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ORIGINAL PAPER

# Spiro- and substituted tetrahydrobenzo[*b*]thiophene-triazaphospholes and phosphoramidates as potent antineoplastic agents: synthesis, biological evaluation, and SAR studies

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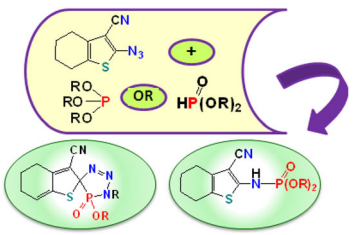
**Abstract** New and efficient conjugate addition reaction of trimethyl, triethyl, and triisopropyl phosphites with 2-azido-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbonitrile was developed and furnished spiro-triazaphosphole-oxide derivatives in ≈70 % yield. Contrary to these results, linear substituted phosphoramidates were obtained from the reaction of the azide with dimethyl, diethyl, and diisopropyl phosphites. *N*-Alkylamino- or 2-aminotetrahydrobenzo[*b*]thiophene-3-carbonitrile was also isolated in ∼10 % yield from the previous two reactions. In the context of this work, hexaalkylphosphorus triamides were caused to react with the same substrate afforded the corresponding phosphoric triamides only in the presence of a protonating agent (dil. alcohol). The three reactions proceeded smoothly, cleanly, and were completed within ∼6 h at r.t. Pharmacological evaluation results of antibreast, anticolon, and antiprostate carcinoma cell lines properties for the products were discussed in terms of structure–activity relationship to define a chromophore for lead compounds.

*Graphical abstract*

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**Keywords** Trialkyl phosphites · Dialkyl phosphites · Azides · Triazaphospholes · Phosphoramidates · Anticancer agents

## Introduction

The search for biologically promising new chemical entities against the deadly cancer disease remains an important theme in drug discovery [1]. The preliminary cancer treatment options are usually a combination of surgery, radio-, and chemotherapy. The latter one is considered one of the effective approaches in suppressing tumor growth and eradication of tumors. However, many patients, who undergoing chemotherapy, suffer from associated serious side effects emphasizing the need to new anticancer agents with improved efficacy and reduced side effects are still needed. Generally, cancers of the breast, lung, colon, and prostate are the most frequent types of cancer worldwide [1–3]. This paper along with our recent efforts focuses on developing, identifying, and optimizing new entities of anticancer properties [4–10].

Organophosphonates, over the last three decades, have become notably recognized for their pharmacological antiinflammatory [11, 12] and anticancer activity [13, 14], especially when associated with various heterocycles [15]. One of the most important of these bioactive heterocycles is the triazoles, which have not been widely reported in the literature [16, 17]. Also, phosphoramidates in particular constitute an important class of compounds that attracts medicinal chemists because of their wide use in drug development [18–20].

Based on these considerations and with the aim of synthesizing new phosphor esters containing one, two or

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three amino functions directly linked to the phosphorus atom, we describe herein the reactions between 2-azido-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbonitrile (**1**) and the phosphorus reagents trialkyl phosphites (TAPs), dialkyl phosphites (DAPs), and hexaalkylphosphorus triamides. Pharmacological evaluation results of antibreast, anticolon, and antiprostate carcinoma cell lines properties for the products were also discussed in terms of structure–activity relationship (SAR) in an attempt to define a chromophore for lead compounds.

## Results and discussion

### Chemistry

The azide **1** readily reacted with trimethyl, triethyl, and triisopropyl phosphites (**2a–2c**) in absolute tetrahydrofuran (THF) under ambient conditions in 4–6 h to give spiro-triazaphosphole-oxides **4a–4c** in good yields. Alkylated 2-aminotetrahydrobenzo[*b*]thiophene-3-carbonitriles **5a–5c** were also isolated (≈10 % yield) from the reactions.

Compounds **4a-4c** could be formed in a one-step mechanism [1 + 4] cycloaddition to give initially the intermediates **3** [21]. Further extrusion of the appropriate alcohol moiety, and an alkyl group shift led to the formation of the triazaphosphole-oxide products **4a–4c** [21, 22]. The latter step was provoked by the formation of the highly stable P=O bond [23]. Similar triazaphosphole ring was previously obtained from the reaction of trialkyl phosphites with 3-$\omega$-azidoacetyl coumarin [24]. Furthermore, 4*H*-isooxazol-4-ylphosphonate was formed via [1 + 4] cycloaddition mechanism from the reaction of triketoindan-2-oxime with phosphorus reagents [25]. In support of the formation of the intermediates **3**, the $^{31}$P NMR spectrum was recorded in an early stage of the reaction for the crude mixture of trimethyl phosphite and azide **1**. The spectrum (after 2 h) revealed two big peaks at $\delta = 141.3$ ppm $P(OMe)_3$, and at 11.7 ppm that corresponds to the phosphazole product **4a** whereas only a minor peak was displayed at −9.6 ppm assigned to the intermediate **3**, which indicated the short life of this structure. Unfortunately, all trials to obtain any of **4a–4c** in proper crystallized form for running single crystal crystallography failed. On the other hand, the amines **5a–5c** arose from slight collapse of the intermediates **3** (due to unfortuitous moisture), resulting in its denitrogenation and the loss of phosphorus moiety (Scheme 1). $^{31}$P NMR spectra of the crude mixtures of the reaction of $(MeO)_3P$ and azide **1** after 2h (a), and at the end of the reaction (b) was displayed in Fig. 1.

Compounds **4a–4c** showed $^{31}$P NMR chemical shifts around 12 ppm confirming the presence of N–P–C linkage in an azaphosphole nucleus [23, 24]. In their EI mass spectra, **4a–4c** showed the molecular ion peaks in addition to the expected fragmentations of the corresponding

