Asian Journal of Chemistry; Vol. 28, No. 4 (2016), 917-920

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2016.19555

Synthetic Approach for Novel Fluorine Substituted Thiadiazaphosphole Fused 1,2,4-Triazinopyridiazine Moieties as Bactericidal Agents

MOHAMMED SALEH TAWFEK MAKKI, REDA MOHAMMADY ABDEL RAHMAN and OLA AHMAD ABU ALI*

Chemistry Department, Faculty of Science, King Abdul Aziz University, Jeddah 80203, Kingdom of Saudi Arabia

*Corresponding author: E-mail: lolo_aa4@hotmail.com

Received: 10 August 2015; *Accepted*: 13 October 2015; *Published online*: 30 December 2015; AJC-17716

Novel fluorine substituted thiadiazaphosphole fused 1,2,4-triazino pyridiazines (**7** and **8**) were synthesized by refluxing of 4-amino-6-styryl-3-mercapto-1,2,4-triazin-5-one (**2**) with triethylphosphite and/or triethylphospate in dry ethyl benzene followed by cycloaddition with hydrazine in warm ethanol-piperidine and finally boil with trifluoroacetic anhydride in dioxane. Structure of the products was elucidated with the help of elemental analysis and spectral data. All the target compounds evaluated as bactericidal agents against *Escherichia coli* compared with chloromycetin as standard antibiotic.

Keywords: Synthetic, Thiadiazaphospholo-1,2,4-triazine, Bactericidal.

INTRODUCTION

The introduction of phosphorus atom to heterocyclic systems, often enhance their biological properties [1,2]. The presence of phosphorus tends to more physical and chemical activities [3]. Abdel-Rahman *et al.* [4,5] reported the incorporation of phosphorus-atom within a 1,2,4-triazinnes and pyrazoles enhance that activity. 1,3,4-Thiadiazolo-1,2,4-triazinone showed an anti HIV and anticancer activities. On the other hand, fluorine substituted heterocyclic nitrogen molecules use as biocidal probes [6-12]. Based on these observations, the present work reports the synthesis of fluorine substituted thiadiazaphosphole fused with 1,2,4-triazinopyridiazine moieties in view of their bactericidal activity.

EXPERIMENTAL

Melting points of the products were determined on Stuart SMP_3 (UK) and uncorrected. UV absorption spectra (λ_{max}, nm) were recorded in DMF on Shimadzu UV and visable 310 IPC-spectrophotometer. A Perkins Elmer Model RXI-FT IR system 55529 was used for recording IR spectra of the prepared compounds γcm^{-1}. A Brucker advanced D P X 400 MHz model using TMS as internal standard was used for recording the ^1H NMR and ^{13}C NMR spectra of the compounds on deuterated ($CDCl_3$, d_6, δ ppm). Mass spectrum was measured on GCMS Q 1000 Ex at 70 eV. Elemental microanalysis was performed by the microanalytical at Cairo- University, Egypt. Compounds **1** [4] and **10** [6] were prepared according the published methods.

Compound **1** was prepared [13] by stirring sodium pyruvate with *p*-chlorobenzaldehyde in 10 % aqueous NaOH at 0-5 °C.

4-Amino-6-(4'-chlorophenyl)ethenyl-3-mercapto-1,2,4-triazin-5-one (2): A mixture of **1** (0.01 mol) and thiocarbohydrazide (0.01 mol) in absoluted ethanol (100 mL) containing a few drops of conc. HCl, then refluxed for 4 h, cooled. The solid obtained was filtered off and crystallized from ethanol to **2** as orange crystals, yield 70 %, m.p.: 284-285 °C. UV (λ_{max}) 280 nm. IR (ν_{max}, cm^{-1}): 1700 (C=O), 1630 (NH_2), 1480 (deformation CH=CH) 820, 780 (*p*-substituted phenyl), 710 (C-Cl). ^1H NMR (DMSO-d_6) δ (ppm): 8.7 (α-CH=), 7.8 (β-CH=), 5.1 (CH=CH- coupling), 3.8 (NH_2). ^{13}C NMR (DMSO-d_6) δ (ppm): 179 (C=S), 160 (C=O), 132-128 (aromatic carbons), 120 (C=N), 77-75 (aliphatic carbons). CHNSCl analysis for $C_{11}H_9N_4OClS$ (280). Calcd: C, 47.14; H, 3.21; N, 20.0; Cl, 12.5; S, 11.42 %. Found: C, 46.86; H, 3.11; N, 19.70; Cl, 12.31; S, 11.23 %.

