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$SnCl_2$-catalyzed Kabachnik–Fields synthesis of α-aminophosphonates with potent antioxidant activity

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A novel and efficient method for synthesizing α-aminophosphonates was developed through a Kabachnik–Fields multicomponent reaction using 6-aminocoumarin or 6-aminobenzodioxane, benzaldehyde, triethyl phosphite, and a catalytic amount of $SnCl_2$ in ethanol. The resulting 25 compounds **1a–l** (71–92%) and **6a–m** (45–96%) were obtained in moderate to excellent yields. Antioxidant activity, assessed *via* the FRAP and CUPRAC assays, the results demonstrated that several of these compounds exhibit comparable or even superior reducing power to ascorbic acid, particularly at low concentrations. These findings underscore the potential of these α-aminophosphonates as promising antioxidant agents for future applications. ADME analysis predicts good oral bioavailability, limited brain and skin penetration, and potential CYP450 inhibition.

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1. Introduction

Phosphonates are a type of organophosphorus molecule featuring a carbon–phosphorus bond that remains stable under biological, thermal, and photochemical conditions.[1] Organophosphate compounds constitute a diverse and functionally important class of molecules widely utilized in industrial, agricultural, and medical applications. Recently, increasing attention has been directed toward α-aminophosphonate esters and α-aminophosphonic acids, recognized as structural analogs of amino acids. This resemblance contributes to their diverse biological properties, including antibiotic,[2] antibacterial,[3] antiviral,[4] and herbicidal activities.[5] Presently, organophosphates are employed in a broad spectrum of products, ranging from pharmaceuticals and detergents to insecticides, flame retardants, fuel additives, flotation agents, antioxidants, and complexing agents.[6] On the other hand, α-aminophosphonates are esters derived from α-aminophosphonic acids and are structurally similar to α-amino acids incorporating N–C–P moiety. Due to their wide array of biological activities, these compounds have gained considerable attention in recent years. Consequently, researchers have focused on developing effective synthetic methodologies to obtain α-aminophosphonates and their derivatives. A general method for the formation of α-aminophosphonates with very good yields is known, which consists of the reductive phosphination of amides (Scheme 1(I)).[7] A synthetic procedure from aldehydes, diethyl phosphite, and azides leads to α-aminophosphonates in the presence of iodine and iron and can be carried out without solvents (Scheme 1(II)).[8]

Although one of the most efficient and widely used approaches was the Kabachnik–Fields reaction, which entails a one-step condensation of an aldehyde, an amine, and a dialkyl phosphite.[9–12] This is a Mannich type condensation and the formation of the intermediate imine is proposed as a key element to obtain the aminophosphonate derivatives. This multi-component reaction can be carried out with or without catalysis and can be modified in other ways, such as in the presence or absence of solvent (Scheme 1(III) and (IV)).[13,14]

Of the many biological activities of α-aminophosphonates the most important one is their antioxidant activity. These compounds have received much attention with regards to their free radical scavenging activities and the inhibition of oxidative stress[15] which is central to the pathogenesis of many diseases such as cancer, neurodegenerative diseases, and cardiovascular diseases. Several studies have demonstrated the effectiveness of α-aminophosphonates as potent antioxidant agents and the results were encouraging both *in vitro* and *in vivo*.[16] Thus, their antioxidant ability remains the subject of research aimed at understanding the mechanisms of their action and the extent of their potential.

Besides, oxygen-containing heterocyclic compounds are commonly occurring structural units in organic synthesis. Indeed, coumarin and its derivatives are widely used in the synthesis of these heterocyclic systems. The broad pharmacology activities of coumarins, namely their antibacterial,[17]

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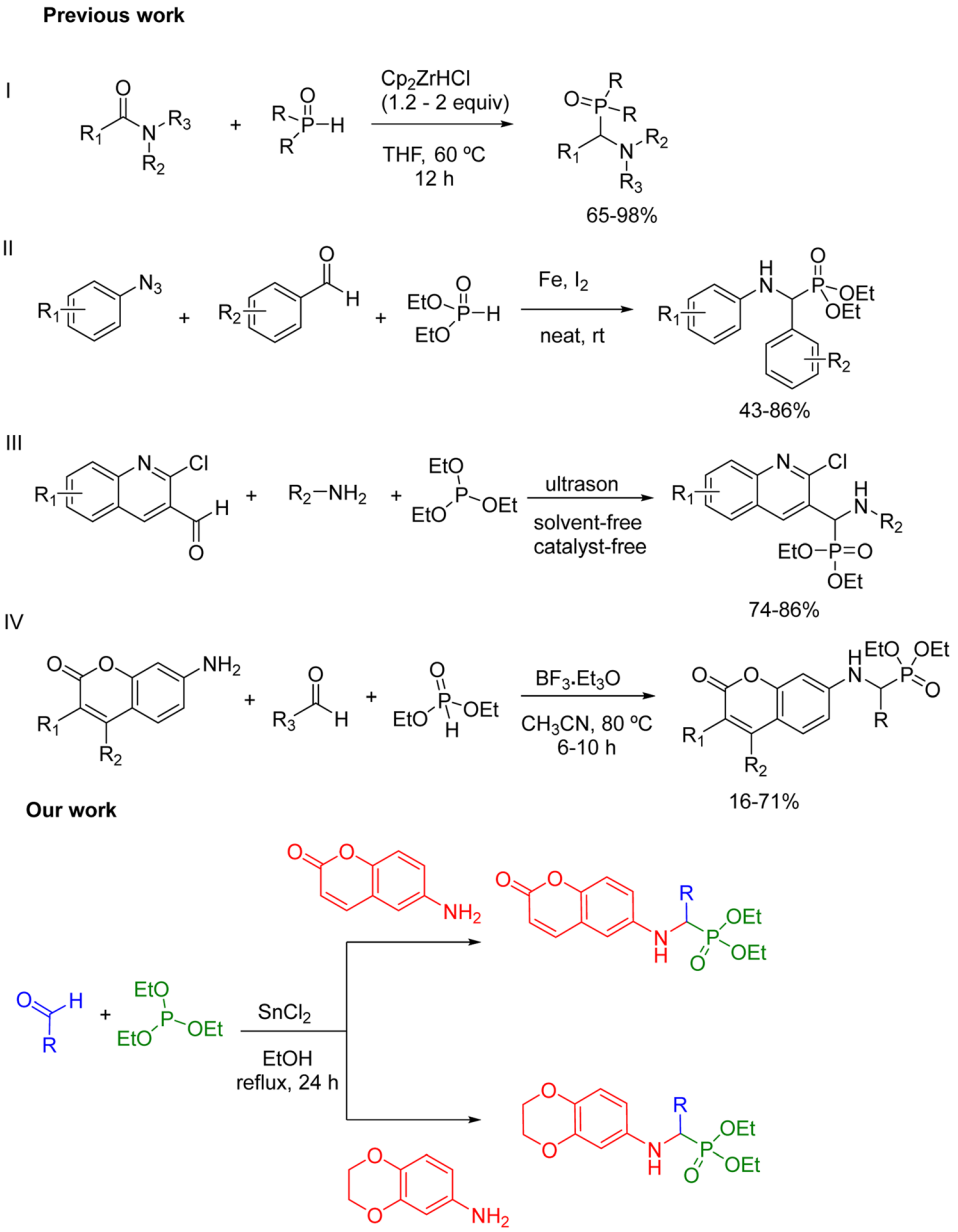


Scheme 1 Methods for the synthesis of α-aminophosphonates.

antifungal,[18] antioxidant,[19] anti-inflammatory,[20] anti HIV,[21] anticancer,[22] anti-tuberculosis,[23] anticoagulant,[24] antiviral[25] and antidiabetic[26] activities (Fig. 1).

In this work, after an initial focus on the synthesis of the new α-aminophosphonates compounds containing coumarin and benzodioxane moiety *via* the Kabachnik-fields reaction. Their potential as antioxidant were evaluated using the FRAP method.

2. Results and discussion

2.1. Synthesis

We aim to develop a sequence of procedures to generate α-aminophosphonate derivatives **1** with a view to potential biological activity. Firstly, we have used 2*H*-chromen-2-one (**2**) as an easily accessible aromatic compound with versatile synthetic intermediates, described previously in the literature, to obtain α-aminophosphonate derivatives in satisfactory yields, according to the retrosynthetic scheme (Scheme 2).

Following study by Cao *et al.*[27] the nitration of 2*H*-chromen-2-one (**2**) using potassium nitrate (KNO_3) in concentrated sulfuric acid at room temperature leads to the formation of 6-nitro-2*H*-chromen-2-one **3** in 92% yield (Scheme 3). The compound **3** obtained by precipitation in a mixture of water and ice was used directly in the following steps without any further purification.

Alternatively, 6-amino-2*H*-chromen-2-one (**4**) was obtained by reduction of 6-nitro-2*H*-chromen-2-one (**3**). The latter was treated with metalic iron in an acidic medium under reflux in ethanol to give compound **4** in good yield (61%) (Scheme 3).

Initially, in the Kabachnik–Fields reaction, the amine (NH) and the phosphonate proton (PH) can react with the aldehyde.

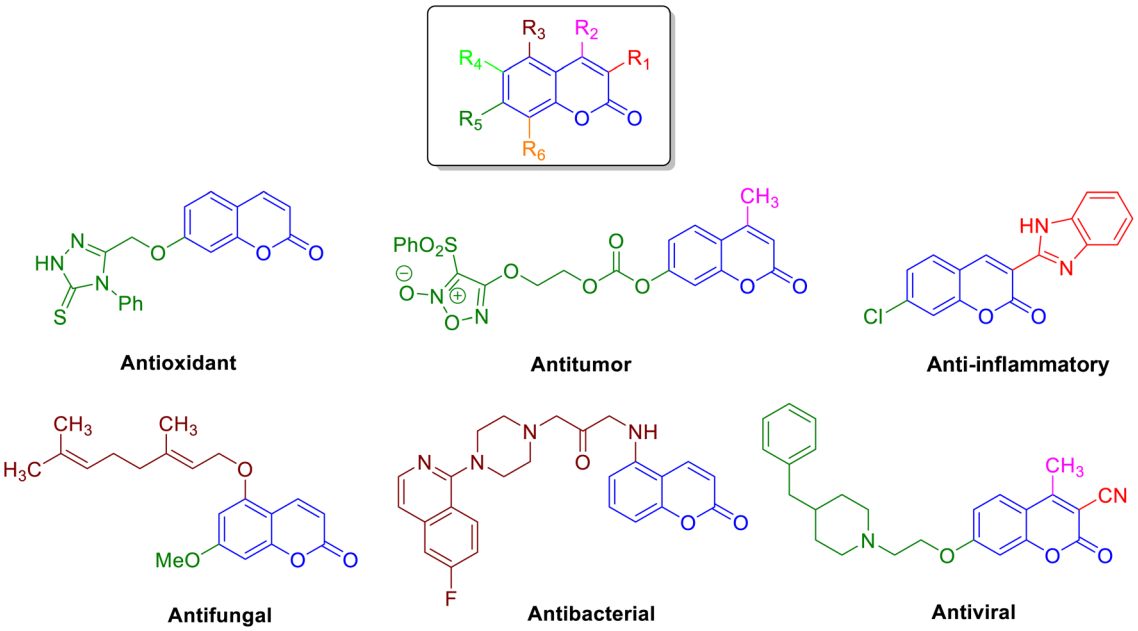
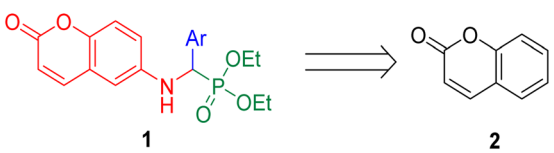


Fig. 1 Coumarin and some biological activities.



Scheme 2 Retrosynthesis of α-aminophosphonate derivatives.

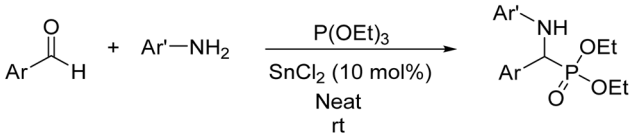
Therefore, we are faced with a competitive addition of N–H or P–H fragments to the C=O bond. However, amines generally react preferentially due to their superior nucleophilicity. However, weaker nucleophiles such as aniline may exhibit reduced reactivity. It should be noted that the use of trialkylphosphorus reagents without P–H bonds prevents unwanted P–H bond activation and improves the selectivity of the amination process.

In the initial tests, the operating conditions developed by Nakayama *et al.*[28] were employed to synthesize α-aminophosphonates from an aldehyde, amine, and triethyl phosphite. This process utilized a Lewis acid ($SnCl_2$) as a catalyst in a multicomponent reaction conducted at room temperature (Scheme 4).

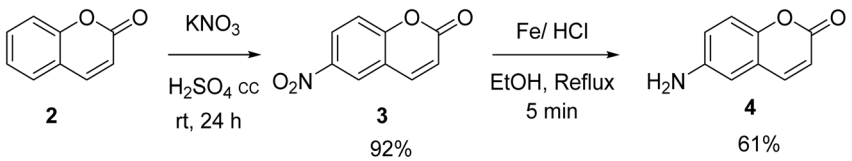
A number of investigations reported in the literature have shown that when the Kabachnik–Field reaction was carried out in the presence of catalysts such as lithium perchlorate,[29] lanthanide triflates with magnesium sulphate,[30] magnesium perchlorate,[31] indium trichloride,[32] aluminium trichloride,[33] tantalum pentachloride combined with SiO_2 silica and samarium diiodide,[34,35] the reaction always leads a single product, α-aminophosphonate.

