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ORIGINAL ARTICLE

Synthesis and antitumor activity of novel indole derivatives containing α-aminophosphonate moieties

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Abstract A series of novel indole derivatives containing α-aminophosphonate moieties were synthesized as antitumor agents. The in vitro cytotoxic activity of the compounds was evaluated against human hepatoma cells (HepG2) and human gastric cancer cells (MGC-803) by MTT assay, revealing that most of target compounds exhibited moderate to high antitumor activities. Among them, compound **C5** (IC_{50} = 34.2 μM) demonstrated superior inhibitory activities against HepG2 compared with 5-fluorouracil (IC_{50} = 78.7 μM). It is noteworthy that compound **B7** (IC_{50} = 35.7 μM) displayed higher inhibitory activities against MGC-803 than that of 5-fluorouracil (IC_{50} = 82.0 μM).

1. Introduction

Cancer has been considered as one of the most important public health problems for a long time (Fidler et al., 2018), accounting for nearly 10 million deaths worldwide in 2020 (Ferlay et al., 2020). Despite many efforts to fight against cancer, the successful treatment of certain tumor types continues to be a challenge owing to their aggressiveness, the complex mechanisms of malignant cell metastasis, chemoresistance and the lack of selectivity for some drugs (Colombano et al., 2010). As the continuous progress of therapies, such as hyperthermia, photodynamic therapy and immunotherapy, chemotherapy is still the most commonly used method to cure cancer and prolong the life of patients (Priestman, 2012). Therefore, the development of novel anticancer agents with low toxicity, low cost and high efficiency is the key way to solve this problem.

Heterocyclic compounds are key structural motifs prevalent in numerous agrochemicals, natural products and pharmaceuticals. As privileged *N*-heterocyclic compounds, the indole derivatives exhibit unique physic-chemical and biological properties as well as important biological and pharmaceutical activities. They have been widely existed in many natural products and bioactive molecules, such as the antibacterial (Osawa and Namiki, 1983; Ryu et al., 2007), the anti-inflammatory (Jiang et al., 2013) and the anti-virus (Chen et al., 2000; Lu

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et al., 2007; Yeung et al., 2013). It is worth noting that the indole derivatives have been used as a core scaffold in the anti-cancer agents design (de Sá Alves et al., 2009; Dadashpour and Emami, 2018; Friberg et al., 2013; Garg et al., 2019; Panathur et al., 2013; Rathi et al., 2017; Wan et al., 2019). As phosphorus analogs of a-amino acids and their esters, α-aminophosphonates present unique biological activities (Kukhar and Hudson, 2000; Naydenova et al., 2010; Orsini et al., 2010) and can act as enzyme inhibitors (Sieńczyk and Oleksyszyn, 2009), anti-inflammatory (Sujatha et al., 2017), antimicrobials (Abdel-Megeed et al., 2012; Abdel-Rahman and Ali, 2013, Sujatha et al., 2017), antivirals (Xu et al., 2006; Zhang et al., 2010), anti-HIV (Bhattacharya et al., 2012), antitubercular agents (Li et al., 2017), anticancer (Bhattacharya et al., 2013; Guo et al., 2015; Ma et al., 2013; Rezaei et al., 2009; Zhu et al., 2017) antioxidants (Devineni et al., 2013) and antitumor (Gu and Cheng, 2012). The introduction of aminophosphonate group to a pharmacophore can further enhance the anticancer activity against human tumors (Chinthaparthi et al., 2013; Huang et al., 2013; Reddy et al., 2012).

Since both indole derivatives and α-aminophosphonates showed unique biological and pharmaceutical activities, structural modifications of the indole derivatives by introducing α-aminophosphonates groups to improve the pharmacological potency have been recognized as a cutting-edge strategy. Recently, we found that α-aminophosphonate groups could enhance the antitumor activity of heterocyclic compounds (Ma et al., 2013; Guo et al., 2015; Zhu et al., 2017). As a continuation of our previous research, we presently designed and synthesized indole derivatives containing α-aminophosphonate moieties to establish a new strategy for human hepatoma and human gastric cancer therapy (Scheme 1).

Based on the concept of bioisosterism and assorted mechanisms, we proposed to graft α-aminophosphonate moieties onto indole nucleus. Herein, we synthesize 22 novel indole derivatives containing α-aminophosphonate moieties and the structures of these compounds (**A1-A8, B1-B8 and C1-C6**) were characterized by ^{1}H NMR, ^{13}C NMR, ^{31}P NMR, IR, MS and HRMS. Moreover, the absolute configurations of **A2**, **B1** and **C3** were further confirmed by X-ray single crystal diffraction test. These target compounds were tested for their antiproliferation activity against HepG2 and MGC-803 at different concentrations. Our work represents the first report about the synthesis and in vitro antitumor activity evaluation of indole derivatives containing α-aminophosphonate moieties.

2. Results and discussion

2.1. Chemistry

The synthetic routes of the target compounds are depicted in Scheme 1. In this experiment, compound **1** was synthesized by the Fischer indole synthesis with *p*-methylphenylhydrazine and ethyl pyruvate as raw materials. Compound **2** underwent nucleophilic methylation, reduction and oxidation, producing compound **4** (Li et al., 2015; Li et al., 2017). Finally, indole formaldehyde, aromatic amine and phosphite via the "one-pot cooking" reaction in toluene under reflux conditions gave the target compounds. All the new compounds were characterized using ^{1}H NMR and ^{13}C NMR, mass spectrometry and high resolution mass spectrometry.

In anhydrous THF, 1,5-dimethyl-1H-indole 1,5-dimethyl-1H-indole-2-carboxylic acid ethyl ester **2** originating from 5-methyl-*1H*-indole-2-carboxylic acid ethyl ester **1** was obtained in a high yield. Otherwise, the ester group was hydrolyzed to carboxylic acid. When reducing the ester group in compound **2** to alcohol **3**, the combination of $CaCl_2$ and $NaBH_4$ in batches under stirring at room temperature was used. For a period of time, the reaction temperature is increased to 50 °C, the reaction proceeds smoothly. The one-pot three-component Mannich reaction was used for the direct synthesis of the target compounds, which not only greatly improved the conversion rate of raw materials, but also accelerated the reaction speed and simplified the reaction steps.

