derivatives of compound **1** bearing electron-withdrawing groups at the *para* and/or *meta* positions of the B ring. This strategy was pursued both for improving the antibacterial activity and for collecting additional information concerning the SAR of this scaffold.

For the synthesis of the amide and α-aminophosphonate derivatives **9** and **10,** respectively, the corresponding 5-(3-bromophenyl)-1,3,4-oxadiazol-2-amine (**8a**) and

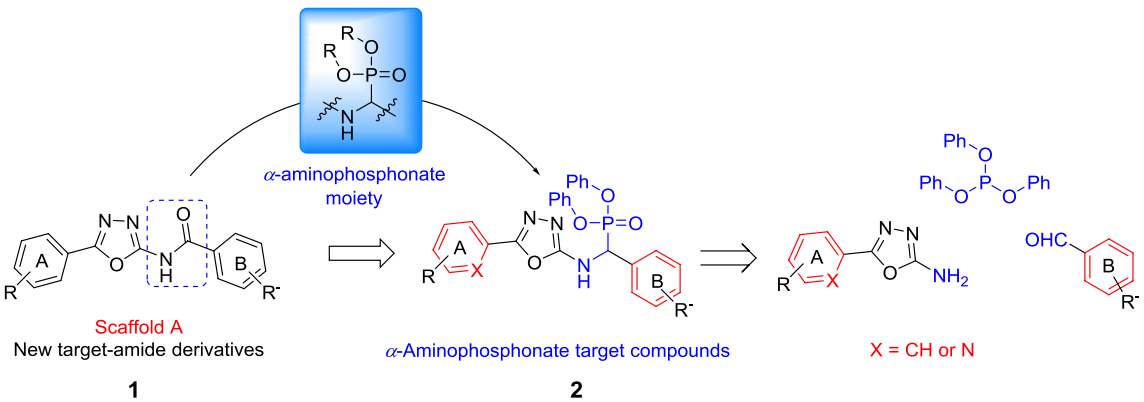


Fig. 1 Design of novel 2-acylamino-1,3,4-oxadiazoles and 2-α-aminophosphonate-1,3,4-oxadiazoles

5-(6-bromopyridin-2-yl)-1,3,4-oxadiazol-2-amine (**8b**) were selected as suitable starting materials. These intermediates were synthesized from the commercially available esters **3**. The first attempt, employing hydrazine hydrate in ethanol at reflux temperature, afforded the undesired dihydrazide **5b**, as a result of the simultaneous nucleophilic aromatic substitution on the heterocyclic ring. Treatment of this intermediate with cyanogen bromide gave the corresponding oxadiazolyl hydrazinylpyridinium bromide **6b** in high purity, as confirmed by liquid chromatography–mass spectrometry (LC–MS) analysis. When the hydrazinolysis was performed under mild conditions (room temperature for 1 h), afforded the corresponding hydrazide **7** which undergoes cyclization with cyanogen bromide to give the desired amino oxadiazole derivatives **8** (Scheme 1).

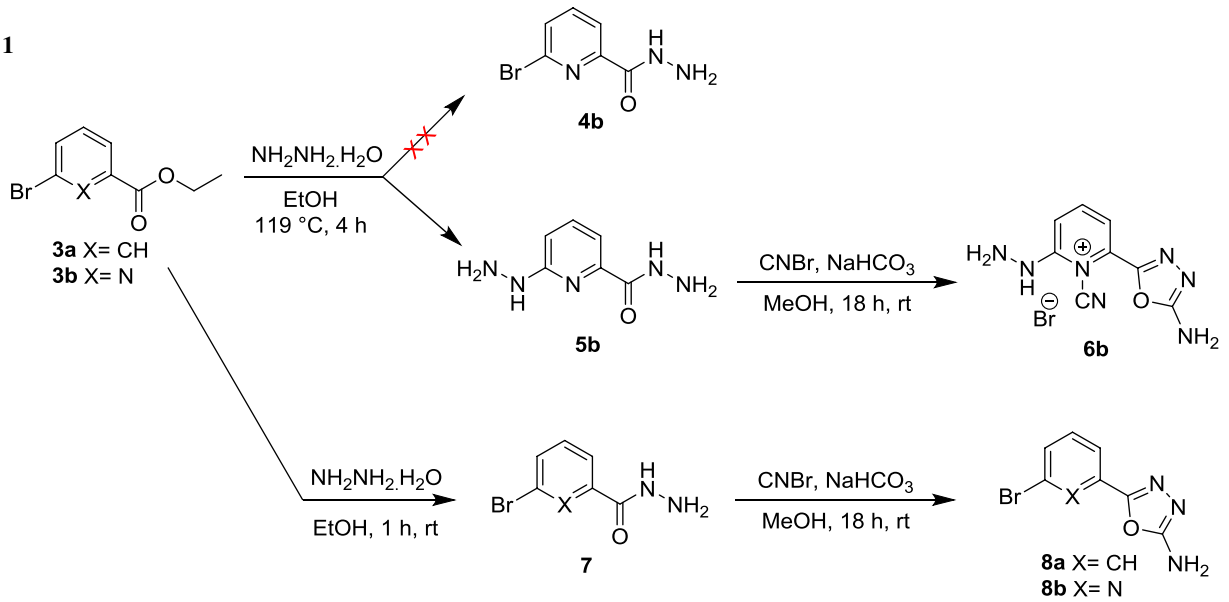
The synthetic strategy of the amide derivatives **9a**–**9h** is the amide coupling between the key intermediate **8a** and appropriate carboxylic acids. The amide bond was formed between carboxylic acid chloride and the amine derivatives in the presence of base. Thus, the reaction between **8a** and the corresponding carboxylic acid chloride in the presence of triethylamine (TEA) was first attempted. Control by thin layer chromatography (TLC) and LC–MS analysis showed that only traces of the amide product was formed after 18 h or after heating the mixture for 5 h at 40 °C. No significant change could be observed and mainly unreacted starting material was present. These results indicated that other conditions for the amide coupling might be required. To optimize the amide coupling conditions, we used propanephosphonic acid anhydride (T3P) as an amide coupling reagent in the presence of TEA as a base, which provides amides in high yields with easy reaction setup and product isolation. Satisfying yields of the product were obtained by precipitation and filtration from the reaction mixture (Scheme 2, Table 1).

