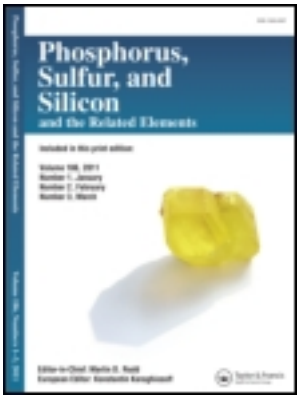


Phosphorus, Sulfur, and Silicon and the Related Elements

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

Synthesis and Antimicrobial Activities of Diphenyl(Arylamino)(1-Phenyl-3-(Pyridin-2-Yl)-1H-Pyrazol-4-Yl)Methylphosphonates

Mohamed F. Abdel-Megeed [a], Badr E. Badr [b], Mohamed M. Azaam [a] & Gamal A. El-Hiti [a c]

[a] Department of Chemistry, Faculty of Science, Tanta University, Tanta, Egypt

[b] Department of Botany, Faculty of Science, Tanta University, Tanta, Egypt

[c] School of Chemistry, Cardiff University, Cardiff, UK

Accepted author version posted online: 09 May 2012.Version of record first published: 10 Sep 2012.

To cite this article: Mohamed F. Abdel-Megeed, Badr E. Badr, Mohamed M. Azaam & Gamal A. El-Hiti (2012): Synthesis and Antimicrobial Activities of Diphenyl(Arylamino)(1-Phenyl-3-(Pyridin-2-Yl)-1H-Pyrazol-4-Yl)Methylphosphonates, Phosphorus, Sulfur, and Silicon and the Related Elements, 187:12, 1462-1468

To link to this article: http://dx.doi.org/10.1080/10426507.2012.690117

Phosphorus, Sulfur, and Silicon, 187:1462–1468, 2012

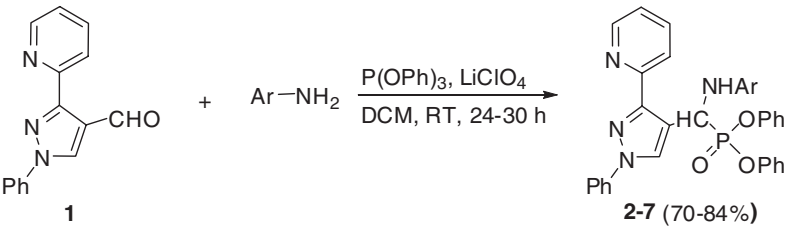
ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426507.2012.690117

SYNTHESIS AND ANTIMICROBIAL ACTIVITIES OF DIPHENYL(ARYLAMINO)(1-PHENYL-3-(PYRIDIN-2-YL)-1*H*-PYRAZOL-4-YL)METHYLPHOSPHONATES

Mohamed F. Abdel-Megeed,[1] Badr E. Badr,[2] Mohamed M. Azaam,[1] and Gamal A. El-Hiti[1,3]

[1]*Department of Chemistry, Faculty of Science, Tanta University, Tanta, Egypt*
[2]*Department of Botany, Faculty of Science, Tanta University, Tanta, Egypt*
[3]*School of Chemistry, Cardiff University, Cardiff, UK*

GRAPHICAL ABSTRACT



Ar = Ph, 4-ClC_6H_4, 4-MeC_6H_4, 4-$Me_2NC_6H_4$, 4-$HO_2CC_6H_4$, 4-$MeOC_6H_4$

Abstract *A series of novel diphenyl(arylamino)(1-phenyl-3-(pyridin-2-yl)-1*H*-pyrazol-4-yl)methylphosphonates have been synthesized in high yields. They were screened for their antibacterial activities against Escherichia coli (NCIM2065) as a Gram-negative bacterium, Bacillus subtilis (PC1219) and Staphylococcus aureus (ATCC25292) as Gram-positive bacteria, and Schccaromycies cerevisiae as a fungus. The minimum inhibitory concentrations (MICs) of the synthetic compounds showed moderate antibacterial and antifungal activities at low concentrations (10–1000 μg/mL).*

