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ORIGINAL PAPER

Some new compounds with P(E)NHC(O) (E = lone pair, O, S) linkage: synthesis, spectroscopic, crystal structures, theoretical studies, and antimicrobial evaluation

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Abstract New phosphinoamides, chalcogenides, and amidophosphates were synthesized and characterized by ^{1}H, ^{13}C, ^{31}P NMR, IR spectroscopy, and elemental analysis. The ^{13}C NMR spectra of two phosphinoamides exhibit obvious differences between their $^{1}J(P,C)$ coupling constants (128.3 Hz in one compound vs. 439.2 Hz in another compound). Natural bond orbital analysis was performed to clarify the electronic behavior of the title molecules. The crystal structures of three derivatives were determined by X-ray crystallography. The structure of *N*-(Diphenylphosphino)-2-pyrazinecarboxamide contains two symmetry-independent forms of the molecule with equal occupancy in the lattice. Density functional theory calculations indicate that two conformers of this compound are identical from an energy point of view. Strong intermolecular N–H···O(P) hydrogen bonds lead to a centrosymmetric dimer in Diphenyl *N*-(2-pyrazinylcarbonyl)phosphoramidate, whereas N–H···(O)C and N–H···N hydrogen bonds in *N*-(Diphenylphosphino)-2-pyrazinecarboxamide and *N*-(Diphenylphosphinothioyl)-2-pyrazinecarboxamide sulfide, respectively, form a one-dimensional polymeric chain in their structures. The in vitro antimicrobial activity of the amidophosphates was evaluated against various microbial strains of Gram positive and Gram negative bacteria and fungi.

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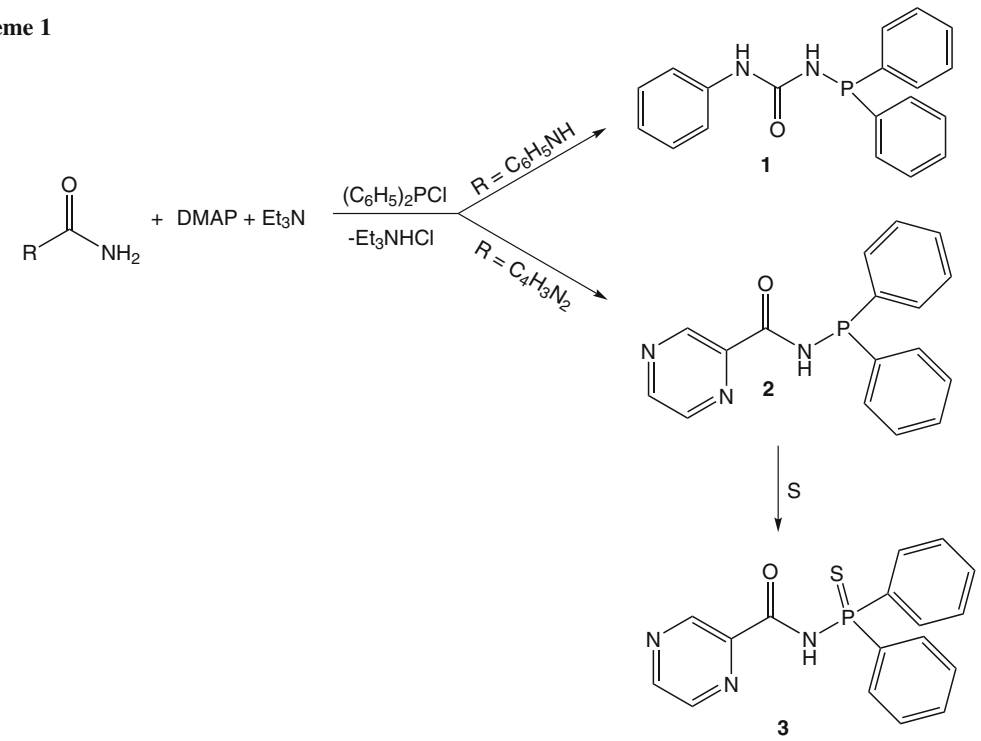
Introduction

The study on phosphorus(III) and (V) derivatives is important owing to their crucial role in various areas of science including synthesis, coordination, biomedicine, and theoretical matters [1–4]. On the other hand, carboxamide compounds such as nicotinamide, isonicotinamide, pyrazineamide (PZA), and urea are materials with a wide range of chemical and biological applications [5–14]. The presence of these amides together with the phosphorus atom has led to extensive structural and functional diversity of these compounds. Synthesis [15–20], coordination chemistry [21–24], and biological activities [25–27] of derivatives containing the corresponding amides (except PZA) with a C(O)NHP(E) (E = lone pair, O, S, Se) skeleton have been reported in the literature. To further study this area, six new derivatives (**1**–**3** and **5**–**7**) were synthesized and characterized. The known compounds **4** and **8** [28, 29] were also prepared to investigate the effect of the phosphorus substituent on structural and biological properties. Molecules **2**, **3**, and **5** reported in this work are the first examples of phosphorus compounds bearing a PZA moiety. The crystal structures of these compounds were determined by X-ray crystallography. Additionally, natural bonding orbital (NBO) analysis was used to get a more detailed insight into orbital interactions in molecules **1** and **2**. Compounds **5**–**8** were also screened for antimicrobial activity against *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *S. epidermidis*, *Aspergillus niger* and *Candida albicans*.