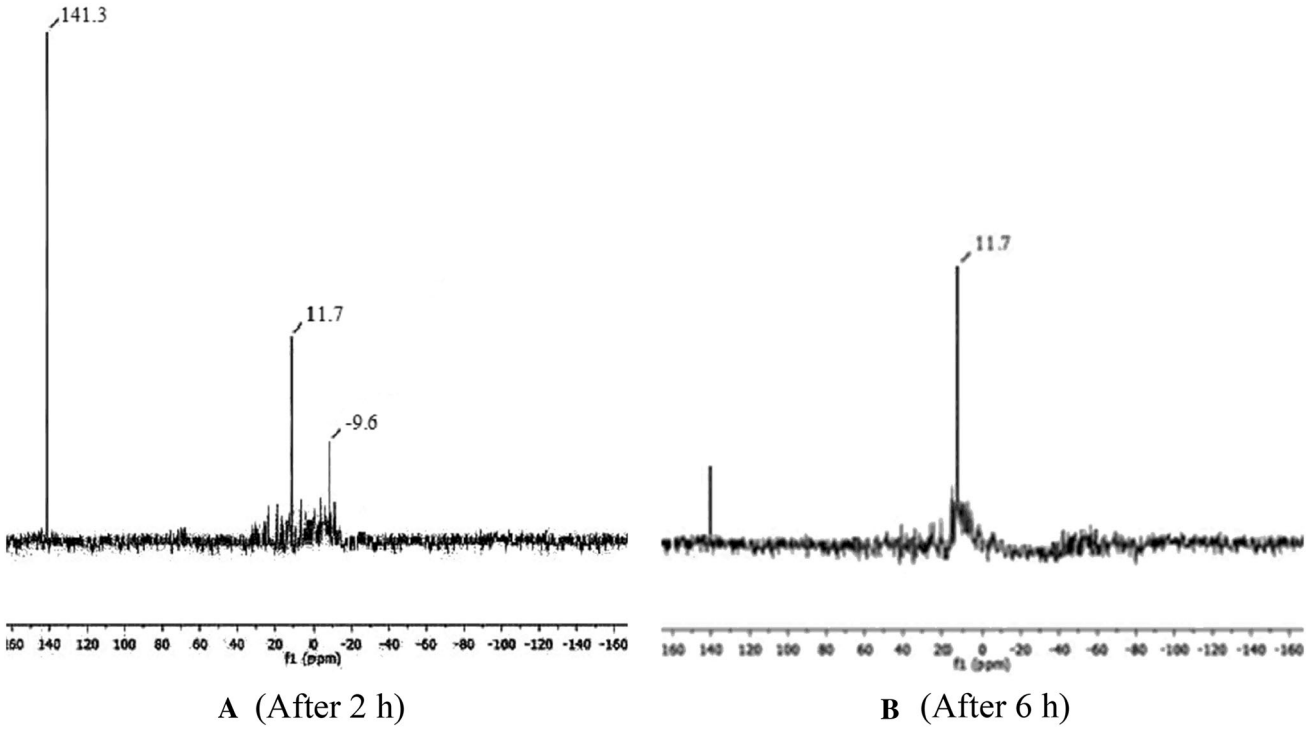
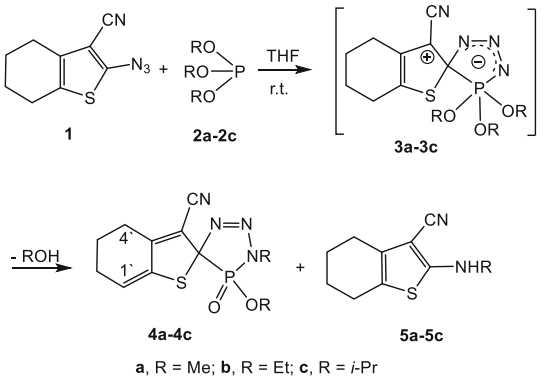



**Fig. 1** $^{31}$P NMR spectra of the crude mixtures of the reaction of $(MeO)_3P$ and azide **1** after 2h (**a**), and at the end of the reaction (**b**)

**Scheme 1**




**a**, R = Me; **b**, R = Et; **c**, R = *i*-Pr

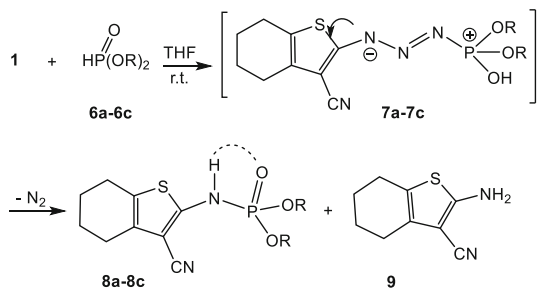
compound. The IR spectrum of **4b** showed the presence of absorption bands at 2211 (CN), 1243 (P=O, free), and at 1029 (P–O–C) $cm^{-1}$. The strong presence of azide frequency in the IR spectrum of **1** at 2090 $cm^{-1}$ was absent in the IR spectrum of **4a**–**4c**. In the $^{1}H$ NMR spectrum of **4b**, the two ethyl–methyl groups were observed as a multiplet within the range 1.16–1.25 ppm (6H, Me.C–N and MeC.OP), while the 1-H proton of the trihydrobenzene nucleus was displayed as a triplet ($^{3}J_{HH} = 6.6$ Hz) at 6.93 ppm. A doublet of quartet (2H, $^{3}J_{HH} = 6.7$ Hz, $^{3}J_{PH} = 8.3$ Hz) was revealed at 3.79 ppm due to $CH_2$ protons linked to 3-N in the triazaphosphole ring. A quintet (2 H, $^{3}J_{HH} = 5.6$, $^{3}J_{PH} = 8.9$ Hz) at 4.02 ppm due to $OCH_2$ protons attached to the phosphorus atom. Moreover, the spiro-C was located as a doublet ($^{1}J_{PC} = 133.6$ Hz) at $\delta = 110.3$ ppm in the $^{13}C$ NMR spectrum of **4b**.

The reaction of dialkylphosphonates, dimethyl, diethyl, and diisopropyl phosphites (**6a**–**6c**) with the azide **1**, however, did not proceed in the same way, but gave the respective phosphoramidates **8a**–**8c** (~72 % yield) along with the known [26] 2-amino-4,5,6,7-tetrahydrobenzo-[*b*]thiophene-3-carbonitrile (**9**, 10 % yield; Scheme 2). The reaction sequence firstly included the reaction of the azide with phosphites to give phosphorimidates **7a**–**7c**, which are analogous to the iminophosphoranes formed during the Staudinger reaction of azides with phosphines [27, 28]. Phosphorimidates **7** underwent rearrangement to their corresponding phosphoramidates **8** via a 1,2-proton shift by Lewis acid activation, whereas the amine **9** was formed through the Staudinger reduction [29, 30] (Scheme 2).

Structural reasons for **8** are: (a) elementary analyses and molecular weight determination (MS) confirmed the assigned structure; (b) the IR spectra (KBr) of **8a**–**8c** revealed the presence of NH and CN absorption bands around 3322 and 2198 $cm^{-1}$; (c) The $^{1}H$ NMR spectrum of **8a** ($CDCl_3$) showed a signal at 11.35 ppm (NH) and a doublet ($^{3}J_{PH} = 11.5$ Hz) at 3.79 ppm due to the two methoxyl groups attached to the phosphorus atom; and (d) $^{31}P$ NMR signals of **8a**–**8c** were found at ≈18 ppm.