6-(4'-Chlorophenyl)ethenyl-2,4,5-thiadiazaphospholo-[2,3-c][1,2,4]triazin-5-one (3) and/or 6-(4'-chlorophenyl)-ethenyl-2,4,5-thiadiazaphospholo[2,3-c][1,2,4]triazin-2,5-dione (4): Equimolar mixture of **2** and triethylphosphite or triethylphosphate in dry ethyl benzene (100 mL) was refluxed for 6 h and cooled. The solid produced filtered off and crystallized from benzene to give **3** and/or **4** respectively. **3**: yield 65 %; m.p.: 274-275 °C. **4**: yield 68 %; m.p.: 268-269 °C. **3**: UV (λ_{max}): 310 nm. IR (ν_{max}, cm^{-1}): 1680 (C=O), 1200 (P=N), 1480 (deformation CH=CH), 880 (*p*-substituted phenyl). **4**:

UV (λ_{max}): 420. IR (ν_{max}, cm^{-1}): 1685 (C=O), 1445 (deformation CH=CH), 1230 (P=O), 1050 (P-O). ^{1}H NMR (DMSO-d_6) δ (ppm): 8.55 (α-CH=), 7.7 (B-CH=), 5.5 (Coupling CH=CH), 7.4-7.2 (m, 4H, aromatic). ^{31}P NMR (DMSO-d_6) δ (ppm): 18.9. **3**: CHNClSP analysis for $C_{11}H_6N_4OClSP$ (308). Calcd: C, 42.83; H, 1.94; N, 18.18; Cl, 11.36; S, 10.38 %. Found C, 42.55; H, 1.80; N, 17.89; Cl, 11.15; S, 10.13 %. **4**: CHNClSP analysis for $C_{11}H_6N_4ClSPO_2$ (324). Calcd: C, 40.74; H, 1.85; N, 17.28; Cl, 10.80; S, 9.87 %. Found C, 40.33; H, 1.55; N, 17.11; Cl, 10.72; S, 9.70 %.

7-(4'-Chlorophenyl)-6H-2,4,5-thiadiazaphospholo[2,3-c][1,2,4]triazino[5,6-c]pyridiazine (5) and/or 7-[4'-chlorophenyl]-6H-2,4,5-thiadiazaphospholo[2,3-c][1,2,4]-triazino[5,6-c]pyridiazin-2-one (6): Equimolar mixture of **3** and/or **4** with hydrazine hydrate in absolute ethanol (100 mL) with a few drops of piperidine, was refluxed for 6 h, cooled then added drops of glacial acetic acid-ice. The produced solid was filtered off and crystallized from dioxane to give **5** and/or **6** respectively. **5**: yield 55 %; m.p.: 280-282 °C. **6**: yield 60 %; m.p.: 242-244 °C. **5**: IR (ν_{max}, cm^{-1}): 3150 (NH), 2900, 1488 (aliphatic CH), 1210 (P=N), ^{1}H NMR (DMSO-d_6) δ (ppm): 8.0 (s, 1H, NH), 7.8, 4.9 (-CH=CH-), 7.6 (s, 1H, CH of pyridiazine). CHNClSP analysis for $C_{13}H_8N_6ClSP$ (346). Calcd: C, 45.08; H, 2.31; N, 24.27; Cl, 10.11; S, 9.24 %. Found: C, 44.88; H, 2.25; N, 24.03; Cl, 9.85; S, 8.91 %. **6**: IR (ν_{max}, cm^{-1}): 3130 (NH), 2890, 1440 (aliphatic CH), 1230 (P=O), 1055 (P-O), 860 (*p*-substituted phenyl), 690 (C-Cl). ^{1}H NMR (DMSO-d_6) δ (ppm): 8.9 (s, 1H, NH), 7.9 (s, 1H, CH of pyridiazine), 7.7-7.5 (m, 4H, aromatic CH). CHNClSP analysis for $C_{13}H_8N_6ClSPO$ (362). Calcd: C, 43.09; H, 2.20; N,23.20; Cl, 9.66; S, 8.83 %. Found: C, 42.81; H, 2.11; N, 22.91; Cl, 9.55; S, 8.55 %.

