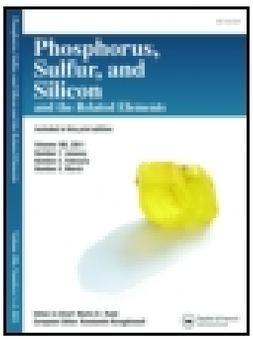

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Synthesis of 2-phenoxyl-2-oxo-1,4,2-oxazaphosphinanes from a three component reaction

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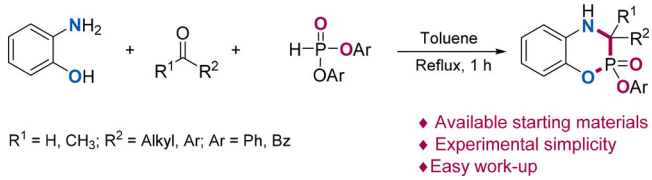
ABSTRACT

A one-pot synthetic strategy was developed for the synthesis of heterocyclic 1,4,2-oxazaphosphinanes via a three component Kabachnik-Fields reaction of 2-aminophenol, diphenyl *H*-phosphonate and carbonyl compounds. Through this newly developed method, 12 organophosphorus heterocycles and 2 related chrysin derivatives were synthesized with high yields. The target compounds were characterized by ^{1}H, ^{31}P and 13C NMR and MS.

GRAPHICAL ABSTRACT



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Introduction

Organophosphorus heterocycles have received considerable attention owing to their unique structural features and wide range of biological and physiological activities, such as herbicidal, insecticidal, bactericidal, antitumor, antiviral activity, etc.[1] Therefore, a good deal of organophosphorus heterocyclic compounds have been synthesized in the past two decades. Among these countless types of phosphorus heterocyclics, 1,4,2-oxazaphosphinanes belong to the pharmacologically and industrially important heterocyclic α-aminophosphates, which are the bioisosterism of natural α-amino acid esters.[2] However, to the best of our knowledge, there are very few approaches in ther literature about the synthesis of this important kind of 1,4,2-oxazaphosphinanes, and most of them were based on the intramolecular transesterification or phosphinic acid esterification,[3] multicomponent cyclization of *o*-aminophenol with dichloro(phenyl)-phosphane[4] or dialkyl phosphorodichloridite.[5] These methods suffer obvious drawbacks including non-availability of the starting materials, toxic phosphorous reagents and narrow substitute scopes. *H*-Phosphonates are a type of readily available, environmental stable and low-cost organic phosphorous compounds, which occupy a major position in organophosphorus chemistry and are frequently used as starting materials for the synthesis of a variety of phosphorus containing compounds.[6] Several works relating to the application of *H*-phosphonates have been reported from our laboratory.[7] As to the synthesis of novel heterocyclic α-aminophosphates, we have developed a convenient approach starting from 2-hydroxyacetophenones or 2-hydroxybenzaldehyes together with amines and dialkyl *H*-phosphonates (Scheme 1a).[8] Therefore, in the course of our synthesis, we continuously committed our efforts to obtain six-membered heterocyclic organophosphorus compounds using an amino group on the benzene ring instead of carbonyl or aldehyde groups (Scheme 1b). Herein, we would like to describe a facile and convenient approach for the synthesis of 1,4,2-oxazaphosphinanes from *o*-aminophenol, carbonyl compounds and easily available, nontoxic diphenyl *H*-phosphonates in toluene. Different carbonyl compounds including ketones and aldehydes are all tolerated in this new method. Starting from 8-aminochrysin, two phosphorous-containing chrysin derivatives were successfully synthesized in satisfactory isolated yields.

Results and discussion

Initially, the optimal reaction conditions for the synthesis of 1,4,2-oxazaphosphinanes were investigated by the use of 2-

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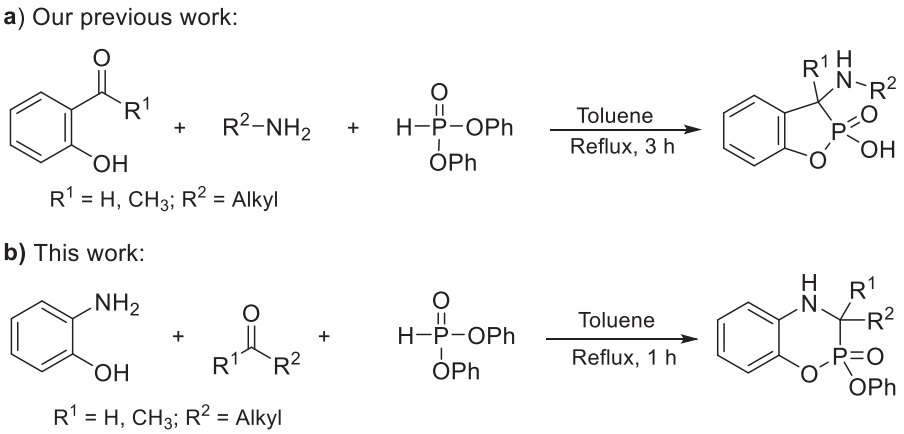
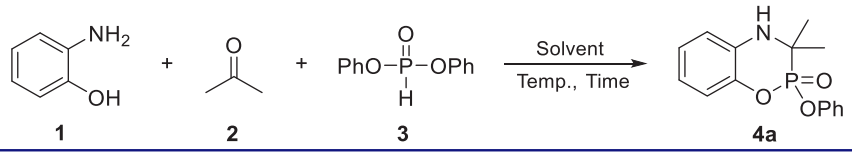


Scheme 1. Comparison of our previous work with the present work.

Table 1. Optimization of the reaction conditions[a].