A typical synthetic method for the α-aminophosphonate derivatives (Kabachnik–Fields reaction) is the one-pot reaction of three components, aldehyde, amine and phosphite derivatives. In the view of the increasing biological importance and the chemical applications of the α-aminophosphonate derivatives, researchers in the last 35 years have been developing a variety of suitable synthetic procedures for the synthesis of these compounds [17, 27–34]. In the present work, we further optimized the conditions for the synthesis of α-aminophosphonate derivatives. The best results were obtained when the amino oxadiazole derivative **8b** was treated with 1.2 equivalents of substituted benzaldehyde and 1 equivalent of triphenyl phosphite in glacial acetic acid at 80 °C for 4 h. The product was recrystallized affording good-to-moderate yields. Detailed synthetic procedure is described in experimental part (Scheme 3, Table 2).

Biological evaluation

The synthesized amide and α-aminophosphonate derivatives bearing 1,3,4-oxadiazole moiety were then evaluated for their in vitro antibacterial activity against MRSA strain by agar disc diffusion method [35] as recommended by Clinical and Laboratory Standards Institute (CLSI) [36]. The assay was carried out by impregnation of synthesized compounds (10 µg/cm^3) in dimethyl sulfoxide (DMSO) and

Scheme 1



Scheme 2

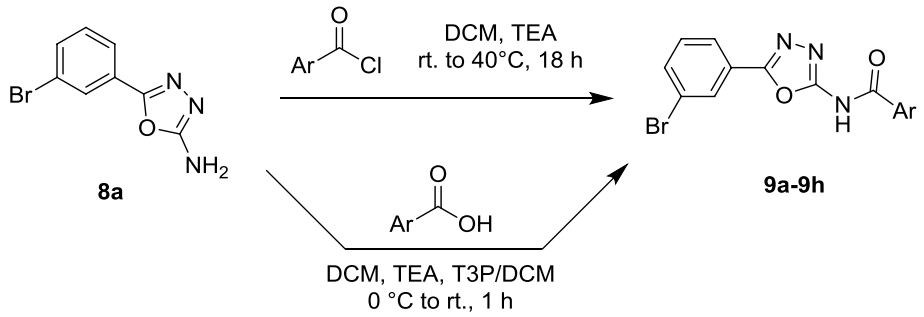
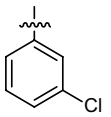
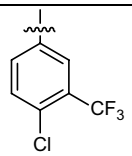
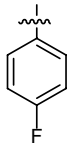
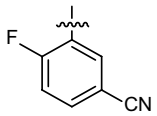
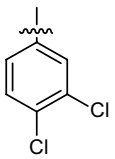
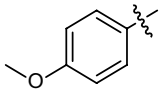
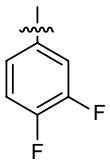
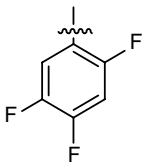


Table 1 2-Acylamino-1,3,4-oxadiazoles **9a–9h**

Product	Ar	Yield / %	Product	Ar	Yield / %
9a		74	**9e**		81
9b		83	**9f**		58
9c		69	**9g**		67
9d		78	**9h**		83

Scheme 3

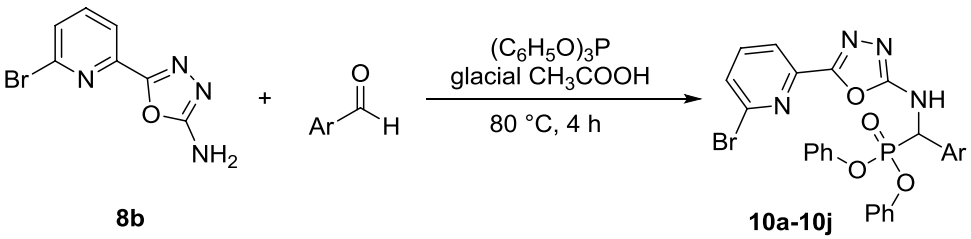
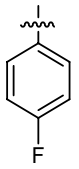
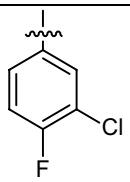
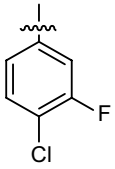
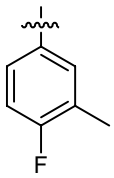
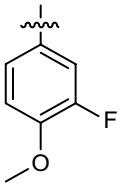
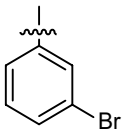
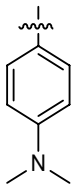
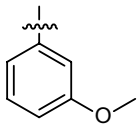
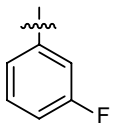
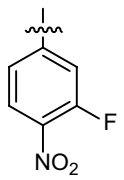


Table 2 α-Aminophosphonates **10a–10j**

Product	Ar	Yield / %	Product	Ar	Yield / %
10a		43	**10f**		39
10b		38	**10g**		65
10c		54	**10h**		49
10d		46	**10i**		32
10e		63	**10j**		27