Scheme 1



Results and discussion

Phosphinoamides **1** and **2** containing a –PNHC(O)– moiety were obtained by the condensation of chlorodiphenylphosphine with *N*-phenylurea and pyrazineamide, respectively, in the presence of excess triethylamine and a catalytic amount of 4-(dimethylamino)pyridine (DMAP) (Scheme 1). The presence of a P(III) atom provides an opportunity for a variety of oxidation products to be synthesized. Two chalcogenides with different functional groups [P(S)NHC(O) (**3**) and P(O)NHC(O) (**4**)] were prepared. Compound **3** was synthesized by reaction of **2** with elemental sulfur in toluene, whereas **4** was obtained by reaction of $C_6H_5NHC(O)Na$ with diphenylphosphinic chloride (Schemes 1 and 2). Syntheses of amidophosphates **5**–**8** were also performed in a similar manner by treatment of the corresponding amide salts RC(O)NHNa [$R = C_4H_3N_2$ (**5**), C_5H_4N (nicotin (**6**) and isonicotin (**7**)), and C_6H_5NH (**8**)] with diphenylchlorophosphate (Scheme 2).

Some spectroscopic data of compounds **1**–**8** are listed in Table 1. The $^{31}P\{^1H\}$ NMR spectra show a single resonance at $\delta(P) = 22.46$ and 51.54 ppm for compounds **2** and **3**, respectively. Results show that the presence of a sulfur atom in **3** leads to the deshielding of the phosphorus atom in this derivative relative to **2**. The phosphorus chemical shift of compounds **5**–**8** is about −12.06 ppm

Scheme 2

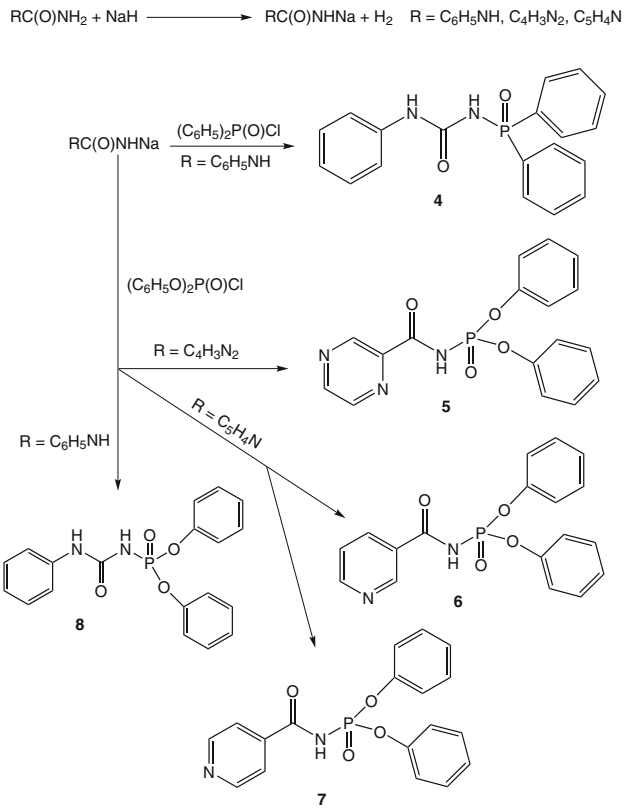


Table 1 Some spectroscopic data of compounds **1**–**8**

Compound	$\delta(^{31}P)$/ppm	$^{2}J_{PH}$/Hz	$^{1}J_{PC}$/Hz	δ(NH)/ppm	$^{2}J_{PC}$/Hz	$^{3}J_{PC}$/Hz
1	16.75	10.06	128.92	8.46	10.19	12.95
2	22.42	–	439.19	9.36	2.64	13.59, 5.63
3	51.54	–	103.85	9.84	11.80	13.57
4	15.61	–	132.49	8.50	10.15	12.43
5	−12.04	12.65	–	9.08	6.92	10.49, 4.70
6	−12.04	–	–	8.60	–	5.09
7	−12.08	–	–	9.08	6.94	4.83
8	−12.08	–	–	6.87	6.77	4.88

which demonstrates the large shift to higher field for these compounds relative to those of **1**–**4**. The ^{1}H NMR spectra exhibit the presence of an amide proton in the range of 6.87–9.84 ppm with ^{2}J(P,H) = 10.06, 12.65 Hz in **1** and **5**. Moreover, the ^{13}C NMR reveals a ^{1}J(P,C) coupling constant of 439.19 Hz for compound **2** that is much larger than ^{1}J(P,C) for molecule **1** (128.92 Hz).

Crystal structure analysis

Single crystals of compounds **2**, **3**, and **5** were obtained after slow evaporation of solutions (see "Experimental") at room temperature. The crystal data and the details of the X-ray analysis are given in Table 2. Selected bond lengths and angles are summarized in Tables 3 and S1 (supplementary material). Hydrogen bonding data are collected in the Supplementary Material (Table S2). Molecular structures of these compounds are presented in Figs. 1, 2, and 3.