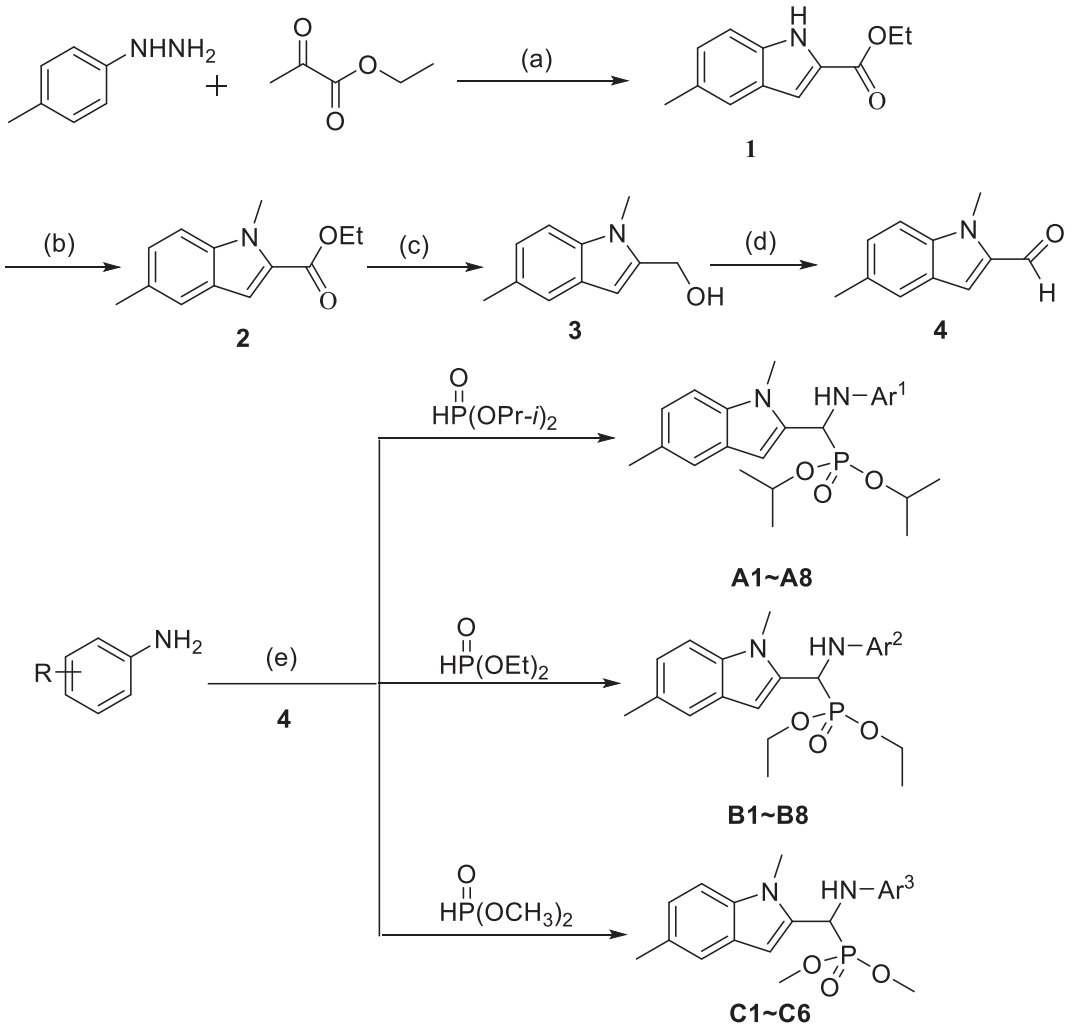
Fortunately, single crystals of compound **A2**, **B1** and **C3** were successfully obtained. High quality and colorless single crystal of the compound **A2** (0.25 mm × 0.2 mm × 0.2 mm) was carefully selected for single crystal X-ray diffraction test. The data were recorded at room temperature on an Agilent xcalibur Eos-II-CCD-diffractometer equipped with a graphite-monochromatic Cu Kα radiation (λ = 1.54184 Å). The entire structure was solved by the direct methods using the SHELXS-97 program and refined by the full-matrix least-squares method on **F2** with anisotropic thermal parameters for all non-hydrogen atoms using SHELXL-97. The hydrogen atoms on organic ligands were generated by the riding mode.

For compound **A2**, 8723 reflections were collected and 4279 were independent reflections (R_{int} = 0.0190, R_{sigma} = 0.0275), among which 4279 ($-11 \le h \le 12$, $-12 \le k \le 9$, $-13 \le l \le 15$) were observed. X-ray diffraction analysis revealed that the molecular structure of **A2** crystallizes in triclinic space group *P*-1 and is illustrated in Figs. 1 and 2. It is found that the structure is stabilized by intermolecular hydrogen bonding interaction (N2-H2···O3 = 2.234(15) Å). CCDC2064712, 2064713 and 2064714 contain the supplementary crystallographic data of compound **A2**, **B1** and **C3**, respectively. They can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

2.2. Biological activity evaluation against HepG2 and MGC-803

In this paper, 5-fluorouracil was used as a positive control drug to study the growth inhibitory activity of target compounds on HepG2 and MGC-803 by MTT assay. The growth inhibitory activity of the target product on HepG2 and MGC-803 was determined by using 100 μg/mL as the primary screening concentration. The corresponding inhibition rate was calculated according to the related formula, as shown in Table 1.

With different substituents on the phenyl ring of aromatic amine, compounds **A1-A8, B1-B8,** and **C1-C6** showed various degrees of inhibitory activity against HepG2 and MGC-803 cells. The target compounds had different degrees of inhibition on HepG2 at a concentration of 100 μg/mL, among which compounds **A2**, **A7**, **B2**, **B7**, **C2** and **C4**-**C6** inhibited the proliferation of HepG2 by more than 75%, and the anticancer activities range from moderate to excellent. The best activity was from compound **C5** with inhibition rate of 84.7%. Compared to the antitumor activity of all the target compounds,



Ar^1 = Ph(**1**), 2-CH_3-Ph(**2**), 3-CH_3-Ph(**3**), 4-CH_3-Ph(**4**), 3-Cl-Ph(**5**), 4-Cl-Ph(**6**), methyl thiophene-3-carboxylate(**7**), 4-OCH_3-Ph(**8**)

Ar^2 = Ph(**1**), 2-CH_3-Ph(**2**), 3-CH_3-Ph(**3**), 4-CH_3-Ph(**4**), 2-Cl-Ph(**5**), 4-Cl-Ph(**6**), methyl thiophene-3-carboxylate(**7**), 4-OCH_3-Ph(**8**)

Ar^3 = Ph(**1**), 2-CH_3-Ph(**2**), 3-CH_3-Ph(**3**), 4-CH_3-Ph(**4**), 4-Cl-Ph(**5**), 4-OCH_3-Ph(**6**)

Scheme 1 Synthetic route of target compounds. [a]Reagents and conditions: (a) CH_3SO_3H, EtOH, 80 °C; CH_3SO_3H, CH_3COOH, 115 °C, 85% for two steps; (b and c) CH_3I, NaH, anhydrous THF, 0 °C to r.t.; $NaBH_4$, $CaCl_2$, anhydrous EtOH, r.t. to 50 °C, 79% for two steps; (d) MnO_2,CH_2Cl_2, r.t., 61%; (e) anhydrous $PhCH_3$, reflux, 45–88%.

it can be found that the introduction of substituents to the benzene ring was beneficial for increasing the antitumor activities. The different substituents R on the compounds **A2**, **B2** and **C2** had no obvious influence on the antitumor activity. When electron-withdrawing group chlorine was at the *para* position of the benzene ring, compounds **A6** and **C5** showed good activity. It was of interest that the introduction of a methyl group to the benzene ring of Ar in compounds **A2-A4** and **B2-B4** was important for improving antitumor activities with the order of *ortho-* > *meta-* > *para-*.

The results also revealed that at a concentration of 100 μg/mL, compounds **A2-A5, A8, B1, B3, B5, B8** and **C1** showed a negative inhibitory effect and promoted the proliferation of MGC-803 cells, which indicates that these compounds may activate the MGC-803 cells. Other target compounds exhibited different degrees of inhibition on MGC-803. Among them, compounds **A6**, **A7**, **B7** and **C6** inhibited the proliferation of MGC-803 by more than 75%, and the best inhibition rate 89.3% was from compound **B7**. The antitumor data indicated that the substitutes of phosphonate have apparently no

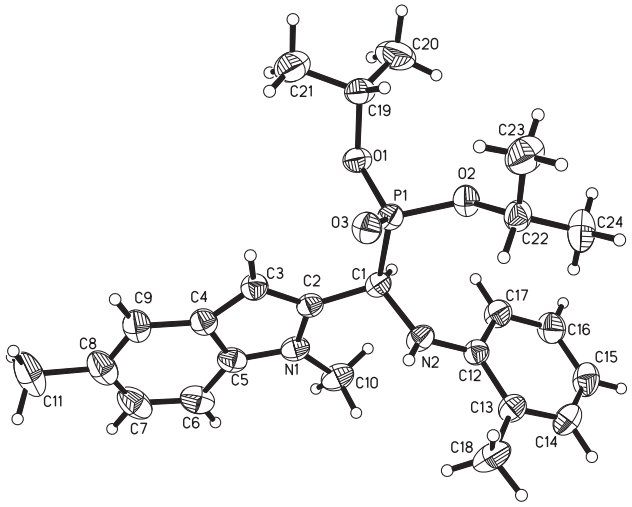


Fig. 1 Molecular structure of Compound **A2.**

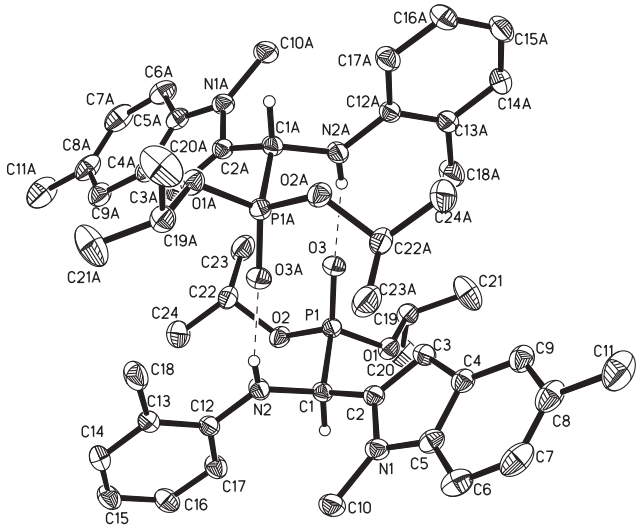


Fig. 2 Single crystal diffraction diagram of compound **A2** with two molecules interacting through hydrogen bonds.

influence on antitumor activity. For example, compounds **A2, B2** and **C2** against HepG2 cells exhibited similar degree of antitumor activity. This same trend was observed for compounds **A7** and **B7** against MGC-803 cells. It was of interest that compound **A6** with a chlorine group to the *para* position of benzene ring as Ar exhibited good antitumor activities against MGC803, and similar results can also be observed in compound **C5**. To our delight, methyl thiophene-3-carboxylate as Ar was crucial for inhibitory activities against MGC-803, while other compounds bearing the methyl substituent to the benzene ring showed weak or negative inhibitory effect.