Supplemental materials are available for this article. Go to the publisher's online edition of Phosphorus, Sulfur, and Silicon and the Related Elements *to view the free supplemental file.*

Keywords α-Aminophosphonates; antimicrobial; Gram-negative and Gram-positive bacteria; fungi; minimum inhibitory concentrations

INTRODUCTION

Organophosphorus derivatives are an important class of biologically active compounds.[1] α-Aminophosphonates are among the most common organophosphorus derivatives and have been used as enzyme inhibitors, inhibitors of serine hydrolase, peptide

Received 26 February 2012; accepted 21 April 2012.
Address correspondence to Gamal A. El-Hiti, School of Chemistry, Cardiff University, Main Building, Park Place, Cardiff CF10 3AT, UK. E-mail: el-hitiga@cardiff.ac.uk; gelhiti@yahoo.co.uk

mimics, antiviral, antibacterial, antifungal, anticancer, anti-HIV, antibiotics, herbicidal, and in other various applications.[2–20] Also, α-aminophosphonates having heterocyclic moieties have shown interesting biological activities.[21–24]

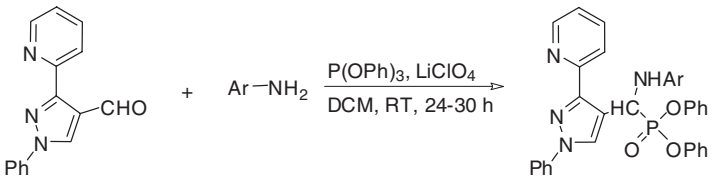
Various methods for the synthesis of α-aminophosphonates were reported.[25–31] However, one pot Mannich-type[32] process of carbonyl compounds, amines, and diphenyl phosphite in the presence of a Lewis acid catalyst remains the most efficient, simple, general, and high yielding method.[33–36]

We have reported efficient syntheses of various heterocycles[37–50] as part of our research in organic chemistry. As part of continuing work in the area of biologically active heterocycles, we have recently reported the synthesis, antimicrobial, and anticancer activities of a novel series of α-aminophosphonates.[51] The present work was aimed to synthesize novel α-aminophosphonates containing pyridine and pyrazole moieties with the hope that new antimicrobial agents could be developed. We now report the successful synthesis of a novel α-aminophosphonates and their antimicrobial properties.

RESULTS AND DISCUSSION

Chemistry

Reactions of 1-phenyl-3-pyridine-2-yl-1*H*-pyrazole-4-carboxaldehyde (**1**; 2 molar equivalents) with aryl amines (aniline, 4-chloroaniline, 4-toluidine, 4-(*N,N*-dimethylamino) aniline, 4-aminobenzoic acid, and 4-anisidine; 4 molar equivalents) and triphenylphosphite (3 molar equivalents) in the presence of lithium perchlorate, as a Lewis acid, were carried out in dichloromethane (DCM) at room temperature for 24–30 h under identical conditions. The crude products obtained were purified by crystallization from ethanol to give the corresponding α-aminophosphonates **2–7** in 70–84% yields (Scheme 1). The reaction represented in Scheme 1 is general, simple, high yielding, involves easy work-up, and accommodates various substituents to produce substituted α-aminophosphonates efficiently.



Ar = Ph, 4-ClC_6H_4, 4-MeC_6H_4, 4-$Me_2NC_6H_4$, 4-$HO_2CC_6H_4$, 4-$MeOC_6H_4$

Scheme 1

The structures of α-aminophosphonates **2–7** were confirmed by infrared (IR), ^{1}H NMR, mass spectroscopy, and elemental analyses. The IR spectra of **2–7** are characterized by the presence of absorption bands within the 3425–3400 cm^{-1} region corresponding to the stretching vibrations of the NH groups. The bands within the 1628–1596 cm^{-1} region are due to the stretching vibration of the C=N groups of the 1*H*-pyrazole ring while the absorption bands in the 1321–1310 cm^{-1} region are due to the symmetric stretching vibrations of the P=O groups and those within the 821–810 cm^{-1} region are attributed to the P–O–C groups.