Compounds **2** and **3** crystallize in orthorhombic and monoclinic systems with $Z = 8$ and 4, respectively. Derivative **2** exists as two crystallographically independent molecules in the crystalline lattice (**A** and **B**) owing to the different torsion angles (Table S1). This phenomenon was observed for some of our previously reported structures [30, 31]. Each conformer is connected to two molecules of the other conformer via C(O)···H–N hydrogen bonds leading to two infinite zigzag polymeric chains in the lattice (Fig. 1). The other molecule contains one conformer with the P=S and C=O groups in a *syn* configuration. The intermolecular N(1)–H(N1)···N(3) hydrogen bonding produces a one-dimensional polymeric chain (Fig. 2). There is also π···π stacking interaction with the centroid-to-centroid distance of 3.56 Å between phenyl and pyrazine rings.

Derivative **5** crystallizes in monoclinic system with $Z = 8$. The structure contains one amidic hydrogen atom and forms a centrosymmetric dimer via intermolecular –P=O···H–N– hydrogen bonds. Further, there is intramolecular P1(O4)···(O2)C1 electrostatic interaction [with d(O(2)···O(4)) = 3.014 Å] in the crystalline network. The phosphoryl and carbonyl groups show an *anti* configuration (Fig. 3). The phosphorus atoms have a slightly distorted tetrahedral configuration with the angles in the range of 100.69(11)–102.32(11)° (in **A**), 102.06(10)–102.23(11)° (in **B**), 101.38(7)–15.57(5)° (in **3**), and 101.77(8)–116.86(8)° (in **5**).

The P–N distances in the derivative **2** (1.728(2) Å in **A** and 1.718(2) Å in **B**) are slightly longer than those in the compounds **3** and **5** (1.703(13) Å and 1.653(17) Å, respectively) and thus are significantly shorter than a typical P–N single bond (1.77 Å) [32]. The sum of the surrounding angles for all of the amidic nitrogen atoms is almost 360° and therefore the environment of the N atoms is practically planar.

The crystal data of molecules **2** and **3** show that the P–C bond lengths do not differ significantly from one another. The phosphorus to sulfur bond length in phosphine sulfide **3** (1.923 Å) is shorter than the typical bond in Ph_3PS (P=S: 1.951(2)–1.954(2) Å) [33, 34].

Computational studies

Similar to some of our previously reported structures, compound **2** exists as two crystallographically independent molecules in a 1:1 ratio in the crystalline lattice [35, 36]. Hence quantum chemical calculations were used to further clarify the conformation of **2**. The experimental and optimized geometric parameters (bond lengths, bond angles, and dihedral angles) by Hartree–Fock (HF) and density functional theory (DFT) (B3LYP) with 6-31+G** basis sets are listed in the Supplementary Material.

The calculated energy for two conformers of **2** is summarized in Tables 4 and S1. These calculated data indicate that the bond lengths and angles are identical and the structural stability of conformer **A** is equal to that of conformer **B** ($\Delta E = 0$). Also, the data show that the two conformers only have differences in their corresponding torsion angles.

Table 2 Crystal data collection and structure refinement parameters for compounds **2**, **3**, and **5**

	2	**3**	**5**
Empirical formula	$C_{17}H_{14}N_3OP$	$C_{17}H_{14}N_3OPS$	$C_{17}H_{14}N_3O_4P$
Formula weight	307.28	339.34	355.28
Temperature/K	120(2)	100(2)	120(2)
Wavelength/Å	0.71073	0.71073	0.71073
Crystal system, space group	Orthorhombic, $P2_12_12_1$	Monoclinic, $P2_1/n$	Monoclinic, $C2/c$
Unit cell dimensions			
a/Å	9.1136(4)	6.6766(3)	22.3843(12)
b/Å	17.9701(8)	26.3223(12)	9.4659(5)
c/Å	18.0500(8)	8.9120(4)	16.0564(8)
α/°	90.0	90.0	90.0
β/°	90.0	90.4280(10)	106.6680(10)
γ/°	90.0	90.0	90.0
V/Å^3	2,956.1(2)	1,566.18(12)	3,259.2(3)
Z	8	4	8
D_{calc}/Mg m^{-3}	1.381	1.439	1.448
Absorption coefficient/mm^{-1}	0.191	0.316	0.197
F(000)	1,280	704	1,472
Crystal size/mm^3	0.40 × 0.20 × 0.20	0.55 × 0.50 × 0.30	0.37 × 0.26 × 0.14
Range for data collection/°	1.60–29.00	1.55–28.00	1.90–27.10
Index ranges	$-12 \le h \le 12$, $-24 \le k \le 23$, $-24 \le l \le 24$	$-8 \le h \le 8$, $-34 \le k \le 34$, $-11 \le l \le 11$	$-28 \le h \le 28$, $-12 \le k \le 12$, $-20 \le l \le 20$
Reflections collected/unique (R_{int})	32,932/7,874 (0.0439)	17,075/3,762 (0.0194)	15,166/3,561 (0.0410)
Completeness to θ/%	(29.00°) 99.9	(28.00°) 99.5	(27.10°) 98.6
Absorption correction	Semiempirical from equivalents	Semiempirical from equivalents	Semiempirical from equivalents
Maximum and minimum transmission	0.967 and 0.9522	0.911 and 0.845	0.9749 and 0.9316
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/restraints/parameters	7,874/0/405	3,762/0/212	3,561/0/226
Goodness-of-fit on F^2	1.011	1.006	1.001
R indices (all data)	$R1 = 0.0609$, w$R2 = 0.1014$	$R1 = 0.0364$, w$R2 = 0.0928$	$R1 = 0.0633$, w$R2 = 0.1017$
Largest difference peak and hole/e Å^{-3}	0.452 and −0.246	0.686 and −0.732	0.353 and −0.500
Absolute structure parameter	−0.05(8)		