For compounds with better activity, the samples were formulated into 6 different concentrations (64 μg/mL, 32 μg/mL, 16 μg/mL, 8 μg/mL, 4 μg/mL and 2 μg/mL). According to the measured OD value, the half effective inhibitory concentration IC_{50} of each compound was calculated by SPSS 17.0 software. The results are summarized in Table 2.

The anticancer activity data in Table 2 showed that all the tested compounds have better inhibitory activities against HepG2 than the positive control 5-fluorouracil. Among them, compound **C5** (IC_{50} = 34.2 μM) and **B2** (IC_{50} = 37.1 μM) exhibited excellent inhibitory activity on HepG2. From the above results, some structure-activity relationships could be concluded: (1) methyl thiophene-3-carboxylate as Ar in compounds **A7** and **B7** was beneficial for improving inhibitory activities against MGC-803. (2) compound **C5** with chlorine atom exerted excellent inhibitory effect on HepG2, when the other compounds bearing the methyl and methoxy group to the benzene ring showed a positive inhibitory effect.

The anticancer activity data in Table 2 showed that compounds **A7**, **B7** and **C5** have better inhibitory activities against MGC-803 than 5-fluorouracil. The IC_{50} values of compound **A7**, **B7** and **C5** on MGC-803 were 45.1 μM, 35.7 μM and 44.8 μM, respectively. More significantly, compound **B7** (IC_{50} = 35.7 μM) displayed superior inhibitory activity on MGC-803 compared with that of 5-fluorouracil (IC_{50} = 82.0 μM). Methyl thiophene-3-carboxylate as Ar was conducive for inhibitory activities against MGC-803. Compound **C5** bearing an electron-withdrawing chlorine on the benzene ring showed high inhibitory effect, while compounds **A2**, **B2**, **C2**, **C4** and **C6** with electron-donating methyl group or methoxy group on the benzene ring showed negative or weak inhibitory effect.

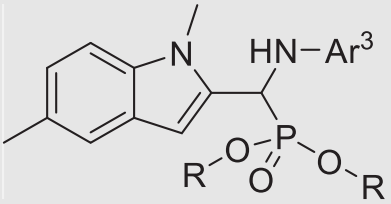
3. Conclusion

In conclusion, we designed and synthesized a series of novel indole derivatives containing α-aminophosphonate moieties. The in vitro cytotoxic activity of the novel compounds was evaluated by the MTT method, revealing that most of target compounds exhibited moderate to high antitumor activities against HepG2 and MGC-803. Among them, compound **C5** (IC_{50} = 34.2 μM) demonstrated more potent inhibitory activities against HepG2 compared with 5-fluorouracil (IC_{50} = 78.7 μM). It is noteworthy that compound **B7** (IC_{50} = 35.7 μM) displayed higher inhibitory activities against MGC-803 than that of 5-fluorouracil (IC_{50} = 82.0 μM). The findings demonstrated that these compounds could be promising and leading bioactive compounds as novel antitumor drugs. Further studies will focus on influence of different substituents, minor structural modification and steric parameters on structure-activity relationships in our lab.

4. Experimental

All starting materials were commercially available and analytically pure. Commercial reagents and solvents were used as received without further purification unless otherwise specified. Toluene was freshly distilled over sodium with the use of diphenyl ketone as an indicator under nitrogen. All manipulations were performed in air atmosphere. All chemicals and reagents were purchased from JK Scientific Co., 9 dingchem. Scientific Co., and used without further purification. ^{1}H NMR and ^{13}C NMR were recorded on a Bruker AVANCE AV 400 (400 MHz for ^{1}H, 100 MHz for ^{13}C) instrument in $CDCl_3$, and ^{31}P chemical shifts were acquired in $CDCl_3$ with H_3PO_4 as the internal standard. Data were reported as follows: chemical shift in ppm (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad signal), coupling constant (Hz), integration. TLC were

Table 1 Inhibitory effects of compounds on human liver cancer cells (HepG2) and human gastric cancer cells (MGC-803) at 100 μg/mL.



comp.	Ar	R	Inhibition rate (%)	
			HepG2	MGC-803
A1	Ph	*i*-Pr	11.7	21.5
A2	2-Me-Ph	*i*-Pr	78.7	−27.4
A3	3-Me-Ph	*i*-Pr	60.2	−8.8
A4	4-Me-Ph	*i*-Pr	48.8	−24.7
A5	3-Cl-Ph	*i*-Pr	60.7	−17.2
A6	4-Cl-Ph	*i*-Pr	73.7	79.2
A7	methyl thiophene-3-carboxylate	*i*-Pr	78.0	80.1
A8	4-MeO-Ph	*i*-Pr	42.9	−11.7
B1	Ph	Et	11.0	−31.7
B2	2-Me-Ph	Et	77.7	1.3
B3	3-Me-Ph	Et	19.1	−29.5
B4	4-Me-Ph	Et	9.9	9.8
B5	2-Cl-Ph	Et	35.0	−6.0
B6	4-Cl-Ph	Et	46.7	1.3
B7	methyl thiophene-3-carboxylate	Et	75.7	89.3
B8	4-MeO-Ph	Et	48.3	−32.2
C1	Ph	Me	26.8	−121.3
C2	2-Me-Ph	Me	76.6	8.1
C3	3-Me-Ph	Me	46.7	47.8
C4	4-Me-Ph	Me	84.4	8.2
C5	4-Cl-Ph	Me	84.7	67.4
C6	4-MeO-Ph	Me	84.0	82.3

Table 2 The second screening compound's growth inhibitory effect on HepG2 and MGC-803.

comp.	Ar	R	IC_{50}(μM)	
			HepG2	MGC-803
A2	2-Me-Ph	*i*-Pr	47.1	–
A7	methyl thiophene-3-carboxylate	*i*-Pr	40.6	45.1
B2	2-Me-Ph	Et	37.1	–
B7	methyl thiophene-3-carboxylate	Et	43.1	35.7
C2	2-Me-Ph	Me	67.4	–
C4	4-Me-Ph	Me	44.4	–
C5	2-Cl-Ph	Me	34.2	44.8
C6	4-MeO-Ph	Me	49.3	90.3
5-Fluorouracil			78.7	82.0

Note: Indicates that there is no second screening inhibitory activity.

performed on silica gel Huanghai HSGF254 plates and visualized by quenching of UV fluorescence (λ_{max} = 254 nm). Silica gel (200–300 mesh) was purchased from Qingdao Haiyang Chemical Co., China. Electron-impact-ionisation mass spectra (EI) were recorded with an Aligent 7890A/5975C GC–MS instrument. High resolution mass spectra (HRMS) were acquired on Varian 7.0 T FTMS. FTIR spectra were obtained with a Bruker Tensor 27 instrument. All IR samples were prepared as thin films and reported in wave numbers (cm^{-1}). 1,5-dimethyl-1H-indole-2-carbaldehydewas synthesized according to the reference (Li et al., 2015; Li et al., 2017).

*4.1. General procedure for the synthesis of compound **A1***

A 50 mL dry round bottom flask was equipped with a magnetic stir bar, and charged with 20 mL of anhydrous toluene,

1,5-dimethyl-1H-indole 2-carboxaldehyde (294 mg, 1.7 mmol), aniline (177 mg, 1.9 mmol), and diisopropyl phosphite (382 mg, 2.3 mmol). The mixture was stirred at 110 °C for 4 h. The resulting solution was then cooled to room temperature, and extracted with EtOAc (3 × 15 mL). The combined organic layer was washed with brine, and dried over anhydrous Na_2SO_4. The volatiles were removed under vacuum, and the residue was purified by column chromatography to give the product. The other target compounds **A2-A8**, **B1-B8** and **C1-C6** were prepared by similar methods.