The ^{1}H NMR spectra of α-aminophosphonates **2–7** showed a characteristic exchangeable singlet within the 10.00–8.01 ppm region due to the NH proton while the CH protons resonated as doublets (J = 12–15 Hz) within the 6.66–5.43 ppm region. The structures of compounds **2–7** were confirmed further by electron impact (EI) and electrospray (ES)-mass spectral and showed either a molecular or pseudomolecular (MH^+) ion. Moreover, the elemental analyses of **2–7** were consistent with the suggested structures.

Antimicrobial Activities

The antimicrobial agents available in the market have various drawbacks such as toxicity, narrow spectrum of activity, and some also exhibit drug–drug interactions.[52] In view of the high incidence of infections in immunocompromised patients, demands for new antimicrobial agents with a broad spectrum of activity and good pharmacokinetic properties have increased.[53]

α-Aminophosphonates **2–7** along with the starting material **1** were screened for their in vitro antibacterial and antifungal activities against *Escherichia coli* (NCIM2065) as a Gram-negative bacterium, *Bacillus subtilis* (PC1219) and *Staphylococcus aureus* (ATCC25292) as Gram-positive bacteria, and *Schccaromycies cerevisiae* as a fungus. The inhibition zones were measured in triplicates and the results are reported in Table S1 (available online in Supplemental Materials).

The results showed that compounds **2–7** showed moderate antimicrobial activities against the tested organisms. It is also clear that α-aminophosphonates **2–7** are more active compared to the starting material **1**.

Minimum Inhibitory Concentrations (MICs)

The MICs of compound **1** and α-aminophosphonates **2–7** were determined for each antimicrobial agent by using the agar diffusion method. The inhibition zone was measured in triplicates in four different concentrations (10–1000 μg/mL) and the mean value $\pm$ standard deviation (SD) is recorded in Table S2 (available online in Supplemental Materials).

Table S2 (available online in Supplemental Materials) showed that all compounds exhibit high antimicrobial activities at a concentration of 10–1000 μg/mL for all microorganisms. Compounds **1–7** showed high antimicrobial activities at a concentration of 1000 μg/mL.

The Lethal Dose

The cytotoxicity lethal dose (LD_{50}) of compounds **1–7** was determined from the larvae of *Artemia salina* using the brine shrimp lethality bioassay. The lethal doses for compounds **1–7** are shown in Figures S1–S7 (available online in Supplemental Materials).

The lethal dose for compounds **2**, **5**, and **6** were found to be 915, 1000, and 2045 μg/mL, respectively while the lethal dose for compound **3** was 544 μg/mL. Clearly, compound **6** is the safest compound to be used followed by compounds **2** and **5**. On the other hand, the starting material **1** and compounds **4** and **7** were the least safe compounds.

CONCLUSION

A convenient high yielding process for the synthesis of α-aminophosphonates, having pyridine and pyrazole moieties, has been developed. The antimicrobial activities of the newly synthesized compounds exhibit Gram-positive, Gram-negative bacteria and fungi

show moderate activities at low concentrations. The lethal dose of the synthetic compounds indicated that the synthesized compounds are safe and are promising for their use as in vivo antimicrobial reagents. Clearly, the introduction of the phosphonate group improved the biological activities and the safety of products for use was comparable to that of the starting material.

