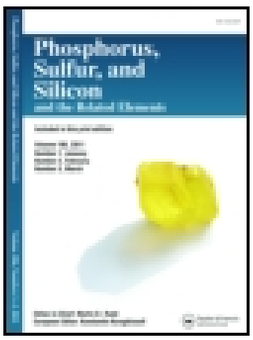

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One-pot synthesis and antimicrobial of novel 6-ethoxy-6-oxido-3-oxo(thioxo) (imino)-5-substituted-2,7-dihydro-1,2,4-triazolo[3,4-*e*][1,2,3]diazaphospholes

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PHOSPHORUS, SULFUR, AND SILICON AND THE RELATED ELEMENTS
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One-pot synthesis and antimicrobial of novel 6-ethoxy-6-oxido-3-oxo(thioxo)(imino)-5-substituted-2,7-dihydro-1,2,4-triazolo[3,4-*e*][1,2,3]diazaphospholes

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ABSTRACT

A series of novel 6-ethoxy-6-oxido-3-oxo(thioxo)(imino)-5-substituted-2,7-dihydro-1,2,4-triazolo[3,4-*e*][1,2,3]diazaphospholes **2a-f** was synthesized and characterized by IR and NMR (^{1}H, ^{13}C, and ^{31}P) spectroscopic analysis. The methodology developed was one-pot three-component reaction of ethyl bromoacetate, triethyl phosphite and carbo(thio)(amino)hydrazides. The synthesized compounds were screened for their antimicrobial activities. 6-Ethoxy-6-oxido-3-oxo(thioxo)-5-phenyl-2,5,7-trihydro-1,2,4-triazolo[3,4-*e*][1,2,3]diazaphospholes (**2c**,**d**) exhibited significantly higher antimicrobial effects against the tested bacterial and fungal strains compared to other compounds and standard drug.

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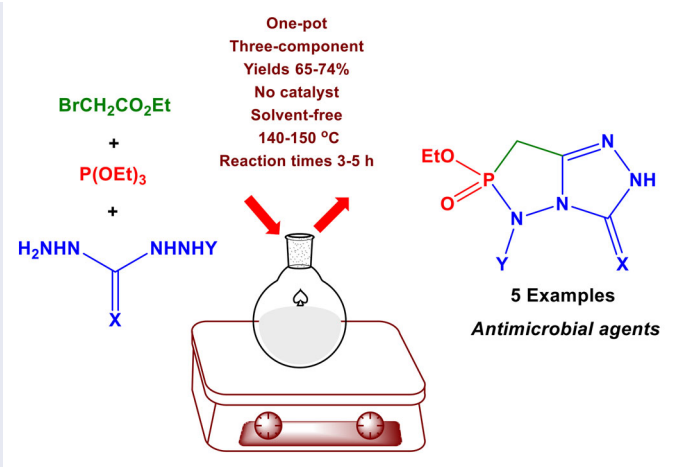
Synthesis; one-pot reaction; 1,2,4-triazole; 1,2,3-diazaphosphole; antimicrobial

GRAPHICAL ABSTRACT



Introduction

Triazoles are a group of heterocyclic compounds with a five-membered ring composed of two carbon atoms and three nitrogen atoms. There are two tautomeric forms that differ in the positions of nitrogen atoms within the ring, namely 1,2,3-triazole and 1,2,4-triazole. Among triazole derivatives, epoxiconazole and propiconazole are used as plant protection products [1]. Also, paclobutrazole and uniconazole are used as plant growth retardants [2]. Furthermore, a wide range of biological effects of triazole derivatives have been confirmed by the literature. This comprises antimicrobial [3–5], antiviral [6], antiproliferative [7], antitumor [8], antioxidant [9], antitubercular [10], anti-inflammatory [11], anticonvulsant [12], and antimalarial [13] activities. On the other hand, 1,2,3-diazaphospholes are well known and have been intensively studied [14–16]. Generally, these compounds were prepared by reaction of hydrazones or azoalkanes with phosphorus trichloride [17]. A variety of substituents on 1,2,3-diazaphosphole molecules led to a wide range of biological activities such as inhibiting activity on calcium transfer across biological membranes [18] and good selective herbicidal activity [19]. Some of these compounds have antivirus activities [20]. This prompted us to extend our research on synthesis and bioactivities of phosphorus heterocycles [21–24] on a combination of triazole and diazaphosphole rings in one molecular frame. Thus, we herein