4.2. Characterization data for products

Diisopropyl ((1,5-dimethyl-*1H*-indol-2-yl)(phenylamino)methyl)phosphonate **A1**: Off-white solid, Yield: 88%, m.p. 158–159 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.34 (s, 1H, ArH), 7.21 (d, J = 8.4 Hz, 1H, ArH), 7.16–7.12 (m, 2H, ArH), 7.04 (d, J = 8.3 Hz, 1H, ArH), 6.73 (t, J = 7.3 Hz, 1H, ArH), 6.66 (d, J = 7.9 Hz, 2H, ArH), 6.59 (d, J = 3.1 Hz, 1H, ArH), 4.97 (d, J = 23.6 Hz, 1H, PC**.**), 4.82–4.74 (m, 1H, C**H**$(CH_3)_2$), 4.62–4.54(m, 1H, C**H**$(CH_3)_2$), 3.84 (s, 3H, NC**H**$_3$), 2.44 (s, 3H, ArC**H**$_3$), 1.37 (d, J = 6.2 Hz, 3H, CH(C**H**$_3)_2$), 1.31–1.27 (m, 6H, 2 × CH(C**H**$_3)_2$), 0.93 (d, J = 6.2 Hz, 3H, CH(C**H**$_3)_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 146.5, 136.4, 134.7, 129.2, 128.6, 127.7, 123.1, 120.3, 118.6, 113.8, 108.7, 101.6, 72.4, 72.3, 50.2 (d, CH, $^1J_{C,P}$ = 159.1 Hz), 30.3, 24.3, 23.8, 23.3, 21.3; ^{31}P NMR ($CDCl_3$, 162 MHz) δ: 19.44; IR (KBr) v: 3276, 2975, 1602, 1537, 1498, 1383, 1327, 1236, 1104, 977, 791, 746, 694; ESI-MS m/z: 415.1 $[M+H]^+$; HRMS (pos.): 415.2163 ($[M+H]^+$, $C_{23}H_{31}N_2O_3PH$; calc. 415.2151).

Diisopropyl ((1,5-dimethyl-*1H*-indol-2-yl)(o-tolylamino)methyl)phosphonate **A2**: Brown yellow solid, Yield: 85%, m.p. 108–110 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.33 (s, 1H, ArH), 7.22 (d, J = 8.4 Hz, 1H, ArH), 7.09–6.97 (m, 3H, ArH), 6.68 (t, J = 7.4 Hz, 1H, ArH), 6.55 (s, 1H, ArH), 6.50 (d, J = 8.0 Hz, 1H, ArH), 4.99 (d, J = 23.5 Hz, 1H, PC**H**), 4.80–4.72 (m, 1H, C**H**$(CH_3)_2$), 4.63–4.55 (m, 1H, C**H**$(CH_3)_2$), 3.85 (s, 3H, NC**H**$_3$), 2.44 (s, 3H, ArC**H**$_3$), 2.28 (s, 3H, ArC**H**$_3$), 1.37 (d, J = 6.2 Hz, 3H, CH(C**H**$_3)_2$), 1.32–1.28 (m, 6H, 2 × CH(C**H**$_3)_2$), 0.96 (d, J = 6.2 Hz, 3H, CH(C**H**$_3)_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 144.5, 136.5, 134.9, 130.2, 128.6, 127.8, 127.1, 123.1, 122.9, 120.3, 118.2, 111.1, 108.7, 101.4, 72.4, 72.3, 50.2 (d, CH, $^1J_{C,P}$ = 159.1 Hz), 30.4, 24.3, 24.3, 23.9, 23.4, 21.4, 17.6; ^{31}P NMR ($CDCl_3$, 162 MHz) δ: 19.37; IR (KBr) v: 3423, 3325, 2975, 1604, 1527, 1454, 1383, 1311, 1246, 1104, 997, 872, 788, 743; ESI-MS m/z: 429.2 $[M+H]^+$; HRMS (pos.): 429.2303 ($[M+H]^+$, $C_{24}H_{33}N_2O_3PH$; calc. 429.2307).

Diisopropyl ((1,5-dimethyl-*1H*-indol-2-yl)(m-tolylamino)methyl)phosphonate **A3**: White solid, Yield: 88%, m.p. 163–165 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.34 (s, 1H, ArH), 7.21 (d, J = 8.4 Hz, 1H, ArH), 7.05–6.99 (m, 2H, ArH), 6.59–6.54 (m, 2H, ArH), 6.51 (s, 1H, ArH), 6.44 (d, J = 8.0 Hz, 1H, ArH), 4.96 (d, J = 23.2 Hz, 1H, PCH), 4.81–4.73 (m, 1H, C**H**$(CH_3)_2$), 4.60–4.49(m, 1H, C**H**$(CH_3)_2$), 3.83 (s, 3H, NC**H**$_3$), 2.44 (s, 3H, ArC**H**$_3$), 2.25 (s, 3H, ArC**H**$_3$), 1.37 (d, J = 6.2 Hz, 3H, CH(C**H**$_3)_2$), 1.29 (t, J = 13.4 Hz, 6H, 2 × CH(C**H**$_3)_2$), 0.92 (d, J = 6.2 Hz, 3H, CH(C**H**$_3)_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 146.6, 138.9, 136.4, 134.9, 129.1, 128.6, 127.8, 123.1, 119.7, 114.8, 110.8, 108.7, 101.6, 72.4, 72.3, 50.2 (d, CH, $^1J_{C,P}$ = 159.2 Hz), 30.4, 24.4, 24.3, 23.9, 23.4, 21.6, 21.4; ^{31}P NMR ($CDCl_3$, 162 MHz) δ: 19.44; IR (KBr) v: 3440, 3286, 2973, 1605, 1590, 1543, 1492, 1383, 1333, 1235, 1180, 1104, 976, 871, 791, 763, 695; ESI-MS m/z: 429.1 $[M+H]^+$; HRMS (pos.): 429.2305 ($[M+H]^+$, $C_{24}H_{33}N_2O_3PH$; calc. 429.2307).

Diisopropyl ((1,5-dimethyl-*1H*-indol-2-yl)(p-tolylamino)methyl)phosphonate **A4**: Light yellow solid, Yield: 86%, m.p. 132–134 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.33 (s, 1H, ArH), 7.20 (d, J = 8.4 Hz, 1H, ArH), 7.03 (d, J = 8.3 Hz, 1H, ArH), 6.94 (d, J = 8.2 Hz, 2H, ArH), 6.57 (d, J = 8.2 Hz, 3H, ArH), 4.92 (d, J = 23.6 Hz, 1H, PC**H**), 4.82–4.74 (m, 1H, C**H**$(CH_3)_2$), 4.61–4.54(m, 1H, C**H**$(CH_3)_2$), 3.82 (s, 3H, NC**H**$_3$), 2.43 (s, 3H, ArC**H**$_3$), 2.20 (s, 3H, ArC**H**$_3$), 1.37 (d, J = 6.2 Hz, 3H, CH(C**H**$_3)_2$), 1.29 (t, J = 10.1 Hz, 6H, 2 × CH(C**H**$_3)_2$), 0.93 (d, J = 6.2 Hz, 3H, CH(C**H**$_3)_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 144.2, 136.3, 134.9, 129.7, 128.5, 127.9, 127.7, 123.0, 120.2, 114.0, 108.7, 101.5, 72.3, 72.2, 50.6 (d, CH, $^1J_{C,P}$ = 168.7 Hz), 30.3, 24.3, 24.2, 23.8, 23.3, 21.3, 20.3; ^{31}P NMR ($CDCl_3$, 162 MHz) δ: 19.48; IR (KBr) v: 3272, 2978, 2922, 1616, 1530, 1384, 1237, 1007, 984, 796; ESI-MS m/z: 429.2 $[M+H]^+$; HRMS (pos.): 429.2306 ($[M+H]^+$, $C_{24}H_{33}N_2O_3PH$; calc. 429.2307).