EXPERIMENTAL

General Experimental

Melting point determinations were performed by the open capillary method using an Electrothermal MEL-TEMP II apparatus (Tanta, Egypt) and are reported uncorrected. IR spectra were recorded on a PerkinElmer 1430 Spectrophotometer (Tanta, Egypt) using the KBr disc technique. ^{1}H NMR spectra were recorded on a Bruker AC400 spectrometer (Cardiff, United Kingdom) operating at 400 MHz. The spectra were recorded in DMSO-d_6. Chemical shifts δ are reported in parts per million (ppm) relative to tetramethylsilane (TMS). Assignments of signals are based on integration values and expected chemical shift values, and have not been rigorously confirmed. EI mass spectra were recorded at energy 70 eV with a 7070 EQ mass spectrometer (Cardiff, United Kingdom). ES analyses were performed on a ZQ4000 spectrometer (Cardiff, United Kingdom) in the positive ionization mode. Microanalysis was performed by analytical service at both the Universities of Tanta and Cairo, Egypt. Reagents and solvents were obtained from commercial sources and used without purification.

1-Phenyl-3-(pyridin-2-yl)-1*H*-pyrazole-4-carbaldehyde (**1**) was prepared according to the literature procedure, mp 190–192 °C; lit. 190–192 °C.[54]

Chemistry

General Procedure for the Synthesis of Diphenyl(arylamino)(1-phenyl-3-(pyridin-2-yl)-1*H*-pyrazol-4-yl)methylphosphonates 2–7. A mixture of **1** (0.50 g, 2.0 mmol) and a solution of $LiClO_4$ in DCM (3 mL, 5.0 M; 15.0 mmol) in DCM (10 mL) was stirred for 2 min and aromatic amine (4.0 mmol) was then added. The mixture was stirred for 10 min and triphenylphosphite (0.93 g, 3.0 mmol) was then added. The mixture was stirred at room temperature for 24–30 h during which the progress of the reaction was monitored by thin-layer chromatography (TLC). Water (10 mL) was added to the reaction mixture and the organic phase was separated and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give the crude product that recrystallized from ethanol to give the pure products **2**–**7**.

*Diphenyl(1-phenyl-3-(pyridin-2-yl)-1*H*-pyrazol-4-yl)(phenylamino)methylphosphonate (**2**).* White crystal; yield: 75%; mp 153–156 °C; IR (KBr): 3420 (NH), 1620 (C=N), 1310 (P=O), and 810 (P–O–C) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 8.70 (br s, exch., 1H, NH), 8.49–6.97 (m, 25H, Ar–H) and 6.66 (d, J = 15 Hz, 1H, CH). EI–MS: *m*/*z* (%) 558 (M^+, 2), 357 (81), 232 (91), 170 (15), 94 (100), and 65 (87). ES$^+$–MS: *m*/*z* (%) 558 (M^+, 7), 465 (100), 428 (10), 390 (24), and 372 (22). Anal. calcd for $C_{33}H_{27}N_4O_3P$ (558.57 g mol^{-1}): C, 70.96; H, 4.87; N, 10.03; P, 5.55. Found: C, 71.02; H, 4.88; N, 10.07; P, 5.52.

*Diphenyl(4-chlorophenylamino)(1-phenyl-3-(pyridin-2-yl)-1*H*-pyrazol-4-yl)methylphosphonate (**3**).* White crystal; yield: 70%; mp 170–172 °C; IR (KBr): 3425 (NH), 1628 (C=N), 1320 (P=O), and 816 (P–O–C) cm^{-1}. ^{1}H NMR (DMSO-d_6):

δ 8.01 (br s, exch., 1H, NH), 8.86–6.63 (m, 24H, Ar–H), and 5.43 (d, $J = 14$ Hz, 1H, CH). EI–MS: *m/z* (%) 594 ($[M^{37}Cl]^+$, 1), 592 ($[M^{35}Cl]^+$, 3), 531 (2), 455 (3), 357 (16), 232 (10), and 95 (100). Anal. calcd for $C_{33}H_{26}ClN_4O_3P$ (593.01): C, 66.84; H, 4.42; N, 9.45; P, 5.22. Found: C, 66.90; H, 4.45; N, 9.44; P, 5.25.