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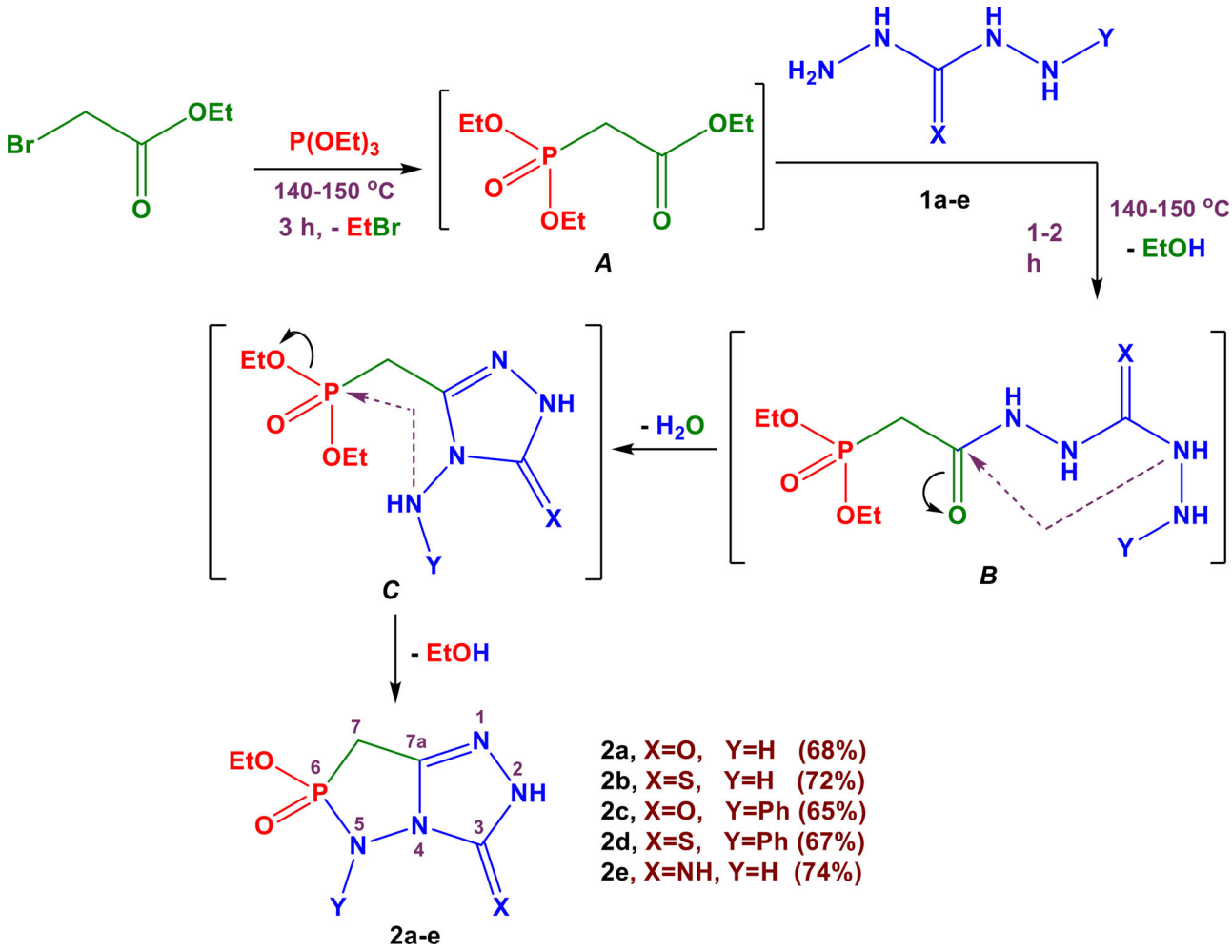

Scheme 1. Reaction of ethyl bromoacetate, triethyl phosphite and carbo(thio)hydrazides 1a-d.

design and synthesize novel substituted of 1,2,4-triazolo[3,4-*e*][1–3]diazaphospholes as potent antimicrobial agents.