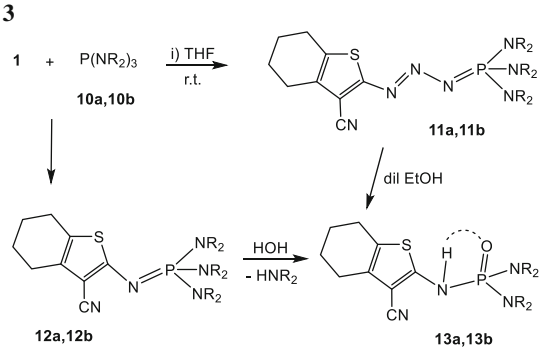
Next, the azide **1** was allowed to react also with hexaalkyl-phosphorus triamides **10a** and **10b** in THF at 20 °C. The resulting crystalline 1:1 adducts (≈90 % yield) were formulated as phosphoranylidene-triazenes **11a**, **11b** [31, 32]. The $^{31}P$ NMR signals of **11a**, **11b** were observed at ≈40 ppm. Correct elemental analyses and expected $^{1}H$, $^{13}C$ NMR data also confirmed the assigned structure **11** (Scheme 3). Compounds **11a** and **11b** were water sensitive, quite stable only for few days in a desiccator. When a protonating agent (2 $cm^3$ dil. EtOH) was present in the reaction medium, the reaction markedly accelerated leading to the formation of the phosphoric triamides **13a** and **13b** (≈82 % yield). Furthermore, when compounds **11** were warmed in dil. alcohol, **13a** and **13b** were again obtained. According to the Staudinger mechanism, the first step is the nucleophile attack of the trivalent phosphorus reagent **10** on the terminal nitrogen of the azide **1** that results in the formation of the phosphazide **11** [29, 30]. Compound **11** is stable under drastic conditions due to the presence of the strong donor, hexaalkylphosphorane triamides moiety [33]. Quenching **11** with a molecule of $H_2O$ afforded **13** via the intermediate **12** with concomitant loss of dialkylamine molecule (Scheme 3). The $^{31}P$ NMR spectrum of these compounds showed signals around $\delta = 34$ ppm. The $^{1}H$ NMR spectrum of **13a** revealed a

**Scheme 2**




**a**, R = Me; **b**, R = Et; **c**, R = *i*-Pr

**Scheme 3**




**a**, R = Me; **b**, R = Et

doublet centered at 2.45 ppm ($^3J_{PH}$ = 9.4 Hz) due to 12 H of the two magnetically equivalent dimethylamino groups.

## Pharmacology

Evaluation of anticancer activity on the synthesized stable phosphorus compounds **4a–4c**, **8a–8c**, **13a**, and **13b** was performed at the Cancer Research Institute (CRI). First, all these compounds were evaluated in primary anticancer assay at $10^{-4}$ M concentration against MCV7 (breast), COLO205 (colon), and PC-3 (prostate cancer) cell lines (Table 1).

For CRI criteria, compounds that reduce the growth of any one of the cell lines to approximately 32 % or less are passed on for evaluation in a full panel of cell lines over a 3-long dose range. Triazaphospholes **4a**, **4b** and phosphoramidates **8a**, **8b** that met these criteria were evaluated for their anticancer activity following the known in vitro disease-oriented antitumor screening program, which is based on the use of a multiple panels of 12 human tumor cell lines [34]. Each compound is tested as a minimum of three concentrations at 10-fold dilution against every cell line in the panel. A 48 h continuous drug exposure protocol is used and sulforhodamine B (SRB) protein assay is used to estimate cell viability or growth [35, 36]. The response parameters $GI_{50}$, TGI, and $LC_{50}$ (Table 2) refer to the drug concentration that produce 50 % inhibition, total growth inhibition, and 50 % cytotoxicity, and are expressed in $10^{-5}$ molar concentration. In the table, we report only the activity of those compounds, which exhibited $GI_{50}$, TGI, and $LC_{50}$ less than $10 \times 10^{-5}$ M. The $GI_{50}$ reported data in Table 2 indicated that nominated compounds **4a**, **4b**, **8a**, and **8b** showed a good level of cytostatic activity at $10^{-5}$ M and in some cases at $10^{-6}$ M concentration against all subpanel cell lines. Compound **4a** displayed a significant growth inhibitory activity on the 12 cell lines showing $GI_{50}$ values between 6.35 and $28.56 \times 10^{-6}$ M, and total growth inhibitory activity at $2.789–8.888 \times 10^{-5}$ M. **4a** also showed cytotoxic activity against all cell lines ($4.411–8.564 \times 10^{-6}$ M concentrations) with particular selectivity against breast and prostate cancer cell lines. Compound **4b** indicated more or less close activity to **4a** against all tested cell lines. On the other hand, phosphoramidates **8a** and **8b** showed excellent response to the three parameters $GI_{50}$, TGI, and $LC_{50}$ of the 5 colon cell lines. As such, **8b** produced $GI_{50}$ between 6.84 and $21.36 \times 10^{-6}$ M concentration, TGI between 3.542 and $5.942 \times 10^{-5}$ M, and $LC_{50}$ value between 5.084 and $6.306 \times 10^{-5}$ M. For comparison, the standard drug, 5-fluorouracil showed $GI_{50}$ between 11.36 and $41.63 \times 10^{-6}$ M concentration, TGI between 3.368 and $6.651 \times 10^{-5}$ M, and $LC_{50}$ value between 3.894 and $8.894 \times 10^{-5}$ M concentrations.

**Table 1** Antiproliferative activity of **4a–4c**, **8a–8c**, **13a**, and **13b** at $10^{-4}$ M concentration expressed in growth percentage

| Compounds | MCF7 | COLO205 | PC-3 |
|---|---|---|---|
| **4a** | 10 | 18 | 4 |
| **4b** | 35 | 42 | 24 |
| **4c** | 78 | 89 | 84 |
| **8a** | 22 | 33 | 14 |
| **8b** | 56 | 64 | 32 |
| **8c** | 87 | 101 | 73 |
| **13a** | 72 | 62 | 67 |
| **13b** | 73 | 101 | 77 |

Considering the structure–activity relationship (SAR), as shown in Tables 1 and 2, the highest protection was observed for **4a**, followed by **4b** while **8a** and **8b** displayed less activity. On the other hand, compounds **4c**, **8c**, **13a**, and **13b** revealed only a weak antitumor activity toward all tested cell lines. It seems that the phosphonate group is essential for the biological activity. As far as cyclic substituted pyrazol-based phosphonate is concerned, it is obvious that the moieties attached to phosphorus determine the potency. As such, cyclic triazaphospholes (**4a**, **4b**) are more favorable for antitumor activity compared to open-chain phosphoramidates (**8a** and **8b**). Furthermore, the introduction of a long chain (e.g., isopropyl) or replacing the alkoxy group (Me or Et) with the amino group at the phosphor atom was totally unfavorable and dramatically decreased the antitumor potencies of compounds (**4c**, **8c**; **13a**, **13b**).

