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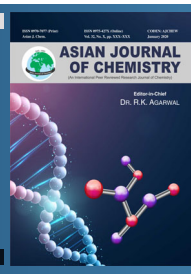

Synthesis, Characterization and Enzyme Inhibition Activity of Organophosphorus Trichalcones Containing Core-Phosphate Moiety

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Facile synthesis of various organophosphorus trichalcones, possessing substantial insecticidal activity, by using *tris*(4-acetylphenyl)-phosphate (**3**) and substituted benzaldehydes as a precursor has been reported. Key precursor **3** has been prepared under mild conditions in presence of tetrabutylammonium bromide (TBAB) as a phase transfer catalyst. All the synthesized compounds (**5a-h**) were screened for their antibacterial activity and inhibition of α-amylase of insect pest, *Tribolium castaneum* (Herbst) (Coleoptera: Tenebrionadeae). Biological activity evaluation study revealed that among all the compounds screened, compound **5g** found to have promising inhibition of α-amylase of insect pest, *Tribolium castaneum*. All the synthesized compounds revealed insignificant antimicrobial activity against pathogenic bacteria even at 500 µg/mL.

Keywords: Phosphoryl chloride, Tetrabutylammonium bromide, Trichalcones, Antibacterial activity.

INTRODUCTION

Organophosphorus compounds are well known for their widespread biological activities [1-10]. The organophosphate derivatives play a significant role as environment friendly pesticides and insecticides in agriculture, horticulture, veterinary medicines and residential settings [11-19]. Phosphoroxy pesticides have been widely used as these are comprehensively effective against pest, economically affordable, degrades within shorter period of time [20] and their decreased likelihood for pest resistance [21]. Phosphate moiety at the core of organophos-phorus pesticides is a common mode of action as an insecticide which works by inhibiting acetyl cholinesterase (AChE) [20,22]. Certain organophosphorus insecticides namely melathian, naled, *etc*. are registered for the mosquito control in USA. These are also used as herbicides [23].

Phosphate esters have been found number of industrial applications such as flame retardants [20,24], surfactants and brighteners in detergents [25], lubricant additives [26] and photo responsive monomers to synthesize cross linked polymer in optical materials, food industry and holographic recording technology [27].

Some organophosphorus derivatives successfully used as antibacterial, antifungal, chemotherapeutic drugs [28] and chemical warfare agents [29]. Organophosphate derivatives derived from benzthiazole were found to be less toxic antifungal agents [30]. Recently phosphates, monophosphates and mono-phosphonate derivatives have been designed for *vivo* health applications such as a more water soluble prodrug, potent drug against cancer and viral infection [31,32].

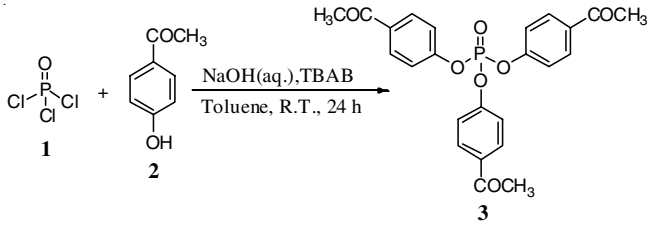
There are plethora of methods reported for the synthesis of phosphorylated compounds [33-35], possessing physical, chemical and biological activities. However, these methods suffer from the limitations such as vigorous conditions, long reaction time, time consuming complex purification method and low product yield. In view of the above facts and in order to develop novel, efficient and further mild protocol for the synthesis of trichalcones (**5a-h**), herein we have reported the phase transfer catalalyzed [36], environmentally benign protocol for the synthesis of structurally diverse phosphate

based trichalcones *via* Claisen-Schmidt condensation reaction. The newly synthesized trichalcone derivatives are studied for antibacterial activity and inhibition of α-amylase of insect pest, *Tribolium castaneum* (Herbst) (Coleoptera: Tenebrionadeae) which is a most destructive pest of flourmills and other stored grain products [37,38].