Results and discussion

We have synthesized a series of novel 6-ethoxy-6-oxido-3-oxo(thioxo)(imino)-5-substituted-2,7-dihydro-1,2,4-triazolo[3,4-*e*][1,2,3]diazaphospholes **2a-f** using the synthetic route depicted in Scheme 1. In the first step, ethyl bromoacetate reacted with triethyl phosphite at 140-150 °C under *Arbuzov* reaction conditions [25] to form triethyl phosphonoacetate (**A**). In the second step, carbo(thio)hydrazides **1a-d** or 1,3-diaminoguanidine hydrochloride **1e** were added to the intermediate **A** and heated under reflux at 140–150 °C for 1–2 h to form the nonisolable diethyl phosphorohydrazides **B**. In the third step, the intermediates **B** underwent cyclization *via* removal of a water molecule forming the nonisolable diethyl phosphonyl triazoles **C** [26]. In the last step, the N-amino group attacked the diethyl phosphonate moiety to eliminate ethanol, allowing to isolate the target products **2a-e** (Scheme 1).

The structures of compounds **2a-e** were established by various spectral (^{1}H, ^{13}C-NMR, ^{31}P-NMR, IR and MS) and elemental analyses. The IR spectra revealed wide stretching absorption bands between 3105 and 3440 cm^{-1} for NH groups and 1241–1276 cm^{-1} assigned for P = O as well as the characteristic C = O groups in 1714–1719 cm^{-1} in the products **2a,c** [27]. In their ^{1}H-NMR spectra, only one ethoxy group appeared in the region 1.29–1.37 (CH_3) and 4.36–4.45 (OCH_2) ppm confirmed the ring-closure to the 1,2,3-diazaphosphole system [28]. The endocyclic protons of CH_2 in 1,2,3-diazaphosphole rings were expected to appear as doublet due to geminal coupling J(HH) and coupling with phosphorus atom J(PCH). However, one doublet appeared in all products **2a-e** in the range δ 2.64–2.79 ppm (J_{PCH}=21.0–23.4 Hz). It seems possible that the exocyclic O and OEt substituents at phosphorus atom have very similar effects on the chemical shift of the two protons of CH_2 and prevents the expected geminal H-H coupling [29, 30]. In ^{13}C-NMR spectra, the chemical shifts between δ 41.9–42.5 ppm (d, J_{PC}=135.0–151.5 Hz) were assigned to carbons of CH_2–P fragments while carbon atoms of C = O, C = S, C = NH and C–7a appeared at δ 159.5–161.8 (compounds **2a,c**), 180.7–183.8 (compounds **2 b,d**), 161.4 (compound **2e**) and 157.1–158.2 ppm, respectively. ^{13}C-NMR signals of the ethoxy carbon atoms were displayed in range δ 13.8–13.9 (CH_3) and 61.9–64.5 ppm (OCH_2) [28]. The ^{31}P-NMR spectroscopic data of the products **2a-e** were displayed as singlets in the region δ 15.32–19.14 ppm. The lower P-chemical shifts might be attributed to the stronger

electron-withdrawing action of the anellated triazole ring [31]. Additionally, the mass spectra also confirmed the molecular ions in accordance with the formation of final compounds.

Antimicrobial activities

The *in vitro* antibacterial activities of the synthesized compounds were screened against three organisms, namely *Streptococcus pyogenes, Staphylococcus aureus* and *Escherichia coli*. Moreover, all the synthesized compounds were also screened for their *in vitro* antifungal activities against three organisms, namely *Aspergillus niger, Aspergillus clavatus* and *Candida albicans* [32,33]. Minimum inhibitory concentration (MIC) of all synthesized compounds was determined and given in Table S1 (Supplemental Materials). MIC is defined as the lowest concentration of inhibitor at which organism growth was not visually apparent. Ciprofloxacin and Ketoconazole were used as standard drugs for the antibacterial and antifungal activities, respectively. All the products recorded good to excellent antimicrobial activities toward the used microorganisms. The products **2a,b,e** showed acceptable inhibitory activities toward all bacteria organisms and moderate effects toward all fungi organisms in comparison with the standard drugs. On the other hand, the products **2c** and **2d** recorded excellent antibacterial and antifungal effects equal to the standard drugs. The presence of phenyl rings attached to triazolodiazaphosphole system in one molecular frame exhibited extremely excellent antibacterial and antifungal activities.