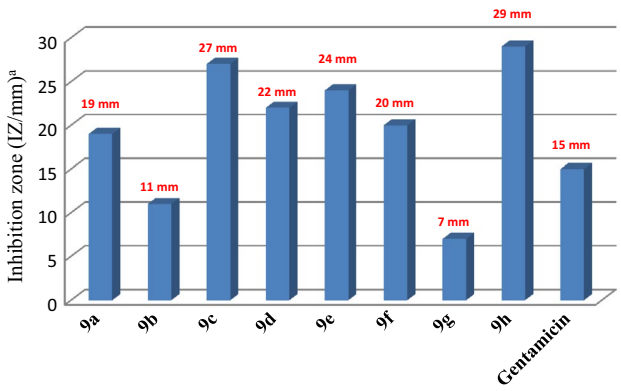


Fig. 2 In vitro antibacterial activity against MRSA for amide derivatives. [a] The IZ for each sample is measured three times using standard micrometer of high accuracy (error = ± 0.005 mm) then the average value is represented

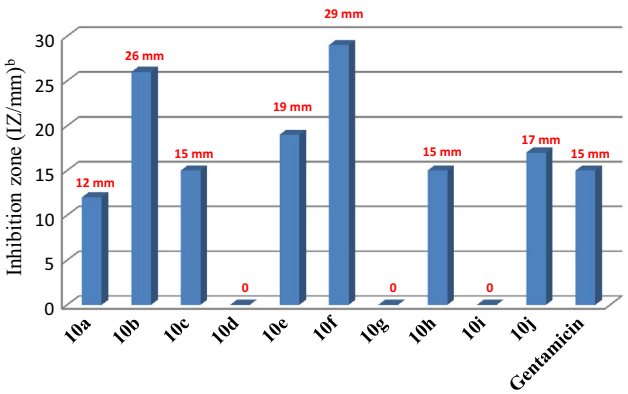


Fig. 3 In vitro antibacterial activity against MRSA for α-aminophosphonate derivatives. [b] The IZ for each sample is measured three times using standard micrometer of high accuracy (error = ± 0.005 mm) then the average value is represented

the inhibition zone for each derivative surrounding the disc is measured in mm scale and the results are compared with the commercial reference drug gentamicin [37]. Figures 2 and 3 show summary of the results.

Figure 2 shows that the novel amide derivatives **9a**, **9c**, **9d**, **9e**, **9f** and **9h** could effectively inhibit the growth of the tested MRSA strain with inhibition zone (IZ) values in the range of 19–29 mm. In detail, the rank order of activity for these derivatives was as following **9h**, IZ = 29 mm > **9c**, IZ = 27 mm > **9e**, IZ = 24 mm > **9d**, IZ = 22 mm > **9f**, IZ = 20 mm > **9a**, IZ = 19 mm. These results are consistently higher than the results from the standard drug gentamicin with IZ = 15 mm. Compounds **9b** and **9g** showed instead a moderate-to-poor activity with IZ values 11 and 7 mm, respectively, which is less effective than the standard drug gentamicin.

On the other hand, the novel α-aminophosphonate derivatives **10b**, **10e**, **10f** and **10j** could also effectively inhibit the growth the tested MRSA strain with inhibition zone values in the range of 17–29 mm. The rank order of activity was as following **10f**, IZ = 29 mm > **10b**, IZ = 26 mm > **10e**, IZ = 19 mm > **10j**, IZ = 17 mm, all surpassing the activity of the standard drug gentamicin, analogously to the series of amide derivatives. Among α-aminophosphonate derivatives, compounds **10a**, **10c** and **10h** showed moderate activity with IZ values of 12, 15 and 15 mm, respectively. The synthesized derivatives **10d**, **10g** and **10i** showed no activity against the tested MRSA strain.

Concerning the structure–activity relationship (SAR), the results in Figs. 2 and 3 showed that the nature (electron withdrawing or electron donating) and the substituted position (*ortho*-, *meta*-, or *para*-) of the substituent groups attached to ring B directly affected on the rank order of activity against MRSA strain. The set of amide derivatives **9c**, **9d**, and **9e** containing electron withdrawing groups at *meta*- and *para*-positions exhibited high anti-MRSA activity, following the rank of order (3-Cl, 4-Cl > 3-CF_3, 4-Cl > 3-F, 4-F), respectively. Furthermore, adding on additional electron withdrawing group (F) to *ortho*-position of ring B provided compound **9h** with the highest anti-MRSA activity. On the other hand, mono-substitution with an electron-withdrawing group (Cl) at *meta*-position showed only a moderate activity (compound **9a**). The mono-substitution affording the *p*-fluoro derivative **9b** and *m*-methoxy derivative **9g**, rendered the compound having moderate-to-poor activity against MRSA strain.

One of the most important targets of this study is to investigate the SAR and the compatibility of the α-aminophosphonate derivatives with substitution of ring B towards the anti-MRSA activity. In this context, the biological results suggested that di-substitution at *meta*- and *para*-positions with electron-withdrawing groups of ring B (3-Cl, 4-F > 3-F, 4-Cl) contributed to the highest activity against MRSA strain, compounds **10f** and **10b,** respectively. Mono-substitution with an electron-withdrawing group (F or Br) at *meta*-position showed good-to-moderate activity, compounds **10e** and **10h,** respectively. Comparable with **10e**, adding one methoxy group or nitro group to *p*-position provided compound **10c** and **10j** with weaker anti-MRSA activity. The mono-substitution using electron-withdrawing groups (F) at *p*-position provided compound **10a** that showed lower activity than **10e** and adding one methyl group to *m*-position afforded compound **10g,** leading to a dramatic decrease in the activity against MRSA strain. The results of compounds **10d** and **10i** having dimethyl amine and methoxy group, respectively, showed no activity against MRSA strain.

In this context, the SAR results further proves that the presence of electron-withdrawing substituents at *meta*- and *para*-positions of the ring B is essential for anti-MRSA activity. In addition, this is in agreement with the previous SAR preliminary results from the HTS study. Moreover, the SAR results confirmed that the α-aminophosphonate derivatives well-tolerated against the MRSA strain and serve as bio-isosteric analogues of the corresponding amide derivatives.