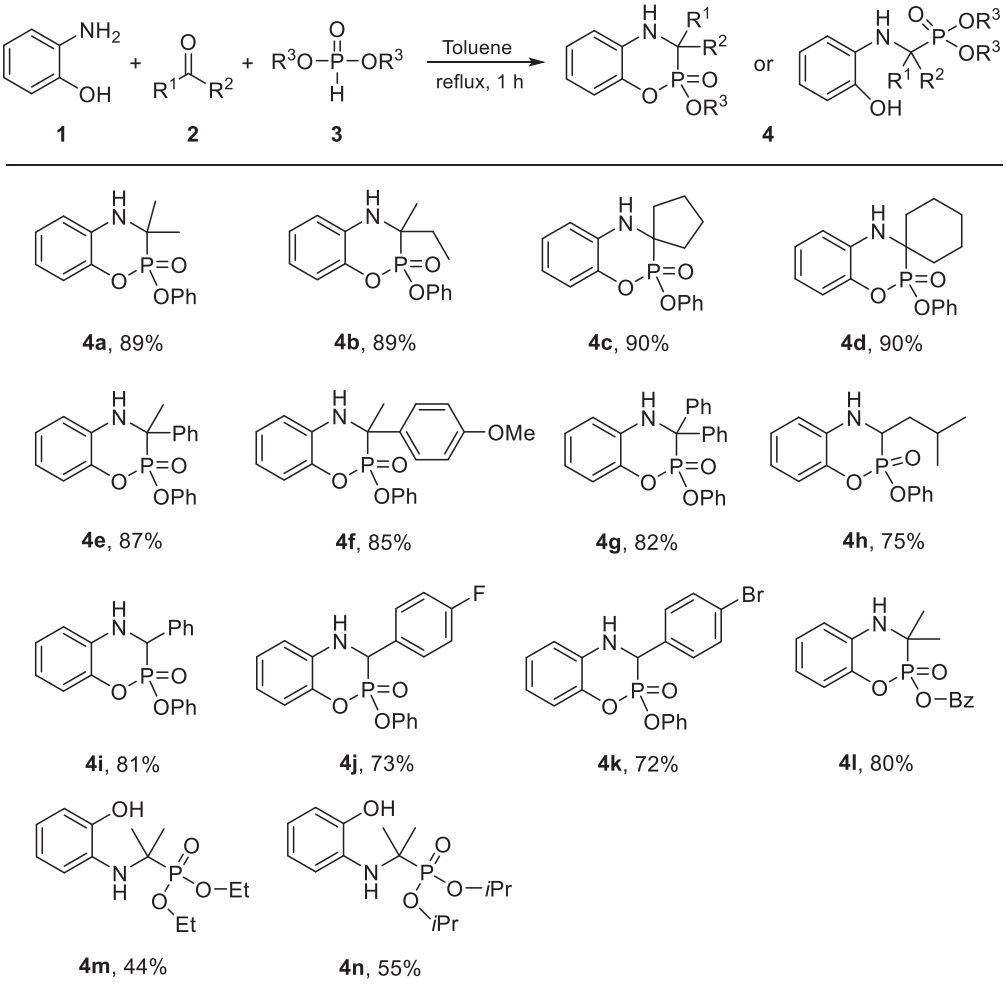


1 **2** **3** **4a**

Entry	Solvent	Temperature (°C)	Time (h)	Yield%[b]
1	*n*-Hexane	Reflux (~68)	1	ND[c]
2	CCl_4	Reflux (~76)	1	20
3	C_2H_5OH	Reflux (~78)	1	ND[c]
4	THF	Reflux (~80)	1	44
5	*i*-C_3H_7OH	Reflux (~82)	1	Trace[c]
6	*p*-Dioxane	Reflux (~102)	1	ND[c]
7	Toluene	Reflux (~110)	1	89
8	None	Reflux (~125)	1	14
9	DMF	Reflux (~153)	1	ND[c]
10	Toluene	30	1	Trace[c]
11	Toluene	50	1	11
12	Toluene	70	1	46
13	Toluene	90	1	61
14	Toluene	Reflux (~110)	0.3	38
15	Toluene	Reflux (~110)	0.5	57
16	Toluene	Reflux (~110)	0.8	89
17	Toluene	Reflux (~110)	1.2	88
18	Toluene	Reflux (~110)	1	81[d]
19	Toluene	Reflux (~110)	1	83[e]

[a]Reaction conditions: 2-aminophenol (5.0 mmol), acetone (5.0 mmol) and DPPH (5.0 mmol) were refluxed in toluene (10 mL).
[b]Isolated yields were provided. ND = not detected.
[c]Detected by ^{31}P NMR.
[d]Acetone (6.0 mmol).
[e]DPPH (6.0 mmol).

aminophenol **1**, acetone **2** and diphenyl *H*-phosphonate **3** (DPPH) as starting materials. Several solvent systems at reflux temperatures as well as a solvent-free system at approximately 125 °C were firstly employed to explore the optimal reaction condition for the synthesis of cyclic compound 3,3-dimethyl-2-phenoxy-3,4-dihydrobenzo[e][1,4,2] oxazaphosphinine 2-oxide (**4a**) (Table 1, entries 1–9). These reaction solutions were refluxed for 1 h, respectively. The results showed that nearly no products were formed in *n*-hexane, C_2H_5OH, *i*-C_3H_7OH, *p*-dioxane and DMF, and relatively low yields were found in CCl_4 and THF. When the reaction was carried out under solvent-free conditions, we obtained a viscous oil, which was difficult to handle and purify (entry 8). When the mixture was refluxed in toluene, a satisfactory isolated yield was obtained (89%, entry 7). Subsequently, the influence of the reaction temperature was investigated. The reaction mixtures were stirred at different temperatures, i.e., 30, 50, 70, 90 and 110 °C for 1 h (Table 1, entries 7, 10–13). It can be seen that the yield was very low (< 50%) when the reaction temperature was below 70 °C, and quickly increased from 46% to 89% over the range of 70–110 °C. However, the reaction temperature could not be further increased after the mixture began to reflux at approximately 110 °C, the boiling point of toluene. The reaction time was also investigated as can be seen in entries 7, 14–17 in Table 1. The results showed that at least 1 h was



Scheme 2. Reaction Scopes[a]. [a]Reaction conditions: 2-aminophenol (5.0 mmol), carbonyl compounds (5.0 mmol) and *H*-phosphonates (5.0 mmol) were refluxed in toluene (10 mL) for 1 h. Isolated yields are provided.

necessary for this conversion and an extended time might cause a decreased isolated yield of **4a**. Finally, the molar ratio of **1**, **2** and **3** were investigated. 1.2 eq. of acetone (6.0 mmol) or DPPH (6.0 mmol) employed in this reaction could cause a decreased isolated yield of **4a** (Table 1, entries 18–19). Therefore, the optimal reaction conditions for the synthesis of **4a** were 5.0 mmol of 2-aminophenol **1**, 1 eq. of acetone **2** and 1 eq. of diphenyl *H*-phosphonate **3** in toluene at 110 °C for 1 h as shown in entry 7.