Experimental

The melting points were measured on a digital Stuart SMP-3 apparatus in an open capillary tube. Infrared spectra were measured on FT-IR spectrophotometer (Nicolet iS10) using KBr disks. The NMR spectra were recorded on a Bruker 600 MHz instrument in DMSO using TMS as an internal standard. Mass spectra were recorded on direct probe controller inlet part to single quadropole mass analyzer in (Thermo Scientific GCMS). Elemental microanalysis was performed on Perkin-Elmer 2400II at the Chemical War department, Ministry of Defense, Egypt. The purity of the synthesized compounds was checked by thin layer chromatography (TLC) and elemental microanalysis. The Supplemental Materials contains sample ^{1}H, ^{13}C and ^{31}P NMR spectra of the products 2 (Figures S1–S15).

General procedure for synthesis of 6-ethoxy-6-oxido-3-oxo(thioxo)(imino)-2,5,7-trihydro-1,2,4-triazolo[3,4-e][1,2,3]diazaphospholes 2a-e

A mixture of triethyl phosphite (5 mmol, 0.82 mL) and ethyl bromoacetate (5 mmol, 0.4 mL) was heated under reflux at 140 − 150 °C for 3 h. The reaction progress was observed by thin layer chromatography. The excess materials were removed under vacuum to form the intermediate residue **A**. An equimolar amount of the corresponding carbo(thio)hydrazide **1a-d** or 1,3-diamino-guanidine hydrochloride **1e** (5 mmol) was added to the previous residue and heated under reflux at 140 − 150 °C for 1 − 2 h. After disappearance of the reactants as monitored by TLC (ethyl acetate: petroleum ether 2:1), the mixtures were cooled and treated with water (30 mL). The formed solids were filtered off and crystallized from ethanol.

6-Ethoxy-6-oxido-3-oxo-2,5,7-trihydro-1,2,4-triazolo[3,4-e][1,2,3]diazaphosphole (2a)

Yellow solid in 68% yield; mp 201 − 202 °C. IR (KBr), (*ν* max, cm^{-1}): 3440 (br, 2 NH), 2923, 2893 (C − H$_{aliph}$), 1719 (C = O), 1603, 1592 (C = N), 1241 (P = O), 1069 (P − O − C). ^{1}H-NMR (600 MHz, DMSO-d_6): 1.36 (t, 3H, J = 7.2 Hz, CH_3), 2.64 (d, 2H, J_{PCH}=23.4 Hz, CH_2−P), 4.38 − 4.43 (m, 2H, CH_2O), 5.87 (s, 1H, NH), 11.80 (s, 1H, NH). ^{13}C-NMR (150 MHz, DMSO-d_6): 13.9 (CH_3), 42.4 (d, J_{PC}=139.5 Hz, CH_2−P), 61.9 (CH_2O), 157.4 (C − 7a), 159.5 (C = O). ^{31}P-NMR (242 MHz, DMSO-d_6): 17.32 ppm. MS (*m/z*, I %): 204 (M^+, 18%). Anal. Calcd for $C_5H_9N_4O_3P$ (204.13): C, 29.42%; H, 4.44%; N, 27.45%. Found: C, 29.26%; H, 4.29%; N, 27.28%.