## Conclusion

In conclusion, we have developed a benign convenient and rapid procedure for the synthesis of two types of phosphor families: spiro-triazaphosphole-oxides and phosphoramidate derivatives in significant yields. The products were evaluated for their in vitro antitumor activities against 12 carcinoma cell lines represent (breast, colon, and prostate cancer diseases). Four compounds out of 8 phosphor ester derivatives exhibited micromolar remarkable inhibition against several cancer cell lines in comparison to 5-flourouracil.

## Experimental section

Melting points were determined with open capillary tube on an Electrothermal (variable heater) melting point apparatus and were corrected. IR spectra were recorded on a JASCO FT-IR 6100 using KBr disc (JASCO, Japan). NMR spectra were measured with a JEOL E.C.A-500 MHz ($^{13}$C: 125.4 MHz, $^1$H: 500.7 MHz, $^{31}$P: 200.7 MHz) spectrometer (JEOL, Japan). $^{31}$P NMR spectra were recorded with $H_3PO_4$ (85 %) as external reference. $^1$H and $^{13}$C NMR spectra were recorded with trimethylsilane as internal standard in $CDCl_3$. Chemical

**Table 2** $GI_{50}$, TGI, and $LC_{50}$ values of compounds **4a**, **4b** and **8a**, **8b**

| Panel/cell lines Type of test | **4a** | | | **4b** | | | **8a** | | | **8b** | | | 5-Fluorouracil | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | $GI_{50}$ | TGI | $LC_{50}$ | $GI_{50}$ | TGI | $LC_{50}$ | $GI_{50}$ | TGI | $LC_{50}$ | $GI_{50}$ | TGI | $LC_{50}$ | $GI_{50}$ | TGI | $LC_{50}$ |
| Breast cancer | | | | | | | | | | | | | | | |
| MCF7 | 0.635 | 4.662 | 5.084 | 0.503 | 4.732 | 3.190 | 0.947 | 8.852 | 6.143 | 0.764 | 6.864 | – | 2.284 | 4.831 | 7.521 |
| MDA-MB-231/ATCC | 1.445 | 3.025 | 5.284 | 1.457 | 3.186 | 4.780 | 2.205 | 4.946 | 6.985 | 1.843 | 7.893 | 6.874 | 2.635 | 6.572 | 3.894 |
| MDA-MB-435 | 0.828 | 2.789 | 8.076 | 0.954 | 3.433 | 8.063 | 1.766 | 5.780 | 8.864 | 0.366 | 7.075 | – | 3.022 | 4.073 | 5.776 |
| NCl/ADR-RES | 1.409 | 4.062 | 6.053 | 1.273 | 4.689 | 6.423 | 1.684 | 6.250 | 8.974 | 2.065 | 8.443 | 8.531 | 4.163 | 6.651 | 8.894 |
| HS578T | 1.924 | 5.864 | 4.762 | 1.746 | 6.786 | 4.628 | 1.336 | 6.876 | 6.740 | 0.541 | – | 8.468 | 2.065 | 4.101 | 6.184 |
| Colon cancer | | | | | | | | | | | | | | | |
| COLO205 | 1.843 | 8.748 | 7.962 | 1.780 | 8.042 | 8.053 | 0.865 | 6.947 | 5.234 | 0.945 | 3.542 | 6.306 | 1.168 | 3.479 | 6.032 |
| HCC-2998 | 1.278 | 8.432 | 6.895 | 2.942 | 8.353 | 8.756 | 0.761 | 4.037 | 5.846 | 0.684 | 4.314 | 6.143 | 1.434 | 4.673 | 5.074 |
| HCT-15 | 2.633 | 8.888 | 8.564 | 3.653 | 6.406 | 8.684 | 1.776 | 3.621 | 6.346 | 2.136 | 5.942 | 5.084 | 1.776 | 4.055 | 8.063 |
| HCT-116 | 2.062 | 5.562 | 7.053 | 2.064 | 4.985 | – | 0.764 | 6.875 | 5.647 | 0.857 | 4.634 | 5.173 | 2.148 | 3.435 | 4.079 |
| SW-620 | 2.856 | 5.883 | 6.941 | 2.868 | 8.043 | – | 0.982 | 4.043 | 7.023 | 0.906 | 4.959 | 5.430 | 2.982 | 3.368 | 7.653 |
| Prostate cancer | | | | | | | | | | | | | | | |
| PC-3 | 1.243 | 3.356 | 4.411 | 0.997 | 4.636 | 4.650 | 1.053 | 6.620 | 5.878 | 0.788 | 2.865 | – | 1.439 | 4.658 | 6.008 |
| DU-145 | 1.053 | 4.325 | 4.664 | 2.843 | 3.513 | 5.844 | 1.448 | 5.974 | 5.036 | 0.816 | 3.906 | – | 1.136 | 4.502 | 6.016 |

(–) means values $>10 \times 10^{-5}$

shifts ($\delta$) are given in ppm. The mass spectra were performed at 70 eV on an MS-50 spectrometer provided with a data system spectrometer (Kratos, UK). Elemental analyses (C/H/N/S) were carried out at the Microanalysis Laboratory, Cairo University, Cairo, Egypt, using elementary Analysen-systeme GmbH-Vario EL III Element Analyzer, Germany. The values obtained are favorably agreed with the calculated ones (±1). The appropriate precautions in handling moisture-sensitive compounds were observed and solvents were dried by standard techniques. TLC: Merck 0.2 mm silica gel 60 F154 anal aluminum plates. Column chromatography (CC): silica gel (Kieselgel 60 mesh, particle size 0.2–0.5 mm; E. Merck, Darmstadt). The substrate 2-azido-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbonitrile (**1**) was prepared according to the reported method [37].

*Preparation of compounds **4a–4c** and **5a–5c** by reaction of azide **1** with trialkyl phosphites **2a–2c***

A mixture of 0.8 g of the azide **1** (3.9 mmol) and 4.1 mmol trimethyl, triethyl, or triisopropyl phosphite (**2a–2c**) in 15 $cm^3$ THF was stirred at r.t. for ≈4–6 h (TLC). Excess of the volatile materials was removed under vacuum, and the resulting residue was chromatographed on silica gel. Elution with *n*-hexane/$CHCl_3$ (9:1 v/v) produced alkylated amines **5a–5c**. Elution with *n*-hexane/$CHCl_3$ (7:3 v/v) afforded triazaphospholes **4a–4c**.