The scope of the reactants was then enlarged to cover various carbonyl compounds and *H*-phosphonates as shown in Scheme 2. Firstly, a series of ketones, including alkyl ketone such as butan-2-one, cyclopentanone and cyclohexanone as well as aromatic ketones such as acetophenone, 1-(4-methoxyphenyl)ethan-1-one and benzophenone, were employed to react with *o*-aminophenol and diphenyl *H*-phosphonate in toluene under reflux conditions for 1 h. It is worth illustrating here that only the corresponding cyclic 1,4,2-oxazaphosphinanes (**4a**–**4g**) were afforded in relatively good yields ranging from 82% to 90%, as shown in Scheme 2. Following that, four representative aldehydes were used in this transformation. As can be seen, four corresponding 3-mono-substituted 1,4,2-oxazaphosphinanes (**4h**–**4k**) were successfully obtained in good isolated yields (72–81%). It is well known that aldehydes are usually more reactive toward nucleophilic additions than ketones because of both steric and electronic effects. However, herein, the use of ketones led to much better yields than those of aromatic or aliphatic aldehydes. This result strongly suggested that the relatively high steric hindrance of ketones forced the formation of the heterocyclic 1,4,2-oxazaphosphinanes. Moreover, three more dialkyl *H*-phosphonates, including dibenzyl *H*-phosphonates, diethanyl *H*-phosphonates and diisopropyl *H*-phosphonates, were used to react with **1** and **2** under our optimal reaction conditions, respectively. As expected, cyclic product **4l** was formed by employing dibenzyl *H*-phosphonate as a phosphoryl reagent. However, instead of affording the cyclic product, the reaction of **1**, **2** with diethanyl or diisopropyl *H*-phosphonates mainly led to acyclic α-aminophosphonates (**4m**–**4n**) according to Kabachnik-Fields reaction[9] (Scheme 2). It may be attributed to the better leaving ability of the phenoxide anion than that of the alkoxide anion or more positive of phosphorus atom in case of diphenyl *H*-phosphonate than dialkyl *H*-phosphonate.

1D and 2D NMR spectra data were used to identify the structures of the heterocyclic 1,4,2-oxazaphosphinanes. Compounds **4a** was taken as an example for structural identification (see 1D and 2D NMR spectrum and data in Supplemental Materials). The 13C NMR and DEPT-135 of

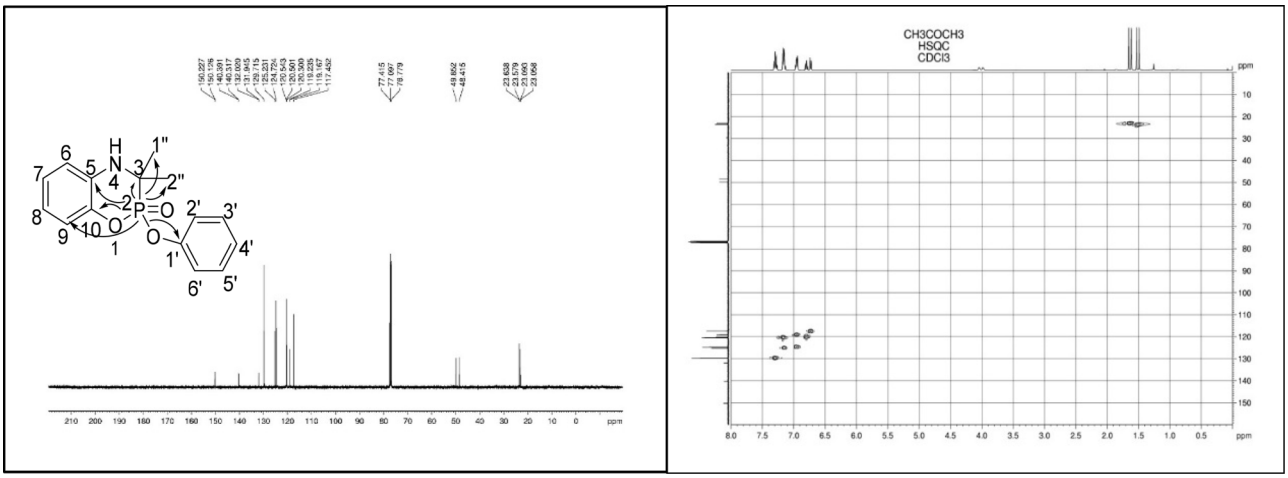
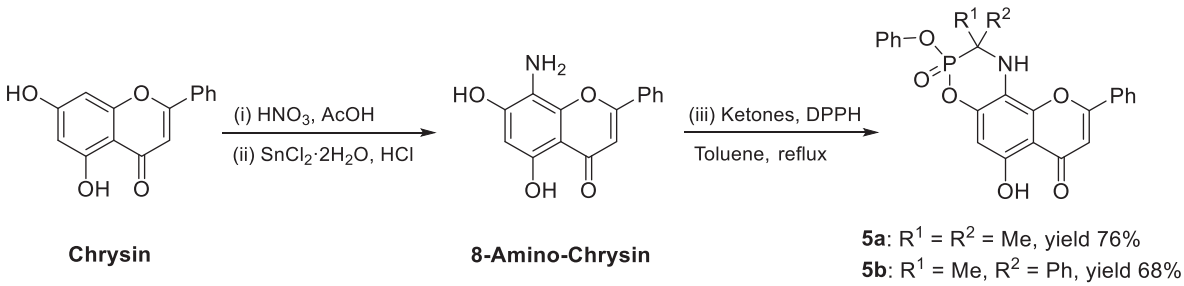


Figure 1. ^{13}C NMR and HSQC spectrum diagram of **4a**.



Scheme 3. Synthesis of chrysin derivatives[a]. [a]Reaction conditions: (i) chrysin, AcOH, conc. HNO3, 65 °C, 2 h; (ii) $SnCl_2{\cdot}2H_2O$, EtOH, conc. HCl, 80 °C,7 h; (iii) 8-amino-chrysin, ketones, DPPH, toluene, reflux, 6 h.

compound **4a** showed 13 carbon peaks, including four quaternary carbon atoms and 8 double peaks due to the phosphorus atom. The 3-C at δ 49.1 was greatly split by the adjacent phosphorus atom with bigger coupling constant ($J_{(P\text{-}C)}$ = 143.7 Hz). According to the ^1H NMR spectrum of compound **4a** along with H-H COSY and HSQC spectra, we could conclude that these quaternary carbon atoms are C-3, C-5, C-10 and C-1' and these double peaks are C-3, C-5, C-9, C-10, C-1', C-2', C-1" and C-2". In the remote related HMBC spectrum diagram of **4a**, the correlation of H and C atoms well matched the configuration of **4a** proposed in our manuscript (Figure 1).

In the course of our syntheses, a further application of this reaction was performed to afford modified natural products. By the use of 8-amino-chrysin and diphenyl *H*-phosphonate together with ketones, two chrysin derivatives **5a** and **5 b** were successfully obtained in satisfactory yields under reflux conditions in toluene for 6 h as shown in Scheme 3.