6-Ethoxy-6-oxido-3-thioxo-2,5,7-trihydro-1,2,4-triazolo[3,4-e][1,2,3]diazaphosphole (2 b)

Yellow solid in 72% yield; mp 210 − 211 °C. IR (KBr), (*ν* max, cm^{-1}): 3295, 3253 (2 NH), 2957, 2863 (C − H$_{aliph}$), 1589, 1525 (C = N), 1258 (P = O), 1197 (C = S), 1066 (P − O − C). ^{1}H-NMR (600 MHz, DMSO-d_6): ^{1}H-NMR (600 MHz, DMSO-d_6): 1.29 − 1.36 (m, 3H, CH_3), 2.76 (d, 2H, J_{PCH}=24.6 Hz, CH_2−P), 4.36 − 4.45 (m, 2H, CH_2O), 5.75 (s, 1H, NH), 11.33 (s, 1H, NH). ^{13}C-NMR (150 MHz, DMSO-d_6): 13.9 (CH_3), 42.5 (d, J_{PC}=135.0 Hz, CH_2−P), 63.7 (CH_2O), 158.2 (C − 7a), 180.7 (C = S). ^{31}P-NMR (242 MHz, DMSO-d_6): 16.94 ppm. MS (*m/z*, I %): 220 (M^+, 12%). Anal. Calcd for $C_5H_9N_4O_2PS$ (220.19): C, 27.27%; H, 4.12%; N, 25.45%; S, 14.56%. Found: C, 27.09%; H, 4.01%; N, 25.31%; S, 14.38%.

6-Ethoxy-6-oxido-3-oxo-5-phenyl-2,5,7-trihydro-1,2,4-triazolo[3,4-e][1,2,3]diazaphosphole (2c)

White solid in 65% yield; mp 223 − 224 °C. IR (KBr), (*ν* max, cm^{-1}): 3120 (NH), 3055 (C − H$_{arom}$), 2946, 2852 (C − H$_{aliph}$), 1714 (C = O), 1597, 1581 (C = N), 1245 (P = O), 1065 (P − O − C). ^{1}H-NMR (600 MHz, DMSO-d_6): 1.37 (t, 3H, J = 7.2 Hz, CH_3), 2.79 (d, 2H, J_{PCH}=21.6 Hz, CH_2−P), 4.38 − 4.42 (m, 2H, CH_2O), 7.20 (t, 1H, J = 9.0 Hz, Ph − H), 7.39 (d, 2H, J = 8.4 Hz, Ph − H), 7.61 (td, 2H, J = 7.2 and 1.2 Hz, Ph − H), 11.93 (s, 1H, NH). ^{13}C-NMR (150 MHz, DMSO-d_6): 13.9 (CH_3), 42.1 (d, J_{PC}=147.0 Hz, CH_2−P), 63.9 (CH_2O), 118.0 (C − 2,6$_{Phenyl}$), 121.6 (C − 4$_{Phenyl}$), 130.0 (C − 3,5$_{Phenyl}$), 140.0 (C − 1$_{Phenyl}$), 157.5 (C − 7a), 161.8 (C = O). ^{31}P-NMR (242 MHz, DMSO-d_6): 19.14 ppm. MS (*m/z*, I %): 280 (M^+, 40%). Anal. Calcd for $C_{11}H_{13}N_4O_3P$ (280.22): C, 47.15%; H, 4.68%; N, 19.99%. Found: C, 47.02%; H, 4.59%; N, 19.73%.

6-Ethoxy-6-oxido-3-thioxo-5-phenyl-2,5,7-trihydro-1,2,4-triazolo[3,4-e][1,2,3]diazaphosphole (2d)

Yellow solid in 67% yield; mp 252 − 254 °C. IR (KBr), (ν max, cm^{-1}): 3105 (NH), 3058 (C − H_{arom}), 2920, 2811 (C − H_{aliph}), 1598, 1552 (C = N), 1276 (P = O), 1123 (C = S), 1052 (P − O − C). ^{1}H-NMR (600 MHz, DMSO-d_6): 1.35 (t, 3H, J = 7.2 Hz, CH_3), 2.64 (d, 2H, J_{PCH}=21.0 Hz, CH_2−P), 4.43 (q, 2H, J = 7.2 Hz, CH_2O), 6.71 (t, 1H, J = 6.6 Hz, Ph − H), 6.82 (d, 2H, J = 8.4 Hz, Ph − H), 7.13 (t, 2H, J = 7.2 Hz, Ph − H), 11.35 (s, 1H, NH). ^{13}C-NMR (150 MHz, DMSO-d_6): 13.9 (CH_3), 41.9 (d, J_{PC}=151.5 Hz, CH_2−P), 64.5 (CH_2O), 157.5 (C − 7a), 183.8 (C = S). ^{31}P-NMR (242 MHz, DMSO-d_6): 18.83 ppm. MS (m/z, I %): 296 (M^+, 28%). Anal. Calcd for $C_{11}H_{13}N_4O_2PS$ (296.28): C, 44.59%; H, 4.42%; N, 18.91%; S, 10.82%. Found: C, 44.41%; H, 4.26%; N, 18.75%; S, 10.71%.