7-(4'-Chlorophenyl)-6-trifluoroacetyl-2,4,5-thiadiazaphospholo[2,3-c][1,2,4]triazino[5,6-c]pyridiazine (7) and/or 7-[4'-chlorophenyl]-6-trifluoroacety-2,4,5-thiadiazaphospholo[2,3-c][1,2,4]triazino[5,6-c]pyridiazin-2-one (8): Equimolar amounts of **5** and/or **6** with triethyl acetic anhydride in dioxane (100 mL) was refluxed for 4 h, cooled. The resulted solid was filtered and crystallized from THF to give **7** and/or **8** respectively. **7**, yield 45 %; m.p.: 248-250 °C. **8**, yield 58 %; m.p.: 232-234 °C.**7**: IR (ν_{max}, cm^{-1}): 1700 (C=O), 1600 (C=N), 1250 (C-F), 1220 (N=P), 810 (*p*-substituted phenyl), 720 (C-F), 700 (C-Cl). CHNClSP analysis for $C_{15}H_7N_6OClSPF_3$ (442). Calcd: C, 40.72; H, 1.58; N, 19.00; Cl, 7.91; F, 12.89; S, 7.23 %. Found: C, 40.44; H, 1.38; N, 18.55; Cl, 7.70; F, 12.63; S, 7.01 %. **8**: IR (ν_{max}, cm^{-1}): 1698 (C=O), 1610 (C=N), 1240 (C-F), 1210 (P=O), 1060 (P-O), 795 (*p*-substituted phenyl). ^{1}H NMR (DMSO-d_6) δ (ppm): 8.2 (s, 1H, CH= of pyridazine), 7.8-7.5 (m, 4H, aromatic protons). ^{13}C NMR (DMSO-d_6) δ (ppm): 165 (C=O), 130-128 (aromatic carbons), 118, 116 (C=N). ^{31}P NMR: 19.1. M/s: (Int. %) 460 (M+2, 5 %) 93 (100). CHNClFPS analysis for $C_{15}H_7N_6O_2ClF_3SP$ (458). Calcd: C, 39.30; H, 1.52; N, 18.34; Cl, 7.64; F, 12.44; S, 6.98 %. Found: C, 38.91; H, 1.33; N, 18.12; Cl, 7.50; F, 12.31; S, 6.55 %.