Conclusion

We synthesized a novel series of amide and α-aminophosphonate derivatives bearing 1,3,4-oxadiazole moiety as new inhibitors against MRSA strain based on the HTS scaffold A. Two series of compounds were synthesized by introducing various substitutes at ring B followed by SAR. The purity of the compounds were monitored at 254 nm and proved to be ≥ 95%. The in vitro antibacterial activity against MRSA strain results showed that: (1) in both series amide and α-aminophosphonate derivatives; (a) mono-electron withdrawing substituent at *meta*-position on the ring B (compounds **9a**, **10e**, and **10h**) shows better activity compared with the one at *para*-position (compounds **9b** and **10a**); (b) compared with that mono-electron withdrawing substitutions on the ring B, two electron withdrawing substituents at *meta*- and *para*-positions contributed to a higher activity against MRSA strain (compounds **9c**, **9d**, **9e**, **10b**, and **10j**), and (2) α-aminophosphonate linker between the 1,3,4-oxadiazole ring and the aromatic ring B serve as bio-isosteric analogues of the corresponding amide linker and gives comparable results with the amide derivatives.

Experimental

All reagents were used in analytical grades. Solvents were desiccated if necessary by standard methods. Reactions were monitored by TLC (silica gel 60F254, Merck, Darmstadt, Germany). Melting points were determined on a Melting

Point Apparatus (Stuart Scientific, Stone, Staffordshire, UK). NMR spectra were carried out with a 400 MHz at Ulm University, Germany. Chemical shifts (δ) are reported in parts per million (ppm) relative to the respective solvent or tetramethylsilane (TMS) as internal standard and standard abbreviations were used (a = apparent; b = broad; s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet). Elemental analyses were determined on a Yanaca CHN Corder MT-3 elemental analyser in the microanalysis laboratory at Cairo University. The purities of isolated products were determined by ESI-mass spectra obtained on an LC–MS instrument (Applied Biosystems API 2000 LC–MS/MS, HPLC Agilent 1100). The required starting materials, 3-bromobenzohydrazide (**7a**) [38], 6-bromopicolinyl hydrazide (**7b**) [39] and 5-(3-bromophenyl)-1,3,4-oxadiazol-2-amine (**8a**) [40] were synthesized according to the literature.

5-(6-Bromopyridin-2-yl)-1,3,4-oxadiazol-2-amine (8b, $C_7H_5BrN_4O$) A suspension of 0.15 g **7b** (0.70 mmol) in 0.40 cm^3 MeOH and 0.20 cm^3 1,4-dioxane was treated with 0.26 cm^3 BrCN (3 M solution in CH_2Cl_2, 0.78 mmol) dropwise at room temperature. Stirring for 1 h, then 0.12 g $NaHCO_3$ (1.42 mmol) was added and the resulting suspension was continued stirring for 18 h. The resulting white precipitate was filtered off, washed with water and dried under high vacuum to afford 145 mg (84%) **8b** as a white solid that recrystallized from ethanol. M.p.: 119–121 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.55 (s, 2H, NH_2), 7.75 (d, J = 7.88 Hz, 1H, Ar–H), 7.90 (t, J = 7.80 Hz, 1H, Ar–H), 7.99 (d, J = 7.70 Hz, 1H, Ar–H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 121.32, 130.60, 140.13, 140.27, 140.79, 151.17, 161.12 ppm; HPLC–UV–MS (254 nm): purity 98%; LC–MS (ESI): *m/z* calcd. 239.96, found 241.0 ([M+H]$^+$).

General procedure for preparation of amides 9a–9h

To a stirred suspension of corresponding acid (1.1 equiv.) in 10 cm^3 dichloromethane, 100 mg aminooxadiazole **8a** (0.42 mmol, 1 equiv.) and 116 mm^3 Et_3N (0.83 mmol, 2 equiv.) were added followed by addition of 291.6 mg T3P (50% in dichloromethane, 0.46 mmol, 1.1 equiv.) at 0 °C then allowed to warm to room temperature. The suspension was cleared up and the product was precipitated after 1 h. The precipitate was filtered off, washed with 100 cm^3 dichloromethane, 100 cm^3 sodium hydrogen carbonate, and 200 cm^3 water to afford the corresponding amides **9** in a high yield and purity after recrystallizing from methanol. In case of amides **9c**, **9f** and **9g** no precipitation formed after the addition of T3P; the reaction was stirred at room temperature overnight until a complete consumption of the respective aniline was detected by TLC. The reaction mixture was poured on a saturated sodium hydrogen carbonate solution and extracted with ethyl acetate (3 × 50 cm^3). The organic layer was combined and washed with water then dried over magnesium sulphate. The solvent was evaporated and the crude product was purified by column chromatography using mixture of dichloromethane and ethyl acetate (8:2) as an eluent to afford the corresponding amide derivatives.

***N*-[5-(3-Bromophenyl)-1,3,4-oxadiazol-2-yl]-3-chlorobenzamide (9a, $C_{15}H_9BrClN_3O_2$** Yield 124 mg (74%) as a pale yellow powder. M.p.: 190–192 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.56 (t, J = 7.82 Hz, 1H, Ar–H), 7.81 (d, J = 7.82 Hz, 1H, Ar–H), 7.82–7.83 (m, 3H, Ar–H),7.92 (d, 8.39 Hz, 1H, Ar–H), 8.04 (d, J = 7.91 Hz, 1H, Ar–H), 8.46 (s, 1H, Ar–H), 12.82 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 120.30, 122.11, 122.86, 125.54, 125.84, 127.18, 127.38, 128.83, 131.54, 132.20, 134.50, 134.98, 135.56, 158.62 ppm; HPLC–UV–MS (254 nm): purity 96%; LC–MS (ESI): *m/z* calcd. 376.96, found 378.0 ([M+H]$^+$).