In our case, the reaction of an equimolar mixture of 6-amino-2*H*-chromen-2-one (**4**), 4-methylbenzaldehyde, and 1.1 equivalent of triethyl phosphite in the presence of $SnCl_2$ without solvent at room temperature for 24 hours unfortunately did not occur due to the low solubility of the starting material. Contrary to the results described in the literature,[28] the solvent-free condensation of 6-amino-2*H*-chromen-2-one (**4**) with 4-methylbenzaldehyde and triethyl phosphite using the Kabachnik–Fields reaction has not resulted in the formation of the desired α-aminophosphonate derivatives.

The $SnCl_2$ catalyst is necessary for obtaining the corresponding aminophosphonates as confirmed in Table 1, entry

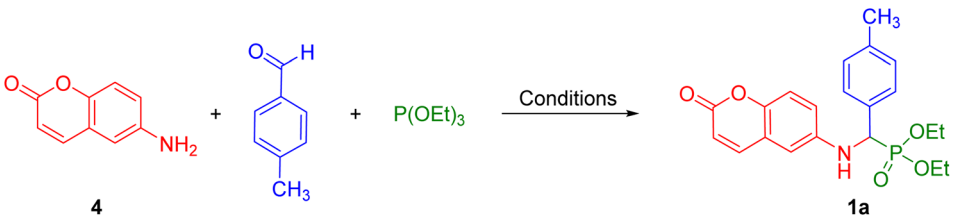


Scheme 4 Kabachnik–Fields reaction catalysed by $SnCl_2$.



Scheme 3 Nitration of 2*H*-chromen-2-one (**2**) and reduction of 6-nitro-2*H*-chromen-2-one (**3**).

Table 1 Effect of solvent, catalyst and temperature on the synthesis of coumarinophosphonates[a]



4 1a

	Conditions			
Entry	Solvent	$SnCl_2$ (mol%)	Temperature	Yield (%)
1	—	10	rt	0
2	EtOH	10	rt	Traces
3	DCM	10	rt	0
4	CH_3CN	10	rt	0
5	H_2O	10	rt	0
6	—	10	100 °C	0
7	**EtOH**	**10**	**Reflux**	**92**
8	DCM	10	50 °C	Traces
9	CH_3CN	10	Reflux	Traces
10	EtOH	5	Reflux	42
11	EtOH	—	Reflux	0

[a] NB: the reaction was optimised with one equivalent of 4-methylbenzaldehyde and 1.1 equivalents of triethylphosphite in 24 h.

11. To determine the reaction supply at its set-up, tests were carried out using aliphatic aldehydes (butanal) that led to a mixture of compounds that are difficult to identify, many of them coming from condensations attributable to the possible enolization of these alcohols that have protons in the alpha carbonyl position.

However, in view of the results obtained, we proceeded to optimize the conditions for the synthesis of these coumarinophosphonate derivatives, by studying the effect of the solvent, the amount of the catalyst and the temperature during the synthesis (Table 1).

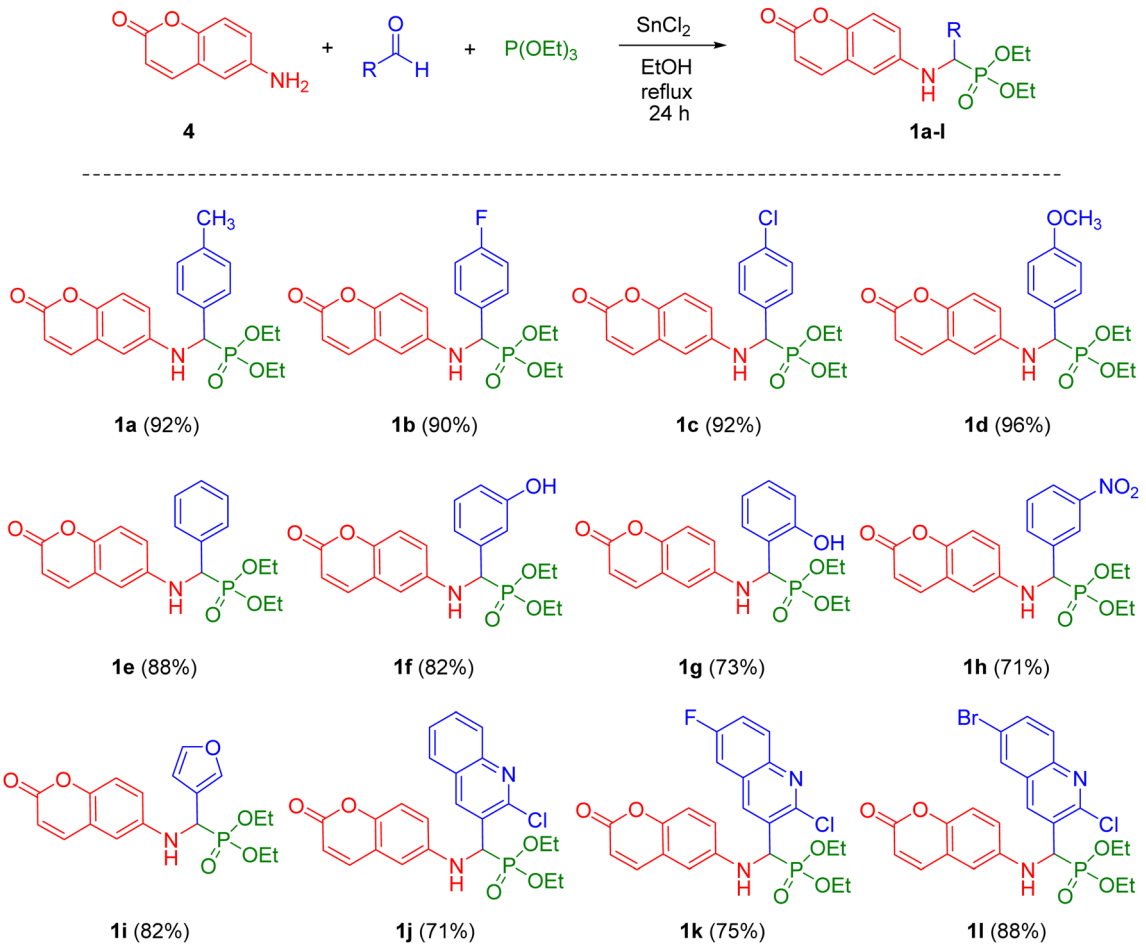
By using conventional heating (reflux), we succeeded to obtain the desired compounds with a very high yield. The results show that the yields of the reaction studied depend on the nature of the solvent and the amount of catalyst used. We found that ethanol was the best solvent for this condensation. In light of the numerous experiments conducted, the optimal conditions are those outlined in Table 1, entry 7. These conditions involve the use of 1 equivalent of 6-amino-2*H*-chromen-2-one (**4**), 1 equivalent of aldehyde, and 1.1 equivalents of triethylphosphite in ethanol under reflux for 24 hours.

Following the optimization of the synthesis conditions, the same strategy was applied to the synthesis of coumarinophosphonate derivatives with different aldehydes, utilizing $SnCl_2$ (10 mol%) in refluxing ethanol (Scheme 5). The desired aminophosphonates **1a–l** were obtained with good to excellent yields.

In continuation of our synthetic efforts, a second series of α-aminophosphonates specifically benzodioxanophosphonate derivatives designated as compounds **6a–m**, was successfully synthesized. The reactions were carried out *via* the Kabachnik–Fields reaction, employing the same optimized conditions as previously established and outlined in Scheme 5. For this series, 6-amino-1,4-benzodioxane **5** was selected as the amine (NH_2) component, playing the role of the core building block for the targeted molecular framework. This choice of substrate allowed for the introduction of the 1,4-benzodioxane moiety into the α-aminophosphonate scaffold, potentially enhancing the biological interest of the resulting derivatives. The complete set of reaction conditions, along with the yields obtained for each individual compound, was comprehensively presented in Scheme 6.

In the case of 3-nitrobenzaldehyde, two products were obtained, **6i** and **6i′** (Scheme 7). The first product **6i** corresponds to the desired α-aminophosphonate according to the Kabachnik–Fields reaction and the second co-product is obtained by direct reaction of 3-nitrobenzaldehyde with triethylphosphine (Scheme 7). The formation of this by-product had not been observed in the case of 6-aminochroman-2-one.

The catalytic feature of tin(II) chloride ($SnCl_2$) in the Kabachnik–Fields reaction can be attributed to its pronounced Lewis acid properties, which enable the simultaneous activation of the carbonyl and phosphite components. Initially, $SnCl_2$ coordinates with the carbonyl oxygen of the aldehyde, thereby enhancing the electrophilicity of the carbonyl group and facilitating its condensation with the amine to give the corresponding imine intermediate (Scheme 8). In parallel, the coordination of $SnCl_2$ to phosphorylated oxygen increases the electrophilic character of the phosphorus centre, favouring nucleophilic addition of the amine (Scheme 8). The activated phosphite then undergoes nucleophilic addition to the electrophilic carbon of the iminium in a typical aza-Pudovik step,



Scheme 5 Synthesis of coumarinophosphonate derivatives **1a–l** using $SnCl_2$ under the optimized conditions.

leading to the formation of the α-aminophosphonate product. Finally, proton transfer and product dissociation regenerate the Sn(II) catalyst.

The compounds of this series of aminophosphonates have not been previously described except for **6c**, **6g**, **6e** and **6i** which appear in a publication but the analytical data are not detailed.[36]

2.2. Antioxidant activity

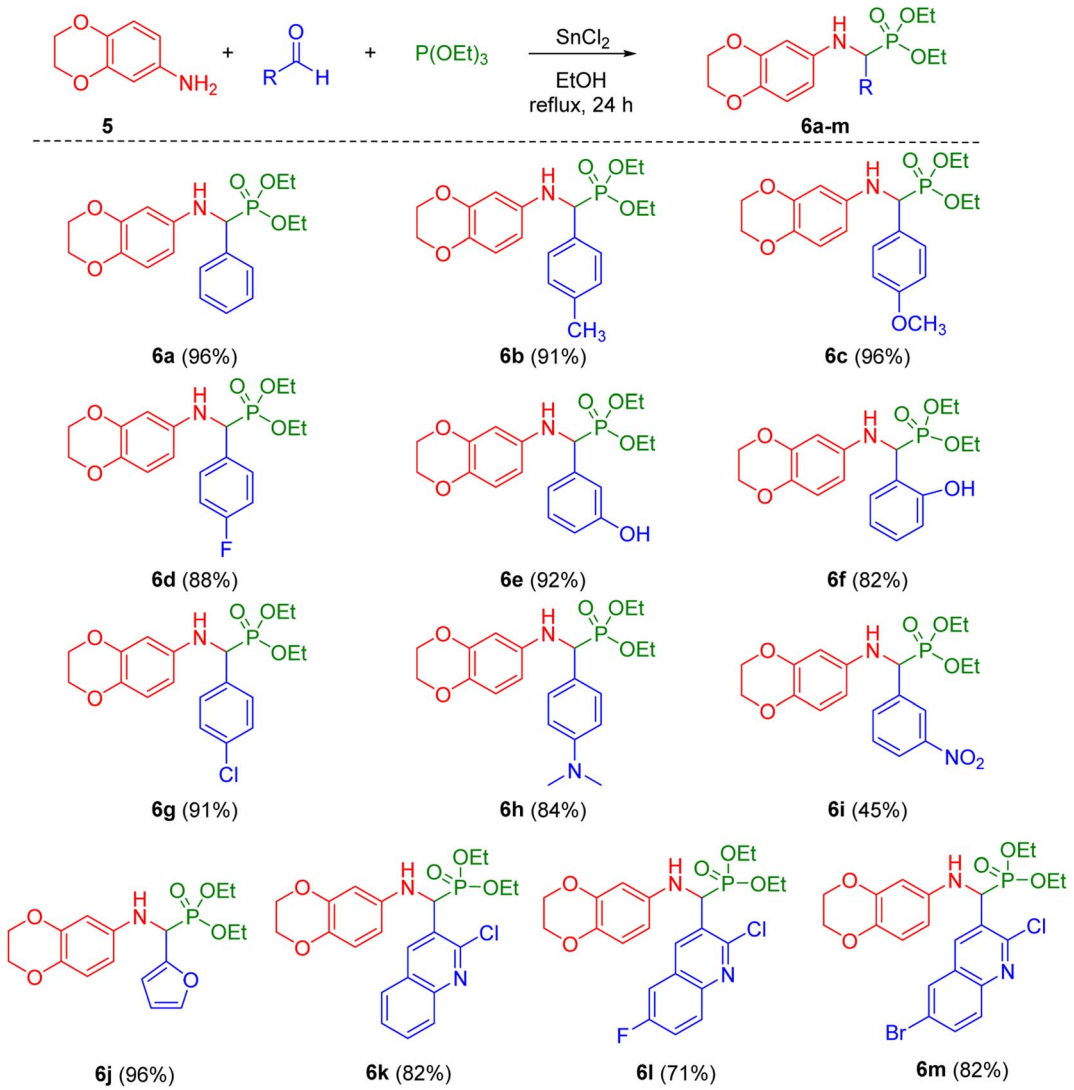
Antioxidant activity can be determined by various validated methods, including DPPH (2,2-diphenyl-1-picrylhydrazyl), ABTS (2,2′-azinobis(3-ethylbenzothiazoline-6-sulfonic)), ORAC (oxygen radical absorbance capacity) and FRAP (ferric reducing antioxidant potential).[37] In this work, the FRAP method was used, based on the principle that antioxidants are substances capable of reducing Fe^{3+} (ferric ion) to Fe^{2+} (ferrous ion). The Fe^{2+} ion forms a blue complex with 2,4,6-tripyridyl-5-triazine (TPTZ). The blue colour can be measured spectrophotometrically at 593 nm, and the absorption obtained was considered to be directly proportional to the oxidative power, as demonstrated by its reduction capacity. $FeSO_4$ has been used as an external standard for quantification. The absorbance results obtained have been directly proportional to the antioxidant power.