Conclusions

In summary, a convenient one-pot three-component strategy for the synthesis of 1,4,2-oxazaphosphinane compounds was developed via the use of 2-aminophenol, diphenyl *H*-phosphonate and carbonyl compounds as starting materials. Besides, this method was further applied for the synthesis of modified chrysin derivatives. This newly developed synthetic strategy has significant advantages including experimental simplicity, mild reaction conditions and easy work-up.

Experimental section

All reagents were of analytical grade, commercially available. Toluene and acetone were distilled immediately prior to use. All reagents were weighed and handled in air at room temperature. Flash column chromatography was performed on silica gel (200–300 mesh), and thin layer chromatography (TLC) analyses were performed on silica gel plates (GF 254). ^1H NMR, 13C NMR ^{31}P NMR and ^{19}F NMR spectra were recorded on a Bruker 400 MHz spectrometer with $CDCl_3$ as the solvent and TMS was used as an internal standard for ^1H NMR and 13C NMR. All NMR spectra were recorded at room temperature (20 ± 3 °C). ^1H and 13C chemical shifts are quoted in parts per million downfield from TMS. ^{31}P NMR spectra were recorded on the same instrument with 85% H_3PO_4 as an external standard. ESI-MS spectra were recorded on a Bruker Esquire 3000. IR spectra were recorded on a Shimadazu IR-408 Fourier Transform Infrared spectrophotometer using a thin film supported on KBr pellets. The Supplemental Materials contains sample ^1H, 13C and ^{31}P NMR for products 4 and 5 (Figures S8–S53).

General procedure for the synthesis of compounds 4a–n

2-Aminophenol (5.0 mmol), carbonyl compounds (5.0 mmol) and *H*-phosphonates (5.0 mmol) were dissolved in toluene (10 mL) in a round bottom flask (25 mL). The mixture was

refluxed with drying pipe for 1 h. Then, the solvent was removed in vacuum and the resulting oil was purified by column chromatography on silica gel by using petroleum ether/ethyl acetate (v/v = 1/1) as eluent to give the desired products **4a–n**.

3,3-Dimethyl-2-phenoxy-3,4-dihydrobenzo[e][1,4,2]oxazaphosphinine 2-oxide (4a)

Orange solid, yield 89%, m.p. 98–100 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.51 (d, $3J_{P\text{-}H}$ = 16.0 Hz, 3H, –CCH_3), 1.63 (d, $3J_{P\text{-}H}$ = 16.8 Hz, 3H, –CCH_3), 4.03 (d, $3J_{P\text{-}H}$ = 23.50 Hz, 1H, N–H), 6.71–6.74 (m, 1H), 6.79 (t, $J_{H\text{-}H}$ = 7.6 Hz, 1H), 6.93–6.97 (m, 2H), 7.12–7.17 (m, 3H), 7.26–7.31 (m, 2H). 13C NMR (100 MHz, $CDCl_3$) δ: 23.1 (d, $2J_{P\text{-}C}$ = 3.5 Hz), 23.6 (d, $2J_{P\text{-}C}$ = 5.9 Hz), 49.1 (d, $1J_{P\text{-}C}$ = 143.7 Hz), 117.4, 119.2 (d, $3J_{P\text{-}C}$ = 6.8 Hz), 120.3, 120.5 (d, $3J_{P\text{-}C}$ = 4.2 Hz), 124.7, 125.2, 129.7, 132.0 (d, $3J_{P\text{-}C}$ = 7.5 Hz), 140.4 (d, $2J_{P\text{-}C}$ = 7.4 Hz), 150.2 (d, $2J_{P\text{-}C}$ = 10.1 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ: 13.57. IR (KBr) ν_{max} (cm^{-1}): 3439 (NH), 2978, 2928 (CH_3), 1614 (Ar), 1264 (P = O), 1199 (P–O–Ar), 736 (Ar–H). ESI MS found m/z: 290.1 $[M+H]^+$, 312.1 $[M+Na]^+$, 601.1 $[2M+Na]^+$.

3-Ethyl-3-methyl-2-phenoxy-3,4-dihydrobenzo[e][1,4,2]oxazaphosphinine 2-oxide (4b)

White solid, yield: 89%, m.p. 90–93 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.98–1.22 (m, 3H, CCH_2CH_3), 1.51 (q, $3J_{P\text{-}H}$ = 16.4 Hz, 3H, CCH_3), 1.85–2.21 (m, 2H, CCH_2CH_3), 3.91 (d, $3J_{P\text{-}H}$ = 29.76 Hz, 1H, N–H), 6.74–6.78 (m, 1H), 6.79–6.85 (m, 1H), 6.95–7.00 (m, 2H), 7.16–7.20 (m, 3H), 7.30–7.34 (t, $J_{P\text{-}H}$ = 7.72 Hz, 2H). 13C NMR (100 MHz, $CDCl_3$) δ: 6.2 (d, $J_{P\text{-}C}$ = 10.4 Hz), 7.9 (d, $J_{P\text{-}C}$ = 6.8 Hz), 19.0 (d, $J_{P\text{-}C}$ = 4.1 Hz), 20.0 (d, $J_{P\text{-}C}$ = 5.7 Hz), 7.2 (d, $J_{P\text{-}C}$ = 6.2 Hz), 29.2 (d, $J_{P\text{-}C}$ = 2.4 Hz), 52.5 (m), 117.1, 117.5, 119.0 (d, $J_{P\text{-}C}$ = 2.6 Hz), 119.1 (d, $J_{P\text{-}C}$ = 2.3 Hz), 120.0, 120.2, 120.6 (d, $J_{P\text{-}C}$ = 4.2 Hz), 124.7 (d, $J_{P\text{-}C}$ = 4.6 Hz), 125.2 (d, $J_{P\text{-}C}$ = 4.3 Hz), 129.7, 131.9 (d, $J_{P\text{-}C}$ = 7.6 Hz), 132.0 (d, $J_{P\text{-}C}$ = 7.3 Hz), 140.2 (d, $J_{P\text{-}C}$ = 7.3 Hz), 140.5 (d, $J_{P\text{-}C}$ = 7.5 Hz), 150.1 (d, $J_{P\text{-}C}$ = 7.6 Hz), 150.2 (d, $J_{P\text{-}C}$ = 7.6 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ: 12.77, 12.44. IR (KBr) ν_{max} (cm^{-1}): 3439 (NH), 2972, 2934 (CH_3, C_2H_5), 1611 (Ar), 1262 (P = O), 1197 (P–O–Ar), 744 (Ar–H). ESI MS found m/z: 304.1 $[M+H]^+$, 326.1 $[M+Na]^+$, 629.2 $[2M+Na]^+$.