NBO analysis

The electronic delocalizations Lp(N) → σ*(P–*X*) and Lp(N) → π*(C=O), where Lp(N) is a lone pair on a nitrogen atom and $X = Cl$, have been well known and reported previously for compounds **I** and **II** with an RC(O)NHP(O)Cl_2 ($R = CF_3$ (**I**), CCl_3 (**II**)) skeleton [37, 38] (Table 5). To further study this system, we investigated two other molecules (**III** and **IV**) with $R = C_6H_5$ and C_6H_5NH. As shown in Table 5, such electronic effects are influenced by the electronic nature of substituent *R*. The aim of the present work is to investigate the factors that affect the intensity of the Lp(N) → π*(C=O) and Lp(N) → σ*(P–C) interactions in compounds **1** and **2**. The electronic delocalization Lp(N) → σ*(P–C) is expected to become more intense on insertion of an NH group between the carbonyl and phenyl ring in the structure $C_6H_5NHC(O)NHP(C_6H_5)_2$ (**1**), assuming that the $Lp(N_{amide})$ in compound **1** tends to contribute more in Lp(N) → σ*(P–C) when the $Lp(N_{aniline})$ participates in resonance interaction with the π*(C=O) π-antibonding orbital. The NBO calculations were performed at HF/6-31+G** level for the structures **1** and **2**. The results of NBO calculations are summarized in Table 5. A stabilization energy of 318.36 kJ/mol was obtained for the $Lp(N_{aniline})$ → π*(C=O) delocalization effect that causes a decrease in the stabilization energy of the $Lp(N_{amide})$ → π*(C=O) interaction from 379.68 kJ/mol in **2** to 257.46 kJ/mol in **1**. Also, this effect attenuates the $Lp(N_{amide})$ → σ*(P–C) interaction and decreases the strength of the P–N bond in the latter compound. These results explain the ^{13}C NMR spectra in which a large value for ^1J(P,C) was observed for the

Table 3 Selected bond lengths/Å and angles/° for compounds **3** and **5**

3		**5**	
Bond lengths/Å			
P(1)–N(1)	1.7026(13)	P(1)–N(1)	1.6529(17)
P(1)–S(1)	1.9232(6)	P(1)–O(1)	1.4612(15)
P(1)–C(14)	1.7976(15)	P(1)–O(3)	1.5690(15)
P(1)–C(8)	1.8080(15)	P(1)–O(4)	1.5793(14)
Bond angles/°			
N(1)–P(1)–C(14)	105.56(7)	O(1)–P(1)–O(3)	116.86(8)
N(1)–P(1)–C(8)	101.38(7)	O(1)–P(1)–O(4)	115.12(8)
C(14)–P(1)–C(8)	107.29(7)	O(3)–P(1)–O(4)	101.77(8)
N(1)–P(1)–S(1)	115.57(5)	O(1)–P(1)–N(1)	111.56(9)
C(14)–P(1)–S(1)	115.28(5)	O(3)–P(1)–N(1)	102.63(8)
C(8)–P(1)–S(1)	110.57(5)	O(4)–P(1)–N(1)	107.64(8)
C(1)–N(1)–P(1)	122.50(11)	C(1)–N(1)–P(1)	125.68(14)
C(1)–N(1)–H(1N1)	116.3(15)	C(1)–N(1)–H(1A)	117.2
P(1)–N(1)–H(1N1)	121.1(15)	P(1)–N(1)–H(1A)	117.2

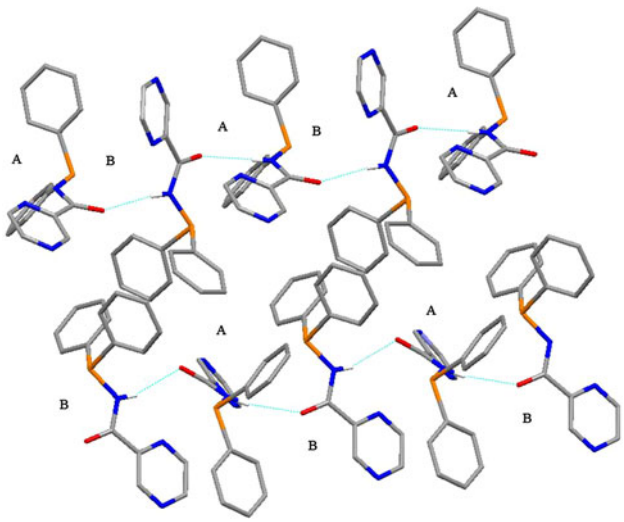


Fig. 1 Two independent polymeric chains in compound **2**

coupling of the *ipso* carbon atom of the phenyl ring with the phosphorus atom in compound **2** (Table 1).