The compounds tested (**1a–l**) and (**6a–m**) and (**6i′**) showed an antioxidant activity comparable to ascorbic acid and ellagic acid, at the highest concentration tested (1 mM). Following lower concentrations (0.1 mM and 0.01 mM), several compounds showed interesting antioxidant activities.

Regarding the structure–activity relationships (SAR), it is noteworthy that the derivatives containing the coumarin nucleus exhibit slightly greater antioxidant capacity than the analogues containing the 1,4-benzodioxane nucleus (Fig. 2), particularly at low concentrations (comparing **6e** and **1f**, **6i** and **1h**, and **6j** and **1i**).

Regarding electron-donating substituents such as the hydroxyl group (phenol), the benzodioxane compounds **6e** and **6f** maintained antioxidant activity similar to that of the derivative without the hydroxyl group, **6a**. However, the compound with a methoxyl group (CH_3O^-) has a significantly higher antioxidant capacity than the hydroxylated derivatives. The introduction of a methyl group at the 4-position of the phenyl group **6b** led to an increase in antioxidant activity at low concentrations of the compound (0.1 mM and 0.01 mM). The same is true for the introduction of a dimethylamino group ($N(CH_3)_2$) at the same 4-position.

The presence of halogens (inductively attractive groups) in the benzodioxane compounds of compounds **6d** and **6g** shows

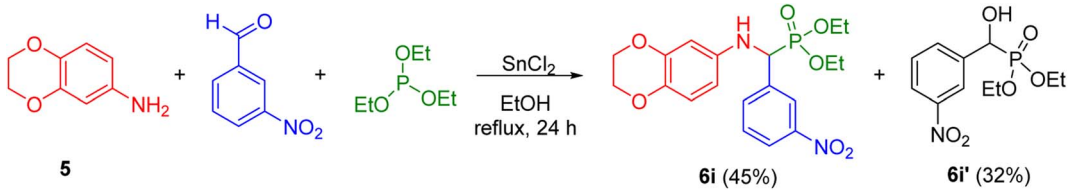


Scheme 6 Synthesis of benzodioxanophosphonate derivatives **6a–m** using $SnCl_2$ under the optimized conditions.

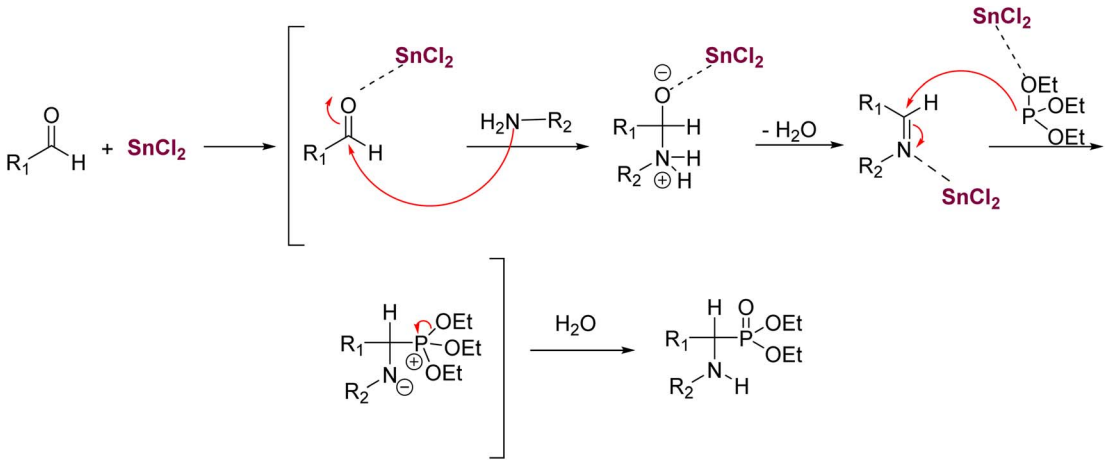
that chlorine exhibits better antioxidant activity than fluorine at low concentrations. However, it appears that fluorine does not enhance the antioxidant properties of chlorine, as is the case with coumarin compounds **1b** and **1c**. Similarly, the presence of $-NO_2$ group, an electron-withdrawing group at the 3-position of phenyl, neither increases nor decreases antioxidant activity, as demonstrated by the comparison between **6i** and **6a**. Furthermore, the introduction of heterocyclic rings such as furan instead of phenyl in the series of derivatives containing 1,4-benzodioxane did not show significant changes in activity (compare **6j** and **6a**), and the antioxidant activities presented are considered to be of the same order.

The presence of the 3-quinoline nucleus (compounds **6k**, **6l**, and **6m**) maintains the activity at the same level as the compound with a phenyl group. The introduction of halogens at the 6-position of quinoline (comparing **6l** and **6m** with **6k**) does not significantly alter the activity results.

In the coumarin series, the presence of donor groups such as hydroxyl (compounds **1f** and **1g**) does not produce significant changes in antioxidant activity compared to the unsubstituted



Scheme 7 Synthesis of diethyl (((2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)amino)(3-nitrophenyl)methyl)phosphonate (**6i**).



Scheme 8 Plausible mechanism for the Kabachnik–Fields reaction using the $SnCl_2$ as a catalyst.

phenyl derivative (compound **1e**). The methoxylated derivative (compound **1d**) exhibits activity at all three concentrations in a range similar to that of the phenyl derivative (**1e**). Furthermore, the introduction of a nitro group at C-3 of the phenyl group in compound **1h** generally results in a slight decrease in activity, which was most pronounced at concentrations of 1 mM and 0.1 mM. Substitution of the phenyl group by heterocyclic rings in the coumarin series, such as the 2-chloroquinolin-3-yl group (compound **1j**), results in a slight reduction in antioxidant activity compared to compound **1e**. Likewise, the incorporation of halogens (F or Br) at C-6 of the quinoline nucleus (compounds **1k** and **1l**) does not significantly affect the activity. In contrast, substitution of the phenyl group by a furan ring results in a slight increase in the activity of the coumarin series at all three concentrations tested (compare **1i** and **1e**).

In general, it is worth noting that the antioxidant activity of these compounds depends on concentration. This is an interesting finding, as it could allow for the regulation of the desired oxidative power by controlling the administered dose (Fig. 2).

In conclusion, the compounds with the greatest Fe-reducing capacity are **1f** (possessing 3-OH-phenyl group), **1d** (with 4-OCH_3-phenyl), **1g** (2-OH-phenyl group), **1e** (without

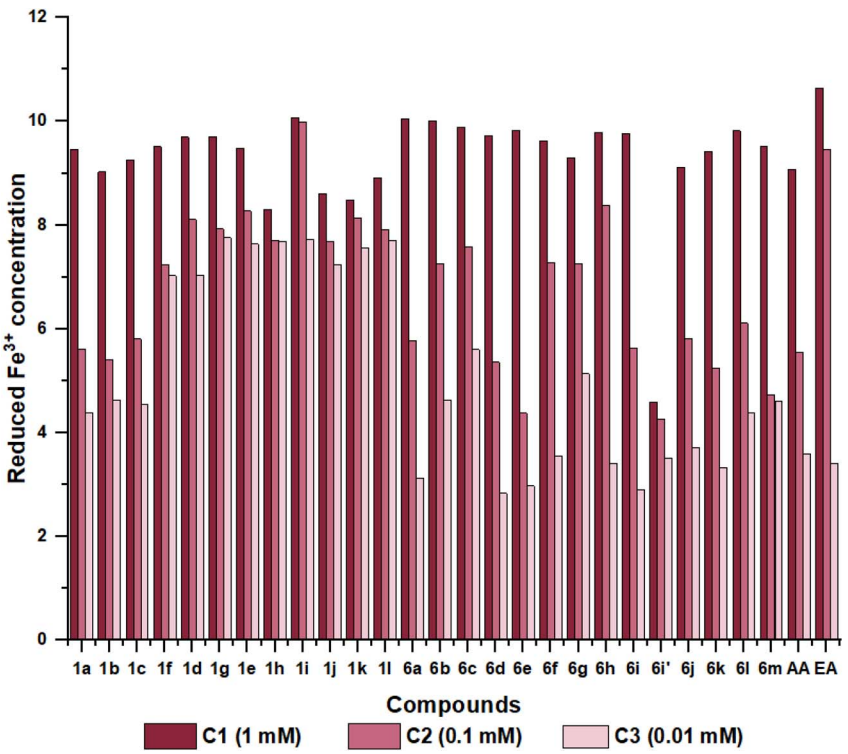


Fig. 2 Reduced Fe^{3+} concentration.

Table 2 Antioxidant activity results determined by absorption and FRAP and log *P*

		Absorbance			FRAP (mmol g^{-1})			
Entry	Compound	1 mM	0.1 mM	0.01 mM	1 mM	0.1 mM	0.01 mM	log *P*
1	**1a**	0.430	0.265	0.213	9.47	5.60	4.38	3.69
2	**1b**	0.411	0.257	0.224	9.02	5.41	4.63	3.66
3	**1c**	0.421	0.274	0.220	9.26	5.81	4.54	3.97
4	**1d**	0.440	0.372	0.326	9.70	8.11	7.03	3.38
5	**1e**	0.431	0.379	0.352	9.49	8.27	7.64	3.41
6	**1f**	0.432	0.335	0.326	9.52	7.24	7.03	2.98
7	**1g**	0.440	0.364	0.357	9.70	7.92	7.76	2.98
8	**1h**	0.380	0.355	0.354	8.30	7.71	7.69	2.67
9	**1i**	0.456	0.448	0.356	10.08	9.98	7.73	2.46
10	**1j**	0.393	0.354	0.335	8.60	7.69	7.24	4.28
11	**1k**	0.388	0.373	0.348	8.48	8.13	7.54	4.56
12	**1l**	0.406	0.363	0.377	8.91	7.90	7.71	4.87
13	**6a**	0.445	0.273	0.160	10.06	5.78	3.13	3.11
14	**6b**	0.453	0.336	0.224	10.01	7.26	4.63	3.48
15	**6c**	0.448	0.350	0.265	9.89	7.59	5.60	3.06
16	**6d**	0.441	0.255	0.147	9.37	5.36	2.83	3.49
17	**6e**	0.445	0.213	0.153	9.82	4.38	2.97	2.76
18	**6f**	0.437	0.328	0.178	9.63	7.08	3.55	2.70
19	**6g**	0.423	0.336	0.245	9.30	7.26	5.13	3.68
20	**6h**	0.442	0.383	0.172	9.78	8.37	3.41	3.14
21	**6i**	0.443	0.266	0.150	9.77	5.62	2.90	2.39
22	**6i′**	0.222	0.208	0.175	4.59	4.26	3.51	0.98
23	**6j**	0.415	0.274	0.185	9.12	5.81	3.72	2.46
24	**6k**	0.428	0.250	0.168	9.42	5.26	3.32	4.04
25	**6l**	0.445	0.287	0.213	9.82	6.11	4.38	4.32
26	**6m**	0.432	0.228	0.223	9.52	4.73	4.61	4.64
27	Ascorbic A	0.413	0.263	0.180	9.07	5.55	3.60	−1.42
28	Ellagic A	0.480	0.430	0.172	10.64	9.47	3.41	1.00

substituents), **1h** (with 3-NO_2-phenyl), **1i** (with furane), **1j** (with 2-chloroquinolin-3-yl), **1k** (with 2-chloro-6-fluoroquinolin-3-yl), **1l** (with 6-bromo-2-chloroquinolin-3-yl) (Table 2 and Fig. 2). All of these compounds contain the coumarin phosphonate system, and the substituent in the alpha position varies. The results show that the coumarin nucleus confers greater antioxidant activity than the benzodioxin nucleus. Regarding the substituents, and according to the results of the FRAP assay, the donor or attractant nature of the substituent does not substantially modify the activity. However, the one with a 3-furyl group shows the best activity profile.

When trying to correlate antioxidant activity with lipophilicity no clear linear relationship was found. The chosen models, ascorbic acid and ellagic acid, exhibit high activity and a very low log *P*, indicating their high degree of polarity. Meanwhile, the compounds **1i**, **6a**, **6c** and **6l** show activities of the same order as the models and their log *P* values indicate higher lipophilicity (ranging from log *P* 2.46 to 4.32). It is also worth nothing that compound **6i′**, which exhibits a log *P* value close to that of ellagic acid, has demonstrated lower antioxidant activity (Table 2).

While FRAP is a classic method for the evaluation of antioxidant capacity, CUPRAC is a procedure dating back to 2004 and is based on the reduction of Cu(II) to Cu(I). The CUPRAC method (copper reducing antioxidant capacity) is a simple, selective, stable and sensitive procedure for different types of antioxidants. The CUPRAC test is similar to the FRAP test, but is based on the reduction of Cu(II) ions in the presence of neocuproine (2,9-dimethyl-1,10-phenanthroline) at pH 7, which implies faster kinetics.[38]

Regarding the second antioxidant test, the experimental results indicate that the compounds tested show interesting antioxidant activities, being in some cases even superior to the controls (Table 3 and Fig. 3). This would be the case of compounds containing chroman-2-one system **1a**, **1e** and **1g** which at concentrations of 0.01 mM exceed ascorbic acid and ellagic acid in TAC.

Compound **6d** shows slightly higher activity than ascorbic acid at a concentration of 0.1 mM. In general, it is observed that coumarin derivatives, with the exception of **1j**, show greater activity at lower concentrations, while 1,4-benzodioxane derivatives show greater activity at higher concentrations.