***N*-[5-(3-Bromophenyl)-1,3,4-oxadiazol-2-yl]-4-fluorobenzamide (9b, $C_{15}H_9BrFN_3O_2$)** Yield 130 mg (83%) as a pale yellow powder. M.p.: 182–184 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.58 (t, J = 7.93 Hz, 1H, Ar–H), 7.71 (d, J = 8.97 Hz, 1H, Ar–H), 7.78 (d, J = 7.84 Hz, 1H, Ar–H), 7.84 (d, J = 8.97 Hz, 1H, Ar–H), 7.94 (d, J = 7.83 Hz, 1H, Ar–H), 8.05–8.07 (m, 1H, Ar–H), 8.15 (s, 1H, Ar–H), 8.35 (d, 8.62 Hz, 1H, Ar–H), 12.56 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 115.76, 122.21, 122.37, 123.95, 125.05, 125.49, 126.46, 127.32, 127.37, 128.34, 131.22, 131.29, 131.46, 132.97, 134.40, 158.45 ppm; HPLC–UV–MS (254 nm): purity 97%; LC–MS (ESI): *m/z* calcd. 360.99, found 361.9 ([M+H]$^+$).

***N*-[5-(3-Bromophenyl)-1,3,4-oxadiazol-2-yl]-3,4-dichlorobenzamide (9c, $C_{15}H_8BrCl_2N_3O_2$)** Yield 128 g (69%) as a white solid. M.p.: 186–188 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.58 (t, J = 7.93 Hz, 1H, Ar–H), 7.84–7.88 (m, 2H, Ar–H), 7.96 (dd, J = 1.04, 7.82 Hz, 1H, Ar–H), 8.00 (dd, J = 2.08, 8.39 Hz, 1H, Ar–H), 8.05 (s, 1H, Ar–H), 8.27 (d, J = 2.07 Hz, 1H, Ar–H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 122.37, 125.04, 125.40, 128.32, 128.56, 130.28, 130.96, 131.48, 131.71, 133.28, 134.45, 135.58, 158.50 ppm; HPLC–UV–MS (254 nm): purity 96%; LC–MS (ESI): *m/z* calcd. 410.92, found 411.0 ([M+H]$^+$).

***N*-[5-(3-Bromophenyl)-1,3,4-oxadiazol-2-yl]-3,4-difluorobenzamide (9d, $C_{15}H_8BrF_2N_3O_2$)** Yield 124 mg (78%) as a light yellow solid. M.p.: 201–203 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.46–7.66 (m, 2H, Ar–H), 7.76–7.89 (m, 1H, Ar–H), 7.94 (d, J = 7.84 Hz, 1H, Ar–H), 7.99–8.10 (m, 2H, Ar–H), 8.25 (dd, J = 2.19, 7.11 Hz, 1H, Ar–H), 12.55 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 117.19, 117.34, 120.01, 122.36, 125.03, 125.40, 128.31, 129.80, 130.97, 131.70, 134.44, 158.96 ppm; HPLC–UV–MS

(254 nm): purity 97%; LC–MS (ESI): *m/z* calcd. 378.98, found 380.0 ($[M+H]^+$).

***N*-[5-(3-Bromophenyl)-1,3,4-oxadiazol-2-yl]-4-chloro-3-(trifluoromethyl)benzamide (9e, $C_{16}H_8BrClF_3N_3O_2$)** Yield 151 mg (81%) as a white solid. M.p.: 179–181 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 7.58$ (t, $J = 7.93$ Hz, 1H, Ar–H), 7.84 (dd, $J = 1.51$, 8.50 Hz, 1H, Ar–H), 7.95–7.98 (m, 2H, Ar–H), 8.06 (s, 1H, Ar–H), 8.31 (dd, $J = 2.04$, 8.36 Hz, 1H, Ar–H), 8.48 (d, $J = 1.99$ Hz, 1H, Ar–H), 12.83 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 40.06$, 119.81, 121.62, 122.37, 123.44, 125.06, 125.35, 126.69, 126.90, 127.69, 128.34, 131.72, 132.20, 134.01, 134.50, 135.07, 158.52 ppm; HPLC–UV–MS (254 nm): purity 95%; LC–MS (ESI): *m/z* calcd. 444.94, found 446.0 ($[M+H]^+$).

***N*-[5-(3-Bromophenyl)-1,3,4-oxadiazol-2-yl]-5-cyano-2-fluorobenzamide (9f, $C_{16}H_8BrFN_4O_2$)** Yield 93 mg (58%) as a pale brown powder. M.p.: 187–189 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 7.54$-7.63 (m, 2H, Ar–H), 7.71–7.78 (m, 2H, Ar–H), 7.83 (d, $J = 7.75$ Hz, 1H, Ar–H), 7.95 (d, $J = 7.52$ Hz, 1H, Ar–H), 8.04 (s, 1H, Ar–H), 12.53 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 119.76$, 119.93, 121.93, 122.35, 125.06, 125.41, 125.82, 127.90, 128.32, 131.76, 134.42, 157.72, 158.42, 160.12 ppm; HPLC–UV–MS (254 nm): purity 98%; LC–MS (ESI): *m/z* calcd. 385.98, found 387.0 ($[M+H]^+$).