RESULTS AND DISCUSSION

The key intermediate in these study is the 4-amino-6-stryle-3-mercapto-1,2,4-triazin-5-one (**2**) was obtained from ring closure reaction of (E) *trans*-4-(4'-chlorophenyl-2-oxo-3-buteneoic acid (**1**) [13] with thiocarbohydrazide in ethanol-HCl [6] (Fig. 1). Reflux of compound **2** with triethylphosphite in dry ethyl benzene [14] to give 2,4,5,1-thiadiazaphospholo[2,3-c]1,2,4-triazine-5-one (**3**), while that reaction in use triethylphosphate yielded 2,5-dioxo-6-(4'-chlorophenyl)ethylenic-1,4,5,2-thiadiazaphosphole (**4**) (**Scheme-I**). The spectral data are in good agreement with the proposed structure. IR spectrum of **2** showed absorption bands at 1700, 1630 and 1480 cm^{-1} for C=O, NH_2 and aliphatic CH=CH groups, while that of **3** recorded mainly bands at 3050 and 2880 cm^{-1} for aromatic and aliphatic functional groups. IR spectrum of **4** showed a characteristic band at 1230 and 1050 cm^{-1} attribute to presence of P=O and P-O groups [15]. IR spectra of **3** and **4** recorded a lack's both NH_2 and SH groups.

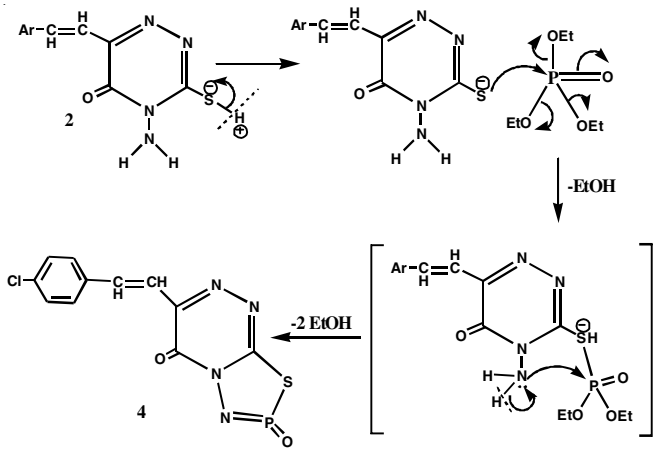
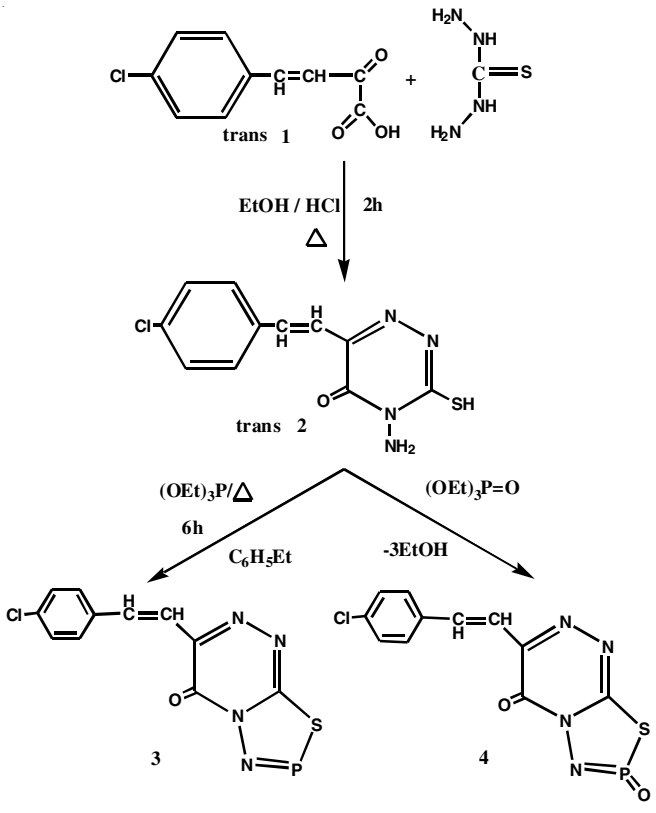