Relating the structure of coumarines with the antioxidant power, the compounds **1a** (with –CH_3), **1e** (without substituent) and **1g** (whit –OH) that have shown greater antioxidant activity at small doses have few differences, **1e** presents phenyl without substituent, while **1a** presents a 4-methylphenyl and **1g** has a 2-hydroxyphenyl. The derivative **1f** also has a high antioxidant power, very similar to **1g**; both have hydroxyl groups, although in different positions. Hydroxyl groups on aromatic rings are highly susceptible to oxidation to quinones or derivatives. These groups would be responsible for the antioxidant capacity of phenolic derivatives.

Table 3 Antioxidant activity results determined by CUPRAC method

	Absorbance			TAC (μM)		
Compounds	C1 (1 mM)	C2 (0.1 Mm)	C3 (0.01 Mm)	C1 (1 mM)	C2 (0.1 Mm)	C3 (0.01 Mm)
1a	0.306	0.250	0.382	278.181	227.954	347.500
1b	0.326	0.208	0.333	296.363	189.090	303.409
1c	0.2885	0.151	0.349	262.272	137.727	317.727
1d	0.3305	0.238	0.316	300.454	216.590	287.272
1e	0.284	0.255	0.383	258.636	231.818	348.863
1f	0.344	0.290	0.346	312.954	263.863	315.000
1g	0.320	0.206	0.378	291.590	187.727	343.636
1h	0.352	0.275	0.299	320.227	250.000	272.045
1i	0.309	0.230	0.324	280.909	209.545	294.545
1j	0.327	0.284	0.270	297.727	258.409	245.681
1k	0.331	0.251	0.327	301.136	228.181	297.727
1l	0.324	0.279	0.296	294.772	254.090	269.772
6a	0.354	0.286	0.327	322.500	260.227	297.500
6b	0.401	0.255	0.274	365.227	232.500	249.772
6c	0.369	0.290	0.315	335.454	263.636	286.363
6d	0.392	0.339	0.261	357.045	308.636	237.727
6e	0.325	0.306	0.255	295.909	278.636	232.272
6f	0.429	0.311	0.241	390.227	282.727	219.090
6g	0.365	0.309	0.291	331.818	281.363	264.545
6h	0.367	0.327	0.183	334.318	297.727	166.590
6i	0.307	0.293	0.255	279.772	266.818	232.045
6j	0.393	0.297	0.293	357.727	270.227	266.590
6k	0.341	0.285	0.266	310.227	259.772	242.045
6l	0.371	0.334	0.176	337.727	303.863	160.227
6m	0.320	0.279	0.324	291.136	254.318	295.000
AA	0.357	0.306	0.278	324.772	278.863	252.954
EA	0.372	0.345	0.316	338.636	314.318	287.727

Derivatives containing the 1,4-benzodioxin nucleus maintain very similar behavior to ascorbic and ellagic acids. In this case, too, the phenolic derivative **6f** (with 2-OH-phenyl) has been shown to be the most oxidizing in the series (Table 3 and Fig. 3). It is followed in activity by **6b** (with 4-CH_3-phenyl), **6d** (with 4-fluorophenyl), and **6j** (with 3-furyl). The results confirm

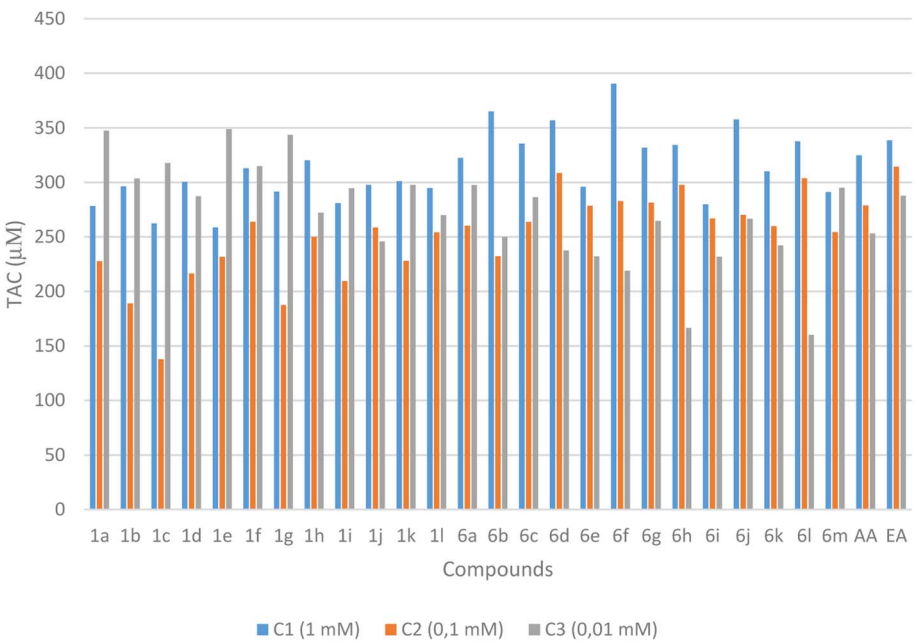


Fig. 3 Total antioxidant capacity TAC (μM).

that their antioxidant activity is more dependent on concentration than the series containing the chroman-2-one nucleus (comparing **6f** and **1g**).

The two methods used to determine the antioxidant capacity of the synthesized phosphonates confirm that all compounds present antioxidant activity and, except for minor differences, the compounds with the greatest activity coincide in both procedures.

2.3. ADME (absorption, distribution, metabolism, and excretion) theoretical studies

From the theoretical study using SwissADME program shows that all compounds comply with Lipinski's rule, which predicts good oral bioavailability. Likewise, the GI values indicates high absorption except for the compounds **1j**, **1k**, **1l** and **6m** (Table 4).

According to the studies carried out, these compounds would not be affected their absorption by the P-gp protein, this being an important cause of multi-drug resistance. Also, polarity does not allow passage through the blood–brain (BBB permeant) (Table 5).

These are structures that are metabolized by cytochrome P450 proteins, and many of them behave as inhibitors of certain cytochrome forms, which should be considered when administering them with other drugs metabolized with these enzymes. The log K_p values provides information on the ability of compounds to penetrate the skin and induce toxicity. For all compounds studied these values are negative (−5.82 to −8.54). Negative log K_p values suggest limited skin penetration, and a larger negative values indicates reduced penetration potential (theoretically these values are between −1 to −8).

Values of bioavailability score of 0.55 suggests that these compounds exhibit excellent absorption by the body.

Cytochrome P450 (CYP) is the most important enzyme system catalyzing phase I microsomal metabolism. CYP induction and inhibition involve highly significant pharmaceutical interactions as they impact the metabolism of ingested substances. Theoretical prediction of the effect of various substances on the different CYP isoforms is necessary to prevent potential adverse effects while maintaining a safety margin. According to theoretical results, most compounds would exhibit inhibitory capacity for the CYP isoforms studied.[39] If these results are confirmed in *in vivo* studies, they would limit their simultaneous use with drugs or other substances that must be metabolized by these enzymes, as their metabolism and subsequent elimination would be reduced. Among the compounds, **6i′** does not inhibit CYP2C9, CYP2D6, or CYP3A4. While **6h** does not inhibit CYP1A2 and **1c** and **1l** do not inhibit CYP2D6.

Table 4 Pharmacokinetic theoretical results by SwissADME program

	Pharmacokinetics								
Compound	GI absorption	BBB permeant	P-gp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	log K_p (cm s^{-1})
1a	High	No	No	No	Yes	Yes	No	Yes	−6.01
1b	High	No	No	Yes	Yes	Yes	Yes	Yes	−6.22
1c	High	No	No	Yes	Yes	Yes	No	Yes	−5.94
1d	High	No	No	Yes	Yes	Yes	Yes	Yes	−6.38
1e	High	No	No	Yes	Yes	Yes	Yes	Yes	−6.18
1f	High	No	No	Yes	Yes	Yes	Yes	Yes	−6.53
1g	High	No	No	Yes	Yes	Yes	Yes	Yes	−6.53
1h	Low	No	No	Yes	Yes	Yes	No	Yes	−6.57
1i	High	No	No	Yes	Yes	Yes	Yes	Yes	−6.78
1j	Low	No	No	Yes	Yes	Yes	No	Yes	−5.83
1k	Low	No	Yes	Yes	Yes	Yes	Yes	Yes	−7.06
1l	Low	No	No	Yes	Yes	Yes	No	Yes	−5.82
6a	High	No	Yes	Yes	Yes	Yes	Yes	Yes	−6.31
6b	High	No	Yes	Yes	Yes	Yes	Yes	Yes	−6.14
6c	High	No	Yes	Yes	Yes	Yes	Yes	Yes	−6.51
6d	High	No	Yes	Yes	Yes	Yes	Yes	Yes	−6.35
6e	High	No	Yes	Yes	Yes	Yes	Yes	Yes	−6.66
6f	High	No	Yes	Yes	Yes	Yes	Yes	Yes	−6.66
6g	High	No	Yes	Yes	Yes	Yes	Yes	Yes	−6.07
6h	High	No	Yes	No	Yes	Yes	Yes	Yes	−6.49
6i	High	No	Yes	Yes	Yes	Yes	Yes	Yes	−6.70
6i′	High	No	No	Yes	Yes	No	No	No	−7.37
6j	High	No	Yes	Yes	Yes	Yes	Yes	Yes	−6.89
6k	High	No	Yes	Yes	Yes	Yes	Yes	Yes	−5.96
6l	High	No	Yes	Yes	Yes	Yes	Yes	Yes	−6.00
6m	Low	No	Yes	Yes	Yes	Yes	Yes	Yes	−5.95
AA	High	No	No	No	No	No	No	No	−8.54
EA	High	No	No	Yes	No	No	No	No	−7.36

Table 5 Druglikeness of compounds **1a–l** and **6a–m**

	Druglikeness					
Compound	Lipinski	Ghose	Veber	Egan	Muegge	Bioavailability score
1a	Yes	Yes	Yes	Yes	Yes	0.55
1b	Yes	Yes	Yes	Yes	Yes	0.55
1c	Yes	Yes	Yes	Yes	Yes	0.55
1d	Yes	Yes	Yes	Yes	Yes	0.55
1e	Yes	Yes	Yes	Yes	Yes	0.55
1f	Yes	Yes	Yes	Yes	Yes	0.55
1g	Yes	Yes	Yes	Yes	Yes	0.55
1h	Yes	Yes	Yes	No (TPSA > 131.6)		0.55
1i	Yes	Yes	Yes	Yes	Yes	0.55
1j	Yes	No (WLOGP > 5.6)	Yes	Yes	Yes	0.55
1k	Yes	No (MW > 480; WLOP > 5.6)	Yes	No (WLOGP > 5.88)	Yes	0.55
1l	Yes (MW > 500)	No (MW > 480; WLOP > 5.6; MR > 130)	Yes	No (WLOGP > 5.88)	No (XLOGP > 5)	0.55
6a	Yes	Yes	Yes	Yes	Yes	0.55
6b	Yes	Yes	Yes	Yes	Yes	0.55
6c	Yes	Yes	Yes	Yes	Yes	0.55
6d	Yes	Yes	Yes	Yes	Yes	0.55
6e	Yes	Yes	Yes	Yes	Yes	0.55
6f	Yes	Yes	Yes	Yes	Yes	0.55
6g	Yes	Yes	Yes	Yes	Yes	0.55
6h	Yes	Yes	Yes	Yes	Yes	0.55
6i	Yes	Yes	Yes	Yes	Yes	0.55
6i′	Yes	Yes	Yes	Yes	Yes	0.55
6j	Yes	Yes	Yes	Yes	Yes	0.55
6k	Yes	Yes	Yes	Yes	Yes	0.55
6l	Yes	No (MW > 480; WLOP > 5.6)	Yes	No (WLOGP > 5.88)	Yes	0.55
6m	Yes (MW > 500)	No (MW > 480; WLOP > 5.6)	Yes	No (WLOGP > 5.88)	No (XLOGP > 5)	0.55
AA	Yes	No (WLOGP < −0.4; MR < 40)	Yes	Yes	No (MW < 40)	0.56
EA	Yes	Yes	No (TPSA > 140)	No (TPSA > 131.6)	Yes	0.55

3. Conclusion

In conclusion, a new synthetic method has been developed for the preparation of α-aminophosphonates **1a–l** and **6a–m** from 6-aminocoumarin and 6-aminobenzodioxane respectively, involving the use of a multicomponent Kabachnik–Fields reaction. This new method requires an amine, benzaldehyde, triethylphosphite and a catalytic amount of $SnCl_2$ in reflux of ethanol. The α-aminophosphonates **1a–l** (71–96%) and **6a–m** (45–96%) were obtained in good to high yields. Furthermore, the antioxidant activity of compounds **1a–l** and **6a–m** was assessed using the FRAP method. At a concentration of 1 mM, the compounds tested (**1a–l**) and (**6a–m**) revealed antioxidant activity of the same order as that of ascorbic acid and ellagic acid at the same concentration. However, at low concentrations (0.1 mM and 0.01 mM), the reducing power of certain compounds (**1f**, **1d**, **1g**, **1e**, **1h**, **1i**, **1j**, **1k**, **1l**) was greater than ascorbic acid and ellagic acid. Theoretical ADME analysis indicated that most compounds have good oral bioavailability, high gastrointestinal absorption, and are not affected by P-gp-mediated drug resistance. They are unlikely to cross the blood–brain barrier and generally show low skin penetration. Some compounds may inhibit cytochrome P450 enzymes, suggesting potential drug–drug interactions. Overall, the bioavailability and pharmacokinetic profiles support their potential as orally active drug candidates.