*2-(Methylamino)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (**5a**)*

Obtained as orange substance; yield: 766 mg (10.4 %). Compound **5a** is commercially available and described in [38], but no physical data have been published. m.p.: 73 °C (from pentane); IR (KBr): $\bar{\nu}$ = 3334 (NH), 2222 (CN) $cm^{-1}$; $^1$H NMR (500.7 MHz, $CDCl_3$): $\delta$ = 2.68 (s, 3H, MeN), 1.82, 2.79 (2 m, 2 × 4H, 4 $H_2$C-hexyl), 6.98 (br, 1H, HN) ppm; $^{13}$C NMR (125.4 MHz, $CDCl_3$): $\delta$ = 163.2 (C–NH), 130.4, 128.3 (C=C-hexyl), 118.7 (CN), 87.3 (*C*–CN), 34.7 (MeN), 26.4, 26.2, 23.5, 21.3 ($CH_2$-hexyl) ppm; MS (EI, 70 eV): *m/z* (%) = 192 (56) [$M^+$], 191 (100) [$M^+$-1].

*2-(Ethylamino)-4,5,6,7-tetrahydrobenzo[b]-thiophene-3-carbonitrile (**5b**)*

Obtained as orange material; yield: 735 mg (9.6 %). Compound **5b** is commercially available, but no physical data have been published. m.p.: 49 °C (from pentane); IR (KBr): $\bar{\nu}$ = 3333 (NH), 2217 (CN) $cm^{-1}$; $^1$H NMR (500.7 MHz, $CDCl_3$): $\delta$ = 1.24 (t, $^3J_{HH}$ = 7.1 Hz, 3H, *Me*$H_2$C), 1.82, 2.95 (2 m, 2 × 4H, 4 $H_2$C-hexyl), 3.54 (q, $^3J_{HH}$ = 6.8 Hz, 2H, $H_2$CMe), 6.88 (br, 1H, HN) ppm; $^{13}$C NMR (125.4 MHz, $CDCl_3$): $\delta$ = 164.3 (C–NH), 130.5, 128.6 (*C*=*C*-hexyl), 118.8 (CN), 87.7 (*C*–CN), 43.6 ($CH_2$.Me), 26.4, 26.2, 23.5, 21.3 ($CH_2$-hexyl), 15.3 ($HC_2$-*Me*) ppm; MS (EI, 70 eV): *m/z* (%) = 206 (64) [$M^+$], 205 (100) [$M^+$-1].

*2-(Isopropylamino)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile* (**5c**, $C_{12}H_{16}N_2S$)

Yellow material; yield: 850 mg (10.3 %); m.p.: 62 °C (from $CH_2Cl_2$/diethylether 1:1); IR (KBr): $\bar{\nu}$ = 3325 (NH), 2218 (CN) $cm^{-1}$; $^1$H NMR (500.7 MHz, $CDCl_3$): $\delta$ = 1.24 (d, $^3J_{HH}$ = 7.1 Hz, 2 × 3H, 2 Me.C), 1.82, 2.93 (2 m, 2 × 4H, 4 $H_2$C-hexyl), 3.01 (m, 1H, *H*C.$(Me)_2$), 7.81 (br,

1H, HN) ppm; $^{13}$C NMR (125.4 MHz, $CDCl_3$): $\delta$ = 162.2 (C–NH), 130.1, 128.6 (*C*=*C*-hexyl), 118.6 (CN), 86.7 (*C*–CN), 45.5 (*C*H.$Me_2$), 26.4, 26.2, 23.5, 21.3 ($CH_2$-hexyl), 23.7 (HC*Me*$_2$) ppm; MS (EI, 70 eV): *m/z* (%) = 219 (47) [$M^+$-1].

*4′-Methoxy-3′-methyl-3′,4′,5,6-tetrahydro-4H-spiro[1-benzothiophene-2,5′-[1,2,3,4]triazaphosphole]-3-carbonitrile 4′-oxide* (**4a**, $C_{11}H_{13}N_4O_2PS$)

Strew yellow needles; yield: 0.77 g (66.4 %); m.p.: 146 °C ($CH_2Cl_2$); IR (KBr): $\overline{\nu}$ = 2214 (CN), 1237 (P=O, free), 1034 (P–O–C) cm$^{-1}$; $^1$H NMR (500.7 MHz, $CDCl_3$): $\delta$ = 1.21, 2.15 (2 m, 2 × 2H, 2 $H_2$C-hexyl), 2.78 (t, $^3J_{HH}$ = 6.8 Hz, 2H, $H_2$C-hexyl), 3.51 (d, $^3J_{PH}$ = 7.1 Hz, 3H, Me.N), 3.78 (d, $^3J_{PH}$ = 6.7 Hz, 3H, Me.O), 6.87 (t, $^3J_{HH}$ = 6.8 Hz, 1H, HC-hexyl) ppm; $^{13}$C NMR (125.4 MHz, $CDCl_3$): $\delta$ = 158.5, 149.7, 115.8, 27.1, 26.2, 21.9 (C-hexyl), 123.1 (CN), 110.6 (d, $^1J_{PC}$ = 136.4 Hz, C–P), 95.1 (*C*–CN), 55.3 (d, $^2J_{PC}$ = 8.7 Hz, MeO), 28.6 (d, $^2J_{PC}$ = 8.4 Hz, MeN) ppm; $^{31}$P NMR (200.7 MHz, $CDCl_3$): $\delta$ = 11.7 ppm; MS (EI, 70 eV): *m/z* (%) = 296 (25) [$M^+$], 268 (37) [$M^+$-28 ($N_2$)], 253 (25) [$M^+$-54 ($N_2$ + CN)], 227 (23) [$M^+$-69 ($N_2$ - + CN + Me)], 149 (100) [$M^+$-147 ($N_2$ + CN + Me + P(O)(OMe))].