Fig. 1. Formation of **4** from **2**



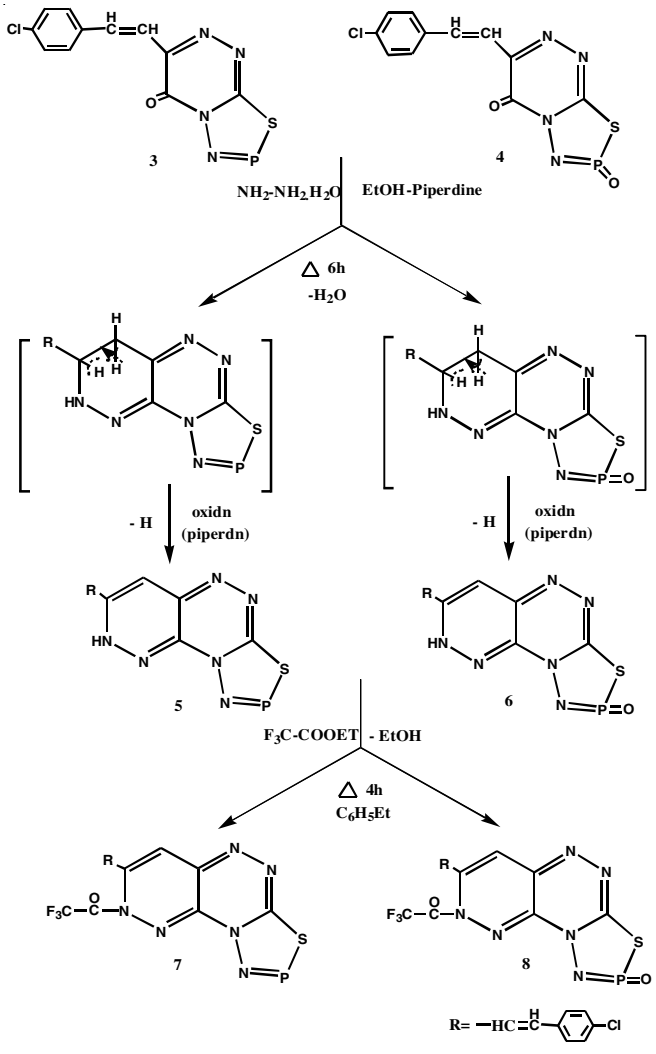
Scheme-I

^{1}H NMR spectra of compounds **2-4** showed a resonated signals at δ 8.8, 7-8 and 6.2 ppm for α-H, β-H and coupling of -CH=CH- (stryl protons). Furthermore, ^{31}P NMR spectrum of **4** recorded a singlet at δ 18.9 ppm for cyclic P=O.

Due the higher nucleophilicity of S^- atoms, formation of compound **4** was deduced from a nucleophilic attack of S^- to a more electrophilic P-atom followed by other nucleophilic attack of NH_2 to that P-atom and loss three mole of EtOH (Fig. 1).

UV absorption spectra of compounds **2-4** give us a good indication about heterocyclization of **2** to **3** and/or **4**. Were λ_{max} of **4** was higher than compound **3** and the start **2**. A higher λ_{max} of **4** is may be due to the extension of hetero-conjugation formed.

Compounds **3** and **4** use as cyclic α,β-unsaturated ketone system. Thus, cycloaddition of **3** and/or **4** with hydrazine hydrate in boiling absolute ethanol drops piperidine afforded the 2,4,5,1-thiadiazaphospholo[2,3-c][1,2,4]triazino[5',6',-c]pyridiazines (**5** and **6**) respectively (**Scheme-II**). IR spectra of compounds **5** and **6** showed a bands at 3150, 2900 and 1488^{-1} cm attribute to NH and CH= groups with lack's of C=O group. ^{1}H NMR spectra of both **5** and **6** showed a new resonated signals at 8.9 and 7.9 ppm for NH and CH= protons of new formed pyridiazine, in addition the aromatic protons at δ 7.7-7.4 ppm. These spectral data, is confirm that cycloaddition reaction tack's place followed by oxidation reaction (**Scheme-II**).