4. Experimental section

4.1. Antioxidant activity

4.1.1 FRAP assay. The method used followed the procedure established by Benzie and Strain.[40] This assay operates on the principle that antioxidants can reduce a ferric-tripyridyltriazine (Fe^{3+}-TPTZ) complex to its ferrous (Fe^{2+}) form, resulting in a blue-colored compound. In brief, the FRAP reagent was freshly prepared by mixing 2.5 mL of 10 mmol per L TPTZ (2,4,6-tripyridyl-*s*-triazine, Sigma) dissolved in 40 mmol per L HCl with 2.5 mL of 20 mmol per L $FeCl_3$ and 25 mL of 0.3 mol per L acetate buffer (pH 3.6), then warmed to 37 °C. Various concentrations of each sample (0.5 mL) were combined with 9 mL of the working FRAP solution and 0.5 mL of distilled water. After incubation at 37 °C for 30 minutes, absorbance was recorded at 593 nm using a spectrophotometer. A 1 mmol per L $FeSO_4$ solution served as the calibration standard. Results were expressed as the antioxidant capacity equivalent to 1 mmol per L $FeSO_4$. Samples with FRAP values exceeding the standard curve's linear range were appropriately diluted before analysis.

4.1.2 CUPRAC assay.[41] The total antioxidant capacity of compounds **1a–l** and **6a–m** was evaluated using the antioxidant assay kit (MAK334, Sigma-Aldrich, St. Louis, MO, USA) following the manufacturer's instructions. In this method, copper(II) ions (Cu^{2+}) are reduced by antioxidant molecules to copper(I) ions (Cu^{+}), which subsequently react with a chromogenic reagent to generate a colored complex. The absorbance of this complex is measured at 570 nm, and the resulting color intensity is directly correlated with the antioxidant capacity of the sample. The outcomes were expressed as micromolar (μM) Trolox equivalents. An important feature is that the evaluation is performed at neutral pH, while FRAP is performed in an acidic medium. This antioxidant assay measures the total antioxidant capacity (TAC) at which Cu^{2+} is reduced by an antioxidant to Cu^{+}. The resulting Cu^{+} specifically forms a colored complex with a dye reagent. The color intensity at 570 nm is proportional to the TAC in the sample. The kit uses 20 μL of sample and has a linear detection range of 1.5–1000 μM Trolox equivalents.[42]

4.2. Chemistry

All chemicals were purchased from commercial sources and were used without further purification. The reactions were monitored by Thin Layer Chromatography (TLC) on commercial silica gel 60 GF254 plates and the reactional mixture were examined under UV light (λ = 254 nm). Column chromatography was carried out using silica gel 60 Merck 0.063–0.200 mm. The reaction solvents used are of analytical quality, except that the solvents used in the column chromatography (hexane and ethyl acetate) are distilled before use. All compounds were characterized in solution by ^{1}H and ^{13}C NMR and when appropriated by using deuterated solvent ($CDCl_3$). The NMR spectra were recorded using Bruker, 400 and 500 spectrometers operating at 400 MHz and 500.13 MHz for ^{1}H and 75.47 MHz, 100.6 MHz and 125.76 MHz for ^{13}C, respectively, with tetramethylsilane (TMS) as the internal standard. Melting points (PF in °C), uncorrected, were determined using a Gallenkamp model MFB.595.010M with an internal thermometer, and were adjusted using an external thermometer.

4.2.1 6-Nitro-2*H*-chromen-2-one (3). Nitro-coumarin was prepared according to a reported procedure using KNO_3 in acidic medium. Coumarin **1** (1.00 g, 6.84 mmol, 1 equiv.) and KNO_3 (0.692 g, 6.84 mmol, 1 equiv.) were added in a single portion to concentrated H_2SO_4 (60 mL) in a 100 mL round-bottom flask equipped with a magnetic stirrer. The mixture was stirred at room temperature for 24 h. After completion of the reaction, as confirmed by TLC, the mixture was slowly poured dropwise into ice-cold water (1000 mL) with constant stirring. The resulting white precipitate was filtered, washed thoroughly with cold water, and dried in an oven. The final product was obtained as a solid of sufficient purity to be used directly in the subsequent step without additional purification, as confirmed by TLC and NMR analyses.

White powder, yield: 92%; m.p.: 200–202 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 8.73 (d, J = 2.8 Hz, 1H, H-5), 8.42 (dd, J = 9.1, 2.8 Hz, 1H, H-7), 8.23 (d, J = 9.1 Hz, 1H, H-4), 7.62 (d, J = 9.7 Hz, 1H, H-8), 6.70 (d, J = 9.7 Hz, 1H, H-3). ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 158.9 (C=O), 157.2 (C8a), 143.5 (C6), 143.3 (C4), 126.5 (C7), 124.3 (C5), 119.1 (C4a), 118.1 (C8), 117.8 (C3).

4.2.2 6-Amino-2*H*-chromen-2-one (4). In a 100 mL round-bottom flask, nitro-coumarin **3** (0.50 g, 2.61 mmol, 1 equiv.) was dissolved in ethanol (10 mL). Iron powder (26.1 mmol, 10 equiv.) was added under vigorous stirring, followed by concentrated HCl (26.1 mmol, 10 equiv.). The reaction mixture was heated to reflux under constant stirring for 5 min. After completion of the reaction, the hot mixture was cooled to room temperature, filtered under pressure, and washed with ethanol. The filtrate was basified with 10% aqueous NaOH and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The crude residue was purified by column chromatography on silica gel using a mixture of ethyl acetate/hexane (4 : 6, v/v) as eluent.

White powder, yield: 92%; m.p.: 200–202 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm): 7.90 (d, J = 9.5 Hz, 1H, H-4), 7.12 (d, J = 8.8 Hz, 1H, H-8), 6.87 (dd, J = 8.8, 2.7 Hz, 1H, H-7), 6.77 (d, J = 2.7 Hz, 1H, H-5), 6.37 (d, J = 9.5 Hz, 1H, H-3), 5.33 (s, 2H, NH_2). ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 160.5 (C=O), 145.4 (C8a), 145.2 (C6), 144.4 (C4), 119.1 (C4a), 118.78 (C7), 116.6 (C8), 115.9 (C3), 110.3 (C5).

4.2.3 General procedure for the synthesis of α-amino-phosphonates coumarine derivatives 1a–l. A solution of 6-amino-2*H*-chromen-2-one (**4**) (1 mmol; 1 equiv.) in ethanol (5 mL), the appropriate aldehyde (1 mmol; 1 equiv.), triethyl phosphite (1.1 mmol; 1.1 equiv.), and tin(II) chloride ($SnCl_2$) (10 mol%) was added, and the reaction mixture was stirred under reflux in ethanol for 24 hours. Once the reaction was deemed complete, ethanol was evaporated under reduced pressure. Then, 15 mL of water was added to the reaction mixture, and the product was extracted using ethyl acetate (20 mL × 3). The organic phase was dried over anhydrous sodium sulfate, filtered under reduced pressure, and the solvent was evaporated under vacuum. The crude product obtained was purified by silica gel column chromatography using a mixture of ethyl acetate/hexane (4 : 6).

*4.2.3.1 Diethyl (((2-oxo-2H-chromen-6-yl)amino)(p-tolyl) methyl)phosphonate (**1a**).* Yellow powder, yield: 92%; m.p.: 155–156 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.49 (d, J = 9.6 Hz, 1H, H-4), 7.33 (dd, J = 8.0, 2.1 Hz, 2H, H-2′, H-6′), 7.15 (d, J = 8.0 Hz, 2H, H-3′, H-5′), 7.11 (d, J = 8.9 Hz, 1H, H-8), 6.83 (dd, J = 8.9, 2.8 Hz, 1H, H-7), 6.53 (d, J = 2.7 Hz, 1H, H-5), 6.32 (d, J = 9.5 Hz, 1H, H-3), 4.88 (t, J = 8.6 Hz, 1H, N–H), 4.69 (d, J = 7.3 Hz, 1H, CH–N), 4.65 (d, J = 7.3 Hz, 1H, CH–N (rotamer)) 4.12 (q, J = 7.1 Hz, 2H, CH_2), 3.94 (cs, 1H, CH_2), 3.68 (cs, 1H, CH_2), 2.33 (s, 3H, CH_3), 1.30 (t, J = 7.1 Hz, 3H, CH_3), 1.13 (t, J = 7.1 Hz, 3H, CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ (ppm) 161.3 (C=O), 147.3 (C8a), 143.3 (C4), 143.2 (C6), 138.1 (C4′), 132.1 (C1′), 129.6 (C3′, C5′), 127.7 (C2′, C6′), 119.3 (C4a), 119.0 (C8), 117.6 (C7), 116.9 (C3), 110.1 (C5), 63.4 (CH–N), 57.0 (CH_2–O), 55.5 (CH_2–O), 21.2 (CH_3), −16.5 (CH_3), 16.3 (CH_3).

*4.2.3.2 Diethyl ((4-fluorophenyl)((2-oxo-2H-chromen-6-yl) amino)methyl)phosphonate (**1b**).* Yellow powder; yield: 90%; m.p.: 138–139 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.49 (d, J = 9.5 Hz, 1H, H-4), 7.43 (ddd, J = 8.5, 5.1, 2.4 Hz, 2H, H-3′, H-5′),

7.12 (d, J = 8.9 Hz, 1H, H-8), 7.04 (t, J = 8.5 Hz, 2H, H-2′, H-6′), 6.82 (dd, J = 8.9, 2.8 Hz, 1H, H-7), 6.50 (d, J = 2.8 Hz, 1H, H-5), 6.33 (d, J = 9.5 Hz, 1H, H-3), 4.91 (dd, J = 10.0, 7.5 Hz, 1H, N–H), 4.65 (d, J = 7.3 Hz, 1H, CH–N), 4.71 (d, J = 7.3 Hz, 1H, CH–N (rotamer)), 4.18–4.06 (q, J = 7.1, 2H, CH_2–O), 3.97 (cs, 1H, CH_2–O), 3.74 (cs, 1H, CH_2–O), 1.30 (t, J = 7.1 Hz, 3H, CH_3), 1.15 (t, J = 7.1 Hz, 3H, CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ (ppm) 162.2 (d, J = 251.5 Hz, C4′), 161.1 (C=O), 147.3 (C8a), 143.3 (C4), 143.1 (C6), 131.1 (d, J = 11.5 Hz, C1′), 129.4 (d, J = 10 Hz, C2′, C6′), 119.3 (C8), 118.9 (C7), 117.7 (C4a), 116.9 (C3), 115.7 (d, J = 21.5 Hz, C3′, C5′), 110.0 (C5), 63.4 (CH–N), 56.6 (CH_2–O), 55.1 (CH_2–O), 16.5 (CH_3), 16.3 (CH_3).

*4.2.3.3 Diethyl ((4-chlorophenyl)((2-oxo-2H-chromen-6-yl) amino)methyl)phosphonate (**1c**).* Yellow powder; yield: 86%; m.p.: 166–167 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.51 (d, J = 9.4 Hz, 1H, H-4), 7.43 (dd, J = 8.5, 2.3 Hz, 2H, H3′, H5′), 7.35 (d, J = 8.5 Hz, 2H, H2′, H6′), 7.15 (d, J = 8.9 Hz, 1H, H-8), 6.84 (dd, J = 8.9, 2.8 Hz, 1H, H-7), 6.51 (d, J = 2.8 Hz, 1H, H-5), 6.36 (d, J = 9.5 Hz, 1H, H-3), 4.91 (dd, J = 10.2, 7.3 Hz, 1H, N–H), 4.72 (d, J = 7.2 Hz, 1H, CH–N), 4.62 (d, J = 7.2 Hz, 1H, CH–N (rotamer)), 4.23–4.09 (q, J = 7.1 Hz, 2H, CH_2–O), 4.01 (sc, 1H, CH_2–O), 3.80 (cs, 1H, CH_2–O), 1.35–1.30 (m, 3H, CH_3), 1.19 (td, J = 7.1, 0.5 Hz, 3H, CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ (ppm) 161.0 (C=O), 147.4 (C8a), 143.1 (C4), 142.8 (C6), 134.1 (C1′), 133.8 (C4′), 129.1 (C3′, C5′), 129.0 (C2′, C6′), 119.3 (C4a), 118.8 (C8), 117.7 (C7), 117.0 (C3), 110.0 (C5), 63.5 (CH–N), 56.7 (CH_2–O), 55.2 (CH_2–O), 16.4 (CH_3), 16.2 (CH_3).

*4.2.3.4 Diethyl ((4-methoxyphenyl)((2-oxo-2H-chromen-6-yl) amino)methyl)phosphonate (**1d**).* Yellow powder; yield: 96%; m.p.: 152–153 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.49 (dd, J = 9.6, 1H, H-4), 7.39–7.34 (m, 2H, H2′, H6′), 7.10 (d, J = 9.0 Hz, 1H, H-8), 6.89–6.86 (m, 2H, H3′, H5′), 6.83 (dd, J = 8.9, 2.8 Hz, 1H, H-7), 6.52 (d, J = 2.8 Hz, 1H, H-5), 6.32 (d, J = 9.5 Hz, 1H, H-3), 4.89 (wide signal, 1H, N–H), 4.67 (cs, 1H, CH–N), 4.18–4.04 (q, J = 7.1 Hz, 2H, CH_2–O), 3.80 (cs, 1H, CH_2–O), 3.78 (s, 3H, O–CH_3), 3.68 (cs, 1H, CH_2–O), 1.29 (td, J = 7.1, 0.5 Hz, 3H, CH_3), 1.13 (td, J = 7.1, 0.6 Hz, 3H, CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ (ppm) 161.1 (C=O), 159.5 (C4′), 159.4 (C8a), 147.1 (C6), 143.4 (C4), 128.4 (C1′), 119.0 (C4a), 117.4 (C8), 116.7 (C3), 114.2 (C3′, C5′), 113.7 (C7), 110.0 (C5), 69.6 (CH–N), 63.4 (CH_2–O), 63.2 (CH_2–O), 55.2 (O–CH_3), 16.4 (CH_3), 16.2 (CH_3).

