Arabian Journal of Chemistry (2015) **xxx**, xxx–xxx

King Saud University

Arabian Journal of Chemistry

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ORIGINAL ARTICLE

One-pot three-component synthesis of peptidomimics for investigation of antibacterial and antineoplastic properties

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Received 22 November 2014; accepted 18 April 2015

KEYWORDS

α-Hydroxyphosphonates;
Peptidomimics;
Multicomponent reactions;
Antimicrobial/antineoplastic properties

Abstract The α-hydroxyphosphonate generated from dialkyl phosphites and 1-phenyl-1*H*-pyrazole-4-carbaldehyde derivative was, in situ, trapped by isothiocyanates, isocyanates or acetic anhydride to produce dialkyl phosphorylmethyl-carbamothioates, -carbamates and/or -methyl acetates in good yields. The reactions were carried out in tetrahydrofuran (THF) in one step at room temperature, using K_2CO_3 catalyst. Antimicrobial and antineoplastic activities of the synthesized compounds were estimated. The results showed that all new compounds cause moderate to good antibiotic activities. However, phosphorylmethylcarbamothioates exhibited the highest growth inhibition. Furthermore, selected nine new synthesized compounds were evaluated for anticancer activity against eight human tumor cell lines (*MCF7*, *MDA-MB-435*, *BT-549*, *IGROVI*, *SK-OV-3*, *PX-3*, *PU-145*, and *HEPG2*). The majority of these compounds revealed moderate to potent activity against *MCF7*, *PU-145*, and *HEPG2*. Among them, two of the phosphorylmethylcarbamo thioates showed excellent broad spectrum of anticancer activity with IC_{50} values ranging from 16.6 to 26.9 and 17.2 to 36.9 μmol L^{-1}, respectively (for 5-fluorouracil IC_{50}: 17.7 to 38.8 μmol L^{-1}). Phosphorylmethyl methylcarbamothioate, in particular was more potent than 5-fluorouracil against all tested human carcinoma cell lines.

1. Introduction

Currently, cancer is among the most critical health issues and considered to be the second leading cause of death worldwide, just behind cardiovascular diseases (Varmus, 2006). Tremendous progress has been made in the war against cancer diseases with the development of many new chemotherapy agents (Harrison et al., 2009), such as paclitaxel, docetaxel (Kingston and Newman, 2007) and ixabepilone (Hunt, 2009), as well as small molecule targeted therapies (Baselga, 2006)

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Peer review under responsibility of King Saud University.

ELSEVIER Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.arabjc.2015.04.014

such as imatinib (Cross and Lyseng-Williamson, 2007) and sorafenib (Wood and Manchen, 2007). Nevertheless, due to the toxicity, problems of mutagenicity, and drug resistance of many currently available treatments, it remains a great challenge to discover and develop more effective drugs to conquer cancer diseases (Varmus, 2006).

In parallel, because of the widespread resistance to antimicrobial drugs, there is an increasing need for developing lead-structures that may be of use in designing new potent and less toxic antimicrobial agents. Furthermore, as it is stated that the antitumor efficacy of many chemotherapeutic agents in many occasions is correlated with antibiotic properties (Sievert et al., 2002; Bremner et al., 2007), new approaches to promote anti-proliferation and apoptosis in cancer cells along with enhancing the antibiotic activity could lead to the development of dual/multiple targets (Hubschwerlen et al., 2003). In addition, these new agents may overcome tumor resistance. In sequel, and in continuation of our cancer-treatment (Abdou et al., 2012a,b,c,d, 2013a,b; Kamel et al., 2012) and antibiotic research programs (Abdou et al., 2009a,b, 2014b,c; Abdou and Khidre, 2010), we have recently considered the anticancer–antibiotic relationship studies (Abdou et al., 2014a).

Over the last three decades, organophosphorus compounds have been notably recognized for their pharmacological anticancer (Pratt, 1989; Wardle et al., 2005) and antibiotic activity (Duncanson et al., 2012), especially when they are associated with various heterocycles (Franco et al., 1995). One of the most important of these bioactive heterocycles is the pyrazole nucleus (Lee et al., 2003; Elguero, 1996).

We have focused, in this work on the synthesis of dialkoxyphosphoryl peptides. The demand for modified peptides with improved stability profiles and pharmacokinetic properties is driving extensive research efforts in this field. Many structural modifications of peptides guided by rational design and molecular modeling have been established to develop novel synthetic approaches (Goodman, 2003).

2. Material and methods

2.1. General data

Melting points were determined with an open capillary tube on an Electrothermal (variable heater, Stuart, UK) melting point apparatus and were corrected. IR spectra were recorded on a JASCO FT-IR 6100 using KBr disk (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 $CDCl_3$ or DMSO-d^6. Chemical shifts (δ) are given in ppm. The mass spectra were recorded at 70 eV on an MS-50 Kratos (A.E.I.) spectrometer (Kratos, UK) provided with a data system. Elemental analyses were carried out at the Microanalysis Laboratory, Cairo University, Cairo, Egypt, using elementary Analysensysteme GmbH-vario EL III Element Analyzer, Germany. Staring aldehyde, 3-(benzofuran-2-yl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde (**1**) was obtained using the procedure reported elsewhere (Goudarshivannanavar et al., 2009). Solvents were dried by standard techniques: TLC, Merck 0.2 mm silica gel 60 F154 anal aluminum plates.

2.2. General procedure for preparation of dialkyl phosphorylmethyl-carbamothioates 5a–5j, -carbamates 6a, 6b and -methylacetate 7a, 7b

A mixture of dimethyl (**2a**) or diethyl phosphite (**2b**, 3.4 mmol), 3-(benzofuran-2-yl)-1-methyl-1*H*-pyrazole-4-carbaldehyde (**1**, 3.4 mmol) in THF (10 mL), and potassium carbonate (5.1 mmol) was stirred for 10 min at room temperature. A solution of isothiocyanates: methyl-, ethyl-, cyclohexane-, phenyl- (**3d**), or allyl-isothiocyanate (**3a–d**, **f**), as well as phenylisocyanate (**3e**), or acetic anhydride (3.4 mmol) in 5 mL THF was then added in one portion; and the reaction mixture was stirred at room temperature for the appropriate time (4–6 h). After completion of the reaction (TLC), the mixture was filtered off and the solid K_2CO_3 washed several times with AcOEt. After removal of the evaporated materials under vacuum, the resulting residue was crystallized from the proper solvent to give the corresponding phosphonate **5a–j**, **6a**, **6b**, **7a**, or **7b**, respectively.

2.2.1. (3-(Benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl)(dimethoxyphosphoryl)methyl-methylcarbamothioate (5a)

Colorless crystals from ethanol, mp 183 °C, yield: 78%. IR (cm^{-1}, KBr): ν_{max} 3364 (NH), 1256 (P═O), 1130 (C═S), 1077 (P—O—C). ^{1}H NMR (DMSO-d^6) ppm: δ 3.33 (s, 3H, *Me*N), 3.59, 3.67 (2d, $^{3}J_{P-H}$ = 10.5 Hz, 2 × 3H, (*Me*CO)$_2$P), 5.42 (d, $^{2}J_{P-H}$ = 15.5 Hz, 1H, *H*C-P), 6.42 (br, 1H, *H*N), 7.33–7.92 (m, 10H, *H*—Ar & hetero), 8.62 (s, 1H, *H*-pyrazole).^{13}C NMR (DMSO-d^6) ppm: δ 180.2 (d, $^{3}J_{P-C}$ = 8.1 Hz, *C*═S), 152.8, 141.7, 141.1, 128.9, 128.4, 126.2, 125.1, 124.4, 122.0, 119.6, 111.4, 109.2 (*C*—Ar & hetero), 136.1 ($^{3}J_{P-C}$ = 8.6 Hz, *C*(3)-pyrazole), 130.2 (d, $^{2}J_{P-C}$ = 14.2 Hz, *C*(4)-pyrazole), 126.2 ($^{3}J_{P-C}$ = 10.2 Hz, *C*(5)-pyrazole), 68.9 (d, $^{1}J_{P-C}$ = 121.5 Hz, HCP), 53.5 (d, $^{2}J_{P-C}$ = 8.8 Hz, *Me*OP), 31.2 (N-*Me*). ^{31}P NMR (DMSO-d^6) ppm: δ 22.6. EI-MS: in *m*/*z* (%): 471 (18) [M$^+$], 470 (37) [M$^+$ − 1], 288 (100) [M$^+$ − (C(S)NHMe + P(O)(OMe)$_2$)]. Anal. Calcd for $C_{22}H_{22}N_3O_5PS$ (471.1): C, 56.05; H, 4.70; N, 8.91; P, 6.57; S, 6.80. Found: C, 56.11; H, 4.62; N, 8.78; P, 6.66; S, 6.93.