EXPERIMENTAL

All the chemicals and reagents were purchased from commercial suppliers and used without further purification. Melting points were determined in open glass capillaries and may be uncorrected. The purity of compounds was checked by TLC. The IR spectra of all compounds were recorded in KBr on Shimadzu FT-IR spectrophotometer in the range of 4000-400 cm^{-1}. ^1H and ^{13}C NMR spectra of *tris*(4-acetylphenyl)phosphate was recorded in $CDCl_3$ and ^1H , ^{13}C and ^{31}P NMR spectra of trichalcones were recorded in (DMSO-d_6) on a Brucker Avance 400 MHz spectrometer using TMS as an internal standard. The mass spectra were recorded on EI-Shimadzu-GC-MS spectrometer.

Synthesis of intermediate *tris*(4-acetylphenyl)phosphate (3): To a solution of phosphorus oxychloride (1.53 g, 10 mmol) and tetrabutylammonium bromide (TBAB) (15 mg) taken in a toluene (50 mL), sodium salt of *p*-hydroxy benzaldehyde (*p*-hydroxy benzaldehyde, 3.66 g, 30 mmol and NaOH, 1.8 g in 30 mL water) was added and subjected to fast stirring at room temperature for 24 h. The progress of reaction was monitored on TLC. After completion of reaction two layers were separated and the organic layer (benzene layer) was then washed 2 to 3 times with 10 % NaOH followed by distilled water. The organic layer was dried over anhydrous sodium sulphate, filtered and evaporated under *vacuo* to get white crystalline product of *tris*(4-acetylphenyl)phosphate (**3**), which was recrystallized in absolute ethanol (**Scheme-I**). Yield: 80 %; m.p.: 108-114 ºC, IR(KBr, ν_{max}, cm^{-1}): 1681 (C=O), 1285 (P=O *str.*), 1114 (P-O-C(phenyl) *str.*); ^1H NMR ($CDCl_3$) ppm: δ 2.55 (s, 9H, $-CH_3$-H), 7.33-7.35 (m, 6H, Ar-H), 7.99 (d, 6H, *J* = 12 Hz, Ar-H). EI-MS (*m/z*, %): 453.3(M^++1). ^{31}P NMR: 19.36 ppm.



Scheme-I: Synthesis of *tris*(4-acetylphenyl)phosphate (**3**)

Synthesis of trichalcones (method A)

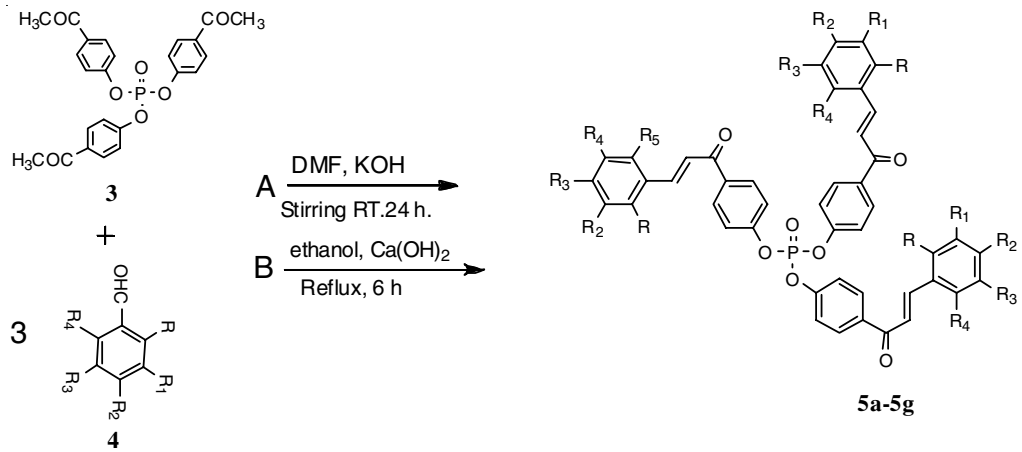
***Tris*(4-(3-phenylacryloyl)phenyl)phosphate (5a):** *Tris*-(4-acetylphenyl)phosphate (**3**) (0.453 g, 1 mmol) was dissolved in DMF (20 mL) and unsubstituted benzaldehyde (**4**) (0.319 g, 3 mmol) was added to it. Then solution of KOH (0.240 g, 6 mmol in 2 mL water) was added to reaction mixture with constant stirring at room temperature for 24 h. The progress of the reaction was monitored on TLC plate. After completion, the reaction mixture was poured over crushed ice and neutralized with dil. HCl. The solid product precipitated out was separated, washed with water and dried. The product purified by recrystallization using the mixture of acetic acid:water (9:1) to give compound **5a**. The same procedure was followed for compounds **5b** and **5e** (**Scheme-II**).