*4.2.3.5 Diethyl (((2-oxo-2H-chromen-6-yl)amino)(phenyl) methyl)phosphonate (**1e**).* Yellow powder; yield: 88%; m.p.: 143–144 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.48 (d, J = 9.6 Hz, 1H, H-4), 7.47–7.42 (m, 2H, H2′, H6′), 7.37–7.32 (m, 2H, H3′, H5′), 7.31–7.27 (m, 1H, H4′), 7.10 (d, J = 8.9 Hz, 1H, H-8), 6.84 (dd, J = 8.9, 2.8 Hz, 1H, H-7), 6.52 (d, J = 2.8 Hz, 1H, H-5), 6.31 (d, J = 9.6 Hz, 1H, H-3), 4.96 (dd, J = 10.0, 7.6 Hz, 1H, N–H), 4.73 (d, J = 7.5 Hz, 1H, CH–N), 4.70 (d, J = 7.5 Hz, 1H, CH–N (rotamer)), 4.20–4.02 (q, J = 7.1 Hz, 2H, CH_2–O), 3.93 (cs, 1H, CH_2–O), 3.66 (cs, 1H, CH_2–O), 1.29 (td, J = 7.0, 0.7 Hz, 3H, CH_3), 1.11 (td, J = 7.1, 0.7 Hz, 3H, CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ (ppm) 161.1 (C=O), 147.2 (C8a), 143.3 (C4), 143.2 (C6), 135.2 (C1′), 128.8 (C3′, C5′), 127.8 (C4′), 127.7 (C2′, C6′), 119.2 (C4a), 118.9 (C8), 117.5 (C7), 116.8 (C3), 110.0 (C5), 63.5 (CH_2–O), 63.3 (CH_2–O), 57.1 (CH–N), 16.4 (CH_3), 16.1 (CH_3).

*4.2.3.6 Diethyl ((3-hydroxyphenyl)((2-oxo-2H-chromen-6-yl) amino)methyl)phosphonate (**1f**).* Off-white powder; yield: 82%; m.p.: 171–172 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.46 (d, J = 9.5 Hz, 1H, H-4), 7.23 (t, J = 7.7 Hz, 1H, H-5′), 7.08 (s, large, 2H, H-2′, H-6′), 6.96 (d, J = 7.7 Hz, 1H, H-4′), 6.84–6.80 (m, 1H, H-8), 6.78 (d, J = 2.9 Hz, 1H, H-7), 6.50 (d, J = 2.8 Hz, 1H, H-5), 6.32 (d, J = 9.5 Hz, 1H, H-3), 4.90 (t, J = 8.9 Hz, 1H, N–H), 4.70 (d, J = 7.4 Hz, 1H, CH–N), 4.66 (d, J = 7.4 Hz, 1H, CH–N (rotamer)), 4.12 (q, J = 7.0 Hz, 2H, CH_2–O), 3.94 (cs, 1H, CH_2–O), 3.62 (cs, 1H, CH_2–O), 1.29 (t, J = 7.1 Hz, 3H, CH_3), 1.10 (t, J = 7.0 Hz, 3H, CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ (ppm) 161.2 (C=O), 157.1 (C3′), 147.3 (C8a), 143.3 (C4), 142.9 (C6), 136.6 (C1′), 130.0 (C5′), 120.0 (C6′), 119.9 (C8), 119.2 (C4a), 118.9 (C7), 117.6 (C3), 116.9 (C4′), 115.8 (C2′), 110.0 (C5), 63.9 (CH_2–O), 63.6 (CH_2–O), 57.1 (CH–N), 16.4 (CH_3), 16.1 (CH_3).

*4.2.3.7 Diethyl ((2-hydroxyphenyl)((2-oxo-2H-chromen-6-yl) amino)methyl)phosphonate (**1g**).* Orange powder; yield: 73%; m.p.: 180–181 °C. 1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.49 (d, J = 9.5 Hz, 1H, H-4), 7.23 (dt, J = 7.7, 2.0 Hz, 1H, H-5′), 7.20–7.14 (m, 1H, H-3′), 7.11 (dd, J = 9.0, 1.2 Hz, 1H, H-8), 6.95 (dd, J = 8.2, 3.5 Hz, 1H, H-5), 6.90–6.85 (m, 2H, H-4′, H-6′), 6.62 (d, J = 2.8 Hz, 1H, H-7), 6.32 (dd, J = 9.5, 0.8 Hz, 1H, H-3), 5.01 (d, J = 2.4 Hz, 1H, CH–N), 4.94 (d, J = 2.4 Hz, 1H, CH–N (rotamer)), 4.2 (q, J = 7.1, 2H, CH_2–O), 4.06 (cs, 1H, CH_2–O), 3.95 (cs, 1H, CH_2–O), 1.27 (t, J = 7.1 Hz, 3H, CH_3), 1.21 (t, J = 7.1 Hz, 3H, CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ (ppm) 161.2 (C=O), 155.5 (C2′), 147.6 (C8a), 143.3 (C4), 142.9 (C6), 129.8 (C6′), 128.8 (C4′), 121.2 (C1′), 120.9 (C5′), 119.3 (C4a), 118.6 (C8), 117.6 (C7), 116.8 (C3), 110.6 (C5), 64.2 (CH_2–O), 63.8 (CH_2–O), 54.5 (CH–N), 16.4 (CH_3), 16.2 (CH_3).

*4.2.3.8 Diethyl ((3-nitrophenyl)((2-oxo-2H-chromen-6-yl) amino)methyl)phosphonate (**1h**).* Orange powder; yield: 71%; m.p.: 70–71 °C. 1H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.39 (d, J = 2.3 Hz, 1H, H2′), 8.16 (d, J = 8.2 Hz, 1H, H4′), 7.81 (d, J = 8.2 Hz, 1H, H6′), 7.56 (t, J = 8.2 Hz, 1H, H5′), 7.50 (d, J = 9.5 Hz, 1H, H4), 7.13 (d, J = 9.0 Hz, 1H, H8), 6.83 (dd, J = 9.0, 2.8 Hz, 1H, H7), 6.49 (d, J = 2.8 Hz, 1H, H5), 5.12 (d, J = 7.1 Hz, 1H, N–H), 4.88 (d, J = 7.1 Hz, 1H, CH–N), 4.80 (d, J = 7.1 Hz, 1H, CH–N (rotamer)), 4.29 (s large, 2H, CH_2–O), 4.12–4.08 (m, 4H, CH_2–O), 3.85 (cs, 1H, CH_2–O (rotamer)), 1.31–1.25 (m, 6H, CH_3 ×2), 1.23 (t, J = 7.1 Hz, 3H, CH_3 (rotamer)).

*4.2.3.9 Diethyl (furan-2-yl((2-oxo-2H-chromen-6-yl)amino) methyl)phosphonate (**1i**).* Yellow powder; yield: 82%; m.p.: 112–113 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.55 (dd, J = 9.6, 0.6 Hz, 1H, H-4), 7.39 (td, J = 1.9, 0.8 Hz, 1H, H-5′), 7.14 (d, J = 9.0 Hz, 1H, H-8), 6.88 (dd, J = 9.0, 2.8 Hz, 1H, H-7), 6.64 (d, J = 2.7 Hz, 1H, H-5), 6.39 (tt, J = 3.2, 0.7 Hz, 1H, H-2′), 6.35–6.32 (m, 1H, H-4′), 4.87 (d, J = 8.0 Hz, 1H, CH–N), 4.83 (d, J = 8.0 Hz, 1H, CH–N (rotamer)), 4.68 (t, J = 8.0 Hz, 1H, N–H), 4.18 (q, J = 7.1 Hz, 2H, CH_2–O), 4.06 (cs, 1H, CH_2–O), 3.87 (cs, 1H, CH_2–O), 1.30 (td, J = 7.1, 0.6 Hz, 3H, CH_3), 1.20 (td, J = 7.1, 0.6 Hz, 3H, CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ (ppm) 161.1 (C=O), 148.7 (C8a), 147.6 (C6), 143.2 (C4), 142.9 (C5′), 142.8 (C2′), 119.3 (C4a), 117.6 (C8), 116.9 (C7), 111.0 (C3), 110.3 (C4′), 109.0 (C5), 63.6 (CH–N), 51.4 (CH_2–O), 49.8 (CH_2–O), 16.4 (CH_3), 16.2 (CH_3).

*4.2.3.10 Diethyl ((2-chloroquinolin-3-yl)((2-oxo-2H-chromen-6-yl)amino)methyl)phosphonate (**1j**).* Yellow powder; yield: 71%; m.p.: 128–129 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.37 (dd, J = 3.3, 0.7 Hz, 1H, H-4′), 8.01 (dd, J = 8.5, 1.0 Hz, 1H, H-8′), 7.80–7.76 (m, 1H, H-7′), 7.73 (dddd, J = 8.5, 6.9, 1.5, 0.8 Hz, 1H, H-5′), 7.54 (ddd, J = 8.2, 6.9, 1.2 Hz, 1H, H-6′), 7.50 (dd, J = 9.6, 0.6 Hz, 1H, H-4), 7.14 (d, J = 8.9 Hz, 1H, H-8), 6.89 (dd, J = 8.9, 2.8 Hz, 1H, H-7), 6.55 (d, J = 2.8 Hz, 1H, H-5), 6.33 (d, J = 9.6 Hz, 1H, H-3), 5.46 (d, J = 8.2 Hz, 1H, CH–N), 5.40 (d, J = 8.2 Hz, 1H, CH–N (rotamer)), 5.20 (dd, J = 10.0, 8.2 Hz, 1H, N–H), 4.30 (t, J = 7.1 Hz, 2H, CH_2), 3.96 (cs, 1H, CH_2–O), 3.75 (cs, 1H, CH_2–O), 1.38 (td, J = 7.1, 0.6 Hz, 3H, CH_3), 1.07 (td, J = 7.1, 0.6 Hz, 3H, CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ (ppm) 160.9 (C=O), 150.0 (C2′), 147.6 (C8a), 147.2 (C6), 143.1 (C4), 142.5 (C8′a), 137.5 (C4′), 131.1 (C3′), 128.3 (C7′), 128.2 (C5′), 127.8 (C8′), 127.5 (C6′), 127.2 (C4′a), 119.4 (C4a), 118.7 (C8), 117.9 (C7), 117.1 (C3), 109.5 (C5), 64.0 (CH_2–O), 63.7 (CH_2–O), 52.1 (CH–N), 16.5 (CH_3), 16.1 (CH_3). HMRS (ESI(+)): m/z calculated for $C_{23}H_{23}ClN_2O_5P$: 473.1033; $[M + H]^+$ found: 473.1255.

*4.2.3.11 Diethyl ((2-chloro-6-fluoroquinolin-3-yl)((2-oxo-2H-chromen-6-yl)amino)methyl)phosphonate (**1k**).* Yellow powder; yield: 75%; m.p.: 187–188 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.34 (d, J = 2 Hz, 1H, H-4′), 8.01 (dd, J = 9.2, 5.1 Hz, 1H, H-8′), 7.51 (d, J = 9.0 1H, H-4), 7.50–7.48 (m, 1H, H-5′),7.39 (dd, J = 8.6, 2.8 Hz, 1H, H-7′), 7.14 (d, J = 8.9 Hz, 1H, H-8), 6.87 (dd, J = 9.0, 2.8 Hz, 1H, H-7), 6.54 (d, J = 2.8 Hz, 1H, H-5), 6.33 (d, J = 9.5 Hz, 1H, H-3), 5.47 (d, J = 7.4 Hz, 1H, CH–N), 5.38 (d, J = 7.4 Hz, 1H CH–N (rotamer)), 5.23 (t, J = 9.1 Hz, 1H, N–H), 4.28 (t, J = 7.1, 2H, CH_2–O), 3.98 (cs, 1H, CH_2–O), 3.78 (cs, 1H, CH_2), 1.38 (td, J = 7.0, 0.6 Hz, 3H, CH_3), 1.08 (td, J = 7.0, 0.6 Hz, 3H, CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ (ppm) 161.0 (d, J = 250 Hz, C6′), 160.9 (C=O), 149.4 (d, J = 6 Hz, C2′) 147.6 (C8a), 143.1 (C4), 142.4 (C8′a), 136.9 (C6), 130.8 (d, J = 9 Hz, C3′), 130.7 (C4′a), 128.2 (d, J = 10 Hz, C8′), 122.2 (d, J = 25 Hz, C7′), 119.4 (C4a), 118.6 (C8), 117.9 (C7), 117.1 (C3), 111.1 (d, J = 27 Hz, C5′), 109.5 (C5), 63.8 (CH_2–O), 63.7 (CH_2–O), 52.9 (CH–N), 51.4 (CH–N (rotamer)), 16.5 (CH_3), 16.16 (CH_3).