2.2.2. (3-(Benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl)(diethoxyphosphoryl)methyl methylcarbamothioate (5b)

Colorless crystals from ethanol, mp 161.5 °C, yield: 70%. IR (cm^{-1}, KBr): ν_{max} 3419 (NH), 1249 (P═O), 1132 (C═S), 1063 (P—O—C). ^{1}H NMR (DMSO-d^6) ppm: δ 1.24, 1.26 (2dt, $^{3}J_{H-H}$ = 6.7, $^{4}J_{P-H}$ = 4.4 Hz, 2 × 3H, (*Me*.CO)$_2$P), 3.36 (s, 3H, *Me*N), 4.15, 4.30 (2dq, $^{3}J_{H-H}$ = 6.7, $^{3}J_{P-H}$ = 6.2 Hz, 2 × 2H, (C*H*$_2$O)$_2$P), 5.63 (d, $^{2}J_{P-H}$ = 17.8 Hz, 1H, *H*C—P), 7.31–7.92 (m, 10H, *H*—Ar & hetero), 8.57 (s, 1H, *H*-pyrazole), 9.52 (br, 1H, *H*N). ^{13}C NMR (DMSO-d^6) ppm: δ 180.4 (d, $^{3}J_{P-C}$ = 8.4 Hz, *C*═S), 152.7, 141.6, 141.1, 128.8, 128.3, 126.1, 125.1, 124.6, 122.6, 119.3, 111.1, 109.2 (*C*—Ar & hetero), 136.1 ($^{3}J_{P-C}$ = 8.8 Hz, *C*(3)-pyrazole), 130.2 (d, $^{2}J_{P-C}$ = 14.7 Hz, *C*(4)-pyrazole), 126.2 ($^{3}J_{P-C}$ = 10.2 Hz, *C*(5)-pyrazole), 70.1 (d, $^{1}J_{P-C}$ = 120.6 Hz, HCP), 64.7 (d, $^{2}J_{P-C}$ = 7.8 Hz, H$_2$*C*OP), 31.6 (N-*Me*), 16.5 (d, $^{3}J_{P-C}$ = 6.8 Hz, *Me*.COP). ^{31}P NMR (DMSO-d^6) ppm: δ 23.9. EI-MS: in *m*/*z* (%): 499 (23) [M$^+$], 498 (35) [M$^+$ − 1], 288 (100) [M$^+$ − (C(S)NHMe + P(O)(OEt)$_2$)]. Anal. Calcd for $C_{24}H_{26}N_3O_5PS$ (499.1): C, 57.71; H, 5.25; N, 8.41; P, 6.20; S, 6.42. Found: C, 57.80; H, 5.12; N, 8.27; P, 6.23; S, 6.55.

Please cite this article in press as: Abdou, W.M., Bekheit, M.S. One-pot three-component synthesis of peptidomimics for investigation of antibacterial and antineoplastic properties. Arabian Journal of Chemistry (2015), http://dx.doi.org/10.1016/j.arabjc.2015.04.014

*2.2.3. (3-(Benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl) (dimethoxyphosphoryl)methyl-ethylcarbamothioate (**5c**)*

Colorless crystals from ethanol, mp 176 °C, yield: 75%. IR (cm^{-1}, KBr): ν_{max} 3332 (NH), 1256 (P═O), 1138 (C═S), 1075 (P─O─C). ^{1}H NMR ($CDCl_3$) ppm: δ 1.20 (t, $^3J_{H-H}$ = 6.4, 3H, *Me*C─N), 3.60 (q, $^3J_{H-H}$ = 6.4 Hz, 2H, C*H*$_2$N), 3.68, 3.82 (2d, $^3J_{P-H}$ = 11.4 Hz, 2 × 3H, (*Me*O)$_2$P), 5.60 (d, $^2J_{P-H}$ = 16.2 Hz, 1H, *H*C─P), 6.41 (br, 1H, *H*N), 7.25–7.78 (m, 10H, *H*─Ar & hetero), 8.41 (s, 1H, *H*-pyrazole). ^{13}C NMR ($CDCl_3$) ppm: δ 180.9 (d, $^3J_{P-C}$ = 8.2 Hz, *C*═S), 152.8, 141.5, 140.8, 128.8, 128.1, 126.1, 125.1, 124.6, 122.0, 119.6, 111.8, 108.8 (*C*─Ar & hetero), 136.2 ($^3J_{P-C}$ = 9.6 Hz, *C*(3)-pyrazole), 130.1 (d, $^2J_{P-C}$ = 14.7 Hz, *C*(4)-pyrazole), 126.2 ($^3J_{P-C}$ = 9.8 Hz, *C*(5)-pyrazole), 69.7 (d, $^1J_{P-C}$ = 124.2 Hz, H*C*P), 53.5 (d, $^2J_{P-C}$ = 7.2 Hz, *Me*OP), 43.1 (N─*C*H$_2$), 41.2 (N─C*Me*). ^{31}P NMR ($CDCl_3$) ppm: δ 20.5. EI-MS: in *m*/*z* (%): 485 (38) [M^+], 484 (56) [$M^+ - 1$], 288 (100) [M^+ – (C(S)NHEt + P(O)(OMe)$_2$)]. Anal. Calcd for $C_{23}H_{24}N_3O_5PS$ (485.1): C, 56.90; H, 4.98; N, 8.66; P, 6.38; S, 6.60. Found: C, 56.82; H, 4.92; N, 8.55; P, 6.29; S, 6.72.

*2.2.4. (3-(Benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl) (diethoxyphosphoryl)methyl ethylcarbamothioate (**5d**)*

Colorless crystals from ethanol, mp 143 °C, yield: 70%. IR (cm^{-1}, KBr): ν_{max} 3421 (NH), 1255 (P═O), 1134 (C═S), 1035 (P─O─C). ^{1}H NMR ($CDCl_3$) ppm: δ 1.18 (t, $^3J_{H-H}$ = 7.6, 3H, *Me*C─N), 1.28, 1.32 (2dt, $^3J_{H-H}$ = 7.8, $^4J_{P-H}$ = 5.4 Hz, 2 × 3H, (*Me*.CO)$_2$P), 3.48 (q, $^3J_{H-H}$ = 7.6 Hz, 2H, C*H*$_2$N), 4.17, 4.20 (2dq, $^3J_{H-H}$ = 7.8, $^3J_{P-H}$ = 10.8 Hz, 2 × 2H, (C*H*$_2$O)$_2$P), 5.58 (d, $^2J_{P-H}$ = 16.6 Hz, 1H, *H*C─P), 7.25–7.78 (m, 10H, *H*─Ar & hetero), 8.38 (s, 1H, *H*-pyrazole), 8.58 (br, 1H, *H*N). ^{13}C NMR ($CDCl_3$) ppm: δ 180.7 (d, $^3J_{P-C}$ = 8.2 Hz, *C*═S), 152.2, 141.6, 141.1, 128.3, 127.7, 126.1, 125.6, 124.2, 122.1, 119.0, 111.2, 108.9 (*C*─Ar & hetero), 136.5 ($^3J_{P-C}$ = 9.2 Hz, *C*(3)-pyrazole), 130.1 (d, $^2J_{P-C}$ = 13.8 Hz, *C*(4)-pyrazole), 126.0 ($^3J_{P-C}$ = 10.4 Hz, *C*(5)-pyrazole), 71.1 (d, $^1J_{P-C}$ = 121.3 Hz, H*C*P), 64.5 (d, $^2J_{P-C}$ = 8.6 Hz, H$_2$*C*OP), 43.2 (N─*C*H$_2$), 41.5 (N─C*Me*), 16.4 (d, $^3J_{P-C}$ = 7.5 Hz, *Me*.COP). ^{31}P NMR ($CDCl_3$) ppm: δ 19.7. EI-MS: in *m*/*z* (%): 513 (28) [M^+], 512 (49) [$M^+ - 1$], 288 (100) [M^+ – (C(S)NHEt + P(O)(OEt)$_2$)]. Anal. Calcd for $C_{25}H_{28}N_3O_5PS$ (513.1): C, 58.47; H, 5.50; N, 8.18; P, 6.03; S, 6.24. Found: 58.37; H, 5.56; N, 8.25; P, 5.59; S, 6.35.