*Diphenyl(1-phenyl-3-(pyridin-2-yl)-1*H*-pyrazol-4-yl)(4-tolylamino)methyl phosphonate (**4**).* White crystal; yield: 81%; mp 141–143 °C; IR (KBr): 3424 (NH), 1596 (C=N), 1320 (P=O), and 811 (P–O–C) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 10.00 (br s, exch., 1H, NH), 8.95–6.78 (m, 24H, Ar–H), 5.81 (d, $J = 15$ Hz, 1H, CH), and 2.10 (s, 3H, CH_3). EI–MS: *m/z* (%) 357 (5), 338 (34), 232 (82), 94 (100). ES^+–MS: *m/z* (%) 636 ($[M + MeCNNa]^+$, 51), 595 ($[M + Na]^+$, 9), 573 (MH^+, 100), 466 (10), 401 (7), 277 (12), and 229 (11). Anal. calcd for $C_{34}H_{29}N_4O_3P$ (572.59): C, 71.32; H, 5.10; N, 9.78; P, 5.41. Found: C, 71.51; H, 4.91; N, 9.35; P, 5.39.

*Diphenyl(4-(dimethylamino)phenylamino)(1-phenyl-3-(pyridin-2-yl)-1*H*-pyrazol-4-yl)methylphosphonate (**5**).* White solid; 84%; mp 153–155; IR (KBr): 3412 (NH), 1611 (C=N), 1321 (P=O), and 821 (P–O–C) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 9.04 (br s, exch., 1H, NH), 8.78–6.75 (m, 24H, Ar–H), 6.01 (d, $J = 12$ Hz, 1H, CH), and 3.00 (s, 6H, 2 CH_3). EI–MS: *m/z* (%) 601 (M^+, 5), 524 (43), 447 (70), 370 (34), 338 (100). Anal. calcd for $C_{35}H_{32}N_5O_3P$ (601.63): C, 69.87; H, 5.36; N, 11.64; P, 5.15. Found: C, 69.68; H, 5.27; N, 11.72; P, 5.29.

*Diphenyl(4-carboxyphenylamino)(1-phenyl-3-(pyridin-2-yl)-1*H*-pyrazol-4-yl)methylphosphonate (**6**).* White solid; yield: 77%; mp 177–179 °C; IR (KBr): 3420 (NH/OH), 1700 (C=O), 1612 (C=N), 1318 (P=O), and 820 (P–O–C) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 9.29 (br s, exch., 1H, NH), 8.86–6.53 (m, 24H, Ar–H), and 5.90 (d, $J = 13$ Hz, 1H, CH). EI–MS: *m/z* (%) 602 (M^+, 2), 339 (26), 220 (73), and 93 (100). Anal. calcd for $C_{34}H_{27}N_4O_5P$ (602.57): C, 67.77; H, 4.52; N, 9.30; P, 5.14. Found: C, 67.60; H, 4.32; N, 9.41; P, 5.25.

*Diphenyl(4-methoxyphenylamino)(1-phenyl-3-(pyridin-2-yl)-1*H*-pyrazol-4-yl)methylphosphonate (**7**).* White solid; yield: 80%; mp 166–168 °C; IR (KBr): 3400 (NH), 1606 (C=N), 1318 (P=O), and 818 (P–O–C) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 9.14 (br s, exch., 1H, NH), 8.68–6.96 (m, 24H, Ar–H), 6.55 (d, $J = 13$ Hz, 1H, CH), and 3.77 (s, 3H, OCH_3). EI–MS: *m/z* (%) 588 (M^+, 5), 511 (24), 325 (71), 221 (23), 93 (100). Anal. calcd for $C_{34}H_{29}N_4O_4P$ (588.59): C, 69.38; H, 4.97; N, 9.52; P, 5.26. Found: C, 69.43; H, 4.90; N, 9.39; P, 5.35.

Biological Assay

Gram-Negative Bacteria. The Gram-negative bacterium used in this study was *E. coli*, which is known as the backbone example for Gram-negative bacteria and causes urinary infection, wound infection, and gastroenteritis.