2-Phenoxy-4H-spiro[benzo[e][1,4,2]oxazaphosphinine-3,1′-cyclopentane] 2-oxide (4c)

White solid, yield: 90%, m.p. 123–124 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.79–1.80 (m, 6H), 2.20–2.26 (m, 1H), 2.46–2.52 (m, 1H), 4.39 (s, 1H, N–H), 6.72–6.79 (m, 2H), 6.89–6.95 (m, 2H), 7.10–7.17 (m, 3H), 7.24–7.28 (m, 2H). 13C NMR(100 MHz, $CDCl_3$) δ: 24.2–24.6(m), 34.6, 35.1 (d, $J_{P\text{-}C}$ = 9.1 Hz), 58.7 (d, $J_{P\text{-}C}$ =147.3 Hz), 117.9, 119.2 (d, $J_{P\text{-}C}$ = 6.7 Hz), 120.2, 120.7 (d, $J_{P\text{-}C}$ = 4.1 Hz), 124.5, 125.2, 129.6, 132.5 (d, $J_{P\text{-}C}$ = 6.9 Hz), 140.9 (d, $J_{P\text{-}C}$ = 7.3 Hz), 150.3 (d, $J_{P\text{-}C}$ = 9.7 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ: 13.95. IR (KBr) ν_{max} (cm^{-1}): 3440 (NH), 2965 (CH_2), 1612 (Ar), 1261 (P = O), 1201 (P–O–Ar), 754 (Ar–H). ESI MS found m/z: 316.0 $[M+H]^+$, 338.1 $[M+Na]^+$, 653.1 $[2M+Na]^+$.

2-Phenoxy-4H-spiro[benzo[e][1,4,2]oxazaphosphinine-3,1′-cyclohexane] 2-oxide (4d)

White solid, yield: 90%, m.p. 145–146 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.45–1.50 (m, 1H), 1.54–1.60 (m, 1H), 1.66–1.71 (m, 3H), 1.82–1.83 (m, 2H), 1.94–2.08 (m, 2H), 2.18–2.25 (m, 1H), 4.12 (d, $3J_{P\text{-}H}$ = 22.5 Hz, N–H), 6.81–6.85 (m, 2H), 6.97–7.02 (m, 2H), 7.15–7.19 (m, 3H), 7.30–7.34 (m, 2H). 13C NMR (100 MHz, $CDCl_3$) δ: 19.7–20.3 (m), 24.97, 29.5–30.0 (m), 51.4 (d, $J_{P\text{-}C}$ = 144.4 Hz), 117.6, 119.1 (d, $J_{P\text{-}C}$ = 8.7 Hz), 120.3 (d, $J_{P\text{-}C}$ = 1.3 Hz), 120.5 (d, $J_{P\text{-}C}$ = 4.2 Hz), 124.6, 125.1, 129.7, 131.5 (d, $J_{P\text{-}C}$ = 7.4 Hz), 140.7 (d, $J_{P\text{-}C}$ = 7.50 Hz), 150.2 (d, $J_{P\text{-}C}$ = 10.1 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ: 11.77. IR (KBr) ν_{max} (cm^{-1}): 3439 (NH), 2935, 2857 (CH_2), 1597 (Ar), 1253 (P = O), 1192 (P–O–Ar), 748 (Ar–H). ESI MS found m/z: 330.0 $[M+H]^+$, 352.1 $[M+Na]^+$, 682.1 $[2M+Na]^+$.

3-Methyl-2-phenoxy-3-phenyl-3,4-dihydrobenzo[e][1,4,2]oxazaphosphinine 2-oxide (4e)

White solid, yield: 87%, m.p. 161–162 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.93 (d, $3J_{P\text{-}H}$ = 16.8 Hz, 3H, CH_3), 4.42 (d, $3J_{P\text{-}H}$ = 20.2 Hz, 1H, N–H), 6.76 (t, $J_{P\text{-}H}$ =7.84 Hz, 1H), 6.82–6.90 (m, 2H), 7.00–7.04 (m, 1H), 7.12–7.16 (m, 3H), 7.26–7.34 (m, 5H), 7.64–7.67 (m, 2H). 13C NMR (100 MHz, $CDCl_3$) δ: 25.3 (d, $J_{P\text{-}C}$ = 4.1 Hz), 56.0 (d, $J_{P\text{-}C}$ = 141.3 Hz), 116.5, 119.5 (d, $J_{P\text{-}C}$ = 6.7 Hz), 120.0, 120.6 (d, $J_{P\text{-}C}$ = 4.2 Hz), 125.1, 125.3, 126.7 (d, $J_{P\text{-}C}$ = 4.8 Hz), 128.0 (d, $J_{P\text{-}C}$ = 2.3 Hz), 128.6 (d, $J_{P\text{-}C}$ = 2.0 Hz), 129.7, 132.7 (d, J = 8.6 Hz), 139.4 (d, $J_{P\text{-}C}$ = 3.8 Hz), 140.1 (d, $J_{P\text{-}C}$ = 7.2 Hz), 150.2 (d, $J_{P\text{-}C}$ = 10.2 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ: 8.22. IR (KBr) ν_{max} (cm^{-1}): 3439 (NH), 2936 (CH_3), 1612 (Ar), 1263 (P = O), 1192 (P–O–Ar), 751 (Ar–H). ESI MS found m/z: 352.1 $[M+H]^+$, 374.1 $[M+Na]^+$, 725.2 $[2M+Na]^+$.

3-(4-Methoxyphenyl)-3-methyl-2-phenoxy-3,4-dihydrobenzo[e][1,4,2]oxazaphosphinine 2-oxide (4f)

White solid, yield: 85%, m.p. 142–144 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.91 (d, $3J_{P\text{-}H}$ = 16.8 Hz, 3H, –CCH_3), 3.75 (s, 3H, –OCH_3), 4.45 (d, $3J_{P\text{-}H}$ = 20.88 Hz, 1H, N–H), 6.75–6.77 (m, 1H), 6.82–6.88 (m, 4H), 6.98–7.00 (m, 1H), 7.11–7.16 (m, 3H), 7.25–7.29 (m, 2H), 7.54–7.57 (m, 2H). 13C NMR (100 MHz, $CDCl_3$) δ: 25.2 (d, $J_{P\text{-}C}$ = 3.66 Hz), 55.0 (d, $J_{P\text{-}C}$ = 49.6 Hz), 56.2, 114.0 (d, $J_{P\text{-}C}$ = 2.0 Hz), 116.5, 119.4, 119.4, 119.8, 120.6 (d, $J_{P\text{-}C}$ = 4.2 Hz), 125.0, 125.2, 128.0 (d, $J_{P\text{-}C}$ = 4.8 Hz), 129.7, 131.3 (d, $J_{P\text{-}C}$ = 3.5 Hz), 132.9 (d, J = 8.5 Hz), 140.0 (d, $J_{P\text{-}C}$ = 7.2 Hz), 115.2 (d, J = 10.1 Hz), 159.2 (d, $J_{P\text{-}C}$ = 2.5 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ: 8.70. IR (KBr) ν_{max} (cm^{-1}): 3439 (NH), 2935 (CH_3), 1611 (Ar), 1261 (P = O), 1195 (P–O–Ar),

1068 (O-CH_3), 833 (Ar-H). ESI MS found m/z: 382.2 $[M+H]^+$, 404.1 $[M+Na]^+$,753.3 $[2M+Na]^+$.