*2.2.5. (3-(Benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl) (dimethoxyphosphoryl)methyl cyclohexylcarbamo-thioate (**5e**)*

Colorless crystals from ethanol, mp 176 °C, yield: 62%. IR (cm^{-1}, KBr): ν_{max} 3372 (NH), 1256 (P═O), 1136 (C═S), 1076 (P─O─C). ^{1}H NMR (DMSO-d^6) ppm: δ 1.32–2.02 (m, 10H, CH_2^chex), 3.32 (m, 1H, *H*-^{c}hex), 3.64, 3.72 (2d, $^3J_{P-H}$ = 10.8 Hz, 2 × 3H, (*Me*O)$_2$P), 5.41 (d, $^2J_{P-H}$ = 20.2 Hz, 1H, *H*C─P), 6.39 (br, 1H, *H*N), 7.28–7.92 (m, 10H, *H*─Ar & hetero), 8.39 (s, 1H, *H*-pyrazole). ^{13}C NMR (DMSO-d^6) ppm: δ 183.9 (d, $^3J_{P-C}$ = 8.3 Hz, C═S), 152.6, 141.6, 141.0, 128. 5, 128.1, 126.1, 125.3, 124.9, 121.8, 119.6, 112.0, 109.0 (*C*─Ar & hetero), 136.0 ($^3J_{P-C}$ = 10.2 Hz, *C*(3)-pyrazole), 130.3 (d, $^2J_{P-C}$ = 14.2 Hz, *C*(4)-pyrazole), 126.2 ($^3J_{P-C}$ = 10.2 Hz, *C*(5)-pyrazole), 69.7 (d, $^1J_{P-C}$ = 122.1 Hz, H*C*P), 54.2 (*C*H-^{c}hex), 53.6 (d, $^2J_{P-C}$ = 7.4 Hz, *Me*OP), 39.7, 25.4, 24.2 (*C*-^{c}hex). ^{31}P NMR (DMSO-d^6) ppm: δ 23.1. EI-MS: in *m*/*z* (%): 539 (40) [M^+], 538 (55) [$M^+ - 1$], 288 (100) [M^+ – (C(S)NH-^{c}hex + P(O)(OMe)$_2$)]. Anal. Calcd for $C_{27}H_{30}N_3O_5PS$ (539.1): C, 60.10; H, 5.60; N, 7.79; P, 5.74; S, 5.94. Found: 60.21; H, 5.55; N, 7.68; P, 5.79; S, 6.88.

*2.2.6. (3-(Benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl) (diethoxyphosphoryl)methyl cyclohexylcarbamo-thioate (**5f**)*

Colorless crystals from ethanol, mp 149 °C, yield: 64%. IR (cm^{-1}, KBr): ν_{max} 3415 (NH), 1254 (P═O, free), 1130 (C═S), 1060 (P─O─C). ^{1}H NMR ($CDCl_3$) ppm: δ 1.24, 1.28 (2dt, $^3J_{H-H}$ = 7.4, $^4J_{P-H}$ = 5.6 Hz, 2 × 3H, (*Me*.CO)$_2$P), 1.30–2.04 (m, 10H, CH_2^chex), 3.43 (m, 1H, *H*-^{c}hex), 4.18, 4.24 (2dq, $^3J_{H-H}$ = 7.4, $^3J_{P-H}$ = 10.4 Hz, 2 × 2H, (CH$_2$O)$_2$P), 5.71 (d, $^2J_{P-H}$ = 14.7 Hz, 1H, *H*C─P), 6.86 (br, 1H, *H*N), 7.25–7.72 (m, 10H, *H*─Ar & hetero), 8.36 (s, 1H, *H*-pyrazole). ^{13}C NMR ($CDCl_3$) ppm: δ 183.7 (d, $^3J_{P-C}$ = 8.6 Hz, *C*═S), 152.5, 141.3, 139.8, 128.4, 128.0, 126.1, 125.2, 124.8, 121.8, 119.5, 112.1, 108.7 (*C*─Ar & hetero), 136.2 ($^3J_{P-C}$ = 8.9 Hz, *C*(3)-pyrazole), 130.2 (d, $^2J_{P-C}$ = 14.5 Hz, *C*(4)-pyrazole), 126.2 ($^3J_{P-C}$ = 9.8 Hz, *C*(5)-pyrazole), 69.5 (d, $^1J_{P-C}$ = 125.4 Hz, H*C*P), 64.3 (d, $^2J_{P-C}$ = 7.6 Hz, H$_2$*C*OP), 53.8 (*C*H-^{c}hex), 31.3, 25.6, 24.6 (*C*-^{c}hex), 16.4 (d, $^3J_{P-C}$ = 7.3 Hz, *Me*.COP). ^{31}P NMR ($CDCl_3$) ppm: δ 20.8. EI-MS: in *m*/*z* (%): 567 (45) [M^+], 566 (65) [$M^+ - 1$], 288 (100) [M^+ – (C(S)NH-^{c}hex + P(O)(OEt)$_2$)]. Anal. Calcd for $C_{29}H_{34}N_3O_5PS$ (567.2): C, 61.36; H, 6.04; N, 7.40; P, 5.46; S, 5.65. Found: C, 61.45; H, 5.95; N, 7.33; P, 5.38; S, 5.76.

*2.2.7. (3-(Benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl)(dimethoxyphosphoryl)methyl phenylcarbamothioate (**5g**)*

Colorless crystals from ethanol, mp 146 °C, yield: 66%. IR (cm^{-1}, KBr): ν_{max} 3417 (NH), 1262 (P═O), 1124 (C═S), 1035 (P─O─C). ^{1}H NMR (DMSO-d^6) ppm: δ 3.62, 3.72 (2d, $^3J_{P-H}$ = 10.5 Hz, 2 × 3H, (*Me*O)$_2$P), 5.42 (d, $^2J_{P-H}$ = 17.6 Hz, 1H, *H*C─P), 6.12 (br, 1H, *H*N), 7.22–7.73 (m, 15H, *H*─Ar & hetero), 8.32 (s, 1H, *H*-pyrazole). ^{13}C NMR (DMSO-d^6) ppm: δ 180.1 (d, $^3J_{P-C}$ = 8.4 Hz, C═S), 152.5, 141.7, 141.2, 138.3, 129.0, 128.8, 128.3, 126.1, 125.5, 125.0, 124.4, 121.3, 120.4, 119.4, 111.7, 109.2 (*C*─Ar & hetero), 135.9 ($^3J_{P-C}$ = 8.8 Hz, *C*(3)-pyrazole), 130.4 (d, $^2J_{P-C}$ = 14.7 Hz, *C*(4)-pyrazole), 126.3 ($^3J_{P-C}$ = 10.2 Hz, *C*(5)-pyrazole), 66.1 (d, $^1J_{P-C}$ = 124.8 Hz, H*C*P), 53.6 (d, $^2J_{P-C}$ = 7.4 Hz, *Me*OP). ^{31}P NMR (DMSO-d^6) ppm: δ 21.8. EI-MS: in *m*/*z* (%): 533 (24) [M^+], 532 (57) [$M^+ - 1$], 288 (100) [M^+ – (C(S)NHPh + P(O)(OMe$_2$)]. Anal. Calcd for $C_{27}H_{24}N_3O_5PS$ (533.1): C, 60.78; H, 4.53; N, 7.88; P, 5.81; S, 6.01. Found: C, 60.88; H, 4.47; N 7.79; P, 5.82; S, 6.14.

*2.2.8. (3-(Benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl)(diethoxyphosphoryl)methyl phenylcarbamothioate (**5h**)*

Colorless crystals from ethanol, mp 140 °C, yield: 78%. IR (cm^{-1}, KBr): ν_{max} 3399 (NH), 1257 (P═O), 1137 (C═S), 1033 (P─O─C). ^{1}H NMR (DMSO-d^6) ppm: δ 1.04, 1.11 (2dt, $^3J_{H-H}$ = 8.6, $^4J_{P-H}$ = 4.5 Hz, 2 × 3H, (*Me*.CO)$_2$P), 4.03, 4.12 (2dq, $^3J_{H-H}$ = 8.6, $^3J_{P-H}$ = 10.2 Hz, 2 × 2H, (C*H*$_2$O)$_2$P), 5.37 (d, $^2J_{P-H}$ = 16.8 Hz, 1H, *H*C─P), 6.37 (br, 1H, *H*N), 7.26–7.92 (m, 15H, *H*─Ar & hetero), 8.58 (s, 1H, *H*-pyrazole). ^{13}C NMR (DMSO-d^6) ppm: δ 180.7 (d, $^3J_{P-C}$ = 7.9 Hz, *C*═S), 152.5, 141.6, 140.8, 138.3, 129.2, 128.5, 128.0, 126.1, 125.8, 124.8, 124.0, 121.3, 120.4, 118.9,

111.5, 109.3 (*C*—Ar & hetero), 135.4 ($^3J_{P-C}$ = 8.8 Hz, *C*(3)-pyrazole), 133.2 (d, $^2J_{P-C}$ = 14.5 Hz, *C*(4)-pyrazole), 126.5 ($^3J_{P-C}$ = 11.2 Hz, *C*(5)-pyrazole), 66.3 (d, $^1J_{P-C}$ = 127.3 Hz, H*C*P), 64.4 (d, $^2J_{P-C}$ = 7.8 Hz, H_2*C*OP), 15.9 (d, $^3J_{P-C}$ = 7.9 Hz, *Me*.COP). ^{31}P NMR (DMSO-d^6) ppm: δ 20.4. EI-MS: in *m*/*z* (%): 561 (31) [M$^+$], 560 (53) [M$^+$ − 1], 288 (100) [M$^+$ − (C(S)NHPh + P(O)(OEt)$_2$)]. Anal. Calcd for $C_{29}H_{28}N_3O_5PS$ (561.1): C, 62.02; H, 5.03; N, 7.48; P, 5.52; S, 5.71. Found: C, 62.20; H, 4.95; N, 7.42; P, 5.63; S, 5.81.