6-Ethoxy-3-imino-6-oxido-2,3,5,7-tetrahydro-1,2,4-triazolo[3,4-e][1,2,3]diazaphosphole (2e)

Pale yellow solid in 68% yield; mp 203 − 205 °C. IR (KBr), (ν max, cm^{-1}): 3317, 3252, 3139 (3 NH), 2961 (C − H_{aliph}), 1617, 1596 (C = N), 1251 (P = O), 1062 (P − O − C). ^{1}H-NMR (600 MHz, DMSO-d_6): 1.36 (t, 3H, J = 7.2 Hz, CH_3), 2.75 (d, 2H, J_{PCH}=22.8 Hz, CH_2−P), 4.39 (q, 2H, J = 7.2 Hz, CH_2O), 4.97 (s, 1H, NH), 8.89 (s, 1H, NH), 10.43 (s, 1H, NH). ^{13}C-NMR (150 MHz, DMSO-d_6): 13.9 (CH_3), 42.2 (d, J_{PC}=135.0 Hz, CH_2−P), 63.8 (CH_2O), 157.1 (C − 7a), 161.4 (C = NH). ^{31}P-NMR (242 MHz, DMSO-d_6): 15.32 ppm. MS (m/z, I %): 203 (M^+, 70%). Anal. Calcd for $C_5H_{10}N_5O_2P$ (203.06): C, 29.56%; H, 4.96%; N, 34.48%. Found: C, 29.38%; H, 4.89%; N, 34.29%.

Evaluation of antimicrobial activities

All the synthesized products were investigated for their in *vitro* antimicrobial activity against bacterial strains namely, *Streptococcus pyogenes, Staphylococcus aureus* and *Escherichia coli* and fungal strains namely, *Aspergillus niger, Aspergillus clavatus* and *Candida albicans* by disk diffusion method [32,33]. Ciprofloxacin and Ketoconazole were used as standard drugs for bacteria and fungi, respectively. The inhibitions were recorded by measuring the diameter of the inhibition zone at the end of 24 h for bacteria and 72 h for fungi. Each experiment was repeated twice. Based on the results of zone of inhibition, the minimum inhibitory concentration (MIC) of the synthesized compounds against all bacterial and fungal strains was determined by liquid dilution method. Stock solutions of tested compounds with 500, 250, 125, 62.5, 31.25, 15.62, and 7.84 μg/mL concentrations were prepared with DMSO solvent. The solutions of standard drugs, Ciprofloxacin and Ketoconazole were prepared in the same concentrations. Inoculums of the bacterial and fungal culture were also prepared. To a series of tubes containing 1 mL each of the used compound solution was added with different concentrations and 0.2 mL of the inoculums. A further, 3.8 mL of the sterile water was added to each of the test tubes. These tubes were incubated for 24 h at 37 °C and observed for the presence of turbidity. The minimum inhibitory concentration at which no growth was observed was taken as the MIC values (Table S1, Supplemental Materials).

Conclusion

One-pot three-component reaction of ethyl bromoacetate, triethyl phosphite and carbo(thio)(amino)hydrazides as starting materials, led to the formation of a series of novel 6-ethoxy-6-oxido-3-oxo(thioxo)(imino)-5-substituted-2,7-dihydro-1,2,4-triazolo[3,4-*e*][1,2,3]diazaphosphole **2a-f** as bioactive antimicrobial agents. The method is simple, efficient, solvent-free, catalyst-free, with simple work up and wide application range of the substrate. It conforms to the basic standard of green chemistry.

Disclosure statement

No potential conflict of interest was reported by the authors.

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