Antimicrobial activity

Molecules **5**–**8** were screened for in vitro antimicrobial activities against two Gram negative bacteria (*E. coli* and *P. aeruginosa*), three Gram positive bacteria (*B. subtilis*, *S. aureus*, and *S. epidermidis*), and two fungi (*A. niger* and *C. albicans*) by using cup-plate agar and microdilution methods. Known antibiotics like gentamicin and

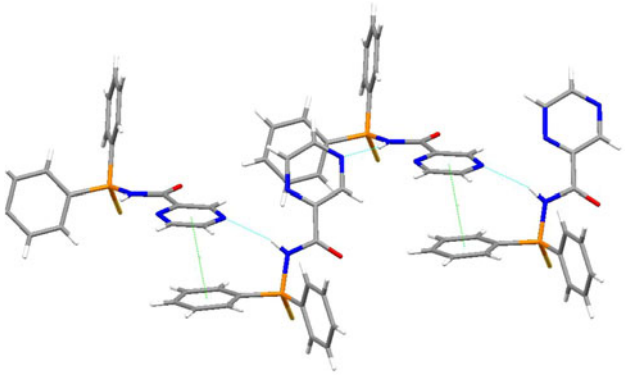


Fig. 2 A one-dimensional polymeric chain and π···π stacking interaction in compound **3**

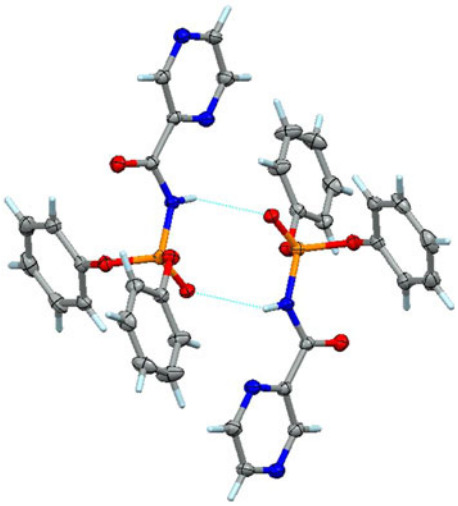


Fig. 3 Centrosymmetric dimer of compound **5**, produced by hydrogen bonds

clotrimazole were used for comparison. The results are presented in Table 6. The screening data reveal that derivative **5** exhibited effective activity against all the bacterial species, probably owing to antimycobacterial properties of the PZA group [39]. Additionally, the MIC values of new compounds against certain microbial strains indicate that **8** was the most potent compound against *S. aureus* at 165 μg/cm^3. All the molecules were less active than gentamicin. The antifungal activity of the compounds was also studied against two pathogenic fungi. Derivative **5** inhibited the growth of *C. albicans* at 510 μg/cm^3. Generally, it may be concluded that the structure of the tested derivatives is the principal factor influencing the antimicrobial activity, and changing the substituents on –P(O)(OPh)$_2$ leads to compounds with different antimicrobial activity.

Table 4 Calculated energy for conformers **A** and **B** of compound **2** by HF and DFT methods

Level of theory	Energy/a.u.		Dipole moment/D	
	Conformer **A**	Conformer **B**	Conformer **A**	Conformer **B**
B3LYP/6-31+G**	−1,237.141077	−1,237.141077	4.9555	4.9535
HF/6-31+G**	−1,230.921633	−1,230.921633	5.2450	5.2448

Table 5 Delocalization effects and stabilization energies of compounds **I–IV**, **1**, and **2**

Compound	Formula	Stabilization energies (kJ/mol)		
		$Lp(N_{amide}) \rightarrow \pi^*(C{=}O)$	$Lp(N_{amide}) \rightarrow \sigma^*(P{-}X)^c$	$Lp(N_{aniline}) \rightarrow \pi^*(C{=}O)$
I	$CF_3C(O)NHP(O)Cl_2$[a,b]	217.14	42.42	–
II	$CCl_3C(O)NHP(O)Cl_2$[a,b]	221.76	42.42	–
III	$C_6H_5C(O)NHP(O)Cl_2$	120.12	50.82	–
IV	$C_6H_5NHC(O)NHP(O)Cl_2$	133.56	55.86	332.22
1	$C_6H_5NHC(O)NHP(C_6H_5)_2$	257.46	39.48	318.36
2	$C_4N_2H_3C(O)NHP(C_6H_5)_2$	379.68	38.22	–

[a] For these compounds, see Refs. [34, 35]

[b] The values are related to the B3LYP/6-31+G** level

[c] X = Cl (**I–IV**), C (**1**, **2**)

Experimental

Chlorodiphenylphosphine, diphenyl chlorophosphate, diphenylphosphinic chloride, 2-pyrazinecarboxamide, 3-pyridinecarboxamide, 4-pyridinecarboxamide, and *N*-phenylurea were used as supplied. All reactions were carried out under argon atmosphere. ^1H, ^{13}C, and ^{31}P NMR spectra were recorded on a Bruker Avance DRS 500 MHz spectrometer. ^1H and ^{13}C chemical shifts were determined relative to TMS, and ^{31}P chemical shifts relative to 85 % H_3PO_4 as external standards. Infrared spectra were obtained by using KBr pellets on a Shimadzu IR-60 spectrophotometer. Elemental analysis was performed by using a Heraeus CHN-O-RAPID apparatus. Melting points were determined on an Electrothermal apparatus.

X-ray crystal structure analysis

X-ray data were collected on a Bruker SMART 1000 CCD for compounds **2** and **5** and a Bruker APEX II CCD single-crystal diffractometer for compound **3** with graphite monochromated Mo Kα radiation ($\lambda = 0.71073$ Å). The structures were refined with SHELXL-97 [40] by full-matrix least-squares on F^2. The positions of hydrogen atoms were obtained from the difference Fourier map. Routine Lorentz and polarization corrections were applied and an absorption correction was performed for compounds using the SADABS program [41].