*4.2.3.12 Diethyl ((6-bromo-2-chloroquinolin-3-yl)((2-oxo-2H-chromen-6-yl)amino)methyl)phosphonate (**1l**).* Off-white powder; yield: 88%; m.p.: 201–202 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.27 (dd, J = 3.3, 0.7 Hz, 1H, H-4′), 7.94 (d, J = 2.1 Hz, 1H, H-5′), 7.88 (d, J = 9.0 Hz, 1H, H-8′), 7.79 (ddd, J = 9.0, 2.2, 0.8 Hz, 1H, H-7′), 7.50 (dd, J = 9.6, 0.7 Hz, 1H, H-4), 7.14 (d, J = 8.9 Hz, 1H, H-8), 6.86 (dd, J = 8.9, 2.8 Hz, 1H, H-7), 6.52 (d, J = 2.8 Hz, 1H, H-5), 6.33 (d, J = 9.5 Hz, 1H, H-3), 5.45 (d, J = 8.1 Hz, 1H, CH–N), 5.39 (d, J = 8.1 Hz, 1H, CH–N (rotamer)), 5.20 (dd, J = 10.1, 8.1 Hz, 1H, N–H), 4.28 (t, J = 7.1, 1.0 Hz, 2H, CH_2–O), 3.98 (cs, 1H, CH_2–O), 3.78 (cs, 1H, CH_2–O), 1.38 (td, J = 7.1, 0.6 Hz, 3H, CH_3), 1.09 (td, J = 7.1, 0.6 Hz, 3H, CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ (ppm) 160.9 (C=O), 147.6 (C8a), 143.1 (C4), 136.3 (C6), 134.5 (C4′), 129.9 (C3′), 129.8 (C8′), 119.4 (C4a), 118.6 (C8), 118.0 (C7), 117.1 (C3), 109.5 (C5), 63.8 (CH–N), 53.0 (CH_2–O), 51.4 (CH_2–O), 16.5 (CH_3), 16.18 (CH_3).

4.2.4 General procedure for the synthesis of α-aminophosphonates benzodioxane derivatives 6a–m. To a solution of 2,3-dihydrobenzo[*b*][1,4]dioxin-6-amine (**5**) (1 mmol; 1 equiv.) in ethanol (5 mL), the appropriate aldehyde (1 mmol; 1 equiv.), triethyl phosphite (1 mmol; 1 equiv.), and tin(II) chloride ($SnCl_2$) (10 mol%) were added. The reaction mixture was stirred under reflux in ethanol for 24 hours. Once the reaction was deemed complete, ethanol was evaporated under reduced pressure. Then, 15 mL of water was added to the reaction mixture, and the product was extracted using ethyl acetate (20 mL × 3). The organic phase was dried over anhydrous sodium sulfate, filtered under reduced pressure, and the solvent was evaporated under reduced pressure. The crude reaction product was purified by silica gel column chromatography using an ethyl acetate/hexane (5 : 5) mixture.

*4.2.4.1 Diethyl (((2,3-dihydrobenzo[b][1,4]dioxin-6-yl)amino)(phenyl)methyl)phosphonate (**6a**).* White powder; yield: 96%; m.p.: 110–111 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.47–7.41 (m, 2H, H-2′, H-6′), 7.35–7.29 (m, 2H, H-3′, H-5′), 7.28–7.23 (m, 1H, H-4′), 6.62 (d, J = 8.5 Hz, 1H, H-8), 6.12 (d, J = 8.5 Hz, 1H, H-7), 6.10 (d, J = 2.0 Hz, 1H, H-5), 4.67 (s, 1H, CH–N (rotamer)) 4.61 (s, 1H, CH–N), 4.18–4.14 (m, 2H, O–CH_2), 4.14–4.11 (m, 2H–O–CH_2), 4.11–4.03 (m, 2H, CH_2), 3.92 (cs, 1H, CH_2), 3.67 (cs, 1H, CH_2), 1.28 (td, J = 7.1, 0.6 Hz, 3H, CH_3), 1.10 (td, J = 7.1, 0.6 Hz, 3H, CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ (ppm) 143.9 (C4a), 141.3 (C6), 136.3 (C1′), 136.0 (C8a), 128.6 (C3′, C5′), 127.9 (C2′, C6′), 127.8 (C4′), 117.6 (C7), 107.7 (C5), 102.74 (C8), 64.6 (CH_2–O (dioxane)), 64.1 (CH_2–O (dioxane)), 63.3 (CH_2–O), 63.2 (CH_2–O), 57.5 (CH–N), 56.0 (CH–N (rotamer)), 16.5 (CH_3), 16.2 (CH_3).

*4.2.4.2 Diethyl (((2,3-dihydrobenzo[b][1,4]dioxin-6-yl)amino)(p-tolyl)methyl)phosphonate (**6b**).* White powder; yield: 91%; m.p.: 102–103 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.31 (dd, J = 8.2, 2.3 Hz, 2H, H-2′, H-6′), 7.12 (dd, J = 8.2, 0.6 Hz, 2H, H-3′, H-5′), 6.61 (dd, J = 8.4, 0.6 Hz, 1H, H-8), 6.16–6.09 (m, 2H, H-5, H-7), 4.64 (s, 1H, CH–N), 4.61 (s, 1H, CH–N (rotamer)), 4.50 (s, large, 1H, N–H), 4.18–4.14 (m, 2H, O–CH_2), 4.12 (td, J = 2.5, 1.3 Hz, 2H, O–CH_2), 4.11–4.04 (m, 2H, CH_2), 3.93 (cs, 1H, CH_2), 3.69 (cs, 1H, CH_2), 2.30 (s, 3H, CH_3), 1.28 (td, J = 7.1, 0.5 Hz, 3H, CH_3), 1.12 (td, J = 7.0, 0.6 Hz, 3H, CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ (ppm) 143.9 (C4a), 141.3 (C6), 137.6 (C4′), 136.3 (C8a), 132.9 (C1′), 129.3 (C3′, C5′), 127.8 (C2′, C6′), 117.6 (C8), 107.7 (C7), 102.8 (C5), 64.6 (CH_2–O (dioxane)), 64.1 (CH_2–O (dioxane)), 63.3 (CH_2–O), 63.1 (CH_2–O), 57.2 (CH–N (rotamer)), 55.7 (CH–N (rotamer)), 21.2 (CH_3–Ar), 16.4 (CH_3), 16.21 (CH_3).

*4.2.4.3 Diethyl (((2,3-dihydrobenzo[b][1,4]dioxin-6-yl)amino)(4-methoxyphenyl)methyl)phosphonate (**6c**).* White powder; yield: 96%; m.p.: 99–100 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.37 (d, J = 7 Hz, 2H, H-3′, H-5′), 6.86 (d, J = 7 Hz, 2H, H-2′, H-6′), 6.62 (d, J = 8.5 Hz, 1H, H-8), 6.12 (dd, J = 8.5, 2 Hz, 1H, H-7) 6.10 (d, J = 2 Hz, 1H, H-5), 4.62 (s, 1H, CH–N), 4.56 (s, 1H, CH–N (rotamer)), 4.48 (s, 1H, N–H), 4.18–4.14 (m, 2H, O–CH_2), 4.14–4.11 (m, 2H, O–CH_2), 4.11–4.04 (m, 2H, CH_2), 3.93 (cs, 1H, CH_2), 3.77 (s, 3H, O–CH_3), 3.69 (cs, 1H, CH_2), 1.28 (td, J = 7.1, 0.6 Hz, 3H, CH_3), 1.13 (td, J = 7.1, 0.6 Hz, 3H, CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ (ppm) 159.3 (C4′), 143.9 (C4a), 141.3 (C6), 136.3 (C8a), 128.9 (C2′, C6′), 127.8 (C1′), 117.6 (C3′, C5′), 114.1 (C8), 107.8 (C7), 102.8 (C5), 64.6 (CH_2–O (dioxane)), 63.3 (CH_2–O (dioxane)), 63.2 (CH–N), 63.1 (CH–N (rotamer)),

56.8 (CH_2–O), 55.3 (CH_2–O), 55.2 (O–CH_3), 16.5 (CH_3), 16.31 (CH_3).

*4.2.4.4 Diethyl (((2,3-dihydrobenzo[b][1,4]dioxin-6-yl) amino)(4-fluorophenyl)methyl)phosphonate (**6d**).* White powder; yield: 88%; m.p.: 120–121 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.42 (ddd, J = 8.9, 5.2, 2.4 Hz, 2H, H-3′, H-5′), 7.06–6.98 (m, 2H, H-2′, H-6′), 6.63 (d, J = 8.6 Hz, 1H, H-8), 6.12 (dd, J = 8.6, 2.8 Hz, 1H, H-7), 6.08 (d, J = 2.7 Hz, 1H, H-5), 4.65 (s, 1H, CH–N), 4.59 (s, 1H, CH–N (rotamer)), 4.17 (dq, J = 5.8, 1.8 Hz, 2H, O–CH_2), 4.15–4.12 (m, 2H, O–CH_2), 4.12–4.03 (m, 2H, CH_2), 3.96 (cs, 1H, CH_2), 3.75 (cs, 1H, CH_2), 1.28 (td, J = 7.1, 0.6 Hz, 3H, CH_3), 1.14 (td, J = 7.1, 0.6 Hz, 3H, CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ (ppm) 162.1 (d, J = 246 Hz, C4′), 143.9 (C4a), 141.0 (d, J = 15 Hz, C1′), 136.4 (C6), 137.7 (C8a), 129.4 (d, J = 8 Hz, C2′, C6′), 117.6 (C8), 115.5 (d, J = 21 Hz, C3′, C5′), 107.7 (C7), 102.7 (C5), 64.1 (CH_2–O (dioxane)), 63.4 (CH_2–O (dioxane)), 63.2 (CH–N), 63.1 (CH–N (rotamer)), 56.8 (O–CH_2), 55.3 (O–CH_2), 16.5 (CH_3), 16.3 (CH_3).

*4.2.4.5 Diethyl (((2,3-dihydrobenzo[b][1,4]dioxin-6-yl) amino)(3-hydroxyphenyl)methyl)phosphonate (**6e**).* Brown powder; yield: 92%; m.p.: 131–132 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.93 (s, 1H, OH), 7.18 (td, J = 7.9, 1.0 Hz, 1H, H-5′), 7.12 (q, J = 2.2 Hz, 1H, H-2′), 6.90 (ddt, J = 7.7, 2.6, 1.2 Hz, 1H, H-4′), 6.78 (dtd, J = 8.2, 2.3, 1.0 Hz, 1H, H-6′), 6.63–6.56 (m, 1H, H-8), 6.12 (d, J = 1.1 Hz, 1H, H-5), 6.11–6.09 (m, 1H, H-7), 4.60 (d, J = 6.4 Hz, 1H, CH–N), 4.58 (d, J = 6.4 Hz, CH–N (rotamer)) 4.51 (d, J = 8.9 Hz, 1H, N–H), 4.18–4.14 (m, 2H, O–CH_2), 4.13 (td, J = 3.0, 1.5 Hz, 2H, O–CH_2), 4.11–4.03 (m, 2H, CH_2), 3.92 (cs, 1H, CH_2), 3.63 (cs, 1H, CH_2), 1.28 (t, J = 7.1 Hz, 3H, CH_3), 1.08 (td, J = 7.1, 0.7 Hz, 3H, CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ (ppm) 157.5 (C3′), 143.9 (C4a), 141.2 (C6), 137.0 (C1′), 136.3 (C8a), 129.7 (C5′), 119.8 (C6′), 117.5 (C8), 115.7 (C4′), 114.4 (C2′), 108.4 (C8), 102.8 (C5), 63.9 (CH_2–O (dioxane)), 63.8 (CH_2–O (dioxane)), 63.7 (CH–N), 57.4 (CH_2–O), 55.9 (CH_2–O), 16.4 (CH_3), 16.2 (CH_3).

*4.2.4.6 Diethyl (((2,3-dihydrobenzo[b][1,4]dioxin-6-yl) amino)(2-hydroxyphenyl)methyl)phosphonate (**6f**).* Brown powder; yield: 82%; m.p.: 148–149 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.19 (dt, J = 5.7, 1.8 Hz, 1H, H-6′), 7.18–7.13 (m, 1H, H-4′), 6.90 (d, J = 9.2, 1H, H-3′), 6.86 (tt, J = 7.5, 1.1 Hz, 1H, H-5′), 6.64 (d, J = 8.6 Hz, 1H, H-8), 6.24 (d, J = 2 Hz, 1H, H-5), 6.22 (d, J = 8.6 Hz, 1H, H-7) 4.80 (s, 1H, CH–N), 4.77 (s, 1H, CH–N (rotamer)), 4.18–4.15 (m, 2H, O–CH_2), 4.15–4.12 (m, 2H, O–CH_2), 4.12–4.06 (m, 2H, CH_2), 4.05–3.91 (m, 2H, CH_2), 1.26 (td, J = 7.1, 0.6 Hz, 3H, CH_3), 1.22 (td, J = 7.1, 0.6 Hz, 3H, CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ (ppm) 156.0 (C2′), 143.9 (C4a), 140.9 (C6), 137.3 (C8a), 129.5 (C6′), 129.1 (C4′), 121.0 (C1′), 120.5 (C5′), 118.2 (C3′), 117.6 (C8), 108.7 (C7), 104.0 (C5), 64.6 (CH_2–O (dioxane)), 64.1 (CH_2–O (dioxane)), 63.7 (CH_2–O), 63.6 (CH_2–O), 56.3 (CH–N), 54.83 (CH–N (rotamer)), 16.4 (CH_3), 16.3 (CH_3).