Gram-Positive Bacteria. The Gram-positive bacteria used in this study were *B. subtilis* and *S. aureus*. *B. subtilis* are mostly involved in urinary infection, wound, ulceration, and septicemia. *S. aureus* is the milestone of Gram-positive bacteria and it is a causative agent of pneumonia, meningitis, and food poisoning.

Fungi. *S. cerevisiae* was obtained from the culture collection of the Bacteriology Unit, Department of Botany, Faculty of Science, Tanta University, Egypt.

Media Used and Antimicrobial Assay

Nutrient and Sabouraud's broths and Nutrient and Sabouraud's agar were used for growing and maintaining the tested bacteria and yeast, respectively. The plates were then

incubated at 30 °C for 24–48 h, after which the diameters of the inhibition zones were measured. Nutrient and Sabouraud's broths were used for activation of organisms.[55]

Determination of MICs

The MIC was determined by agar diffusion assay using the filter paper disc method. It was carried out by impregnation of different concentrations of synthesized compounds (0–1000 μg/mL) in dimethyl sulfoxide (DMSO) and then placing them on filter paper discs of the same diameter (5 mm). The antimicrobial activities of the tested samples were determined by measuring the diameter of the zone of inhibition expressed in millimeters. The inhibition zones were measured in triplicates and expressed as mean ± SD.[56]

The Lethal Dose

Brine shrimp lethality bioassay is a very simple bench-top assay used to measure cytotoxicity of plant extracts as well as synthetic compounds. Three replicates were used for each concentration and living larvae were counted after 72 h. All data were expressed as mean ± SD.[57]

REFERENCES

1. Ordóñez, M.; Rojas-Cabrera, H.; Cativiela, C. *Tetrahedron* **2009,** 65, 17-49.
2. Hassal, C. H.; Hahn, E. F. *Antibiotics*, vol VI; Springer: Berlin, **1983**; pp. 1-11.
3. Atherton, F. R.; Hassall, C. H.; Lambert, R. W. *J. Med. Chem.* **1986,** 29, 29-40.
4. Allen, M. C.; Fuhrer, W.; Tuck, B.; Wade, R.; Wood, J. M. *J. Med. Chem.* **1989,** 32, 1652-1661.
5. Kafarski, P.; Lejczak, B. *Phosphorous Sulfur Silicon Relat. Elem.* **1991,** 63, 193-215.
6. Lombaert, S. D.; Blanchard, L.; Tan, T.; Akane, Y. S.; Berry, C.; Ghai, R. D. *Bioorg. Med. Chem. Lett.* **1995,** 5, 145-150.
7. Alonso, E.; Alonso, E.; Solis, A.; Del Pozo, C. *Synlett* **2000,** 698-700.
8. Kafarski, P.; Lejczak, B. *Curr. Med. Chem. Anti-Cancer Agents* **2001,** 1, 301-312.
9. Song, B. A.; Wu, Y. L.; Yang, S.; Hu, D. Y. *Molecules* **2003,** 8, 186-192.
10. Li, C.; Song, B.; Yan, K.; Xu, G.; Hu, D.; Yang, S.; Jin, L.; Xue, W.; Lu, P. *Molecules* **2007,** 12, 163-172.
11. Prasad, G. S.; Krishna, J. R.; Manjunath, M.; Reddy, O. V. S.; Krishnaiah, M.; Reddy, C. S.; Puranikd, V. G. *Arkivoc* **2007,** xiii, 133-141.
12. Rao, X.; Song, Z.; He, L. *Heteroatom Chem.* **2008,** 19, 512-516.
13. Naydenova, E. D.; Todorov, P. T.; Topashka-Ancheva, M. N.; Momekov, G. Ts.; Yordanova, T. Z.; Konstantinov, S. M.; Troev, K. D. *Eur. J. Med. Chem.* **2008,** 43, 1199-1205.
14. Tušek-Božić, L.; Juribašić, M.; Traldi, P.; Scarcia, V.; Furlani, A. *Polyhedron* **2008,** 27, 1317-1328.
15. Wang, B.; Miao, Z. W.; Wang, J.; Chen, R. Y.; Zhang, X. D. *Amino Acids* **2008,** 35, 463-468.
16. Rezaei, Z.; Firouzabadi, H.; Iranpoor, N.; Ghaderi, A.; Jafari, M. R.; Jafari, A. A.; Zare, H. R. *J. Med. Chem.* **2009,** 44, 4266-4275.
17. Naydenova, E. D.; Todorov, P. T.; Mateeva, P. I.; Zamfirova, R. N.; Pavlov, N. D.; Todorov, S. B. *Amino Acids* **2010,** 39, 1537-1543.
18. Oniţa, N.; Sisu, I.; Penescu, M.; Purcarea, V. L.; Kurunczi, L. *Farmacia* **2010,** 58, 531-545.
19. Zhang, X.; Qu, Y.; Fan, X.; Bores, C.; Feng, D.; Andrei, G.; Snoeck, R.; De Clercq, E.; Loiseau, P. M. *Nucleosides Nucleotides Nucleic Acids* **2010,** 29, 616-627.
20. Liu, J.; Yang, S.; Li, X.; Fan, H.; Bhadury, P.; Xu, W.; Wu, J.; Wang, Z. *Molecules* **2010**, 15, 5112-5123.