Crystallographic data for the structures **2**, **3**, and **5** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication nos. CCDC 742002 ($C_{17}H_{14}N_3OP$), CCDC 786390 ($C_{17}H_{14}N_3OPS$), and CCDC 742000 ($C_{17}H_{14}N_3O_4P$). Copies of the data may be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

Computational methods

All quantum chemical calculations were performed with the Gaussian 98 [42] system of programs, implemented on a Pentium 4 computer. The calculations were performed for molecules in the gaseous phase. The molecular geometries were optimized by using B3LYP and HF methods with 6-31+G** basis sets. The electronic delocalization was rationalized by a natural bond orbital (NBO) analysis [43], using the HF/6-31+G** method of approximation.

Biological evaluation

The cup-plate agar method [44] was used to determine the antibacterial activity of compounds **5–8** against three Gram positive bacteria, namely *Bacillus subtilis* (ATCC 6633), *Staphylococcus aureus* (ATCC 6538P), and *S. epidermidis* (ATCC 12229); two Gram negative bacteria, namely *Escherichia coli* (ATCC 35218) and *Pseudomonas aeruginosa* (ATCC 9027); and two fungi, namely *Aspergillus niger* (ATCC 16404) and *Candida albicans* (ATCC 10218). Base plates were prepared by pouring of

Table 6 Antimicrobial activity of compounds **5–8**

Compound	*B. subtilis*		*E. coli*		*S. aureus*		*S. epidermidis*	
	GIZ[a]	MIC[a]	GIZ	MIC	GIZ	MIC	GIZ	MIC
5	18	510	–	–	23	510	18	510
6	10	4,500	11	4,500	14	>5000	11	4,500
7	11	4,500	11	>5,000	12	>5000	11	4,500
8	10	4,400	12	>5,000	10	165	12	>5,000
Gentamicin	23	6.25	20	6.25	20	3.12	20	6
Clotrimazole	–	–	–	–	–	–	–	–

Compound	*P. aeruginosa*		*C. albicans*		*A. niger*	
	GIZ	MIC	GIZ	MIC	GIZ	MIC
5	–	–	11	510	–	–
6	12	4,500	–	–	–	–
7	11	4,500	–	–	–	–
8	13	>5,000	11	4,400	–	–
Gentamicin	20	1.5	–	–	–	–
Clotrimazole	–	–	20	0.3	22	2.4

Error values are within ±1 mm; moderately active (8–13), higher active (>14), – not active

[a] The values indicate the diameters in mm for the zone of growth inhibition (GIZ) and minimal inhibitory concentration (MIC) in μg/cm^3 observed after 24 h of incubation at 35 °C

autoclaved Mueller–Hinton (MH) agar (for bacteria) and Sabouraud Dextrose agar (for fungi) into sterile petri dishes and allowing them to settle. The compounds dissolved in dimethyl sulfoxide (DMSO) at a concentration of 7,000 μg/cm^3 were used. Then, the solutions of the compound tested were placed on the well of the media inoculated with the microorganisms. The plates were incubated at 35 °C and 24 h for the microorganism cultures. After incubation, the growth inhibition zones around the discs were measured by diameters of inhibition zones and are shown in Table 6. Gentamicin and clotrimazole were used as reference antibacterial and antifungal drugs, respectively. DMSO was used as a solvent control.

Also, the minimal inhibitory concentration (MIC) values for compounds **5–8** defined as the lowest concentration of the compound preventing the visible growth were determined by using the microdilution broth method [45]. The test compounds dissolved in DMSO were first diluted to the highest concentration (7,000 μg/cm^3) to be tested. Then serial twofold dilutions were prepared in concentration ranges from 50 to 7,000 μg/cm^3 in 10 cm^3 sterile tubes. A prepared suspension of the standard microorganisms was added to each dilution in a 1:1 ratio. The microorganism growth (or lack of it) was determined visually after incubation for 24 h at 35 °C. MIC values were studied for the same microbial strains and are given in Table 6. Gentamicin and clotrimazole were used as reference antibacterial and antifungal drugs, respectively. Control experiments using DMSO were performed. All microdilution experiments were performed in duplicate and repeated three times.

*Synthesis of derivatives **1** and **2***

Derivatives **1** and **2** were prepared according to the literature procedures [46] (Scheme 1). Then, 0.6 cm^3 chlorodiphenylphosphine (3.3 mmol) was added to a solution of 0.45 g *N*-phenylurea (3.3 mmol) for **1** and 0.41 g pyrazinamide (3.3 mmol) for **2**, 0.35 g triethylamine (3.5 mmol), and 0.04 g 4-dimethylaminopyridine (DMAP, 0.33 mmol) in 30 cm^3 THF and refluxed overnight. The reaction mixture was filtered to remove a white solid ($Et_3N{\cdot}HCl$). The solvent was removed in vacuo leaving white and pale yellow solids, respectively. Compound **2** was crystallized from a mixture of ethanol/heptane at room temperature.