***N*-[5-(3-Bromophenyl)-1,3,4-oxadiazol-2-yl]-3-methoxybenzamide (9g, $C_{16}H_{12}BrN_3O_3$)** Yield 104 mg (67%) as a light yellow solid. M.p.: 168–170 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 3.77$ (s, 1H, OCH_3), 7.59 (d, $J = 7.79$ Hz, 1H, Ar–H), 7.63 (d, $J = 7.72$ Hz, 1H, Ar–H), 7.70–7.74 (m, 2H, Ar–H), 7.78 (d, $J = 7.83$ Hz, 1H, Ar–H), 7.82–7.86 (m, 1H, Ar–H), 7.97 (d, $J = 7.84$ Hz, 1H, Ar–H), 8.07 (s, 1H, Ar–H), 12.53 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 55.42$, 119.02, 122.20, 122.37, 123.95, 125.05, 125.52, 126.46, 127.31, 128.34, 131.46, 131.69, 132.96, 134.38, 158.40 ppm; HPLC–UV–MS (254 nm): purity 95%; LC–MS (ESI): *m/z* calcd. 373.01, found 373.9 ($[M+H]^+$).

***N*-[5-(3-Bromophenyl)-1,3,4-oxadiazol-2-yl]-2,4,5-trifluorobenzamide (9h, $C_{15}H_7BrF_3N_3O_2$)** Yield 137 mg (83%) as a pale brown solid. M.p.: 181–183 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 7.58$ (t, $J = 7.94$ Hz, 1H, Ar–H), 7.85–7.87 (m, 2H, Ar–H), 7.97 (d, $J = 8.86$ Hz, 1H, Ar–H), 8.02 (dd, $J = 2.23$, 7.67 Hz, 1H, Ar–H), 8.08 (s, 1H, Ar–H), 12.58 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 119.24$, 122.20, 122.36, 123.94, 125.08, 125.32, 126.46, 127.31, 128.35, 131.46, 132.96, 134.49, 157.54 ppm; HPLC–UV–MS (254 nm): purity 96%; LC–MS (ESI): *m/z* calcd. 396.97, found 397.8 ($[M+H]^+$).

General procedure for preparation of *α*-aminophosphonate derivatives 10a–10j

Aldehyde (1.2 eq), 100 mg 5-(6-bromopyridin-2-yl)-1,3,4-oxadiazol-2-amine (**8b**, 0.41 mmol, 1 eq), and 128.74 mg triphenylphosphite (1 eq) were dissolved in 2 cm^3 glacial acetic acid and stirred at 80 °C for 4 h (TLC analysis showed the complete consumption of the amine). The solvent was evaporated and the residue was dissolved in methanol and left at − 20 °C overnight affording the crystalized product. The product was filtered off, washed with cold methanol to afford the corresponding *α*-aminophosphonate derivative **10** in a good yield and purity. In case of **10b**, **10f**, **10i** and **10j**, the filtered product showed low purity, the column chromatography was used for the purification using a mixture of dichloromethane and ethyl acetate (8:2) as an eluent to afford the aminophosphonate derivatives in moderate yields.

Diphenyl [[5-(6-bromopyridin-2-yl)-1,3,4-oxadiazol-2-yl]amino](4 fluorophenyl)methylphosphonate (10a, $C_{26}H_{19}BrFN_4O_4P$) Yield 140 mg (43%) as a pale brown solid. M.p.: 260–263 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 5.79$ (dd, $J = 9.91$, 22.01 Hz, 1H, N–CH–P), 7.00 (d, $J = 8.25$ Hz, 2H, Ar–H), 7.10 (d, $J = 8.17$ Hz, 2H, Ar–H), 7.19 (t, $J = 7.94$ Hz, 2H, Ar–H), 7.27 (d, $J = 8.74$ Hz, 2H, Ar–H), 7.34–7.37 (m, 4H, Ar–H), 7.74–7.80 (m, 3H, Ar–H), 7.92 (t, $J = 7.82$ Hz, 1H, Ar–H), 8.03 (d, $J = 7.71$ Hz, 1H, Ar–H), 9.68 (d, $J = 11.62$ Hz, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 53.57$, 54.83, 115.31, 115.48, 120.17, 120.78, 125.35, 129.51, 129.84, 130.06, 130.54, 140.77, 141.27, 143.67, 149.75, 149.94, 157.17, 161.10, 163.45 ppm; HPLC–UV–MS (254 nm): purity 96%; LC–MS (ESI): *m/z* calcd. 580.03, found 581.0 ($[M+H]^+$).

Diphenyl [[5-(6-bromopyridin-2-yl)-1,3,4-oxadiazol-2-yl]amino](4-chloro-3-fluorophenyl)methylphosphonate (10b, $C_{26}H_{18}BrClFN_4O_4P$) Yield 135 mg (38%) as a light brown solid. M.p.: 270–272 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 5.90$ (dd, $J = 10.00$, 22.71 Hz, 1H, N–CH–P), 7.05 (d, $J = 8.67$ Hz, 2H, Ar–H), 7.11 (d, $J = 8.68$ Hz, 2H, Ar–H), 7.20 (t, $J = 7.41$ Hz, 2H, Ar–H), 7.31–7.39 (m, 4H, Ar–H), 7.61 (d, $J = 8.48$ Hz, 1H, Ar–H), 7.68 (d, $J = 16.14$ Hz, 1H, Ar–H), 7.79 (d, $J = 14.16$ Hz, 2H, Ar–H), 7.93 (t, $J = 7.83$ Hz, 1H, Ar–H), 8.03 (d, $J = 7.72$ Hz, 1H, Ar–H), 9.69 (d, $J = 11.25$ Hz, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 53.34$, 54.60, 115.17, 116.79, 120.09, 120.82, 125.43, 125.68, 129.56, 129.88, 130.75, 135.61, 140.78, 141.27, 143.64, 149.62, 149.87, 157.28, 163.27 ppm; HPLC–UV–MS (254 nm): purity 98%; LC–MS (ESI): *m/z* calcd. 613.99, found 615.0 ($[M+H]^+$).