*2.2.9. (3-(Benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl)(dimethoxyphosphoryl)methyl phenylcarbamate (**5i**)*

Colorless crystals from ethanol, mp 174 °C, yield: 82%. IR (cm^{-1}, KBr): ν_{max} 3341 (NH), 1703 (C═O), 1256 (P═O), 1075 (P—O—C). ^{1}H NMR ($CDCl_3$) ppm: δ 3.06 (br, 1H, *H*N), 3.69, 3.82 (2d, $^3J_{P-H}$ = 12.3 Hz, 2 × 3H, (*Me*O)$_2$P), 5.62 (d, $^2J_{P-H}$ = 14.6 Hz, 1H, *H*C—P), 7.25–7.77 (m, 15H, *H*—Ar & hetero), 8.41 (s, 1H, *H*-pyrazole). ^{13}C NMR ($CDCl_3$) ppm: δ 154.2 (d, $^3J_{P-C}$ = 6.5 Hz, C═O), 150.9, 140.7, 139.8, 138.1, 128.9, 128.5, 127.3, 126.0, 125.5, 124.8, 123.7, 120.9, 120.3, 119.1, 111.7, 109.4 (*C*—Ar & hetero), 135.8 ($^3J_{P-C}$ = 8.6 Hz, *C*(3)-pyrazole), 130.1 (d, $^2J_{P-C}$ = 14.3 Hz, *C*(4)-pyrazole), 126.4 ($^3J_{P-C}$ = 10.8 Hz, *C*(5)-pyrazole), 68.1 (d, $^1J_{P-C}$ = 125.6 Hz, H*C*P), 53.1 (d, $^2J_{P-C}$ = 7.2 Hz, *Me*OP). ^{31}P NMR ($CDCl_3$) ppm: δ 23.9. EI-MS: in *m*/*z* (%): 517 (28) [M$^+$], 516 (42) [M$^+$ − 1], 288 (100) [M$^+$ − (C(O)NHPh + P(O)(OMe)$_2$)]. Anal. Calcd for $C_{27}H_{24}N_3O_6P$ (517.1): C, 62.67; H, 4.67; N, 8.12; P, 5.99. Found: C, 62.54; H, 4.59; N, 8.03; P, 6.22.

*2.2.10. (3-(Benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl)(diethoxyphosphoryl)methyl phenylcarbamate (**5j**)*

Colorless crystals from ethanol, mp 148.5 °C, yield: 80%. IR (cm^{-1}, KBr): ν_{max} 3365 (NH), 1742 (C═O), 1258 (P═O), 1062 (P—O—C). ^{1}H NMR (DMSO-d^6) ppm: δ 1.04, 1.19 (2dt, $^3J_{H-H}$ = 6.7, $^4J_{P-H}$ = 4.4 Hz, 2 × 3H, (*Me*.CO)$_2$P), 4.03, 4.16 (2dq, $^3J_{H-H}$ = 6.7, $^3J_{P-H}$ = 11.2 Hz, 2 × 2H, (CH_2O)$_2$P), 5.37 (d, $^2J_{P-H}$ = 21.4 Hz, 1H, *H*C—P), 6.40 (br, 1H, *H*N), 7.26–7.91 (m, 15H, *H*—Ar & hetero), 8.58 (s, 1H, *H*-pyrazole). ^{13}C NMR (DMSO-d^6) ppm: δ 153.8 (d, $^3J_{P-C}$ = 6.4 Hz, *C*═O), 151.2, 141.0, 138.6, 137.6, 128.7, 128.1, 127.2, 126.3, 125.2, 124.8, 124.3, 120.8, 120.2, 119.4, 111.8, 109.1 (*C*—Ar & hetero), 135.1 ($^3J_{P-C}$ = 8.6 Hz, *C*(3)-pyrazole), 130.4 (d, $^2J_{P-C}$ = 14.4 Hz, *C*(4)-pyrazole), 125.9 ($^3J_{P-C}$ = 10.2 Hz, *C*(5)-pyrazole), 68.7 (d, $^1J_{P-C}$ = 124.6 Hz, H*C*P), 64.3 (d, $^2J_{P-C}$ = 7.9 Hz, H_2*C*OP),16.0 (d, $^3J_{P-C}$ = 7.5 Hz, *Me*.COP). ^{31}P NMR (DMSO-d^6) ppm: δ 22.4. EI-MS: in *m*/*z* (%): 545 (27) [M$^+$], 544 (30) [M$^+$ − 1], 288 (100) [M$^+$ − (C(O)NHPh + P(O)(OEt)$_2$)]. Anal. Calcd for $C_{29}H_{28}N_3O_6P$ (545.1): C, 63.85; H, 5.17; N, 7.70; P, 5.68. Found: C, 63.91; H, 5.28; N, 7.56; P, 5.62.

*2.2.11. (3-(Benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl)(dimethoxyphosphoryl)methyl propylidenecarbamo-thioate (**6a**)*

Colorless crystals from ethanol, mp 179 °C, yield: 70%. IR (cm^{-1}, KBr): ν_{max} 1610 (N═C, exocycl), 1134 (C═S), 1251 (P═O), 1068 (P—O—C). ^{1}H NMR (DMSO-d^6) ppm: δ 2.33 (t, J_{H-H} = 6.7, 3H, *Me*CH_2), 3.44 (m, 2H, H_2C-Me), 3.66, 3.68 (2d, $^3J_{P-H}$ = 11.8 Hz, 2 × 3H, (*Me*CO)$_2$P), 5.42 (d, $^2J_{P-H}$ = 17.4 Hz, 1H, *H*C—P), 6.46 (t, J_{H-H} = 6.6 Hz, 1H, N═C*H*-exocycl), 7.35–7.92 (m, 10H, *H*—Ar & hetero), 8.60 (s, 1H, *H*-pyrazole). ^{13}C NMR (DMSO-d^6) ppm: δ 185.2 (d, $^3J_{P-C}$ = 7.5 Hz, *C*═S), 164.8 (N═*C*H-exocycl), 152.6, 141.8, 141.1, 128.9, 128.1, 126.2, 125.4, 124.3, 122.4, 119.2, 111.3, 109.4 (*C*—Ar & hetero), 135.2 ($^3J_{P-C}$ = 8.8 Hz, *C*(3)-pyrazole), 130.5 (d, $^2J_{P-C}$ = 14.7 Hz, *C*(4)-pyrazole), 126.2 ($^3J_{P-C}$ = 10.2 Hz, *C*(5)-pyrazole), 71.9 (d, $^1J_{P-C}$ = 123.4 Hz, H*C*P), 53.0 (d, $^2J_{P-C}$ = 7.8 Hz, *Me*OP), 18.7 (N═C*C*H$_2$), 11.1 (C—*C*H$_3$). ^{31}P NMR (DMSO-d^6) ppm: δ 24.1. EI-MS: in *m*/*z* (%): 497 (29) [M$^+$], 496 (53) [M$^+$ − 1], 288 (100) [M$^+$ − (C(S)C_3H_6 + P(O)(OMe)$_2$)]. Anal. Calcd for $C_{24}H_{24}N_3O_5P$ S (497.1): C, 57.94; H, 4.86; N, 8.45; P, 6.23; S, 6.45. Found: C, 58.07; H, 4.80; N, 8.37; P, 6.33; S, 6.51.