21. Zhou, J.; Fan, H. T.; Song, B. A.; Jin, L. H.; Bhadury, P. S.; Hu, D. Y.; Yang, S. *Phosphorus Sulfur Silicon Relat. Elem.* **2011,** 186, 81-87.
22. Hu, D. Y.; Wan, Q. Q.; Yang, S.; Song, B. A.; Bhadury, P. S.; Jin, L. H.; Yan, K.; Liu, F.; Chen, Z.; Xue, W. *J. Agric. Food Chem.* **2008,** 56, 998-1001.
23. Liu, J.-Z.; Song, B.-A.; Fan, H.-T.; Bhadury, P. S.; Wan, W.-T.; Yang, S.; Xu, W.; Wu, J.; Jin, L.-H.; Wei, X.; Hu, D.-Y.; Zeng, S. *Eur. J. Med. Chem.* **2010,** 45, 5108-5112.
24. Jin, L.; Song, B.; Zhang, G.; Xu, R.; Zhang, S.; Gao, X.; Hu, D.; Yang, S. *Bioorg. Med. Chem. Lett.* **2006,** 16, 1537-1543.
25. Fields, E. K. *J. Am. Chem. Soc.* **1952,** 74, 1528-1531.
26. Sawamura, M.; Ito, Y.; Hayashi, T. *Tetrahedron Lett.* **1989,** 30, 2247-2250.
27. Kuntz, H.; Laschat, S. *Synthesis* **1992,** 90-95.
28. Yokommatsu, T.; Shibuya, S. *Tetrahedron: Asymmetry* **1992,** 3, 377-380.
29. Qian, C.; Huang, T. *J. Org. Chem.* **1998,** 63, 4125-4128.
30. Ranu, B. C.; Hajra, A.; Jana, U. *Org. Lett.* **1999,** 1, 1141-1143.
31. Chandrasekhar, S.; Prakash, S. J.; Jagadeshwar, V.; Narsihmulu, Ch. *Tetrahedron Lett.* **2001,** 42, 5561-5563.
32. Wang, Q. M.; Li, Z. G.; Hung, R. Q.; Cheng, J. R. *Heteroatom Chem.* **2001,** 12, 68-72.
33. El Sayed, I.; El Kosy, S. M.; Hawata, M. A.; El Gokha, A. A.-A.; Tolan, A.; Abd El-Sattar, M. M. *J. Am. Sci.* **2011,** 7, 357-361.
34. Caldés, C.; Vilanova, B.; Adrover, M.; Muñoz, F.; Donoso, J. *Bioorg. Med. Chem.* **2011,** 19, 4536-4543.
35. Ning, L.; Wang, W.; Liang, Y.; Peng, H.; Fu, L.; He, H. *J. Med. Chem.* **2012,** 47, 379-384.
36. Reddy, C. B.; Kumar, K. S.; Kumar, M. A.; Reddy, M. V. N.; Krishna, B. S.; Naveen, M.; Arunasree, M. K.; Reddy, C. S.; Raju, C. N. Reddy, C. D. *J. Med. Chem.* **2012,** 47, 553-559.
37. Smith, K.; El-Hiti, G. A.; Abdel-Megeed, M. F.; Abdo, M. A. *J. Org. Chem.* **1996,** 61, 647-655.