Diphenyl [[5-(6-bromopyridin-2-yl)-1,3,4-oxadiazol-2-yl]-amino](3-fluoro-4-methoxyphenyl)methylphosphonate (10c, $C_{27}H_{21}BrFN_4O_5P$) Yield 136 mg (54%) as a white solid. M.p.: 272–274 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.84 (s, 3H, OCH_3), 5.76 (dd, J = 10.27, 21.84 Hz, 1H, N–CH–P), 6.63–6.70 (m, 1H, Ar–H), 6.75–6.81 (m, 2H, Ar–H), 6.85 (s, 1H, Ar–H), 7.01 (d, J = 8.48 Hz, 2H, Ar–H), 7.10 (d, J = 7.59 Hz, 1H, Ar–H), 7.16–7.24 (m, 2H, Ar–H), 7.32–7.40 (m, 4H, Ar–H), 7.50 (d, J = 8.00 Hz, 1H, Ar–H), 7.92 (t, J = 7.83 Hz, 1H, Ar–H), 8.03 (d, J = 7.69 Hz, 1H, Ar–H), 9.65 (d, J = 10.11 Hz, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 53.46, 54.52, 55.90, 113.85, 115.02, 120.17, 120.31, 120.83, 125.39, 125.43, 129.57, 129.72, 129.77, 129.90, 140.83, 141.32, 143.70, 157.21, 163.43 ppm; HPLC–UV–MS (254 nm): purity 95%; LC–MS (ESI): *m/z* calcd. 610.04, found 611.0 ($[M+H]^+$).

Diphenyl [[5-(6-bromopyridin-2-yl)-1,3,4-oxadiazol-2-yl]-amino][4-(dimethylamino)phenyl]methylphosphonate (10d, $C_{28}H_{25}BrN_5O_4P$) Yield 116 mg (46%) as a pale yellow solid. M.p.: 266–268 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.90 (s, 6H, $-NCH_3$), 5.54 (dd, J = 10.17, 21.14 Hz, 1H, N–CH–P), 6.74 (d, J = 8.85 Hz, 2H, Ar–H), 6.98 (d, J = 8.63 Hz, 2H, Ar–H), 7.10 (d, J = 8.64 Hz, 2H, Ar–H), 7.15–7.20 (m, 2H, Ar–H), 7.33–7.36 (m, 4H, Ar–H), 7.46–7.52 (m, 2H, Ar–H), 7.74–7.80 (m, 1H, Ar–H), 7.88–7.93 (m, 1H, Ar–H), 7.98–8.04 (m, 1H, Ar–H), 9.52 (d, J = 11.98 Hz, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 40.02, 53.87, 55.15, 112.03, 115.18, 120.26, 120.72, 125.21, 128.93, 129.51, 129.62, 129.78, 140.72, 141.23, 143.74, 144.12, 149.97, 150.42, 155.99, 157.00, 163.64, 164.66 ppm; HPLC–UV–MS (254 nm): purity 98%; LC–MS (ESI): *m/z* calcd. 605.08, found 605.9 ($[M+H]^+$).

Diphenyl [[5-(6-bromopyridin-2-yl)-1,3,4-oxadiazol-2-yl]amino](3-fluorophenyl)methylphosphonate (10e, $C_{26}H_{19}BrFN_4O_4P$) Yield 152 mg (63%) as a white solid. M.p.: 243–246 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.85 (dd, J = 10.16, 22.50 Hz, 1H, N–CH–P), 7.01 (d, J = 8.69 Hz, 2H, Ar–H), 7.10 (d, J = 8.69 Hz, 2H, Ar–H), 7.16–7.25 (m, 3H, Ar–H), 7.35–7.39 (m, 3H, Ar–H), 7.45–7.52 (m, 2H, Ar–H), 7.58 (t, J = 7.60 Hz, 2H, Ar–H), 7.79 (d, J = 7.93 Hz, 1H, Ar–H), 7.92 (t, J = 7.83 Hz, 1H, Ar–H), 8.03 (d, J = 6.88 Hz, 1H, Ar–H), 9.69 (d, J = 10.25 Hz, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 53.81, 55.06, 115.10, 115.28, 115.45, 120.10, 120.80, 124.57, 125.38, 129.53, 129.86, 130.45, 136.51, 140.77, 141.27, 143.66, 149.65, 149.92, 157.22, 160.97, 162.93, 163.46 ppm; HPLC–UV–MS (254 nm): purity 98%; LC–MS (ESI): *m/z* calcd. 580.03, found 580.9 ($[M+H]^+$).

Diphenyl [[5-(6-bromopyridin-2-yl)-1,3,4-oxadiazol-2-yl]-amino](3-chloro-4-fluorophenyl)methylphosphonate (10f, $C_{26}H_{18}BrClFN_4O_4P$) Yield 100 mg (39%) as a pale brown solid. M.p.: 263–265 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.87 (dd, J = 10.13, 22.85 Hz, 1H, N–CH–P), 7.07 (d, J = 8.56 Hz, 2H, Ar–H), 7.14 (d, J = 8.61 Hz, 2H, Ar–H), 7.25–7.27 (m, 2H, Ar–H), 7.33–7.38 (m, 4H, Ar–H), 7.63 (d, J = 8.37 Hz, 1H, Ar–H), 7.70 (d, J = 15.80 Hz, 1H, Ar–H), 7.83 (d, J = 14.76 Hz, 2H, Ar–H), 7.97 (t, J = 7.76 Hz, 1H, Ar–H), 8.10 (d, J = 7.77 Hz, 1H, Ar–H), 9.71 (d, J = 11.27 Hz, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 53.51, 54.68, 115.21, 117.01, 120.11, 120.87, 125.51, 125.69, 129.61, 129.90, 130.71, 135.62, 140.81, 141.31, 143.66, 149.69, 149.90, 157.25, 163.31 ppm; HPLC–UV–MS (254 nm): purity 96%; LC–MS (ESI): *m/z* calcd. 613.99, found 615.0 ($[M+H]^+$).