*2.2.12. (3-(Benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl)(diethoxyphosphoryl)methyl propylidenecarbamo-thioate (**6b**)*

Colorless crystals from ethanol, mp 158 °C, yield: 74%. IR (cm^{-1}, KBr): ν_{max} 1605 (N═C, exocycl), 1136 (C═S), 1258 (P═O), 1064 (P—O—C). ^{1}H NMR (DMSO-d^6) ppm: δ 1.12, 1.24 (2dt, $^3J_{H-H}$ = 7.6, $^4J_{P-H}$ = 4.4 Hz, 2 × 3H, (*Me*.CO)$_2$P), 2.24 (t, J_{H-H} = 6.4, 3H, CH$_2$*Me*), 3.52 (m, 2H, H_2CMe), 4.08, 4.12 (2dq, $^3J_{H-H}$ = 7.6, $^3J_{P-H}$ = 6.2 Hz, 2 × 2H, (CH_2O)$_2$P), 5.36 (d, $^2J_{P-H}$ = 18.6 Hz, 1H, *H*C—P), 6.35 (t, J_{H-H} = 6.5 Hz, 1H, N═C*H*-exocycl), 7.26–7.92 (m, 10H, *H*—Ar & hetero), 8.58 (s, 1H, *H*-pyrazole). ^{13}C NMR (DMSO-d^6) ppm: δ 184.8 (d, $^3J_{P-C}$ = 7.2 Hz, *C*═S),164.6 (N═*C*H-exocycl), 152.2, 141.5, 141.0, 128.8, 128.1, 126.1, 125.2, 124.0, 122.4, 119.1, 112.1, 108.9 (*C*—Ar & hetero), 135.4 ($^3J_{P-C}$ = 8.6 Hz, *C*(3)-pyrazole), 130.3 (d, $^2J_{P-C}$ = 14.7 Hz, *C*(4)-pyrazole), 126.1 ($^3J_{P-C}$ = 9.6 Hz, *C*(5)-pyrazole), 72.4 (d, $^1J_{P-C}$ = 124.5 Hz, H*C*P), 63.9 (d, $^2J_{P-C}$ = 7.6 Hz, H_2*C*OP), 15.8 (d, $^3J_{P-C}$ = 7.7 Hz, *Me*.COP), 18.2 (N═C*C*H$_2$), 11.4 (C—*C*H$_3$). ^{31}P NMR (DMSO-d^6) ppm: δ 23.7. EI-MS: in *m*/*z* (%): 525 (33) [M$^+$], 288 (100) [M$^+$ − (C(S)NHC_3H_6 + P(O)(OEt)$_2$)]. Anal. Calcd for $C_{26}H_{28}N_3O_5PS$ (525.1): C, 59.42; H, 5.37; N, 8.00; P, 5.89; S, 6.10. Found: C, 59.31; H, 5.8; N, 7.84; P, 5.94 S, 6.23.

*2.2.13. (3-(Benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl)(dimethoxyphosphoryl)methyl acetate (**7a**)*

Colorless crystals from ethanol, mp 149 °C, yield: 82%. IR (cm^{-1}, KBr): ν_{max} 1754 (C═O), 1253 (P═O), 1050 (P—O—C). ^{1}H NMR (DMSO-d^6) ppm: δ 2.12 (s, H, C(O)*Me*), 3.73, 3.78 (2d, $^3J_{P-H}$ = 11.0 Hz, 2 × 3H, (*Me*CO)$_2$P), 6.64 (d, $^2J_{P-H}$ = 14.6 Hz, 1H, *H*C—P), 7.33–7.95 (m, 10H, *H*—Ar & hetero), 8.73 (s, 1H, *H*-pyrazole). ^{13}C NMR (DMSO-d^6) ppm: δ 166.9 (d, $^3J_{P-C}$ = 8.4 Hz, *C*═O), 152.7, 141.7, 141.3, 128.5, 128.1, 126.2, 124.9, 124.2, 122.3, 119.2, 111.3, 109.5 (*C*—Ar & hetero), 136.1 ($^3J_{P-C}$ = 8.8 Hz, *C*(3)-pyrazole), 129.8 (d, $^2J_{P-C}$ = 14.2 Hz, *C*(4)-pyrazole), 126.6 ($^3J_{P-C}$ = 9.8 Hz, *C*(5)-pyrazole), 65.7 (d, $^1J_{P-C}$ = 126.2 Hz, H*C*P), 53.1 (d, $^2J_{P-C}$ = 7.4 Hz, *Me*OP), 20.6 (C(O)*Me*). ^{31}P NMR (DMSO-d^6) ppm: δ 26.7. EI-MS: in *m*/*z* (%): 440(45) [M$^+$], 331 (7) [M$^+$ − 109 (P(OMe)$_2$], 288 (100) [M$^+$ − (C(O)Me + P(O)(OMe)$_2$)]. Anal. Calcd for $C_{22}H_{21}N_2O_6P$ (440.1): C, 60.00; H, 4.81; N, 6.36; P, 7.03. Found: Found: C, 60.21 H, 4.72; N, 6.45; P, 7.17.

Please cite this article in press as: Abdou, W.M., Bekheit, M.S. One-pot three-component synthesis of peptidomimics for investigation of antibacterial and antineoplastic properties. Arabian Journal of Chemistry (2015), http://dx.doi.org/10.1016/j.arabjc.2015.04.014

*2.2.14. (3-(Benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl) (diethoxyphosphoryl)methyl acetate (**7b**)*

Colorless crystals from ethanol, mp 129 °C, yield: 86%. IR (cm^{-1}, KBr): ν_{max} 1750 (C═O), 1260 (P═O), 1058 (P─O─C). ^{1}H NMR (DMSO-d^6) ppm: δ 2.19 (s, H, C(O)*Me*), 1.06, 1.13 (2dt, $^3J_{H-H}$ = 6.5, $^4J_{P-H}$ = 6.8 Hz, 2 × 3H, (*Me*.CO)$_2$P), 4.07, 4.22 (2dq, $^3J_{P-H}$ = 11.0 Hz, 2 × 2H, (C*H*$_2$O)$_2$P), 5.59 (d, $^2J_{P-H}$ = 12.4 Hz, 1H, *H*C─P), 7.28–7.94 (m, 10H, *H*─Ar & hetero), 8.70 (s, 1H, *H*-pyrazole). ^{13}C NMR (DMSO-d^6) ppm: δ 167.1 (d, $^3J_{P-C}$ = 8.2 Hz, *C*═O), 152.2, 141.7, 141.0, 128.9, 128.3, 126.3, 125.4, 124.2, 121.8, 119.1, 111.2, 108.9 (*C*─Ar & hetero), 136.2 ($^3J_{P-C}$ = 8.6 Hz, *C*(3)-pyrazole), 130.0 (d, $^2J_{P-C}$ = 14.7 Hz, *C*(4)-pyrazole), 125.9 ($^3J_{P-C}$ = 10.6 Hz, *C*(5)-pyrazole), 66.7 (d, $^1J_{P-C}$ = 127.3 Hz, H*C*P), 64.2 (d, $^2J_{P-C}$ = 7.8 Hz, H$_2$*C*OP), 20.9 (C(O)*C*H$_3$), 16.1 (d, $^3J_{P-C}$ = 7.5 Hz, *Me*.COP). ^{31}P NMR (DMSO-d^6) ppm: δ 26.2. EI-MS: in *m*/*z* (%): 468 (43) [M$^+$], 331 (12) [M$^+$ − 109 (P(OEt)$_2$], 288 (100) [M$^+$ − (C(O)Me + P(O)(OEt)$_2$)]. Anal. Calcd for $C_{24}H_{25}N_2O_6P$ (468.1): C, 61.54; H, 5.38; N, 5.98; P, 6.61. Found: C, 61.60; H, 5.21; N, 5.88; P, 6.75.

2.3. Pharmacological evaluation

2.3.1. Antimicrobial activity

The antimicrobial activity of the synthesized phosphonates **5a–5j**, **6a**, **6b**, **7a** and **7b** was individually tested against a panel of Gram negative: *Klebsiella pneumoniae* 2011E, *Pseudomonas aeruginosa* 6065 Y; *Escherichia coli* BW54; *Escherichia coli* BW55, *Acinetobacter hemolyticus* BW62; *Stenotrophomonas maltophilia* D457R; and Gram positive bacterial pathogens: Staphylococcus epidermis 887E, bacillus cereus ATCC 11778, *Staphylococcus aureus* ATCC 29213 and *Sarcina lutea*. Ciprofloxacin (**Cipro**) and chloramphenicol (**Chlor**) were used as positive reference standards. The tested compounds and the drugs were used at a concentration 10 μmol mL^{-1} (DMSO). Antimicrobial tests were carried out by the agar well diffusion method (Perez et al., 1990) using 100 mL of a suspension of the proper LB nutrient broth (the medium that is used to grow bacteria) containing 1×10^8 CFU mL^{-1} bacteria. The antimicrobial activity was evaluated by measuring the zone of inhibition against the tested organisms and compared with that of the standards. Antimicrobial activities were expressed as the inhibition diameter zones in millimeters (mm) and presented in Table 1. Each experiment was carried out in triplicate and the average zone of inhibition was calculated.