*4′-Ethoxy-3′-ethyl-3′,4′,5,6-tetrahydro-4H-spiro[1-benzothiophene-2,5′-[1,2,3,4]triazaphosphole]-3-carbonitrile* (**4b**, $C_{13}H_{17}N_4O_2PS$)

Strew yellow needles; yield: 0.94 g (74.2 %); m.p.: 132 °C (cyclohexane); IR (KBr): $\overline{\nu}$ = 2211 (CN), 1243 (P=O, free), 1029 (P–O–C) cm$^{-1}$; $^1$H NMR (500.7 MHz, $CDCl_3$): $\delta$ = 1.16–1.25 (m, 6H, Me.C–N, MeC.OP), 1.11, 2.45 (2 m, 2 × 2H, 2 $H_2$C-hexyl), 2.78 (t, $^3J_{HH}$ = 6.8 Hz, 2H, $H_2$C-hexyl), 3.79 (dq, $^3J_{HH}$ = 6.7, $^3J_{PH}$ = 8.3 Hz, 2H, $H_2$CN), 4.02 (qt, $^3J_{HH}$ = 5.6, $^3J_{PH}$ = 8.9 Hz, 2H, $H_2$CO), 6.93 (t, $^3J_{HH}$ = 6.6 Hz, 1H, HC-hexyl) ppm; $^{13}$C NMR (125.4 MHz, $CDCl_3$): $\delta$ = 159.7, 149.4, 118.6, 26.7, 25.3, 22.4 (C-hexyl), 122.5 (CN), 110.3 (d, $^1J_{PC}$ = 133.6 Hz, C–P), 94.7 (*C*–CN), 63.6 (d, $^2J_{PC}$ = 12.7 Hz, $CH_2$O), 43.7 (d, $^2J_{PC}$ = 11.9 Hz, $CH_2$N), 19.7 (d, $^3J_{PC}$ = 8.3 Hz, *Me*$CH_2$-O), 14.6 (d, $^3J_{PC}$ = 7.9 Hz, *Me*$CH_2$N) ppm; $^{31}$P NMR (200.7 MHz, $CDCl_3$): $\delta$ = 12.4 ppm; MS (EI, 70 eV): *m/z* (%) = 324 (43) [$M^+$], 296 (37) [$M^+$-28 ($N_2$)], 270 (29) [$M^+$-54 ($N_2$ + CN)], 241 (56) [$M^+$-83 ($N_2$ + CN + Et)], 149 (100) [$M^+$-175 ($N_2$ + CN + Et + P(O)(OEt))].

*4′-Isopropoxy-3′-isopropyl-3′,4′,5,6-tetrahydro-4H-spiro[1-benzothiophene-2,5′-[1,2,3,4]triazaphosphole]-3-carbonitrile 4′-oxide* (**4c**, $C_{15}H_{21}N_4O_2PS$)

Strew yellow crystals; yield: 0.98 g (71.2 %); m.p.: 152 °C (MeCN); IR (KBr): $\overline{\nu}$ = 2213 (CN), 1240 (P=O, free), 1031 (P–O–C) cm$^{-1}$; $^1$H NMR (500.7 MHz, $CDCl_3$): $\delta$ = 0.96, 2.12 (2 m, 2 × 2H, 2 $H_2$C-hexyl), 1.26 (dd, $^3J_{HH}$ = 4.6, $^4J_{PH}$ = 3.8 Hz, 2 × 3H, $Me_2$CHN), 1.33 (dd, $^3J_{HH}$ = 6.7, $^4J_{PH}$ = 4.1 Hz, 2 × 3H, $Me_2$CHO), 2.69 (t, $^3J_{HH}$ = 6.5 Hz, 2H, $H_2$C-hexyl), 3.68 (dsept, $^3J_{PH}$ = 7.9 Hz, 1H, HC.N), 4.17 (dsept, $^3J_{PH}$ = 8.2 Hz, 1H, HC.O), 6.49 (t, $^3J_{HH}$ = 6.4 Hz, 1H, HC-hexyl) ppm; $^{13}$C NMR (125.4 MHz, $CDCl_3$): $\delta$ = 161.2, 149.6, 120.6, 26.6, 25.6, 22.6 (C-hexyl), 122.8 (CN), 109.8 (d, $^1J_{PC}$ = 139.5 Hz, C–P), 93.8 (*C*–CN), 75.5 (d, $^2J_{PC}$ = 12.9 Hz, CH.O), 49.6 (d, $^2J_{PC}$ = 11.9 Hz, HC.N), 24.1 (d, $^3J_{PC}$ = 7.9 Hz, $Me_2$CHO), 21.3 (d, $^3J_{PC}$ = 8.5 Hz, $Me_2$CHN) ppm; $^{31}$P NMR (200.7 MHz, $CDCl_3$): $\delta$ = 11.9 ppm; MS (EI, 70 eV): *m/z* (%) = 352 (47) [$M^+$], 324 (36) [$M^+$-28 ($N_2$)], 298 (25) [$M^+$-54 ($N_2$ + CN)], 255 (46) [$M^+$-97 ($N_2$ + CN + $C_3H_7$)], 149 (100) [$M^+$-203 ($N_2$ + CN + $C_3H_7$ + P(O)($OC_3H_7$))].

*Preparation of phosphoramidates **8a–8c** by reaction of azide **1** with dialkyl phosphites **6a–6c***

A mixture of 0.8 g azide **1** (3.9 mmol) and 4.1 mmol of dimethyl, diethyl, or diisopropyl phosphite (**6a–6c**) in 15 cm$^3$ THF was stirred at r.t. for 6–10 h (TLC) and volatile materials were removed under vacuum. The resulting residue was chromatographed on silica gel with *n*-hexane/$CHCl_3$ (8:2, v/v) to give 2-amino-4,5,6,7-tetrahydrobenzo-[*b*]thiophene-3-carbonitrile (**9**) as buff substance in 10.3 % yield; m.p. 147 °C (Ref. [26] 145 °C). Elution with *n*-hexane/$CHCl_3$ (1:1, v/v) afforded **8a–8c**.

*Dimethyl 3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-ylphosphoramidate* (**8a**, $C_{11}H_{15}N_2O_3PS$)

Colorless crystals; yield: 0.76 g (68.2 %); m.p.: 174 °C (EtOH); IR (KBr): $\overline{\nu}$ = 3322 (NH), 2198 (CN), 1234 (P=O, bonded), 1029 (P–O–C) cm$^{-1}$; $^1$H NMR (500.7 MHz, $CDCl_3$): $\delta$ = 1.91, 2.45 (2 m, 4 × 2H, 4 $H_2$C-hexyl), 3.79 (d, $^3J_{PH}$ = 11.5 Hz, 2 × 3H, 2 Me.OP), 11.35 (br, 1H, HN) ppm; $^{13}$C NMR (125.4 MHz, $CDCl_3$): $\delta$ = 151.6 (d, $^2J_{PC}$ = 31.5 Hz, C-NH), 134.4, 130.2 (*C* = *C*-hexyl), 113.8 (CN), 74.3 (*C*–CN), 52.4 (d, $^2J_{PC}$ = 12.9 Hz, 2 MeOP), 26.4, 26.1, 23.6, 22.3 ($CH_2$-hexyl) ppm; $^{31}$P NMR (200.7 MHz, $CDCl_3$): $\delta$ = 17.6 ppm; MS (EI, 70 eV): *m/z* (%) = 285 (53) [$M^+$-1], 259 (34) [$M^+$-27 (H + CN)], 150 (100) [$M^+$-136 (H + CN + P(O)$(OMe)_2$)].