2-Phenoxy-3,3-diphenyl-3,4-dihydrobenzo[e][1,4,2]oxazaphosphinine 2-oxide (4g)

White solid, yield: 82%, m.p. 221–223 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.79 (d, $3J_{P\text{-}H}$ = 21.7 Hz, 1H, N–H), 6.77–6.82 (m, 3H), 6.86–6.89 (m, 1H), 6.93–6.97 (m, 2H), 7.06–7.08 (m, 1H), 7.14–7.18 (m, 2H), 7.23 (d, $J_{H\text{-}H}$ = 7.2 Hz, 1H), 7.29 (d, $J_{H\text{-}H}$ = 7.4 Hz, 2H), 7.34–7.37 (m, 3H), 7.68–7.73 (m, 4H). 13C NMR (100 MHz, $CDCl_3$) δ: 63.5 (d, $J_{P\text{-}C}$ = 141.1 Hz), 118.0, 119.3 (d, $J_{P\text{-}C}$ = 7.2 Hz), 120.3 (d, $J_{P\text{-}C}$ = 4.3 Hz), 121.1, 124.8, 125.0, 127.7, 127.8, 128.0, 128.2, 128.2, 128.4, 128.4, 128.7 (d, $J_{P\text{-}C}$ = 2.15 Hz), 129.4, 132.0 (d, $J_{P\text{-}C}$ = 7.5 Hz), 138.2 (d, $J_{P\text{-}C}$ = 7.5 Hz), 140.0 (d, $J_{P\text{-}C}$ = 7.1 Hz), 141.0 (d, $J_{P\text{-}C}$ = 7.4 Hz), 150.3 (d, $J_{P\text{-}C}$ = 9.7 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ: 5.20. IR (KBr) ν_{max} (cm^{-1}): 3439 (NH), 1612 (Ar), 1262 (P = O), 1199 (P–O–Ar), 751 (Ar–H). ESI MS found m/z: 414.1 $[M+H]^+$, 436.2 $[M+Na]^+$, 849.1 $[2M+Na]^+$.

3-Isobutyl-2-phenoxy-3,4-dihydrobenzo[e][1,4,2]oxazaphosphinine 2-oxide (4h)

White solid, yield: 75%, m.p. 122–123 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.06 (d, $4J_{P\text{-}H}$ = 6.8 Hz, 3H, -$CH(CH_3)_2$), 1.18 (d, $4J_{P\text{-}H}$ = 6.8 Hz, 3H, –$CH(CH_3)_2$), 2.29–2.36 (m, 1H, –$CHCH(CH_3)_2$), 3.45–3.52 (m, 1H, –$CHCH(CH_3)_2$), 4.23 (d, $3J_{P\text{-}H}$ = 26.1 Hz, 1H, N–H), 6.72–6.77 (m, 2H), 6.93–6.97 (m, 2H), 7.1–7.19 (m, 3H), 7.29–7.33 (m, 2H). 13C NMR (100 MHz, $CDCl_3$) δ: 18.4 (d, $J_{P\text{-}C}$ = 7.90 Hz), 20.2 (d, $J_{P\text{-}C}$ = 8.8 Hz), 30.1 (d, $J_{P\text{-}C}$ = 2.8 Hz), 53.2 (d, $J_{P\text{-}C}$ = 136.8 Hz), 116.0, 119.4 (d, $J_{P\text{-}C}$ = 6.8 Hz), 119.6, 120.6 (d, $J_{P\text{-}C}$ = 4.3 Hz), 124.9, 125.4, 129.8, 132.8 (d, $J_{P\text{-}C}$ = 10.2 Hz), 139.8 (d, $J_{P\text{-}C}$ = 7.4 Hz), 149.8 (d, $J_{P\text{-}C}$ = 8.7 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ: 10.25. IR (KBr) ν_{max} (cm^{-1}): 3438 (NH), 2925, 2859 (C_3H_7), 1614 (Ar), 1262 (P = O), 1196 (P–O–Ar), 742 (Ar–H). ESI MS found m/z: 318.2 $[M+H]^+$, 340.2 $[M+Na]^+$, 657.3 $[2M+Na]^+$.

2-Phenoxy-3-phenyl-3,4-dihydrobenzo[e][1,4,2]oxazaphosphinine 2-oxide (4i)

White solid, yield: 81%, m.p. 173–175 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.27 (d, $3J_{P\text{-}H}$ = 29.2 Hz, 1H, N–H), 4.92 (d, $3J_{P\text{-}H}$ =9.9 Hz, 1H, –CHPh), 6.84–6.90 (m, 4H), 7.02–7.11 (m, 3H), 7.18–7.22 (m, 2H), 7.43–7.45 (m, 3H), 7.65–7.68 (m, 2H). 13C NMR (100 MHz, $CDCl_3$) δ: 55.1 (d, $J_{P\text{-}C}$ = 140.6 Hz), 116.5, 119.7, 119.6, 120.3 (d, $J_{P\text{-}C}$ = 4.4 Hz), 120.6 (d, $J_{P\text{-}C}$ = 1.6 Hz), 124.8, 125.1, 128.1 (d, $J_{P\text{-}C}$ = 5.4 Hz), 129.0 (d, $J_{P\text{-}C}$ = 3.1 Hz), 129.1 (d, $J_{P\text{-}C}$ = 3.5 Hz), 129.510, 132.6 (d, $J_{P\text{-}C}$ = 10.9 Hz), 133.7 (d, $J_{P\text{-}C}$ = 6.0 Hz), 140.0 (d, $J_{P\text{-}C}$ = 6.8 Hz), 150.0 (d, $J_{P\text{-}C}$ = 10.1 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ: 5.32. IR (KBr) ν_{max} (cm^{-1}): 3439 (NH), 1614 (Ar), 1257 (P = O), 1199 (P-O-Ar), 1070, 789 (Ar–H). ESI MS found m/z: 338.2 $[M+H]^+$, 359.9 $[M+Na]^+$, 696.9 $[2M+Na]^+$.