Diisopropyl(((3-chlorophenyl)amino)(1,5-dimethyl-*1H*-indol-2-yl)methyl)phos-phornate **A5**: Light yellow solid, Yield: 62%, m.p. 175–176 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.35 (s, 1H, ArH), 7.21 (d, J = 8.4 Hz, 1H, ArH), 7.06–7.01 (m, 2H, ArH), 6.70–6.67 (m, 2H, ArH), 6.58 (d, J = 2.8 Hz, 1H, ArH), 6.52–6.49(m, 1H, ArH), 4.92 (d, J = 23.4 Hz, 1H, PC**H**), 4.80–4.72 (m, 1H, C**H**$(CH_3)_2$), 4.60–4.52(m, 1H, C**H**$(CH_3)_2$), 3.83 (s, 3H, NC**H**$_3$), 2.44 (s, 3H, ArC**H**$_3$), 1.37 (d, J = 6.1 Hz, 3H, CH(C**H**$_3)_2$), 1.29 (t, J = 13.6 Hz, 6H, 2 × CH(C**H**$_3)_2$), 0.91 (d, J = 6.1 Hz, 3H, CH(C**H**$_3)_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 147.7, 136.4, 134.9, 134.2, 130.2, 128.8, 127.7, 123.3, 120.4, 118.5, 113.7, 111.9, 108.8, 101.7, 72.6, 72.4, 49.9 (d, CH, $^1J_{C,P}$ = 159.3 Hz), 30.4, 24.3, 23.9, 23.3, 21.4; ^{31}P NMR ($CDCl_3$, 162 MHz) δ: 18.88; IR (KBr) v: 3272, 2975, 2923, 1605, 1594, 1537, 1485, 1384, 1235, 1102, 999, 793, 774; ESI-MS m/z: 449.2 $[M+H]^+$; HRMS (pos.): 449.1762 ($[M+H]^+$, $C_{23}H_{30}ClN_2O_3PH$; calc. 449.1761).

Diisopropyl (((4-chlorophenyl)amino)(1,5-dimethyl-*1H*-indol-2-yl)methyl)phos-

phornate **A6**: White solid, Yield: 45%, m.p. 152–153 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.34 (s, 1H, ArH), 7.22 (d, J = 8.4 Hz, 1H, ArH), 7.09–7.04 (m, 3H, ArH), 6.58 (t, J_1 = 8.7 Hz, 3H, ArH), 4.91 (d, J = 23.4 Hz, 1H, PC**H**), 4.82–4.72 (m, 1H, C**H**$(CH_3)_2$), 4.63–4.54(m, 1H, C**H**$(CH_3)_2$), 3.82 (s, 3H, NC**H**$_3$), 2.44 (s, 3H, ArC**H**$_3$), 1.38 (d, J = 7.7 Hz, 3H, CH(C**H**$_3)_2$), 1.30 (t, J = 6.3 Hz, 6H, 2 × CH(C**H**$_3)_2$), 0.92 (d, J = 6.2 Hz, 3H, CH(C**H**$_3)_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 145.1, 136.4, 134.2, 129.1, 128.8, 127.7, 123.3, 120.3, 114.9, 108.8, 101.7, 101.64, 72.6, 72.4, 50.3 (d, CH, $^1J_{C,P}$ = 159.3 Hz), 30.4, 24.3, 24.3, 23.9, 23.3, 21.4; ^{31}P NMR ($CDCl_3$, 162 MHz) δ: 19.12; IR (KBr) v: 3286, 2980, 2935, 1597, 1528, 1489, 1384, 1318, 1235, 1178, 1104, 1012, 988, 875, 793; ESI-MS m/z: 449.2 $[M+H]^+$; HRMS (pos.): 449.1765 ($[M+H]^+$, $C_{23}H_{30}ClN_2O_3PH$; calc. 449.1761).

Methyl2-(((diisopropoxyphosphoryl)(1,5-dimethyl-*1H*-indol-2-yl)methyl)amino)-thiophene-3-carboxylate **A7**: Light yellow solid, Yield: 83%, m.p. 120–123 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.58 (t, J = 7.0 Hz, 1H, N**H**), 7.35 (s, 1H,

ArH), 7.24–7.20 (m, 2H, ArH), 7.05 (d, J = 8.3 Hz, 1H, ArH), 6.57–6.55 (m, 2H, ArH), 5.02 (d, J = 23.4 Hz, 1H, PC**H**), 4.74–4.65 (m, 2H, 2 × C**H**$(CH_3)_2$), 3.88 (s, 3H, NC**H**$_3$), 3.85 (s, 3H, OC**H**$_3$), 2.45 (s, 3H, ArC**H**$_3$), 1.35–1.33 (m, 6H, 2 × CH(C**H**$_3)_2$), 1.27 (d, 3H, J = 6.2 Hz, CH(C**H**$_3)_2$), 1.15 (d, J = 6.2 Hz, 3H, CH(C**H**$_3)_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 164.9, 137.2, 136.5, 134.1, 131.8, 128.7, 127.5, 124.1, 123.3, 116.8, 108.8, 102.0, 72.7, 72.5, 51.9 (d, CH, $^1J_{C,P}$ = 158.8 Hz), 51.3, 30.5, 24.2, 24.1, 23.7, 23.6, 21.3; ^{31}P NMR ($CDCl_3$, 162 MHz) δ: 17.17; IR (KBr) v: 3364, 2977, 2945, 1675, 1567, 1446, 1254, 1206, 983, 777, 646; ESI-MS m/z: 479.1 $[M+H]^+$; HRMS (pos.): 479.1768 ($[M+H]^+$, $C_{23}H_{31}N_2O_5PSH$; calc. 479.1770).

Diisopropyl((1,5-dimethyl-*1H*-indol-2-yl)((4-methoxyphe nyl)amino)methyl)phosphonate **A8**: Brown yellow solid, Yield: 49%, m.p. 136–138 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.31 (s, 1H, ArH), 7.18 (d, J = 8.4 Hz, 1H, ArH), 7.03–6.99 (m, 2H, ArH), 6.56 (t, J = 3.1 Hz, 1H, ArH), 6.28–6.23 (m, 2H, ArH), 6.19–6.18 (m, 1H, ArH), 4.99 (d, J = 23.5 Hz, 1H, PC**H**), 4.79–4.71 (m, 1H, C**H**$(CH_3)_2$), 4.59–4.50 (m, 1H, C**H**$(CH_3)_2$), 3.80 (s, 3H, NC**H**$_3$), 3.70 (s, 3H, OCH_3), 2.41 (s, 3H, ArC**H**$_3$), 1.34 (d, J = 6.2 Hz, 3H, CH(C**H**$_3)_2$), 1.27–1.25 (m, 6H, 2 × CH(C**H**$_3)_2$), 0.89 (d, J = 6.2 Hz, 3H, CH(C**H**$_3)_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 160.6, 147.8, 136.3, 134.7, 129.9, 128.6, 127.7, 123.1, 120.2, 108.7, 106.7, 103.6, 101.5, 100.0, 72.4, 72.3, 55.0, 50.1(d, CH, $^1J_{C,P}$ = 159.5 Hz), 30.3, 24.3, 24.2, 23.8, 23.2, 21.3, 17.55; ^{31}P NMR ($CDCl_3$, 162 MHz) δ: 19.26; IR (KBr) v: 3423, 3287, 2974, 2928, 1610, 1498, 1236, 1001, 980, 791; ESI-MS m/z: 445.2 $[M+H]^+$; HRMS (pos.): 445.2257 ($[M+H]^+$, $C_{24}H_{33}N_2O_4PH$; calc. 445.2256).