2.3.2. Minimal inhibitory- (MIC, μmol L^{-1}) and minimal bactericidal concentration (MBC, μmol L^{-1}) evaluation

The bacteriostatic activity of the most active compounds **5a–5d**, **5g**, and **5h**, **Cipro** and **Chlor** was determined by the broth microdilution method on 96-well polystyrene flatbottom microtiter plates (Sarstedt, Germany), according to Clinical Laboratory Standards Institute (CLSI) guidelines specifications (Scott, 1989). The antimicrobial activity was assessed for each compound in the range of concentration from 450 to 10 μmol L^{-1} (450, 200, 100, 50, 25, 10 μmol L^{-1}) in cation-adjusted Mueller Hinton (MH) medium (Fluka). Overnight cultures incubated at 30 °C or 37 °C as appropriate in MH, were standardized to 0.5 McFarland units at 625 nm. Each compound-containing well and the positive control wells were inoculated with 2×10^8 CFU. Each plate included the positive control (bacteria without the antimicrobial) and the negative controls (medium only). MIC was recorded as the lowest concentration of compound that did not result in an observed optical density (*OD*) at a wavelength (λ) of 595 nm higher than its respective control with compound only after 24 h of incubation at 37 °C. Each assay was performed in triplicate. A strain is considered multi-resistant when it is non-susceptible to at least 3 different classes of antimicrobial agents. The lowest concentration showing no growth was taken as the minimum inhibitory concentration (MIC μmol L^{-1}).

After 24 h of incubation, a spotting essay was performed in order to evaluate minimum bacterial concentration (MBC). Plates were prepared using LB nutrient broth solid medium, dried on a laminar flux chamber and inoculated with 5 mL of the content of each microplate pit. Plates were incubated at 37 °C overnight for CFU counting. MBC was recorded as the lowest concentration used that did not result in an eye-observable culture in solid medium after 24 h of incubation. Each assay was performed in triplicate. Data of MIC (μmol L^{-1})/MBC (μmol L^{-1}) are presented in Table 2.

2.3.3. Antitumor activity screening

Antitumor potency of selected phosphonates **5a–5d**, **5f**, **5g**, **5j**, **6a and 7a** was tested at a dose of 10 μmol L^{-1} (DMSO) utilizing 8 different human tumor cell lines. These lines represent breast (MCF7, MDA-MB-435, BT-549), ovarian (IGROVI, SK-OV-3), prostate (PX-3, PU-145), and liver (HEPG2). 5-Fluorouracil was used as a positive reference according to the reported methods (Kitamura et al., 2004; Boyd and Paull, 1995) (Table 3). Using absorbance measurements at a wavelength (λ) 515 nm for each compound for the control growth and for the test growth, the percentage growth inhibition is calculated at each of the tested compound concentration level. The susceptibility testing assays were undertaken three times. Growth inhibition of 50% (GI_{50} μmol L^{-1}) was calculated. Further studies on experimental tumors *in vivo* for evaluating the possible antineoplastic potential of the most promising compounds are in progress.

3. Results and discussion

3.1. Chemistry

We have focused, in this work on the synthesis of dialkoxyphosphoryl peptides. The demand for modified peptides with improved stability profiles and pharmacokinetic properties is driving extensive research efforts in this field. Many structural modifications of peptides guided by rational design and molecular modeling have been established to develop novel synthetic approaches (Goodman, 2003).

Our targets, dialkoxyphosphoryl peptides **5a–5j** were obtained using the three component reaction of 3-(benzofuran-2-yl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde (**1**), dialkyl phosphites **2a**, **2b** and isothiocyanates **3a–3d** (or isocyanates **3e**), successively in tetrahydrofuran (THF) containing potassium carbonate (K_2CO_3). Obviously, the phosphonates **5** were observed through the initial formation of the α-hydroxyhydrocarbylphosphonates **4** *via* the nucleophilic addition of the phosphite reagent to the aldehyde, followed by the hydrophosphonylation of the imine function of **3** (Scheme 1) (Kaboudin

Table 1 Zone of growth inhibition (mm)[a] of the phosphor esters **5a–5j**, **6a**, **6b**, **7a** and **7b**, **Cipro**, and **Chlor** against some bacteria.

Cmpd.	Strain (Gram-negative)						Strain (Gram-positive)			
	K. pneumoniae 2011E	*P. aeruginosa* 6065Y	*E. coli* BW54	*E. coli* BW55	*A. hemolyticus* BW62	*S. maltophilia* D457R	*S. epidermis* 887E	*B. cereus* ATCC 11778	*S. aureus* ATCC 29213	*Sarcina lutea*
Cipro	12	9	11	11	10	9	10	14	12	12
Chlor	10	8	11	7	9	9	12	11	10	10
5a	13	10	12	11	12	10	13	14	14	9
5b	14	10	12	9	11	8	11	12	12	10
5c	10	9	8	7	8	11	6	6	8	7
5d	9	8	10	8	7	6	7	9	7	11
5e	6	5	8	6	8	5	4	6	5	4
5f	6	4	5	6	7	6	4	4	5	7
5g	11	8	10	8	9	6	11	10	10	9
5h	6	7	4	5	5	6	4	6	6	8
5i	8	6	6	7	8	4	5	6	5	7
5j	8	6	6	7	5	4	6	7	5	6
6a	6	8	6	7	5	7	4	6	7	7
6b	7	5	8	4	6	5	7	5	⩽4[b]	6
7a	⩽4	⩽4	⩽4	⩽4	⩽4	⩽4	⩽4	⩽4	⩽4	⩽4
7b	⩽4	⩽4	⩽4	⩽4	⩽4	⩽4	⩽4	⩽4	⩽4	⩽4

[a] Concentration of each used compound is 10 μmol L^{-1} (DMSO).
[b] Compounds, which have < 4 mm growth inhibition, were considered inactive.

Table 2 MIC (μmol L^{-1})/MBC (μmol L^{-1}) of the phosphonates **5a–d**, **5g**, **5h**, **Cipro** and **Chlor** against some bacteria.

Strains	**Cipro**	**Chlor**	**5a**	**5b**	**5c**	**5d**	**5g**	**5h**
K. pneumoniae 2011E	90.6/90.6	55.7/99	61.5/76.4	56.1/176.3	65.9/65.9	97.5/124.7	82.5/375.2	137.2/196.1
P. aeruginosa 6065Y	102.7/187.3	99/99	59.4/138	66.1/100.2	65.9/65.9	124.7/194.9	82.5/375.2	114.1/114.1
E. coli BW54	193.3/193.3	49.5/198.1	42.5/67.9	60.1/200.4	61.8/131.9	68.2/116.9	56.3/120	114.1/213.9
E. coli BW55	362.5/368.5	396.2/396.2	186.8/233.5	128.2/128.2	61.8/131.9	124.7/249.5	60/60	114.1/228.1
A. hemolyticus BW62	362.5/694.9	37.1/46.4	259/329	56.1/56.1	61.8/65.9	48.7/62.4	131.3/375.2	245.9/445.6
S. maltophilia D457R	96.7/135.9	123.8/123.8	63.7/106.1	48.1/66.1	90.7/263.9	62.4/389.9	131.3/375.2	114.1/114.1
S. epidermis 887E	377.6/543.8	191.9/433.4	159.2/271.8	156.3/354.7	185.6/131.9	257.3/194.9	326.4/422.1	276.3/415.3
B. cereus ATCC 11778	66.5/193.3	111.4/173.4	50.9/127.4	160.3/200.4	65.9/131.9	85.7/194.9	75/187.6	228.2/356.5
S. aureus ATCC 29213	181.2/181.2	198.1/619.2	93.4/163.5	92.2/200.4	90.7/113.4	128.6/ 194.9	112.6/120	228.2/356.5
Sarcina lutea	96.7/377.6	198.1/619.2	53.1/212.3	80.1/220.4	82.4/181.4	140.3/ 389.9	103.2/375.2	115.8/392.1

and Nazari, 2001; Li et al., 2008). In the IR (ν_{max} cm^{-1}, KBr) spectra of **5a–5j**, NH bond was observed at about 3421–3332 while the thiocarbamyl (C═S) bond was displayed within 1138–1124 (**5a–5h**) whereas the carbonyl bonds of **5i** and **5j** appeared at 1703 and 1742. In the NMR spectra (δ ppm) of **5b** "as a representative example", the exocyclic methine moiety "chiral" was found at δ_H = 5.63 (d, $^2J_{P-H}$ = 17.8 Hz) and at δ_c 70.1 (d, $^1J_{P-C}$ = 120.6 Hz). *N*-Methyl protons appeared as a singlet at 3.36 (3H) and at δ_c 31.6. ^{13}C NMR spectrum of **5b** also showed the signals at 180.4 (d, $^3J_{P-C}$ = 8.4 Hz, C═S), 136.1 ($^3J_{P-C}$ = 8.8 Hz, *C*(3)-pyrazole) pm. The ^{31}P NMR spectrum of **5b** showed a positive signal at δ_P = 23.9 ppm (*vs* H_3PO_4) that indicates the phosphonate structure. Finally, compound **5b** was correctly identified as $C_{24}H_{26}N_3O_5PS$, {*m*/*z* (%): 499 (23) [M^+], 498 (35) [$M^+ - 1$], and the base peak at 288 (100) [M^+ − (C(S)NHMe + P(O)(OET)$_2$)]}.