3-(4-Fluorophenyl)-2-phenoxy-3,4-dihydrobenzo[e][1,4,2]oxazaphosphinine 2-oxide (4j)

White solid, yield: 73%, m.p. 158–159 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.20 (d, $3J_{P\text{-}H}$ = 29.6 Hz, 1H, N–H), 4.94 (d, $3J_{P\text{-}H}$ = 9.8 Hz, 1H, CHPhF), 6.84–6.91 (m, 4H), 7.03–7.0 8(m, 2H), 7.10–7.17 (m, 3H), 7.23 (t, $J_{H\text{-}H}$ = 7.8 Hz, 2H), 7.64–7.68 (m, 2H). 13C NMR (100 MHz, $CDCl_3$) δ: 53.6–55.1 (m), 115.9, 115.9, 116.0, 116.1, 116.1, 116.2, 116.5, 116.6, 119.7, 119.7 (d, $J_{P\text{-}C}$ = 2.8 Hz), 119.8, 120.2 (d, $J_{P\text{-}C}$ = 4.4 Hz), 120.7, 120.7, 124.9, 125.2, 129.6, 129.8, 129.9 (d, $J_{P\text{-}C}$ = 2.7 Hz), 130.0, 133.4(t, $J_{P\text{-}C}$ = 6.2 Hz), 139.9 (m), 149.9 (d, $J_{P\text{-}C}$ = 10.0 Hz), 161.9, 164.4. ^{31}P NMR (162 MHz, $CDCl_3$) δ: 4.09. ^{19}F NMR (376 MHz, $CDCl_3$) δ: −112.24. IR (KBr) ν_{max} (cm^{-1}): 3432 (NH), 1604 (Ar), 1258 (P = O), 1184 (P–O–Ar), 1108 (–C–F), 742 (Ar–H). ESI MS found m/z: 356.1 $[M+H]^+$, 378.2 $[M+Na]^+$.

3-(4-Bromophenyl)-2-phenoxy-3,4-dihydrobenzo[e][1,4,2]oxazaphosphinine 2-oxide (4k)

White solid, yield: 72%, m.p. 152–154 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.81 (d, $2J_{P\text{-}H}$ = 19.8 Hz, 1H), 6.77–6.82 (m, 2 H), 6.96–7.02 (m, 2H), 7.14–7.18 (m, 3H), 7.29–7.33 (m, 4H), 7.45 (d, $J_{H\text{-}H}$ = 8.3 Hz, 2H). 13C NMR (100 MHz, $CDCl_3$) δ: 52.8 (d, $J_{P\text{-}C}$ = 138.9 Hz), 116.2, 119.7 (d, $J_{P\text{-}C}$ = 6.9 Hz), 120.1, 120.6 (d, $J_{P\text{-}C}$ = 4.2 Hz), 122.8 (d, $J_{P\text{-}C}$ = 3.9 Hz), 125.3, 125.7, 129.3 (d, $J_{P\text{-}C}$ = 5.7 Hz), 129.9, 132.1 (d, $J_{P\text{-}C}$ = 2.6 Hz), 132.7, 132.778, 134.0 (d, $J_{P\text{-}C}$ = 3.0 Hz), 139.4 (d, $J_{P\text{-}C}$ = 6.8 Hz), 149.7 (d, $J_{P\text{-}C}$ = 8.8 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ: 5.51. IR (KBr) ν_{max} (cm^{-1}): 3438 (NH), 1636 (Ar), 1255 (P = O), 1198 (P-O-Ar), 787 (Ar-H), 568 (C–Br). ESI MS found m/z: 416.1 $[M+H]^+$, 338.2 $[M+Na]^+$, 853.3 $[2M+Na]^+$.

2-(Benzyloxy)-3,3-dimethyl-3,4-dihydrobenzo[e][1,4,2]oxazaphosphinine 2-oxide (4l)

White solid, yield: 80%, m.p. 93–95 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.42–1.50 (m, 6H), 4.11–4.16 (m, 1H, N–H), 5.17–5.29 (m, 2H, OCH_2Ph), 6.72–6.80 (m, 2H), 6.90–6.95 (m, 2H), 7.32 (s, 5H). 13C NMR (100 MHz, $CDCl_3$) δ: 23.3 (m), 48.9 (d, $J_{P\text{-}C}$ = 143.6 Hz), 68.5 (d, $J_{P\text{-}C}$ = 7.3 Hz), 117.4, 119.0 (d, $J_{P\text{-}C}$ = 6.7 Hz), 120.1, 124.4, 128.0, 128.6 (d, $J_{P\text{-}C}$ = 3.4 Hz), 132.2 (d, $J_{P\text{-}C}$ = 7.1 Hz), 136.0 (d, $J_{P\text{-}C}$ = 5.4 Hz), 140.5 (d, $J_{P\text{-}C}$ = 7.2 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ: 18.36. IR (KBr) ν_{max} (cm^{-1}): 3439 (NH), 2973, 2932 (CH_3), 1608 (Ar), 1253 (P = O), 1202 (P–O–Ar), 1053 (O–C), 880, 752 (Ar–H). ESI MS found m/z: 303.1 $[M+H]^+$, 326.2 $[M+Na]^+$, 629.3 $[2M+Na]^+$.

Diethyl (2-((2-hydroxyphenyl)amino)propan-2-yl)phosphonate (4m)

Green oil, yield 44%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.31 (m, 6H, CH_2CH_3), 1.40 (d, $3J_{P\text{-}H}$ = 16.0 Hz, 6H, $C(CH_3)_2$), 3.02 (s, 1H, N–H), 4.13–4.18 (m, 4H, CH_2CH_3), 6.77 (m, 1H), 6.93 (d, $J_{H\text{-}H}$ = 7.6 Hz, 1H), 6.99–7.04 (m, 2H), 8.32 (s, 1H, O–H). 13C NMR (100 MHz, $CDCl_3$) δ: 16.5 (d, $J_{P\text{-}C}$ = 6.0 Hz), 23.3 (d, $J_{P\text{-}C}$ = 2.0 Hz), 54.8 (d, $J_{P\text{-}C}$ = 159 Hz), 62.9 (d, $J_{P\text{-}C}$ = 7.7 Hz), 116.3, 119.6, 125.7, 127.4, 130.5 (d, $J_{P\text{-}C}$ = 7.8 Hz), 153.0. ^{31}P NMR (162 MHz, $CDCl_3$) δ: 31.62. ESI MS found m/z: 310.2 $[M+H]^+$, 332.1 $[M+Na]^+$, 642.2 $[2M+Na]^+$.