*Diethyl 3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-ylphosphoramidate* (**8b**, $C_{13}H_{19}N_2O_3PS$)

Colorless crystals; yield: 0.86 g (70.6 %); m.p.: 162 °C (EtOH); IR (KBr): $\overline{\nu}$ = 3325 (NH), 2194 (CN), 1229 (P=O, bonded), 1032 (P–O–C) cm$^{-1}$; $^1$H NMR (500.7 MHz, $CDCl_3$): $\delta$ = 1.32 (dt, $^3J_{HH}$ = 6.7, $^4J_{PH}$ = 4.4 Hz, 2 × 3H, 2 MeCOP), 1.93, 2.46 (2 m, 4 × 2H, 4 $H_2$C-hexyl), 4.17 (dq, $^3J_{HH}$ = 6.7, $^3J_{PH}$ = 10.6 Hz, 2 × 2H, 2 $H_2$COP), 11.29 (br, 1H, HN) ppm; $^{13}$C NMR (125.4 MHz, $CDCl_3$): $\delta$ = 151.3 (d, $^2J_{PC}$ = 29.6 Hz, C–NH), 134.2, 129.7 (*C*=*C*-hexyl), 113.4 (CN), 74.7 (*C*–CN), 62.4 (d, $^2J_{PC}$ = 13.5 Hz, 2$CH_2$.OP), 26.3, 26.1, 23.4, 21.9 ($CH_2$-

hexyl), 16.3 (d, $^3J_{PC} = 8.2$ Hz, 2*Me*.COP) ppm; $^{31}$P NMR (200.7 MHz, $CDCl_3$): $\delta = 19.3$ ppm; MS (EI, 70 eV): *m/z* (%) = 313 (48) [$M^+$-1], 287 (34) [$M^+$-27 (H + CN)], 150 (100) [$M^+$-164 (H + CN + P(O)$(OEt)_2$)].

*Diisopropyl 3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-ylphosphoramidate* (**8c**, $C_{15}H_{23}N_2O_3PS$)
Colorless crystals; yield: 1.02 g (76.4 %); m.p.: 170 °C (EtOH); IR (KBr): $\bar{\nu}$ = 3329 (NH), 2196 (CN), 1231 (P=O, bonded), 1031 (P–O–C) $cm^{-1}$; $^1$H NMR (500.7 MHz, $CDCl_3$): $\delta = 1.34$, 1.56 (2 dd, $^3J_{HH} = 6.7$, $^4J_{PH} = 4.7$ Hz, 4 × 3H, $(Me_2CO)_2P$), 1.93, 2.51 (2 m, 4 × 2H, 4 $H_2C$-hexyl), 4.64-4.81 (2 m, 2H, $(HCO)_2P$), 10.91 (br, 1H, HN) ppm; $^{13}$C NMR (125.4 MHz, $CDCl_3$): $\delta = 151.5$ (d, $^2J_{PC} = 31.2$ Hz, C–NH), 133.9, 129.9 (*C* = *C*-hexyl), 113.5 (CN), 75.6 (*C*–CN), 71.2 (d, $^2J_{PC} = 12.7$ Hz, 2 CH.OP), 26.4, 26.2, 23.5, 21.6 ($CH_2$-hexyl), 24.2 (d, $^3J_{PC} = 8.5$ Hz, 4 Me.COP) ppm; $^{31}$P NMR (200.7 MHz, $CDCl_3$): $\delta = 18.4$ ppm; MS (EI, 70 eV): *m/z* (%) = 341 (56) [$M^+$-1], 315 (43) [$M^+$-27 (H + CN)], 150 (100) [$M^+$-192 (H + CN + P(O)$(OC_3H_7)_2$)].

*Preparation of compounds **11a** and **11b** by reaction of azide **1** with **10a**, **10b***
Hexamethyl- or hexaethylphosphorus triamide (**10a**, **10b**, 5.2 mmol) in 5 $cm^3$ THF was added dropwise to 0.8 g of azide **1** (3.9 mmol) in 10 $cm^3$ THF. The reaction mixture was stirred at r.t. for ≈4 h (TLC). The precipitate was collected and washed several times with light petroleum (40–60 °C) to give **11a** and **11b**. Compounds **11a** and **11b** are pure enough for carrying out the spectroscopic analyses, and stable for a week at −10 °C under argon.

*2-[3-[Tris(dimethylamino)phosphoranylidene]triaz-1-en-1-yl]-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile*
(**11a**, $C_{15}H_{26}N_7PS$)
Yellow material; yield: 1.26 g (90 %); m.p.: 193 °C ($CHCl_3$); IR (KBr): $\bar{\nu}$ = 2206 (CN), 1333 (P=N), 1301, 923 (P$(NMe_2)_3$) $cm^{-1}$; $^1$H NMR (500.7 MHz, $CDCl_3$): $\delta = 1.81$, 2.61 (2 m, 2 × 4H, 4 $H_2C$-hexyl), 2.75, 2.81 (2 d, $^3J_{PH} = 8.9$ Hz, 18H, $(Me_2N)_3P$) ppm; $^{13}$C NMR (125.4 MHz, $CDCl_3$): $\delta = 160.6$ (C–N=N), 131.1, 128.7 (*C*=*C*-hexyl), 117.5 (CN), 69.4 (*C*–CN), 37.8 (d, $^2J_{PC} = 13.5$ Hz, $(Me_2N)_3P$), 26.3, 26.1, 23.6, 21.4 ($CH_2$-hexyl) ppm; $^{31}$P NMR (200.7 MHz, $CDCl_3$): $\delta = 40.2$ ppm; MS (EI, 70 eV): *m/z* (%) = 367 (35) [$M^+$], 339 (24) [$M^+$-28 ($N_2$)], 313 (29) [$M^+$-54 ($N_2$ + CN)], 150 (100) [$M^+$-217 ($N_2$ + CN + $C_6H_{18}N_3P$)].