Scheme-II

Fluorination of both compounds **5** and/or **6** by using trifluoroacetic anhydride in reflux dioxane furnished 6-(trifluoroacetyl)-7-(4'-chlorophenyl)-2,4,5,1-thiadiazaphospholo[2,3-c][1,2,4]triazino[5,6-c]pyridiazine (**7** and **8**), respectively (**Scheme-II**). IR spectra of compounds **7** and **8** showed the lack's of NH groups with presence of a new bands at 1710 and 1250 cm^{-1} for acetyl C=O and C-F functional groups. Also, ^{1}H NMR spectra give us a good indication about lack's of NH proton of **7** and **8**.

^{13}C NMR spectra of these compounds recorded a resonated signals at δ 160 and 140 ppm for C=O and C-F carbons present. Mass fragmentation pattern of compound **8** showed [16] a molecular ion peak which under fragmentation process give a base peak at *m/z* 93 as cyclic NSPO (Fig. 2).

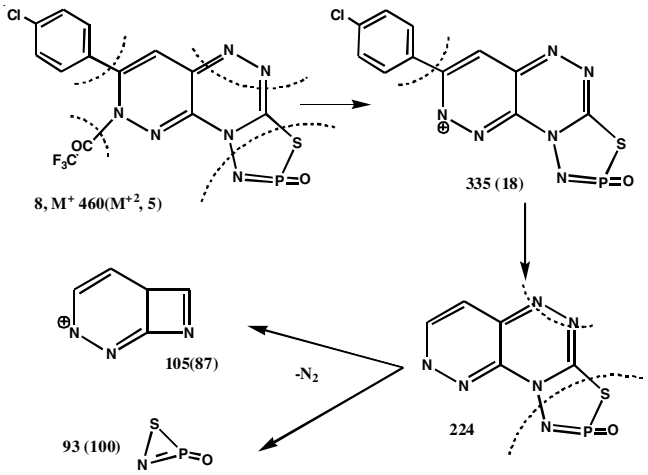


Fig. 2. Mass Fragmentation pattern of compound **8**

Bactericidal activity: Literature survey reveals that cyclic nitrogen-phosphorus as phospholes have attracted considerable attention as they are endowed with wide spectrum of activities [17,18]. Also 1,2,4-triazines are well known and important heterocyclic nitrogen systems [19,20]. *Escherichia coli* is one of the important bacteria widely occurring in green plants. Thus the present investigation, tends to synthesis of fused polyheterocyclic systems containing both nitrogen, sulfur and phosphorus elements (compounds **3-8**) in view of their bactericidal activity against *E. coli*, all the synthesized compounds were evaluated *in vitro* for antibacterial (*E. coli*) *via* the disc diffusion method [21], was applied against *Escherichia coli*. The filter paper discs were soaked in the solutions of synthesized compounds at different concentrations (150, 100 and 50 ppm) in 10 % ethanol and placed at the center of the bacteria seeded agar plates (petri-dishes). These petri dishes were incubated at 28-30 °C for 24 h. The strength is reported by measuring the diameter of zone of inhibition of mm. and the results are standardized against chloromycetin (Table-1).

From the results obtained (Table-1), it is concluded that: compound **2** is highly effective and more than **4** > **6** > **8**. The higher inhibitory of **2** in action on *E. coli* is due to presence of both NH_2 and SH groups which is agreement with biodynamic systems. On the other hand, inhibition zone of compound

TABLE-1
ANTIBACTERIAL ACTIVITY (*in vitro*) OF THE SYNTHESIZED COMPOUNDS **2-8** (ZONE OF INHIBITION, mm)

Compounds	*E. coli*		
	Conc. 50	100	150
2	50	50	50
3	25	28	30
4	25	35	48
5	20	20	25
6	22	31	47
7	15	19	21
8	23	35	46

Control: Chloromycetin at 150 ppm, IZ = 48

4 > 6 > 8 were more than **3 > 5 > 7** which may be the presence of inhibition of cyclic unsaturated ketones (**5-8**). Only compound **8 > 7** which attribute the C-F_3 group.