Diethyl ((1,5-dimethyl-*1H*-indol-2-yl)(phenylamino)methy l)phosphonate **B1**: Light brown solid, Yield: 84%, m.p. 128–131 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.35 (s, 1H, ArH), 7.22 (d, J = 8.4 Hz, 1H, ArH), 7.17–7.13 (m, 2H, ArH), 7.06 (d, J = 8.4 Hz, 1H, ArH), 6.75 (t, J = 7.3 Hz, 1H, ArH), 6.67 (d, J = 8.3 Hz, 2H, ArH), 6.62 (d, J = 3.0 Hz, 1H, ArH), 5.04 (d, J = 23.1 Hz, 1H, PC**H**), 4.25–4.12 (m, 2H, C**H**$_2$CH$_3$), 4.07–4.01 (m, 1H, C**H**$_2$CH$_3$), 3.83 (s, 3H, NC**H**$_3$), 3.81–3.74 (m, 1H, C**H**$_2$CH$_3$), 2.45 (s, 3H, ArC**H**$_3$), 1.33 (t, J = 7.0 Hz, 3H, CH_2C**H**$_3$), 1.15 (t, J = 7.0 Hz, 3H, CH_2C**H**$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 146.2, 136.4, 134.2, 129.2, 128.8, 127.6, 123.3, 120.3, 118.8, 113.8, 108.8, 101.7, 63.6, 63.5, 49.7 (d, CH, $^1J_{C,P}$ = 155.0 Hz), 30.3, 21.3, 16.5, 16.3; ^{31}P NMR ($CDCl_3$, 162 MHz) δ: 21.11; IR (KBr) v: 3277, 2978, 2907, 1602, 1533, 1498, 1488, 1323, 1240, 1048, 1018, 973, 792, 745; ESI-MS m/z: 387.2 $[M+H]^+$; HRMS (pos.): 387.1839 ($[M+H]^+$, $C_{21}H_{27}N_2O_3PH$; calc. 387.1838).

Diethyl ((1,5-dimethyl-*1H*-indol-2-yl)(o-tolylamino)methyl) phosphonate **B2**: White solid, Yield: 82%, m.p. 97–99 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.35 (s, 1H, ArH), 7.24 (d, J = 8.4 Hz, 1H, ArH), 7.10–7.00 (m, 3H, ArH), 6.70 (t, J = 7.4 Hz, 1H, ArH), 6.60 (d, J = 3.2 Hz, 1H, ArH), 6.55 (d, J = 8.0 Hz, 1H, ArH), 5.08 (d, J = 23.2 Hz, 1H, PC**H**), 4.51–4.49(m, 1H, NH), 4.24–4.14 (m, 2H, C**H**$_2$CH$_3$), 4.08–4.00 (m, 1H, C**H**$_2$CH$_3$), 3.85 (s, 3H, NC**H**$_3$), 3.81–3.74 (m, 1H, C**H**$_2$CH$_3$), 2.45 (s, 3H, ArC**H**$_3$), 2.29 (s, 3H, ArC**H**$_3$), 1.34 (t, J = 7.0 Hz, 3H, CH_2C**H**$_3$), 1.17 (t, J = 7.0 Hz, 3H, CH_2C**H**$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 144.3, 136.5, 134.5, 130.3, 128.8, 127.7, 127.1, 123.3, 123.1, 120.4, 118.5, 111.2, 108.8, 101.6, 63.7, 63.5, 49.8 (d, CH, $^1J_{C,P}$ = 156.7 Hz), 30.3, 21.4, 17.6, 16.5, 16.3; ^{31}P NMR ($CDCl_3$, 162 MHz) δ: 21.11; IR (KBr) v: 3329, 2979, 2907, 1603, 1524, 1479, 1309, 1249, 1020, 967, 791; ESI-MS m/z: 401.2 $[M+H]^+$; HRMS (pos.): 401.1982 ($[M+H]^+$, $C_{22}H_{29}N_2O_3$-PH; calc. 401.1994).

Diethyl ((1,5-dimethyl-*1H*-indol-2-yl)(m-tolylamino)methy l)phosphonate **B3**: White solid, Yield: 83%, m.p. 138–140 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.35 (s, 1H, ArH), 7.22 (d, J = 8.4 Hz, 1H, ArH), 7.06–7.01 (m, 2H, ArH), 6.62 (d, J = 3.1 Hz, 1H, ArH), 6.57 (d, J = 7.4 Hz, 1H, ArH), 6.52 (s, 1H, ArH), 6.47 (dd, J_1 = 1.8 Hz, J_2 = 1.8 Hz, 1H, ArH), 5.53 (d, J = 23.5 Hz, 1H, PC**H**), 4.49 (s, 1H, NH), 4.24–4.12 (m, 2H, C**H**$_2$CH$_3$), 4.07–3.99 (m, 1H, C**H**$_2$CH$_3$), 3.83 (s, 3H, NC**H**$_3$), 3.81–3.74 (m, 1H, C**H**$_2$CH$_3$), 2.45 (s, 3H, ArC**H**$_3$), 2.26 (s, 3H, ArC**H**$_3$), 1.33 (t, J = 7.1 Hz, 3H, CH_2C**H**$_3$), 1.15 (t, J = 7.1 Hz, 3H, CH_2C**H**$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 146.3, 139.1, 136.4, 134.5, 129.2, 128. 8, 127.7, 123.3, 120.4, 119.8, 114.8, 110.8, 108.8, 101.7, 63.6, 63.4, 51.0 (d, CH, $^1J_{C,P}$ = 155.1 Hz), 30.3, 21.63, 21.4, 16.5, 16.3; ^{31}P NMR ($CDCl_3$, 162 MHz) δ: 21.09; IR (KBr) v: 3426, 3288, 2978, 2925, 1605, 1542, 1493, 1332, 1239, 1047, 1017, 972, 792, 761; ESI-MS m/z: 401.2 $[M+H]^+$; HRMS (pos.): 401.1992 ($[M+H]^+$, $C_{22}H_{29}N_2O_3PH$; calc. 401.1994).

Diethyl ((1,5-dimethyl-*1H*-indol-2-yl)(p-tolylamino)methyl) phosphonate **B4**: Brown yellow solid, Yield: 81%, m.p. 126–129 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.34 (s, 1H, ArH), 7.21 (d, J = 8.4 Hz, 1H, ArH), 7.04 (d, J = 8.4 Hz, 1H, ArH), 6.95 (d, J = 8.2 Hz, 2H, ArH), 6.60–6.58 (m, 3H, ArH), 5.00 (d, J = 23.1 Hz, 1H, PC**H**), 4.24–4.13 (m, 2H, C**H**$_2$CH$_3$), 4.08–4.01 (m, 1H, C**H**$_2$CH$_3$), 3.82 (s, 3H, NC**H**$_3$), 3.79–3.75 (m, 1H, C**H**$_2$CH$_3$), 2.44 (s, 3H, ArC**H**$_3$), 2.21 (s, 3H, ArC**H**$_3$), 1.33 (t, J = 7.0 Hz, 3H, CH_2C**H**$_3$), 1.15 (t, J = 7.1 Hz, 3H, CH_2C**H**$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 144.0, 136.4, 134.4, 129.7, 128.7, 128.1, 127.7, 123.2, 120.3, 114.0, 108.8, 101.7, 63.6, 63.4, 50.1 (d, CH, $^1J_{C,P}$ = 168.3 Hz), 30.3, 21.3, 20.4, 16.5, 16.3; ^{31}P NMR ($CDCl_3$, 162 MHz) δ: 21.17; IR (KBr) v: 3284, 2990, 2918, 1614, 1524, 1487, 1235, 1049, 1020, 973, 792; ESI-MS m/z: 401.2 $[M+H]^+$; HRMS (pos.): 401.1991 ($[M+H]^+$, $C_{22}H_{29}N_2O_3$-PH; calc. 401.1994).

Diethyl(((2-chlorophenyl)amino)(1,5-dimethyl-*1H*-indol-2-yl)methyl)phosphor-nate **B5**: Yellow solid, Yield: 60%, m.p. 115–117 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.35 (s, 1H, ArH), 7.29 (d, J = 5.7 Hz, 1H, ArH), 7.23 (d, J = 8.4 Hz, 1H, ArH), 7.07–7.01 (m, 2H, ArH), 6.68 (t, J = 7.6 Hz, 1H, ArH), 6.61–6.58 (m, 2H, ArH), 5.30–5.26 (m, 1H, NH), 5.06 (d, J = 23.2 Hz, 1H, PC**H**), 4.24–4.04 (m, 3H, C**H**$_2$CH$_3$), 3.92–3.86 (m, 4H, C**H**$_2$CH$_3$, NC**H**$_3$), 2.45 (s, 3H, ArC**H**$_3$), 1.33 (t, J = 7.0 Hz, 3H, CH_2C**H**$_3$), 1.21 (t, J = 7.0 Hz, 3H, CH_2C**H**$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 142.3, 136.6, 133.7, 129.3, 128.9, 127.8, 127.6, 123.4, 120.4, 120.2, 118.8, 112.5, 108.9, 101.9, 63.9, 63.6, 49.8 (d, CH, $^1J_{C,P}$ = 159.2 Hz), 30.4, 21.4, 16.5, 16.3; ^{31}P NMR ($CDCl_3$, 162 MHz) δ: 20.01; IR (KBr) v: 3405, 2983, 2927, 1597, 1503, 1486, 1320, 1242, 1028, 977, 802, 745; ESI-MS m/z: 421.1 $[M+H]^+$; HRMS (pos.): 421.1447 ($[M+H]^+$, $C_{21}H_{26}ClN_2O_3PH$; calc. 421.1448).