N-Diphenylphosphino-N′-phenylurea (**1**, $C_{19}H_{17}N_2OP$) Yield 20 %; m.p.: 225–226 °C; ^{1}H NMR (DMSO-d_6): δ = 6.98 (t, $^3J_{HH}$ = 7.23 Hz, 1H), 7.24 (t, $^3J_{HH}$ = 7.71 Hz, 2H), 7.33 (d, $^3J_{HH}$ = 7.99 Hz, 2H), 7.53 (t, $^3J_{HH}$ = 7.34 Hz, 4H), 7.58 (t, $^3J_{HH}$ = 7.13 Hz, 2H), 7.80 (dd, $^3J_{HH}$ = 7.45 Hz, $^3J_{PH}$ = 12.34 Hz, 4H), 8.48 (d, $^2J_{PH}$ = 10.06 Hz, 1H, NHP), 8.89 (s, 1H, PhNH) ppm; ^{13}C NMR (DMSO-d_6): δ = 118.26 (s), 122.57 (s), 128.60 (d, $^3J_{PC}$ = 12.95 Hz), 128.79 (s), 131.10

(d, $^{2}J_{PC}$ = 10.19 Hz), 131.92 (d, $^{4}J_{PC}$ = 2.64 Hz), 132.00 (d, $^{1}J_{PC}$ = 128.92 Hz), 138.68 (s), 152.44 (s) ppm; ^{31}P NMR (DMSO-d_6): δ = 16.75 (d, $^{3}J_{PH}$ = 11.11 Hz) ppm; IR (KBr): $\overline{\nu}$ = 3,315 (NH), 3,055, 2,860, 1,685 (C=O), 1,594, 1,543, 1,463, 1,434 (P–Ph), 1,313, 1,179, 1,122, 1,100, 1,077, 1,042, 1,021, 990, 910, 802, 773, 741, 718, 690, 590, 520, 475, 425 cm^{-1}.

N-(Diphenylphosphino)-2-pyrazinecarboxamide
(**2**, $C_{17}H_{14}N_3OP$)
Yield 20 %; m.p.: 132–133 °C; ^{1}H NMR (DMSO-d_6): δ = 7.52 (m, $^{3}J_{HH}$ = 7.55 Hz, 4 Ar–H), 7.61 (t, $^{3}J_{HH}$ = 7.45 Hz, 2 Ar–H), 7.94 (dd, $^{3}J_{PH}$ = 13.25 Hz, $^{3}J_{HH}$ = 7.8 Hz, 4 Ar–H), 8.57 (s, 1 Py–H), 8.83 (d, $^{3}J_{HH}$ = 2.25 Hz, 1 Py–H), 9.07 (s, 1H, NHP), 9.46 (s, 1 Py–H) ppm;^{13}C NMR (DMSO-d_6): δ = 128.7 (d, $^{3}J_{PC}$ = 13.59 Hz), 129.8 (s), 129.9 (s), 130.9 (s), 131.6 (s), 131.7 (s), 131.8 (s), 132.8 (d, $^{2}J_{PC}$ = 2.64 Hz), 142.7 (s), 142.9 (d, $^{3}J_{PC}$ = 5.63 Hz), 144.9 (d, $^{1}J_{PC}$ = 439.19 Hz), 144.1 (s), 144.8 (s), 147.6 (s), 166.6 (s) ppm; ^{31}P NMR (DMSO-d_6): δ = 22.46 (b) ppm; IR (KBr): $\overline{\nu}$ = 3,300 (NH), 1,665 (C=O), 1,469, 1,447 (P–Ph), 1,386, 1,167, 1,128, 1,094, 1,016, 864, 805, 742, 692, 630, 506, 428 cm^{-1}.

N-(Diphenylphosphinothioyl)-2-pyrazinecarboxamide
(**3**, $C_{17}H_{14}N_3OPS$)
Sulfur (1.5 mmol, 0.05 g) was added to a solution of 0.46 g diphenylphosphino-2-pyrazinecarboxamide (1.5 mmol) in 20 cm^3 toluene and refluxed overnight. The solvent was removed in vacuo leaving a solid. This solid was crystallized from a hot toluene solution. Yield 15 %; m.p.: 149–150 °C; ^{1}H NMR (DMSO-d_6): δ = 7.54 (td, $^{3}J_{HH}$ = 7.55 Hz, $^{4}J_{PH}$ = 3.5 Hz, 4 Ar–H), 7.61 (t, $^{3}J_{HH}$ = 7.15 Hz, 2 Ar–H), 7.94 (dd, $^{3}J_{PH}$ = 14.30 Hz, $^{3}J_{HH}$ = 7.5 Hz, 4 Ar–H), 8.80 (d, $^{3}J_{HH}$ = 2.1 Hz, 1 Py–H), 8.95 (d, $^{3}J_{HH}$ = 2.3 Hz, 1 Py–H), 9.16 (s, 1 Py–H), 9.84 (s, 1H, NHP) ppm; ^{13}C NMR (DMSO-d_6): δ = 128.5 (d, $^{3}J_{PC}$ = 13.57 Hz), 131.1 (d, $^{2}J_{PC}$ = 11.80 Hz), 131.7 (d, $^{1}J_{PC}$ = 103.85 Hz), 132.0 (s), 143.5 (s), 143.8 (s), 148.5 (s), 165.2 (s) ppm; ^{31}P NMR (DMSO-d_6): δ = 51.54 (b) ppm; IR (KBr): $\overline{\nu}$ = 3,435 (NH), 3,195, 1,689 (C=O), 1,463, 1,431 (P–Ph), 1,376, 1,221, 1,100, 1,044, 1,018, 825, 746, 720, 680, 637, 498, 405 cm^{-1}.