*4.2.4.7 Diethyl ((4-chlorophenyl)((2,3-dihydrobenzo[b][1,4] dioxin-6-yl)amino)methyl)phosphonate (**6g**).* White powder; yield: 91%; m.p.: 106–107 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.38 (dq, J = 9.0, 2.5 Hz, 2H, H-3′, H-5′), 7.33–7.27 (m, 2H, H-2′, H-6′), 6.63 (d, J = 8.6 Hz, 1H, H-8), 6.11 (dd, J = 8.6, 2.8 Hz, 1H, H-7), 6.06 (d, J = 2.7 Hz, 1H, H-5), 4.64 (s, 1H, CH–N), 4.58 (s, 1H, CH–N (rotamer)), 4.19–4.15 (m, 2H, O–CH_2), 4.13 (td, J = 3.3, 2.0 Hz, 2H, O–CH_2), 4.12–4.05 (m, 2H, O–CH_2), 3.97 (cs, 1H, CH_2), 3.77 (cs, 1H, CH_2), 1.29 (td, J = 7.1, 0.6 Hz, 3H, CH_3), 1.15 (td, J = 7.1, 0.6 Hz, 3H, CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ (ppm) 143.9 (C4a), 140.9 (C6), 136.5 (C8a), 134.7 (C1′), 133.7 (C4′), 129.2 (C3′, C5′), 128.8 (C2′, C6′), 117.7 (C8), 107.7 (C7), 102.7 (C5), 64.7 (CH_2–O (dioxane)), 64.1 (CH_2–O (dioxane)), 63.4 (CH_2–O), 63.3 (CH_2–O), 57.0 (CH–N), 55.5 (CH–N (rotamer)), 16.5 (CH_3), 16.3 (CH_3).

*4.2.4.8 Diethyl (((2,3-dihydrobenzo[b][1,4]dioxin-6-yl) amino)(4-(dimethylamino)phenyl)methyl)phosphonate (**6h**).* Orange powder; yield: 84%; m.p.: 150–151 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.25 (dd, J = 7 Hz, 2H, H-2′, H-6′), 6.66 (d, J = 7 Hz, 2H, H-3′, H-5′), 6.61 (dt, J = 8.7, 1.2 Hz, 1H, H-8), 6.13 (d, J = 8.6 Hz, 1H, H-7), 6.11 (d, J = 1.2 Hz, 1H, H-5), 4.55 (s, 1H, CH–N), 4.49 (s, 1H, CH–N (rotamer)), 4.18–4.14 (m, 2H, O–CH_2), 4.12 (td, J = 3.3, 1.9 Hz, 2H, O–CH_2), 4.11–4.07 (m, 2H, CH_2), 3.92 (cs, 1H, CH_2), 3.67 (sc, 1H, CH_2), 2.95 (s, 1H, N–H), 2.91 (s, 6H, 2× N–CH_3), 1.30–1.26 (m, 3H, CH_3), 1.13 (td, J = 7.1, 0.6 Hz, 3H, CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ (ppm) 150.1 (C4′), 143.8 (C4a), 141.5 (C6), 136.1 (C8a), 128.5 (C2′, C6′), 123.0 (C1′), 117.4 (C8), 112.5 (C3′, C5′), 107.7 (C7), 102.7 (C5), 64.6 (CH_2–O (dioxane)), 63.1 (CH_2–O (dioxane)), 63.0 (CH_2–O), 56.7 (CH_2–O), 40.5 (CH–N), 40.4 (CH–N (rotamer)), 16.4 (CH_3), 16.27 (CH_3).

*4.2.4.9 Diethyl (((2,3-dihydrobenzo[b][1,4]dioxin-6-yl) amino)(3-nitrophenyl)methyl)phosphonate (**6i**).* Red powder; yield: 45%; m.p.: 104–105 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.30 (q, J = 2.2 Hz, 1H, H-2′), 8.12 (dtd, J = 8.2, 2.1, 1.0 Hz, 1H, H-4′), 7.83–7.77 (m, 1H, H-6′), 7.50 (td, J = 8.0, 0.8 Hz, 1H, H-5′), 6.62 (d, J = 8.6 Hz, 1H, H-8), 6.11 (dd, J = 8.7, 2.8 Hz, 1H, H-7), 6.05 (d, J = 2.7 Hz, 1H, H-5), 4.77 (s, 1H, CH–N), 4.71 (s, 1H, CH–N (rotamer)), 4.62 (s, large, 1H, N–H), 4.25–4.16 (m, 2H, O–CH_2), 4.16–4.14 (m, 2H, O–CH_2), 4.13–4.11 (m, 2H, CH_2), 4.11–4.06 (m, 2H, CH_2), 4.02 (sc, 1H, CH_2), 3.88 (cs, 1H, CH_2), 1.31–1.28 (m, 3H, CH_3), 1.17 (td, J = 7.1, 0.6 Hz, 3H, CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ (ppm) 148.4 (C3′), 143.9 (C4a), 140.4 (C6), 139.0 (C1′), 138.8 (C1′ (rotamer)), 136.6 (C6′), 133.7 (C8a), 129.4 (C5′), 122.8 (C2′), 122.7 (C4′), 117.7 (C8), 107.5 (C7), 102.6 (C5), 64.5 (CH_2–O (dioxane)), 64.1 (CH_2–O (dioxane)), 64.0 (CH_2–O), 63.2 (CH_2–O), 56.9 (CH–N), 55.5 (CH–N (rotamer)), 16.3 (CH_3), 16.2 (CH_3).

*4.2.4.10 Diethyl α-hydroxy-3-nitrobenzyl phosphonate (**6i′**).* Orange powder; yield: 32%; m.p.: 97–98 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.40 (d, J = 1.8 Hz, 1H, H-2), 8.17 (dtd, J = 8.2, 2.1, 1.0 Hz, 1H, H-4), 7.82 (dddt, J = 7.7, 2.4, 1.8, 0.9 Hz, 1H, H-6), 7.54 (td, J = 8.0, 0.9 Hz, 1H, H-5), 5.16 (d, J = 4.9 Hz, 1H, CH–N), 5.13 (d, J = 4.9 Hz, 1H, CH–N (rotamer)), 4.77–4.71 (m, 1H, N–H), 4.20–4.04 (m, 4H, O–CH_2), 1.33–1.28 (m, 3H, CH_3), 1.28–1.24 (m, 3H, CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ (ppm) 148.2 (C3), 139.1 (C1), 133.0 (C6), 129.1 (C5), 122.9 (C2), 122.0 (C4), 70.7 (CH_2–O), 69.1 (CH_2–O), 64.0 (CH_2–O), 63.4 (CH_2–O), 16.4 (CH_3), 16.3 (CH_3).

*4.2.4.11 Diethyl (((2,3-dihydrobenzo[b][1,4]dioxin-6-yl) amino)(furan-2-yl)methyl)phosphonate (**6j**).* Off-white powder; yield: 96%; m.p.: 132–133 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.38 (td, J = 1.9, 0.9 Hz, 1H, H-5′), 6.69–6.63 (m, 1H, H-8), 6.36 (tt, J = 3.3, 0.8 Hz, 1H, H-2′), 6.34–6.30 (m, 1H, H-4′), 6.21 (d, J = 9 Hz, 1H, H-7), 6.18 (d, J = 2 Hz, 1H, H-5), 4.76 (d, J =

7.5 Hz, 1H, CH–N), 4.72 (d, J = 7.5 Hz, 1H, CH–N (rotamer)), 4.23–4.19 (m, 2H, O–CH_2), 4.19–4.16 (m, 2H, O–CH_2), 4.16–4.13 (m, 2H, CH_2), 4.05 (cs, 1H, CH_2), 3.87 (cs, 1H, CH_2), 1.31 (td, J = 7.1, 0.6 Hz, 3H, CH_3), 1.20 (td, J = 7.1, 0.6 Hz, 3H, CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ (ppm), 143.2 (C4a), 142.5 (C5′), 140.9 (C6), 140.8 (C2′), 136.7 (C8a), 117.6 (C8), 110.8 (C3′), 108.8 (C4′), 107.9 (C7), 103.1 (C5), 64.6 (CH_2–O (dioxane)), 63.6 (CH_2–O (dioxane)), 63.5 (CH_2–O), 63.2 (CH_2–O), 51.9 (CH–N), 50.3 (CH–N (rotamer)), 16.5 (CH_3), 16.3 (CH_3).

4.2.4.12 Diethyl ((2-chloroquinolin-3-yl)((2,3-dihydrobenzo[b][1,4]dioxin-6-yl)amino)methyl)phosphonate ***(6k)***. Yellow powder; yield: 82%; m.p.: 165–166 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.35 (dd, J = 3.4, 0.7 Hz, 1H, H-6′), 8.00 (dd, J = 8.5, 1.0 Hz, 1H, H-2′), 7.82–7.76 (m, 1H, H-3′), 7.71 (dddd, J = 8.5, 6.9, 1.5, 0.8 Hz, 1H, H-5′), 7.53 (ddd, J = 8.2, 6.9, 1.2 Hz, 1H, H-4′), 6.66–6.59 (m, 1H, H-8), 6.18–6.14 (m, 2H, H-5, H-7), 5.36 (d, J = 8.5 Hz, 1H, CH–N), 5.33 (d, J = 8.5 Hz, 1H, CH–N (rotamer)), 4.82 (dd, J = 9.9, 8.6 Hz, 1H, N–H), 4.26 (dq, J = 8.1, 7.1 Hz, 2H, O–CH_2), 4.18–4.12 (m, 2H, O–CH_2), 4.11–4.04 (m, 2H, CH_2), 3.99–3.87 (sc, 1H, CH_2), 3.74 (sc, 1H, CH_2), 1.36 (td, J = 7.1, 0.6 Hz, 3H, CH_3), 1.06 (td, J = 7.1, 0.6 Hz, 3H, CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ (ppm) 150.3 (C2′), 147.1 (C4a), 144.1 (C8′a), 140.1 (C6), 139.9 (C6 (rotamer)), 137.6 (C8a), 136.7 (C4′), 130.7 (C3′), 129.1 (C7′), 128.2 (C5′), 127.9 (C8′), 127.3 (C4′a), 127.2 (C6′), 117.8 (C8), 107.2 (C7), 102.6 (C5), 64.6 (CH_2–O (dioxane)), 64.1 (CH_2–O (dioxane)), 63.9 (CH_2–O), 63.4 (CH_2–O), 53.2 8 (CH–N), 51.7 (CH–N (rotamer)), 16.5 (CH_3), 16.1 (CH_3). HMRS (ESI(+)): m/z calculated for $C_{22}H_{25}ClN_2O_5P$: 463.1190; $[M + H]^+$ found: 463.1205.

4.2.4.13 Diethyl ((2-chloro-6-fluoroquinolin-3-yl)((2,3-dihydrobenzo[b][1,4]dioxin-6-yl)amino)methyl)phosphonate ***(6l)***. Orange powder; yield: 71%; m.p.: 161–162 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.29 (d, J = 3.3 Hz, 1H, H-4′), 8.00 (dd, J = 9.2, 5.2 Hz, 1H, H-8′), 7.71 (dd, J = 5.7, 3.3 Hz, 1H, H-5′), 7.53 (dd, J = 5.7, 3.3 Hz, 1H, H-7′), 6.66–6.60 (m, 1H, H-8), 6.17–6.13 (m, 1H, H-7), 6.13 (d, J = 1.0 Hz, 1H, H-5), 5.37 (d, J = 7.9 Hz, 1H, CH–N), 5.32 (d, J = 7.9 Hz, 1H, CH–N (rotamer)), 4.80 (t, J = 9.3 Hz, 1H, N–H), 4.31–4.24 (m, 2H, O–CH_2), 4.24–4.19 (m, 2H, O–CH_2), 4.18–4.13 (m, 2H, CH_2), 3.96 (sc, 1H, CH_2), 3.77 (sc, 1H, CH_2), 1.36 (td, J = 7.1, 0.6 Hz, 3H, CH_3), 1.07 (td, J = 7.1, 0.6 Hz, 3H, CH_3).

4.2.4.14 Diethyl ((6-bromo-2-chloroquinolin-3-yl)((2,3-dihydrobenzo[b][1,4]dioxin-6-yl)amino)methyl)phosphonate ***(6m)***. Yellow powder; yield: 82%; m.p.: 213–214 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.25 (d, J = 3.4 Hz, 1H, H-5′), 7.94 (d, J = 2.1 Hz, 1H, H-4′), 7.86 (d, J = 9.0 Hz, 1H, H-8′), 7.76 (ddd, J = 9.0, 2.2, 0.8 Hz, 1H, H-7′), 6.63 (dt, J = 9.0, 1.3 Hz, 1H, H-8), 6.15 (d, J = 9 Hz, 1H, H-7), 6.12 (d, J = 2 Hz, 1H, H-5) 5.38 (d, J = 8.3 Hz, 1H, CH–N), 5.32 (d, J = 8.3 Hz, 1H, CH–N (rotamer)), 4.81 (t, J = 9.2 Hz, 1H, N–H), 4.26 (dq, J = 8.1, 7.1 Hz, 2H, O–CH_2), 4.18–4.15 (m, 2H, O–CH_2), 4.12–4.06 (m, 2H, CH_2), 3.96 (cs, 1H, CH_2), 3.77 (cs, 1H, CH_2), 1.36 (td, J = 7.0, 0.6 Hz, 3H, CH_3), 1.08 (td, J = 7.1, 0.6 Hz, 3H, CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ (ppm) 150.8 (C2′), 150.7 (C8′a), 145.6 (C4a), 139.9 (C6), 136.8 (C4′), 136.5 (C8a), 134.2 (C7′), 130.4 (C3′), 129.9 (C8′), 128.4 (C4′a), 121.2 (C6′), 117.9 (C8), 107.2 (C7), 102.6 (C5), 64.6 (CH_2–O (dioxane)), 64.0 (CH_2–O (dioxane)), 63.5 (CH_2–O), 63.5 (CH_2–O), 53.3 (CH–N (rotamer)), 51.8 (CH–N (rotamer)), 16.5 (CH_3), 16.2 (CH_3).

Conflicts of interest

The authors declare no conflict of interest.

Note added after first publication

This article replaces the version published on 28 November 2025, which was showing as a Review instead of a Paper. The text of the article remains unchanged.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information is available. See DOI: https://doi.org/10.1039/d5ra06186e.

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