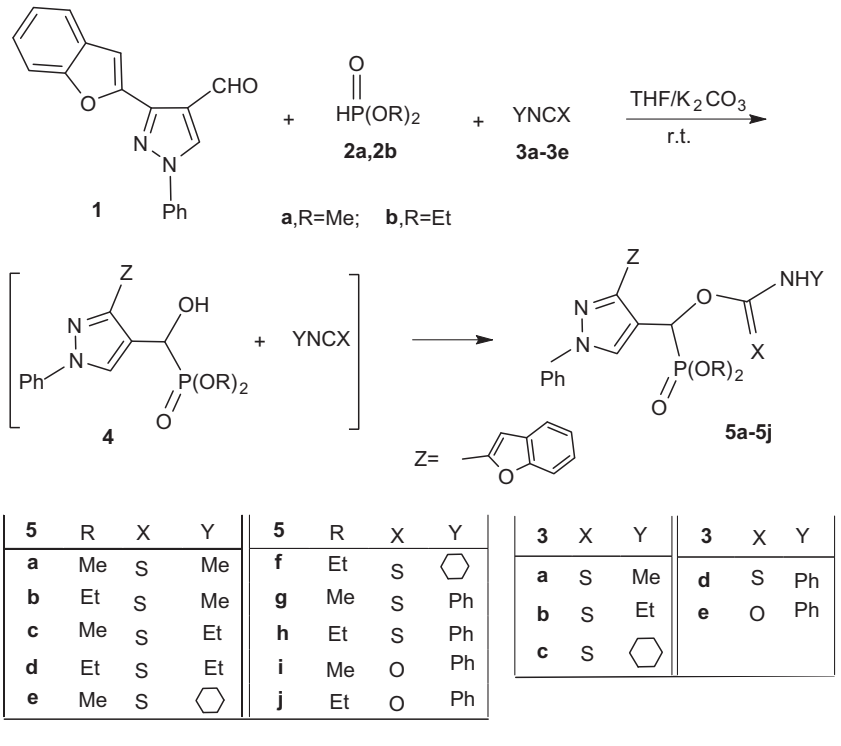
On the other hand, when the unsaturated isothiocyanate **3f** was applied in the above reaction with pyrazole-4-carbaldehyde **1** and dialkyl phosphites **2a**, **2b**, the phosphonates **6a**, **6b** were produced in 70 and 74 yields. Compounds **6a**, **6b** were derived from the rearrangement of **5k** and **5l** (Scheme 2). Structure **6a** was clearly verified by its NMR spectra. ^{1}H NMR (δ ppm) did not show any of NH signal and revealed no D_2O exchanges. However, the two methoxyl (P(OMe)$_2$) protons displayed as two doublets ($^3J_{P-H}$ = 11.8 Hz, 2 × 3H) at 3.66, 3.68 whereas the ethyl (N═CH─C_2H_5) protons resonated at 2.33 (t, J_{H-H} = 6.7 Hz, 3H, *Me*CH_2) and 3.44 (m, 2H, H_2C-Me). The imine proton (N═C*H*) appeared as a triplet at 6.46 ppm (t, J_{H-H} = 6.6 Hz, 1H, N═C*H*-exocycl). ^{13}C NMR spectrum of **6a** showed among others *C*═S (d, $^3J_{P-C}$ = 7.5 Hz) at 186.2, and N = *C*H at 164.8 ppm.

Structure **6a** was clearly verified by its NMR spectra. ^{1}H NMR (δ ppm) did not show any of NH signal and revealed no D_2O exchanges. However, the two methoxyl (P(OMe)$_2$) protons displayed as two doublets ($^3J_{P-H}$ = 11.8 Hz, 2 × 3H) at 3.66, 3.68 whereas the ethyl (N═CH─C_2H_5) protons resonated at 2.33 (t, J_{H-H} = 6.7 Hz, 3H, *Me*CH_2) and 3.44 (m, 2H, H_2C-Me). The imine proton (N═C*H*) appeared as a

Table 3 Concentrations resulting in growth inhibition of 50% (IC_{50} μmol L^{-1})[a,b] of *in vitro* human tumor cell lines of **5a**, **5b**, **5c**, **5d**, **5f**, **5g**, **5j**, **6a**, **7a**.

Panel/Cell line	Control	Compounds								
	Vehicle	**F**[c]	**5a**	**5b**	**5c**	**5d**	**5f**	**5g**	**5j**	**6a**	**7a**
Breast cancer											
MCF7	–	17.7	16.6	17.2	21.8	28	31.4	34.3	31.5	36.6	58.2
MDA-MB-435	–	27.7	23.3	22.3	13.6	24.2	24.7	34.7	28.4	36.4	65.4
BT-549	–	23.6	22.7	29.4	35.7	36.6	20.4	20.2	29.3	33.4	67.3
Ovarian cancer											
IGROVI	–	38.8	24.6	29.2	29.9	24.6	24.2	40.3	51.9	47	60.3
SK-OV-3	–	27.4	26.9	36.9	34	40	23.6	58.2	55.8	55.5	69.4
Prostate cancer											
PX-3	–	22.9	22.7	17.4	23	13.4	27.9	34.1	26	53.7	37.9
PU-145	–	27.5	20.1	28.8	19.6	15.6	24.6	29.3	28.4	36.6	65.2
Liver cancer											
HEPG2	–	25.5	18.2	26.8	29.9	23.8	36.3	22.3	42.7	67.8	62.2

[a] Cell line growth inhibition with >50% at a concentration of 10 μmol L^{-1} was considered to be a noticeable activity.
[b] Data are presented as the means of three independent experiments.
[c] F: 5-Fluorouracil.



5	R	X	Y
a	Me	S	Me
b	Et	S	Me
c	Me	S	Et
d	Et	S	Et
e	Me	S	⬡

5	R	X	Y
f	Et	S	⬡
g	Me	S	Ph
h	Et	S	Ph
i	Me	O	Ph
j	Et	O	Ph

3	X	Y
a	S	Me
b	S	Et
c	S	⬡

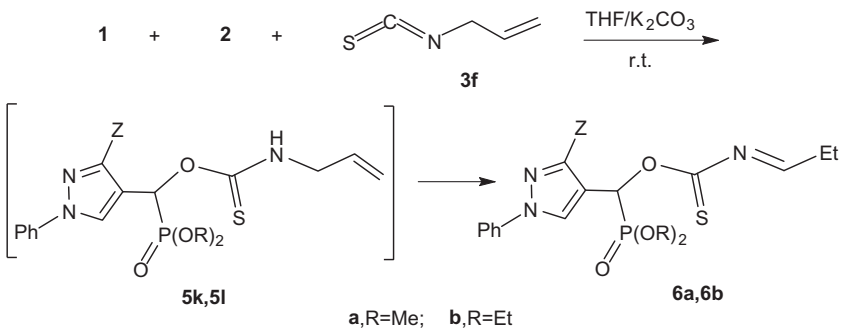
3	X	Y
d	S	Ph
e	O	Ph

Scheme 1 Synthesis of the phosphonates **5a**–**5j**.

triplet at 6.46 ppm (t, J_{H-H} = 6.6 Hz, 1H, N=C*H*-exocycl). ^{13}C NMR spectrum of **6a** showed among others *C*=S (d, $^{3}J_{P-C}$ = 7.5 Hz) at 186.2, and N=*C*H at 164.8 ppm.

Next, we applied the same protocol to the reaction of the aldehyde **1**, dialkyl phosphites **2a**, **2b** and acetic anhydride (instead of the cyanate)/K_2CO_3, using the same ratio 1:1:1:1.5. The reaction proceeded smoothly in 1–3 h at room temperature to give α-acetoxyphosphonates **7a** and **7b** in 82% and 86% yields (Scheme 3). Structure **7** was apparent from their mass spectra, which displayed, in each case, the molecular ion peak at appropriate *m*/*z* values. Its ^{1}H NMR (δ ppm) spectrum exhibited two doublets ($^{3}J_{P-H}$ = 11.0 Hz, 2 × 3H) at 3.73, 3.78 that readily recognized as arising from the two diastereotopic methoxyl groups attached to phosphorus [$(MeO)_2P$]. The singlet at 2.12 belongs to the methyl ester protons. The α-methine proton is coupled to the phosphorus atom and it showed up as a doublet at 6.64 ($^{2}J_{P-H}$ = 14.6 Hz). The proton-decoupled ^{13}C NMR spectrum of **7a** showed distinct resonances in agreement with the proposed structure. ^{31}P NMR shift of **7a** was recorded at δ_p 26.7 ppm.