Diisopropyl (2-((2-hydroxyphenyl)amino)propan-2-yl)phosphonate (4n)

Orange oil, yield 55%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.29 (d, $J_{H\text{-}H}$ = 6.2 Hz, 6H, $C(CH_3)_2$), 1.35 (s, 6H, $C(CH_3)_2$), 1.38 (d, $J_{H\text{-}H}$ = 10.5 Hz, 6H, $C(CH_3)_2$), 4.72–4.79 (m, 2H, $2CH(CH_3)_2$) , 6.77 (t, $J_{H\text{-}H}$ = 7.6 Hz, 1H), 6.94 (d, $J_{H\text{-}H}$ = 8.0 Hz, 1H), 7.03 (m, 2H), 8.41 (s, 1H, O–H). 13C NMR (100 MHz, $CDCl_3$) δ: 23.2 (d, $J_{P\text{-}C}$ = 2.2 Hz), 23.8 (d, $J_{P\text{-}C}$ = 5.0 Hz), 24.2 (d, $J_{P\text{-}C}$ = 3.9 Hz), 54.7 (d, $J_{P\text{-}C}$ = 161.2 Hz), 71.4 (d, $J_{P\text{-}C}$ = 8.1 Hz), 116.4, 119.5, 125.9, 127.8, 130.5 (d, $J_{P\text{-}C}$ = 7.5 Hz), 153.3. ^{31}P NMR (162 MHz, $CDCl_3$) δ: 30.00. ESI MS found m/z: 338.2 $[M+H]^+$, 360.1 $[M+Na]^+$, 677.2 $[2M+Na]^+$.

General procedure for the synthesis of compounds 5a and 5b

Synthesis of 8-amino-chrysin

(i) chrysin (2.0 g, 7.87 mmol) was dissolved in AcOH (250 mL). AcOH (10 mL) containing HNO_3 (0.2 mL, conc.70%) was added dropwise into the chrysin solution. The mixture was stirred and reacted at 65 °C for 2 h. Then, the mixture was poured into ice water (200 mL) and the yellow precipitate was filtered, washed with water and recrystallized from ethanol to provide 8-nitro-chrysin. (ii) 8-nitro-chrysin (250 mg, 0.5 mmol) and $SnCl_2{\cdot}2H_2O$ (1.13 g, 5 mmol) were dissolved in EtOH (100 mL) and 10 mmol of conc. HCl were dropwised in the solutions. Then, the mixture were reacted at 80 °C for 7 h. After the reaction was completed, the solvent was evaporated in vacuum. The residue was extracted by EtOAc, washed by brine and dried over Na_2SO_4. The pure 8-animo-chrysin was obtained as a brick-red solid by evaporation of the solvent.

Synthesis of chrysin derivatives 5a and 5b

8-Amino-chrysin (0.135 g, 0.5 mmol), ketones (0.5 mmol) and DPPH (0.117 g, 0.5 mmol) were dissolved in toluene (30 mL) in a 100 mL round bottom flask. The mixture was refluxed with drying pipe for 6 h. The solvent was removed in vacuum and the resulting oil was purified by column chromatography on silica gel by using petroleum ether/ethyl acetate (v/v = 1/1) as eluent to give the desired products **5a** and **5 b**.

Chrysin derivatives 5a

White solid, yield: 76%, m.p. 205–206 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.60 (d, $3J_{P\text{-}H}$ = 16.3 Hz, 3H, $-C(CH_3)_2$), 1.78 (d, $3J_{P\text{-}H}$ = 16.8 Hz, 3H, $-C(CH_3)_2$), 3.91 (d, $3J_{P\text{-}H}$ = 18.5 Hz, 1H, N-H), 6.55 (s, 1H), 6.73(s, 1H), 7.19–7.24 (m, 1H), 7.34–7.38 (m, 1H), 7.57–7.65 (m, 1H), 7.87–7.91 (m, 1H), 12.08 (s, 1H, O–H). 13C NMR (100 MHz, $CDCl_3$) δ: 23.1 (d, $2J_{P\text{-}C}$ = 2.5 Hz), 23.3 (d, $2J_{P\text{-}C}$ = 5.9 Hz), 48.5 (d, $J_{P\text{-}C}$ = 141.4 Hz), 102.2 (d, $J_{P\text{-}C}$ = 6.9 Hz), 106.7, 108.0, 112.9, 120.4 (d, $J_{P\text{-}C}$ = 4.3 Hz), 125.6, 126.4, 129.3, 129.9, 131.2, 132.2, 146.3–146.4 (m), 149.8, 154.4, 164.1, 182.7. ^{31}P NMR (162 MHz, $CDCl_3$) δ: 13.50. IR (KBr) ν_{max} (cm^{-1}): 3439, 3269 (O–H), 2976, 2896 (CH_3), 1655 (C = O), 1617 (Ar), 1261 (P = O), 1199 (P = O–Ar), 1071 (O–C), 786 (Ar–H). ESI MS found m/z: 450.1 $[M+H]^+$, 472.1 $[M+Na]^+$, 921.2 $[2M+Na]^+$.

Chrysin derivatives 5b

White solid, yield: 68%, m.p. 205–206 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.00 (d, $3J_{P\text{-}H}$ = 16.9 Hz, 3H, CH_3), 4.40 (d, $3J_{P\text{-}H}$ = 26.6 Hz, 1H, N–H), 6.64 (s, 1H), 6.73 (s, 1H), 6.75–6.76 (m, 2H), 7.07–7.11 (m, 1H), 7.17–7.21 (m, 2H), 7.47–7.49 (m, 1H), 7.52–7.62 (m, 5H), 7.59 (m, 2H), 7.85–7.87 (m, 2H), 7.90–7.93 (m, 2H), 12.07 (s, 1H). 13C NMR (100 MHz, $CDCl_3$) δ: 23.2, 55.2 (d, $J_{P\text{-}C}$ = 137.0 Hz), 102.4 (d, $J_{P\text{-}C}$ = 6.5 Hz), 106.9, 108.1, 113.4, 120.0, 125.3, 126.3, 126.9, 128.7, 129.1, 129.4, 129.6, 131.2, 132.3, 137.2, 154.0, 164.1, 182.6. ^{31}P NMR (162 MHz, $CDCl_3$) δ: 8.83. IR (KBr) ν_{max} (cm^{-1}): 3439, 3269 (O–H), 2975, 2896 (CH_3), 1655 (C = O), 1619 (Ar), 1262 (P = O), 1199 (P–O–Ar), 1091 (O–C), 3008, 787 (Ar–H). ESI MS found m/z: 512.2 $[M+H]^+$, 1045.2$[2M+Na]^+$.

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