Diethyl(((4-chlorophenyl)amino)(1,5-dimethyl-*1H*-indol-2-yl)methyl)phosphor-nate **B6**: Light brown solid, Yield: 73%, m.p. 145–147 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.35 (s, 1H, ArH), 7.22 (d, J = 8.4 Hz, 1H, ArH), 7.10–7.05 (m, 3H, ArH), 6.60–6.58 (m, 3H, ArH), 4.97 (d, J = 23.0 Hz, 1H, PC**H**), 4.23–4.17 (m, 2H, C**H**$_2$CH$_3$), 4.06–3.99 (m, 1H,

C**H**$_2$CH$_3$), 3.81–3.73 (m, 4H, C**H**$_2$CH$_3$, NC**H**$_3$), 2.44 (s, 3H, ArC**H**$_3$), 1.33 (t, J = 7.0 Hz, 3H, CH$_2$C**H**$_3$), 1.15 (t, J = 7.1 Hz, 3H, CH$_2$C**H**$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 144.5, 136.5, 134.9, 130.2, 128.6, 127.8, 127.1, 123.1, 122.9, 120.3, 118.2, 111.1, 108.7, 101.4, 72.4, 51.0, 49.4 (d, CH, $^1J_{C,P}$ = 159.2 Hz), 30.4, 21.3, 16.5, 16.3; ^{31}P NMR ($CDCl_3$, 162 MHz) δ: 20.77; IR (KBr) ν: 3441, 3280, 2920, 1594, 1492, 1390, 1285, 1231, 1052, 1021, 974, 654; ESI-MS m/z: 443.1 $[M+H]^+$; HRMS (pos.): 443.1262 ($[M+H]^+$, $C_{21}H_{26}ClN_2O_3PH$; calc. 443.1267).

Methyl2-(((diethoxyphosphoryl)(1,5-dimethyl-*1H*-indol-2-yl)methyl)amino)thiophene-3-carboxylate **B7**: Light yellow solid, Yield: 78%, m.p. 106–108 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.63–7.60 (m, 1H, NH), 7.36 (s, 1H, ArH), 7.25–7.21 (m, 2H, ArH), 7.06 (d, J = 8.4 Hz, 1H, ArH), 6.58–6.55 (m, 2H, ArH), 5.09 (d, J = 23.6 Hz, 1H, PC**H**), 4.19–4.06 (m, 3H, C**H**$_2$CH$_3$), 4.05–3.95 (m, 1H, C**H**$_2$CH$_3$), 3.88 (m, 4H, NC**H**$_3$), 3.84 (s, 3H, OC**H**$_3$), 2.44 (s, 3H, ArC**H**$_3$), 1.34–1.24 (m, 6H, CH$_2$C**H**$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 165.0, 154.2, 136.5, 133.7, 131.9, 128.8, 127.5, 123.4, 120.3, 116.7, 108.9, 102.0, 64.0, 63.6, 51.5 (d, CH, $^1J_{C,P}$ = 164.5 Hz), 51.4, 30.5, 21.3, 16.5, 16.4; ^{31}P NMR ($CDCl_3$, 162 MHz) δ: 19.03; IR (KBr) ν: 3394, 3321, 2989, 1675, 1586, 1478, 1441, 1392, 1245, 1083, 1021, 974, 805, 777; ESI-MS m/z: 473.2 $[M+H]^+$; HRMS (pos.): 473.1271 ($[M+H]^+$, $C_{21}H_{27}N_2O_5PH$; calc. 473.1276).

Diethyl((1,5-dimethyl-*1H*-indol-2-yl)((4-methoxyphenyl)amino)methyl)phosphonate **B8**: Light yellow solid, Yield: 53%, m.p. 128–131 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.35 (s, 1H, ArH), 7.22 (d, J = 8.4 Hz, 1H, ArH), 7.07–7.03 (m, 2H, ArH), 6.62 (d, J = 3.2 Hz, 1H, ArH), 6.32–6.27 (m, 2H, ArH), 6.24–6.23 (m, 1H, ArH), 5.02 (d, J = 23.6 Hz, 1H, PC**H**), 4.58 (t, J = 7.6 Hz, 1H, NH), 4.25–4.13 (m, 2H, C**H**$_2$CH$_3$), 4.08–3.98 (m, 1H, C**H**$_2$CH$_3$), 3.83 (s, 3H, NC**H**$_3$), 3.81–3.73 (m, 4H, C**H**$_2$CH$_3$, OC**H**$_3$), 2.44 (s, 3H, ArC**H**$_3$), 1.33 (t, J = 7.1 Hz, 3H, CH$_2$C**H**$_3$), 1.14 (t, J = 7.1 Hz, 3H, CH$_2$C**H**$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 160.6, 147.6, 136.4, 134.2, 130.0, 128.8, 127.6, 123.3, 120.3, 108.8, 106.6, 103.8, 101.7, 100.0, 63.6, 63.5, 55.0, 49.7 (d, CH, $^1J_{C,P}$ = 159.6 Hz), 30.3, 21.3, 16.5, 16.3; ^{31}P NMR ($CDCl_3$, 162 MHz) δ: 20.94; IR (KBr) ν: 3291, 2977, 2927, 1610, 1599, 1499, 1445, 1236, 1165, 1045, 974, 845, 792, 756; ESI-MS m/z: 417.2 $[M+H]^+$; HRMS (pos.): 417.1941 ($[M+H]^+$, $C_{22}H_{29}N_2O_4PH$; calc. 417.1943).

Dimethyl ((1,5-dimethyl-*1H*-indol-2-yl)(phenylamino)methyl)phosphonate **C1**: Brown yellow solid, Yield: 76%, m.p. 140–143 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.36 (s, 1H, ArH), 7.23 (d, J = 8.4 Hz, 1H, ArH), 7.18–7.14 (m, 2H, ArH), 7.06 (d, J = 8.4 Hz, 1H, ArH), 6.76 (t, J = 7.38 Hz, 1H, ArH), 6.69–6.65 (m, 3H, ArH), 5.07 (d, J = 23.0 Hz, 1H, PC**H**), 3.83–3.81 (m, 6H, NC**H**$_3$, OC**H**$_3$), 3.55 (d, J = 10.6 Hz, 3H, OC**H**$_3$), 2.44 (s, 3H, ArC**H**$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 146.0, 136.4, 133.9, 129.3, 128.9, 127.6, 123.5, 120.4, 119.0, 113.8, 108.9, 101.9, 54.2, 53.9, 49.4 (d, CH, $^1J_{C,P}$ = 159.2 Hz), 30.2, 21.3; ^{31}P NMR ($CDCl_3$, 162 MHz) δ: 23.41; IR (KBr) ν: 3293, 2949, 1603, 1498, 1314, 1242, 1056, 1027, 840, 754; ESI-MS m/z: 359.2 $[M+H]^+$; HRMS (pos.): 359.1520 ($[M+H]^+$, $C_{19}H_{23}N_2O_3PH$; calc. 359.1525).