Please cite this article in press as: Abdou, W.M., Bekheit, M.S. One-pot three-component synthesis of peptidomimics for investigation of antibacterial and antineoplastic properties. Arabian Journal of Chemistry (2015), http://dx.doi.org/10.1016/j.arabjc.2015.04.014



Scheme 2 Synthesis of the phosphonates **6a** and **6b**.

3.2. Pharmacology

3.2.1. Antimicrobial evaluation

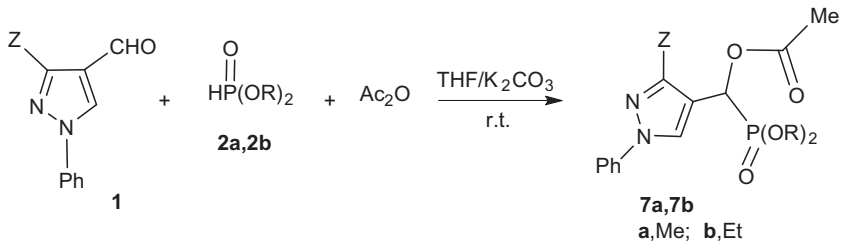
A preliminary screening of new compounds **5a–5j**, **6a**, **6b**, **7a** and **7b** was evaluated *in vitro* against a panel of standard and clinically isolated strains of Gram-negative and Gram-positive bacteria. The antibiotic activity was executed using the disk diffusion method (Perez et al., 1990) and the results are recorded in Table 1. All tested phosphonates exhibited moderate to good antimicrobial activity. The measurement of the zone of growth inhibition for a concentration 10 μmol mL^{-1} (DMSO) of each compound showed that phosphorylthiocarbamates **5a–5d**, followed by phosphorylcarbamates **5i** and **5j** are the most active compounds that inhibited the growth of Gram-negative and/or Gram-positive. The order of activity into the series of the thiocarbamates is **5a** > **5b** > **5c** > **5d** > **5g** > **5h** > **5e** > **5f** > **6a** > **6b**. Four top active compounds **5a–5d** were selected for further screening of minimum concentrations of each compound required to inhibit growth (*MIC* μmol L^{-1}). They all have in common the thiocarbamate moiety, which suggests that the presence of this motif may be enhancing the activity. Even compounds **5g** and **5h**, which were less active, were also selected for comparison.

The minimum concentrations of each compound required to inhibit growth (*MIC* μmol L^{-1}) and the minimum bactericidal concentrations of each compound i.e., the concentration required to kill each pathogen (MBC μmol L^{-1}) were then determined for the phosphonates **5a–5d** and **5g**, **5h** as well as the two reference drugs ciprofloxacin (**Cipro**) and chloramphenicol (**Chlor**). The activity was assessed for each drug in the range of concentration from 450 to 10 μmol L^{-1} (450, 200, 100, 50, 25, 10 μmol L^{-1}) in cation-adjusted Mueller Hinton (MH) medium (Fluka) (Scott, 1989) and the results are displayed in Table 2.

Data displayed in Tables 1 and 2 showed that the most two active phosphonates are **5a** and **5b** with MIC 42.5–259 μmol L^{-1} and 48.1–160.3 μmol L^{-1} values whereas their MBC values are 67.967.–329 and 56.1–354.7 μmol L^{-1} against all pathogens tested. For comparison, MIC/MBC for ciprofloxacin were recorded at 66.5–377.6 (MIC, μmol L^{-1}) and at 90.6–694.9 for MBC μmol L^{-1} values. On the other hand, MIC/MBC for chloramphenicol were recorded at 37.1–396.2(MIC, μmol L^{-1}) and at 46.4–619.2 for MBC μmol L^{-1}.

3.2.2. Antitumor activity

The IC_{50} values (concentration required to inhibit tumor cell proliferation by 50%) for nine of the synthesized compounds (**5a–5d**, **5f**, **5g**, **5j**, **6a**, and **7a**) against eight human cancer cell lines including *MCF7*, *MDA-MB-435*, *BT-549* (human breast carcinoma cell lines), IGROVI, SK-OV-3 (human ovarian carcinoma cell lines), *PX-3*, *PU-145* (human prostate carcinoma cell lines), and *HEPG2* (human liver carcinoma cell line) were determined at a dose of 10 μmol L^{-1} (DMSO) in assays according to the reported methods (Kitamura et al., 2004; Boyd and Paull, 1995). The IC_{50} values are listed in Table 3 and the well known anticancer drug 5-fluorouracil was used as a positive control. From the screening results in Table 3, it was observed that compounds **5a–d** exhibited good to significant anticancer activity against the eight tested human cancer cell lines. Two of the most active compounds are **5a** and **5b** with IC_{50} values against the eight tested human cancer cell lines ranging from 16.6 to 26.9 and 17.2 to 36.9 μmol L^{-1}, respectively (for 5-fluorouracil IC_{50}: 17.7–38.8). Compound **5a** was more cytotoxic than 5-fluorouracil against all tested eight human cancer cell lines while **5b** was more active than 5-fluorouracil only in the case of *MDA-MB-*, *IGROVI* and *PX-3*. On the other hand, α-acetoxyphosphonate **7a** showed a dramatic drop of potency. Replacing the alky substituent



Scheme 3 Synthesis of the phosphonates **7a** and **7b**.

in the isothiocyanates with hexyl or phenyl moiety caused a slight loss of the IC_{50} values (**5f**, **5g**). Nevertheless, the substituent at the isothiocyanates has a profound influence on anticancer activity, such as **5a** (16.6 μmol) as compared to **6a** (36.6 μmol) against *MCF7*. However, phosphoryl carbamates **5j** showed weak or no cytotoxicity against all tested cell lines. It is worth mentioning that it is for the first time to obtain phosphonates of remarkable potency against human liver carcinoma cell line.

In parallel, similar to antitumor data, the antibiotic results showed that phosphorylthiocarbamates **5a** and **5b** possess the highest activity than their phosphorylcarbamates-counterparts **6a**, **6b** or α-acetoxyphosphonate **7a**. On the other hand, while **5g** showed good potency against all tested pathogens, antitumor efficacy was only noticeable for this compound. At this point, a straight correlation between tumor activity and antibiotic efficacy of the tested phosphonates was not found. This result is not surprising, since the targets of these two activities should be different. Furthermore, the observed antibacterial activity, albeit weak, can be the result of non-specific cytotoxic effects (e.g., **6a**, **6b** and **7a**, **7b**), as bacteria can be killed in many ways.

Considering the structure–activity relationship (*SAR*), as shown in Tables 1–3, the highest protection was observed for **5a**, followed by **5b** and **5c**. 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 substituents of the phosphonate moiety determine potency. Thus, the presence of C(S)N group is favorable in this series of compounds. The introduction of hexyl or phenyl substituent to the exo-cyclic amino group led to compounds **5g**, **5h** with decrease activity. Nevertheless, the introduction of both C(O)N and phenyl moieties was totally unfavorable and dramatically decreased the antiinflammatory and the antitumor potencies of compounds **5i** and **5j**.

4. Conclusion

In summary, we have synthesized three types of new phosphonate derivatives: α-phosphorylthiocarbamates (**5a–h**, **6a**, **6b**), α-phosphorylcarbamates (**5i**, **5j**), and α-acetoxyphosphonates (**7a**, **7b**). The described method is efficient and high yielding for the one-pot approach from aldehyde, dialkyl phosphites and cyanates or acetic anhydride using potassium carbonate. Representative examples of the new class of phosphonates were screened for anticancer activity against eight human cancer cell lines. Compounds **5a** and **5b** exhibited excellent broad spectrum of anticancer activity *in vitro*, especially compound **5a**, which was more potent than 5-fluorouracil against all tested human cancer cell lines.

Acknowledgments

Authors would like to thank the National Research Centre, Dokki, Cairo Egypt (project # 10010101) for financial support. Authors are also thankful to the Central Lab, School of Pharmacy, Alexandria University for the antimicrobial evaluation, Egypt; and National Cancer Institute, NY, USA, for carrying out the antitumor screening and taking care of getting the culture cell lines.

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Please cite this article in press as: Abdou, W.M., Bekheit, M.S. One-pot three-component synthesis of peptidomimics for investigation of antibacterial and antineoplastic properties. Arabian Journal of Chemistry (2015), http://dx.doi.org/10.1016/j.arabjc.2015.04.014