*General procedure for the synthesis of derivatives **4–8***

Compounds **4–8** were prepared by two processes (Scheme 2). For the first step, 0.27 g NaH (7.2 mmol) was added to a suspension of the amide (4.8 mmol) in 25 cm^3 toluene . The mixture was refluxed for 4 h. The amide salt was filtered and dried. Afterward, diphenylphosphinic chloride for **4** or diphenylchlorophosphate for **5–8** (4.8 mmol) was added dropwise to a suspension of the amide salt in 10 cm^3 THF. After 24 h, the precipitate of NaCl was filtered, and the solvent was removed in vacuum. Colorless crystals of compound **5** were obtained by slow evaporation of a dichloromethane/heptane solution.

N-(Diphenylphosphinyl)-N′-phenylurea
(**4**, $C_{19}H_{17}N_2O_2P$)
Yield 30 %; m.p.: 201–202 °C (Ref. [28] 205–206 °C).

Diphenyl N-(2-pyrazinylcarbonyl)phosphoramidate
(**5**, $C_{17}H_{14}N_3O_4P$)
Yield 40 %; m.p.: 110–111 °C; ^{1}H NMR (DMSO-d_6): δ = 7.26 (m, 6 Ar–H), 7.42 (m, 4 Ar–H), 8.55 (m, 1 Py–H), 8.83 (d, $^{3}J_{HH}$ = 2.4 Hz, 1 Py–H), 9.08 (d, $^{2}J_{PH}$ = 12.65 Hz, 1H, NHP), 9.46 (d, $^{3}J_{HH}$) = 1.3 Hz, 1 Py–H) ppm; ^{13}C NMR (DMSO-d_6): δ = 119.9 (d, $^{3}J_{PC}$ = 4.70 Hz), 125.2 (s), 129.3 (s), 141.8 (d, $^{3}J_{PC}$ = 10.49 Hz), 142.2 (s), 144.4 (s), 148.1 (s), 149.5 (d, $^{2}J_{PC}$ = 6.92 Hz), 162.9 (s) ppm; ^{31}P NMR (DMSO-d_6): δ = −12.04 (b) ppm; IR (KBr): $\overline{\nu}$ = 3,230 (N–H), 1,712 (C=O), 1,585, 1,481, 1,448, 1,387, 1,284, 1,210, 1,188 (P=O), 1,154, 1,103, 1,062, 1,019, 989, 877, 768, 687, 583, 502, 431 cm^{-1}.

Diphenyl N-(3-pyridinylcarbonyl)phosphoramidate
(**6**, $C_{18}H_{15}N_2O_4P$)
Yield 40 %; m.p.: 100–101 °C; ^{1}H NMR (DMSO-d_6): δ = 7.16 (t, $^{3}J_{HH}$ = 7.8 Hz, 4H), 7.35 (t, $^{3}J_{HH}$ = 8.0 Hz, 2H), 7.90 (s, 1H), 8.11 (d, $^{3}J_{HH}$ = 5.6 Hz, 4H), 8.60 (s, 1H, NHP), 8.90 (d, $^{3}J_{HH}$ = 6.2 Hz, 3H) ppm; ^{13}C NMR (DMSO-d_6): δ = 112.5 (s), 119.6 (d, $^{3}J_{PC}$ = 5.09 Hz), 123.4 (s), 124.3 (s), 129.6 (s), 145.5 (s), 145.9 (s), 164.8 (s) ppm; ^{31}P NMR (DMSO-d_6): δ = −12.04 (s) ppm; IR (KBr): $\overline{\nu}$ = 3,245 (N–H), 3,110, 1,711 (C=O), 1,688, 1,591, 1,487, 1,257, 1,206, 1,168 (P=O), 1,095, 991, 903, 770, 532 cm^{-1}.

Diphenyl N-(4-pyridinylcarbonyl)phosphoramidate
(**7**, $C_{18}H_{15}N_2O_4P$)
Yield 30 %; m.p.: 104–106 °C; ^{1}H NMR (DMSO-d_6): δ = 7.17 (d, $^{3}J_{HH}$ = 8.35 Hz, 4 Ar–H), 7.35 (t,$^{3}J_{HH}$ = 7.75 Hz, 4 Ar–H), 7.58 (t, $^{3}J_{HH}$ = 2.7 Hz, 2 Ar–H), 8.31 (d, $^{3}J_{HH}$ = 7.6 Hz, 2 Py–H), 8.80 (d, $^{3}J_{HH}$ = 4.6 Hz, 2 Py–H), 9.08 (s, 1H, NHP) ppm; ^{13}C NMR (DMSO-d_6): δ = 119.9 (d, $^{3}J_{PC}$ = 4.83 Hz), 124.2 (s), 126.8 (s), 129.6 (s), 137.5 (s), 149.7 (s), 151.2 (d, $^{2}J_{PC}$ = 6.94 Hz), 152.7 (s), 160.9 (s) ppm; ^{31}P NMR (DMSO-d_6): δ = −12.08 (s) ppm; IR (KBr): $\overline{\nu}$ = 3,155 (N–H), 1,719 (C=O), 1,599, 1,526, 1,486, 1,407, 1,287, 1,213, 1,179 (P=O), 1,020, 907, 771, 665, 531 cm^{-1}.

Diphenyl N-(phenylaminocarbonyl)phosphoramidate
(**8**, $C_{19}H_{17}N_2O_4P$)
Yield 20 %; m.p.: 155–156 °C (Ref. [29] 155–156 °C).

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