Dimethyl ((1,5-dimethyl-*1H*-indol-2-yl)(o-tolylamino)methyl)phosphonate **C2**: Light yellow solid, Yield: 79%, m.p. 152–155 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.35 (s, 1H, ArH), 7.23 (d, J = 8.4 Hz, 1H, ArH), 7.10–7.01 (m, 3H, ArH), 6.71 (t, J = 7.4 Hz, 1H, ArH), 6.63 (d, J = 3.2 Hz, 1H, ArH), 6.57 (d, J = 8.0 Hz, 1H, ArH), 5.10 (d, J = 22.9 Hz, 1H, PC**H**), 3.82 (m, 6H, NC**H**$_3$, OC**H**$_3$), 3.56 (d, J = 10.5 Hz, 3H, OC**H**$_3$), 2.45 (s, 3H, ArC**H**$_3$), 2.28 (s, 3H, ArC**H**$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 144.1, 136.5, 134.2, 130.4, 129.0, 127.6, 127.2, 123.5, 123.2, 120.4, 118.7, 111.1, 108.9, 101.8, 54.2, 53.9, 49.5 (d, CH, $^1J_{C,P}$ = 158.1 Hz), 30.3, 22.0, 17.6; ^{31}P NMR ($CDCl_3$, 162 MHz) δ: 23.43; IR (KBr) ν: 3392, 2952, 2851, 1603, 1510, 1484, 1450, 1316, 1246, 1080, 1028, 870, 835, 749; ESI-MS m/z: 373.2 $[M+H]^+$; HRMS (pos.): 373.1678 ($[M+H]^+$, $C_{20}H_{25}N_2O_3PH$; calc. 373.1681).

Dimethyl ((1,5-dimethyl-*1H*-indol-2-yl)(m-tolylamino)methyl)phosphonate **C3**: Brown solid, Yield: 73%, m.p. 133–136 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.36 (s, 1H, ArH), 7.23 (d, J = 8.4 Hz, 1H, ArH), 7.07–7.02 (m, 2H, ArH), 6.66 (d, J = 2.5 Hz, 1H, ArH), 6.59 (d, J = 7.4 Hz, 1H, ArH), 6.53 (s, 1H, ArH), 6.48 (d, J = 8.0 Hz, 1H, ArH), 5.06 (d, J = 23.0 Hz, 1H, PC**H**), 3.83–3.81 (m, 6H, NC**H**$_3$, OCH$_3$), 3.55 (d, J = 10.5 Hz, 3H, OC**H**$_3$), 2.45 (s, 3H, ArC**H**$_3$), 2.26 (s, 3H, ArC**H**$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 146.1, 139.2, 136.5, 134.1, 129.2, 128.9, 127.6, 123.5, 120.4, 120.0, 114.8, 110.7, 108.9, 101.9, 54.2, 53.9, 49.4 (d, CH, $^1J_{C,P}$ = 158.6 Hz), 30.3, 21.6, 21.4; ^{31}P NMR ($CDCl_3$, 162 MHz) δ: 23.38; IR (KBr) ν: 3313, 2949, 2917, 1608, 1589, 1489, 1458, 1326, 1245, 1179, 1060, 1028, 834, 768; ESI-MS m/z: 373.2 $[M+H]^+$; HRMS (pos.): 373.1679 ($[M+H]^+$, $C_{20}H_{25}N_2O_3PH$; calc. 373.1681).

Dimethyl ((1,5-dimethyl-*1H*-indol-2-yl)(p-tolylamino)methyl)phosphonate **C4**: Light yellow solid, Yield: 80%, m.p. 131–133 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.36 (s, 1H, ArH), 7.22 (d, J = 8.4 Hz, 1H, ArH), 7.06 (d, J = 8.4 Hz, 1H, ArH), 6.97 (d, J = 8.2 Hz, 2H, ArH), 6.65–6.60 (m, 3H, ArH), 5.04 (d, J = 23.0 Hz, 1H, PC**H**), 3.84–3.81 (m, 6H, NC**H**$_3$, OCH$_3$), 3.56 (d, J = 10.6 Hz, 3H, OC**H**$_3$), 2.45 (s, 3H, ArC**H**$_3$), 2.23 (s, 3H, ArC**H**$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 143.7, 136.4, 134.1, 129.8, 128.9, 128.3, 127.6, 123.4, 120.4, 114.0, 108.8, 101.9, 54.2, 53.8, 49.8 (d, CH, $^1J_{C,P}$ = 161.17 Hz), 30.2, 21.3, 20.4; ^{31}P NMR ($CDCl_3$, 162 MHz) δ: 23.44; IR (KBr) ν: 3317, 2951, 2850, 1616, 1521, 1486, 1241, 1184, 1063, 1029, 834, 794, 755; ESI-MS m/z: 373.2 $[M+H]^+$; HRMS (pos.): 373.1683 ($[M+H]^+$, $C_{20}H_{25}N_2O_3PH$; calc. 373.1681).

Dimethyl(((4-chlorophenyl)amino)(1,5-dimethyl-*1H*-indol-2-yl)methyl)phosphonate **C5**: Light pink solid, Yield: 63%, m.p. 140–142 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.36 (s, 1H, ArH), 7.23 (d, J = 8.4 Hz, 1H, ArH), 7.11–7.06 (m, 3H, ArH), 6.62–6.59 (m, 3H, ArH), 5.00 (d, J = 22.8 Hz, 1H, PC**H**), 4.60 (s, 1H, NH), 3.83–3.80 (m, 6H, NC**H**$_3$, OC**H**$_3$), 3.54 (d, J = 10.6 Hz, 3H, OC**H**$_3$), 2.44 (s, 3H, ArC**H**$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 144.6, 136.4, 133.3, 129.1, 127.5, 123.6, 120.4, 114.9, 108.9, 102.0, 54.1, 54.0, 49.5 (d, CH, $^1J_{C,P}$ = 159.2 Hz), 30.2, 21.3; ^{31}P NMR ($CDCl_3$, 162 MHz) δ: 22.99; IR (KBr) ν: 3280, 2952, 1598, 1517, 1491, 1320, 1241, 1055, 1027, 834, 793; ESI-MS m/z: 393.1 $[M+H]^+$; HRMS (pos.): 393.1136 ($[M+H]^+$, $C_{19}H_{22}ClN_2O_3PH$; calc. 393.1135).

Dimethyl((1,5-dimethyl-*1H*-indol-2-yl)((4-methoxyphenyl)amino)methyl)phosphornate **C6**: Yellow solid, Yield: 56%, m.p. 127–128 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.36 (s, 1H, ArH), 7.22 (d, J = 8.4 Hz, 1H, ArH), 7.08–7.04 (m, 2H,

ArH), 6.65 (d, J = 3.0 Hz, 1H, ArH), 6.33–6.27 (m, 2H, ArH), 6.25–6.24 (m, 1H, ArH), 5.04 (d, J = 23.0 Hz, 1H, PC**H**), 4.55 (s, 1H, NH), 3.84–3.81 (m, 6H, NC$\mathbf{H}_3$, POC$\mathbf{H}_3$), 3.74 (s, 3H, ArOC$\mathbf{H}_3$), 3.54 (d, J = 10.6 Hz, 3H, POC$\mathbf{H}_3$), 2.44 (s, 3H, ArC$\mathbf{H}_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 147.4, 136.4, 133.8, 130.1, 128.9, 127.6, 123.5, 108.9, 106.6, 104.0, 101.9, 100.0, 55.0, 54.1, 53.9, 49.3 (d, CH, $^1J_{C,P}$ = 159.2 Hz), 30.2, 21.3; ^{31}P NMR ($CDCl_3$, 162 MHz) δ: 23.24; IR (KBr) v: 3450, 3297, 2952, 1613, 1492, 1250, 1163, 1022, 837, 754; ESI-MS m/z: 389.2 $[M+H]^+$; HRMS (pos.): 389.1623 ($[M+H]^+$, $C_{20}H_{25}N_2O_4PH$; calc. 389.1630).

4.3. In vitro anti-proliferative assay

The in vitro cytotoxic activity of compounds **A1-A8**, **B1-B8** and **C1-C6** against HepG2 and MGC-803 was evaluated by the MTT method and the potency was expressed as inhibition rate. A 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay was performed to investigate in vitro cytotoxic activity. HepG2 and MGC-803 seeded into the 96-well plate (100 μL each well) were incubated at 37 °C under 5% CO_2 and 95% O_2 until cell adherence was observed. Cells were exposed to solutions of compounds **A1-A8**, **B1-B8** and **C1-C6** at different concentrations. After 48 h, 20 mL of MTT with a concentration of 5 mg/mL was added into the 96-well plate and incubated for 4 h at 37 °C. Then, the supernatant was aspirated, 150 μL of DMSO was added to each well, and the absorbance was measured at 570 nm. The formula for calculating inhibition of cell proliferation was as follows: inhibition of cell proliferation rate (%) = (OD value of the control group - OD value of drug group)/ control OD value 100%.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

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