Diphenyl [[5-(6-bromopyridin-2-yl)-1,3,4-oxadiazol-2-yl]-amino](4-fluoro-3-methylphenyl)methylphosphonate (10 g, $C_{27}H_{21}BrFN_4O_4P$) Yield 152 mg (65%) as a white solid. M.p.: 255–258 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.38 (s, 3H, CH_3), 5.78 (dd, J = 9.96, 21.91 Hz, 1H, N–CH–P), 7.02 (d, J = 8.19 Hz, 2H, Ar–H), 7.11 (d, J = 8.10 Hz, 2H, Ar–H), 7.23 (t, J = 7.99 Hz, 2H, Ar–H), 7.31 (d, J = 8.82 Hz, 2H, Ar–H), 7.35-7.48 (m, 3H, Ar–H), 7.76–7.82 (m, 4H, Ar–H), 7.90 (t, J = 7.88 Hz, 1H, V), 8.05–8.07 (m, 1H, Ar–H), 9.71 (d, J = 11.90 Hz, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 20.53, 53.72, 54.89, 120.35, 122.25, 122.43, 129.07, 129.20, 130.84, 131.44, 132.69, 136.44, 136.75, 140.73, 141.06, 143.47, 147.98, 150.42, 156.02, 164.69 ppm; HPLC–UV–MS (254 nm): purity 95%; LC–MS (ESI): *m/z* calcd. 594.05, found 595.0 ($[M+H]^+$).

Diphenyl (3-bromophenyl)[[5-(6-bromopyridin-2-yl)-1,3,4-oxadiazol-2-yl]amino]methylphosphonate (10 h, $C_{26}H_{19}Br_2N_4O_4P$) Yield 130 mg (49%) as a pale brown solid. M.p.: 264–266 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.82 (dd, J = 10.19, 22.48 Hz, 1H, N–CH–P), 7.02 (d, J = 8.73 Hz, 2H, Ar–H), 7.10 (d, J = 8.58 Hz, 2H, Ar–H), 7.16–7.23 (m, 3H, Ar–H), 7.34–7.37 (m, 3H, Ar–H), 7.46–7.53 (m, 2H, Ar–H), 7.57 (t, J = 7.71 Hz, 2H, Ar–H), 7.79 (d, J = 7.78 Hz, 1H, Ar–H), 7.91 (t, J = 7.79 Hz, 1H, Ar–H), 8.04 (d, J = 7.12 Hz, 1H, Ar–H), 9.71 (d, J = 10.25 Hz, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 53.28, 56.16, 115.26, 115.90, 116.59, 120.36, 122.43, 125.48, 129.08, 130.85, 131.44, 136.76, 140.74, 141.26, 141.72, 143.48, 144.15, 149.62, 150.06, 156.03, 157.73, 161.30, 163.49 ppm; HPLC–UV–MS (254 nm): purity 96%; LC–MS (ESI): *m/z* calcd. 639.95, found 640.0 ($[M+H]^+$).

Diphenyl [[5-(6-bromopyridin-2-yl)-1,3,4-oxadiazol-2-yl]amino](3-methoxyphenyl)methylphosphonate (10i, $C_{27}H_{22}BrN_4O_5P$) Yield 79 mg (32%) as a pale yellow solid. M.p.: 261–263 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.75 (s, 3H, $-OCH_3$), 5.72 (dd, J = 10.22, 21.98 Hz,

1H, N–CH–P), 6.97 (dd, $J = 8.38$, 29.15 Hz, 3H, Ar–H), 7.06–7.22 (m, 3H, Ar–H), 7.24–7.38 (m, 4H, Ar–H), 7.51 (s, 1H, Ar–H), 7.77–7.80 (m, 2H, Ar–H), 7.87–8.07 (m, 3H, Ar–H), 9.65 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 40.06$, 54.43, 55.20, 114.14, 120.28, 120.82, 125.41, 129.07, 129.56, 129.89, 135.18, 140.73, 141.32, 143.72, 144.14, 149.84, 150.04, 156.03, 157.17, 159.30, 163.53, 164.70 ppm.

Diphenyl [[5-(6-bromopyridin-2-yl)-1,3,4-oxadiazol-2-yl]-amino](3-fluoro-4-nitrophenyl)methylphosphonate (10j, $C_{26}H_{18}BrFN_5O_6P$) Yield 70 mg (27%) as a white solid. M.p.: 275–277 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 5.88$ (dd, $J = 10.10$, 22.79 Hz, 1H, N–CH–P), 7.03 (d, $J = 8.76$ Hz, 2H, Ar–H), 7.12 (d, $J = 8.69$ Hz, 2H, Ar–H), 7.23 (t, $J = 7.51$ Hz, 2H, Ar–H), 7.35–7.39 (m, 4H, Ar–H), 7.60 (d, $J = 8.39$ Hz, 1H, Ar–H), 7.73 (d, $J = 16.10$ Hz, 1H, Ar–H), 7.80 (d, $J = 14.56$ Hz, 2H, Ar–H), 7.91 (t, $J = 7.79$ Hz, 1H, Ar–H), 8.01–8.03 (m, 1H, Ar–H), 9.73 (d, $J = 11.29$ Hz, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 53.50$, 54.71, 114.97, 119.79, 119.95, 120.49, 124.26, 125.11, 129.22, 129.55, 130.21, 136.26, 140.96, 141.89, 143.36, 149.61, 156.91, 163.15 ppm; HPLC–UV–MS (254 nm): purity 95%; LC–MS (ESI): *m/z* calcd. 625.02, found 626.0 ($[M+H]^+$).

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