Conclusion

From the present investigation, it can be concluded that the novel synthesized of fluorine bearing a condensed polyheterocyclic systems containing both sulfur and phosphorus were designed to act as bactericidal probe. These systems were found to be active towards *E. coli* which may plays an important role for antimicrobial activity, were help to control on cellobiace phenomena.

ACKNOWLEDGEMENTS

The authors are grateful to Dr. I.N. Ismail, Biochemistry Department, Faculty of Sciences, Ain Shams University, for antibacterial activity screening studies of the newly synthesized compounds.

REFERENCES

1. R.M. Abdel-Rahman, M.S.T. Makki and A.N. Al-Romaizan, *Int. J. Org. Chem.*, **4**, 247 (2014).
2. A.N. Al-Romaizan, M.S.T. Makki and R.M. Abdel-Rahman, *Inter. J. Org. Chem.*, **4**, 154 (2014).
3. T.E. Ali, R.M. Abdel-Rahman, F.I. Hanafy and S.M. El-Edfawy, *Phosphorus Sulfur Silicon Rel. Elem.*, **183**, 2565 (2008).
4. R.M. Abdel-Rahman, *Trends Heterocycl. Chem.*, **8**, 187 (2002).
5. R.M. Abdel-Rahman, M.A. Ibrahim and T.E. Ali, *Eur. J. Chem.*, **1**, 383 (2010).
6. Z. El-Gendy, J.M. Morsy, H.A. Allimony, W.R. Abdel-Monem and R.M. Abdel-Rahman, *Pharmazie*, **56**, 376 (2001).
7. Z. El-Gendy, J.M. Morsy, H.A. Allimony, W.R. Abdel-Monem and R.M. Abdel-Rahman, *Phosphorus Sulfur Silicon Rel. Elem.*, **178**, 2055 (2003).
8. R.M. Al-Harbi, Abdel-Rahman and A.M. Asiri, *Eur J. Chem.*, **6**, 63 (2015).
9. R.M. Al-Harbi, Abdel-Rahman and A.M. Asiri, *Inter. J. Org. Chem.*, **4**, 142 (2014).
10. M.S.T. Makki, R.M. Abdel-Rahman and K.A. Khan, *J. Chem.*, Article ID 430573 (2014).
11. T.E. Ali and R.M. Abdel-Rahman, *J. Sulfur Chem.*, **33**, 339 (2014).
12. R.M. Abdel-Rahman and T.E. Ali, *Monatsh. Chem.*, **144**, 1243 (2013).
13. H.A. Zaher, R. Mohammady and Y.A. Ibrahim, *J. Heterocycl. Chem.*, **21**, 905 (1984).
14. T.E. Ali and S.S. Halacheva, *Heteroatom Chem.*, **20**, 117 (2009).
15. T.E. Ali, *Phosphorus Sulfur Silicon Rel. Elem.*, **185**, 88 (2009).
16. C.D. Reddy, G.T. Reddy and M.S. Reddy, *Asian J. Chem.*, **5**, 291 (1993).
17. I.B. Paek, S.Y. Kim, M.S. Kim, J. Kim, G. Lee and H.S. Lee, *J. Toxicol. Environ. Health*, **70**, 1356 (2007).
18. J.Y. Winum, M. Rami, A. Scozzafava, J.L. Montero and C. Supuran, *Med. Res. Rev.*, **28**, 445 (2008).
19. R.M. Abdel-Rahman, M.S.T. Makki, T.E. El-Sayed and M.A. Ibrahim, *Curr Org Synth*, **10**, 136 (2013).
20. R.M. Abdel-Rahman, *Pharmazie*, **56**, 18 (2001).
21. C.H. Collins, Microbiological Methods, Butterworths, London, p. 364 (1967).