38. Smith, K.; El-Hiti, G. A.; Abdel-Megeed, M. F.; Abdo, M. A. *J. Org. Chem.* **1996,** 61, 656-661.
39. Smith, K.; El-Hiti, G. A.; Hawes, A. C. *Synthesis* **2003,** 2047-2052.
40. Smith, K.; El-Hiti, G. A.; Mahgoub, S. A. *Synthesis* **2003,** 2345-2348.
41. El-Hiti, G. A. *Synthesis* **2003,** 2799-2804.
42. El-Hiti, G. A. *Synthesis* **2004,** 363-368.
43. Smith, K.; El-Hiti, G. A.; Abdel-Megeed, M. F. *Synthesis* **2004,** 2121-2130.
44. Smith, K.; El-Hiti, G. A.; Hegazy, A. S. *Synthesis* **2005,** 2951-2961.
45. Smith, K.; El-Hiti, G. A.; Hegazy, A. S. *Synlett* **2009,** 2242-2244.
46. Smith, K.; El-Hiti, G. A.; Hegazy, A. S. *Synthesis* **2010,** 1371-1380.
47. Smith, K.; El-Hiti, G. A.; Hegazy, A. S.; Fekri, A. *Heterocycles* **2010,** 80, 941-956.
48. Smith, K.; El-Hiti, G. A.; Hegazy, A. S. *Chem. Commun.* **2010,** 2790-2792.
49. Smith, K.; El-Hiti, G. A.; Hegazy, A. S.; Kariuki, B. *Beilstein J. Org. Chem.* **2011,** 7, 1219-1227.
50. Browne, K. A.; Deheyn, D. D.; El-Hiti, G. A.; Smith, K.; Weeks, I. *J. Am. Chem. Soc.* **2011**, 133, 14637-14648.
51. Abdel-Megeed, M. F.; Badr, B. E.; Azaam, M. M.; El-Hiti, G. A. *Bioorg. Med. Chem.* **2012,** 20, 2252-2258.
52. Shalini, K.; Kumar, N.; Drabu, S.; Sharma, P. K. *Beilstein J. Org. Chem.* **2011,** 7, 668-677.
53. Azizi, N.; Saidi, M. R. *Tetrahedron* **2003,** 59, 5329-5332.
54. El Sayed, I.; El Kosy, S. M.; Abdel-Megeed, M. F.; Hamed, M. A.; El Gokha, A. A.-A.; Abd El-Sattar, M. M. *J. Am. Sci.* **2011,** 7, 604-608.
55. Pridham, T. G.; Lindenfelser, L. A.; Shotwell, O. L.; Stodola, F.; Benedict, R. G.; Foley, C.; Jacks, P. W.; Zaumeeyer, W. J.; Perston, W. H.; Mitchell, J. W. *Phytopathology* **1956,** 46, 568-575.
56. Hsueh, P. R.; Chang, J. C.; Teng, L. J.; Yang, P. C.; Ho, S. W.; Hsieh, W. C.; Luh, K. T. *J. Clin. Microbiol.* **1997,** 35, 1021-1023.
57. Meyer, B. N.; Ferrigni, N. R.; Putnam, J. E.; Jacobsen, L. B.; Nichols, D. E.; McLaughlin, J. L. *Planta Med.* **1982,** 45, 31-34.