*2-[3-[Tris(diethylamino)phosphoranylidene]triaz-1-en-1-yl]-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile*
(**11b**, $C_{21}H_{38}N_7PS$)
Yellow material; yield: 1.49 g (92 %); m.p.: 184 °C (EtOH); IR (KBr): $\bar{\nu}$ = 2210 (CN), 1330 (P=N), 1317, 898 (P$(NEt_2)_3$) $cm^{-1}$; $^1$H NMR (500.7 MHz, $CDCl_3$): $\delta = 0.95$, 1.39 (2 dt, $^3J_{HH} = 8.5$, $^4J_{PH} = 6.4$ Hz, 18H, $\{(Me.C)_2N\}_3P$), 1.84, 2.63 (2 m, 4 × 2H, 4 $H_2C$-hexyl), 2.91, 3.26 (2 dq, $^3J_{HH} = 8.5$, $^3J_{PH} = 9.1$ Hz, 12H, $[(H_2C)_2N]_3P$) ppm; $^{13}$C NMR (125.4 MHz, $CDCl_3$): $\delta = 160.4$ (C–N=N), 131.3, 128.6 (*C*=*C*-hexyl), 117.4 (CN), 69.3 (C–CN), 39.5 (d, $^2J_{PC} = 13.7$ Hz, $[(CH_2)_2N]_3P$), 26.5, 26.2, 23.6, 21.2 ($CH_2$-hexyl), 14.7 (d, $^3J_{PC} = 8.4$ Hz, $[(Me.C)_2N]_3P$) ppm; $^{31}$P NMR (200.7 MHz, $CDCl_3$): $\delta = 40.4$ ppm; MS (EI, 70 eV): *m/z* (%) = 451 (34) [$M^+$], 423 (26) [$M^+$-28 ($N_2$)], 397 (19) [$M^+$-54 ($N_2$ + CN], 150 (100) [$M^+$-301 ($N_2$ + CN + $C_{12}H_{30}N_3P$)].

*Reaction of **1** with hexaalkylphosphorus triamides **10a** and **10b** in the presence of a protonating agent. Preparation of compounds **13a** and **13b***
Phosphorus triamides **10a**, **10b** (5.2 mmol) in 5 $cm^3$ of dry THF were added in one portion to a mixture of 0.8 g azide **1** (3.9 mmol) and 2 $cm^3$ dil. EtOH (1:1) in 10 $cm^3$ THF. The reaction mixture was stirred at r.t. for ≈6 h (TLC). The solvent was evaporated to dryness; the residue was washed several times with light petroleum (40–60 °C), and crystallized from the proper solvent to give **13a** and **13b**, respectively.

*N″-(3-Cyano-4,5,6,7-tetrahydro-1-benzothien-2-yl)-N,N,N′,N′-tetramethylphosphoric triamide*
(**13a**, $C_{13}H_{21}N_4OPS$)
Pale yellow crystals; yield: 0.97 g (79.6 %); m.p.: 165 °C (MeCN); IR (KBr): $\bar{\nu}$ = 3325 (NH), 2205 (CN), 1232 (P=O, bonded) $cm^{-1}$; $^1$H NMR (500.7 MHz, $CDCl_3$): $\delta = 1.91$, 2.32 (2 m, 4 × 2H, 4 $H_2C$-hexyl), 2.45 (d, $^3J_{PH} = 9.4$ Hz, 2 × 6H, $(Me_2N)_2P$), 11.21 (br, 1H, HN) ppm; $^{13}$C NMR (125.4 MHz, $CDCl_3$): $\delta = 150.6$ (d, $^2J_{PC} = 28.3$ Hz, C–NH), 136.1, 130.2 (*C*=*C*-hexyl), 113.7 (CN), 87.3 (*C*–CN), 35.5 (d, $^2J_{PC} = 13.5$ Hz, $(Me_2N)_2P$), 26.4, 26.2, 23.5, 21.8 ($CH_2$-hexyl) ppm; $^{31}$P NMR (200.7 MHz, $CDCl_3$): $\delta = 34.7$ ppm; MS (EI, 70 eV): *m/z* (%) = 311 (45) [$M^+$-1], 285 (34) [$M^+$-27 (H + CN)], 150 (100) [$M^+$-162 (H + CN + $C_4H_{12}N_2OP$)].

*N″-(3-Cyano-4,5,6,7-tetrahydro-1-benzothien-2-yl)-N,N,N′,N′-tetraethylphosphoric triamide*
(**13b**, $C_{17}H_{29}N_4OPS$)
Pale yellow crystals; yield: 1.1 g (82.4 %); m.p.: 153 °C ($CHCl_3$); IR (KBr): $\bar{\nu}$ = 3327 (NH), 2205 (CN), 1228 (P=O, bonded) $cm^{-1}$; $^1$H NMR (500.7 MHz, $CDCl_3$): $\delta = 1.32$ (dt, $^3J_{HH} = 7.7$, $^4J_{PH} = 5.4$ Hz, 2 × 6H, $[MeC.C)_2N]_2P$), 1.92, 2.45 (2 m, 4 × 2H, 4 $H_2C$-hexyl), 3.26 (dq, $^3J_{HH} = 7.7$, $^3J_{PH} = 8.6$ Hz, 2 × 4H, $[(H_2C)_2N]_2P$), 11.25 (br, 1H, HN) ppm; $^{13}$C NMR (125.4 MHz, $CDCl_3$): $\delta = 150.4$ (d, $^2J_{PC} = 28.6$ Hz, C–NH), 135.8, 130.1 (*C*=*C*-hexyl), 113.6 (CN), 88.2 (*C*–CN), 40.8 (d,

$^{2}J_{PC}$ = 13.5 Hz, [(Me$CH_2$)$_2$N]$_2$P), 26.3, 25.9, 23.5, 21.2 ($CH_2$-hexyl), 16.3 (d, $^{3}J_{PC}$ = 8.2 Hz, [(*Me*$CH_2$)$_2$N]$_2$P) ppm; $^{31}$P NMR (200.7 MHz, $CDCl_3$): $\delta$ = 33.3 ppm; MS (EI, 70 eV): *m/z* (%) = 367 (42) [$M^+$-1], 341 (31) [$M^+$-27 (H + CN)], 150 (100) [$M^+$-218 (H + CN + $C_8H_{20}N_2OP$)].

### Antitumor activity screening

Determination of $GI_{50}$, TGI, and $LC_{50}$ values: A total of 12 human tumor cell lines, derived from three cancer types (breast, colon, and prostate), formed the basis of this test [35, 36]. The tumor cells were cultured in RPM11640 medium supplemented with 5 % fetal calf serum and 2 mM L-glutanine. The tumor cells are inoculated over a series of standard 48-well microtiter plates in 100 $cm^3$ of medium. Density of inoculums depends on the type of tumor cell and on its growth characteristics. These cells are then preincubated on the microtiter plate for 24 h before adding the compounds. They were tested in DMSO solution at three different concentrations ($10^{-4}$, $10^{-5}$, and $10^{-6}$ M). After an incubation of the chemical agent for 48 h with the tumor cell lines, a sulforhodamine B (SRB) protein assay was used to estimate cell viability or growth. The cytotoxic effects are evaluated, and the assay was used to estimate cell viability or growth, and the assay results and dose–response parameters were calculated as previously described [34].

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