Synthesis of trichalcones (method B)

***Tris*(4-(3-(3,4,5-F-phenyl)acryloyl)phenyl)phosphate (5c):** To a solution of *tris*(4-acetylphenyl)phosphate (**3**) (0.453 g,1 mmol) and 3,4,5-trifluorobenzaldehyde (0.319 g, 3 mmol) in absolute ethanol (30 mL), $Ca(OH)_2$ (1.11 g, 15 mmol) was added and subjected to reflux for 6 h [39]. The progress of the reaction was monitored on TLC plate. After completion, the reaction mixture was poured over crushed ice and neutralized with dil. HCl. The solid product precipitated out was separated, washed with water and dried. The product purified by recrystallization using the mixture of acetic acid:water (9:1) to give compound **5c**. The same procedure was followed for compounds **5d**, **5f** and **5g** (**Scheme-II**). The analytical data is given in Table-1.

Spectral data

***Tris*(4-(3-Phenylacryloyl)phenyl)phosphate (5a):** IR (KBr, ν_{max}, cm^{-1}): 3133 broad (olefinic =C-H, Ar=C-H), 1656 (conj. C=O *str.*), 1597 (-C=C- *str.*), 1336 (P=O *str.*), 1108 (P-O-C- *str.*); ^1H NMR(DMSO-d_6) ppm: δ 7.36-7.45 (m. 15H, Ar-H, O=C-CH=), 7.72 (d, 3H, Ar-CH=, *J* = 16 Hz), 7.79-7.85 (m, 9H, Ar-H), 8.14-8.17 (m, 6H, Ar-H); ^{13}C NMR (DMSO-



Scheme-II: Synthesis of *tris*(4-(3-phenylacryloyl)phenyl)phosphate

TABLE-1
SYNTHESIS OF ORGANOPHOSPHORUS TRI-CHALCONES (**5a-h**)

Product	R	R_1	R_2	R_3	R_4	Yield (%) (method)	Observed m.p. (°C)
5a	H	H	H	H	H	80(A)	197-201
5b	H	H	Cl	H	H	75(A)	225-228
5c	H	F	F	F	H	82(B)	184-189
5d	H	OMe	OMe	OMe	H	70(B)	210-213
5e	H	H	Br	H	H	77(A)	198-205
5f	H	Cl	H	H	H	78(A)	174-176
5g	H	H	NO_2	H	H	87(B)	207-212
5h	H	H	OMe	H	H	80(B)	182-188

d_6) ppm: δ 187.8 (C=O), 155.6 (P-O-C-Ar), 143.7 (C=C), 134.6 (-C-Ar), 133.2 (C-Ar), 130.5 (C-Ar), 128.8 (C-Ar), 128.8 (C-Ar), 122 (C-Ar), 119.9 (C=C), 119.8 (C-Ar).

***Tris*(4-(3-(4-Chlorophenyl)acryloyl)phenyl)phosphate (5b):** IR (KBr, ν_{max}, cm^{-1}): 3135 broad (olefinic =C-H, Ar=C-H), 1680 (conj. C=O *str*.), 1595 (-C=C- *str*.), 1331 (P=O *str*.), 1109 (P-O-C- *str*.). ^{1}H NMR (DMSO-*d_6*) ppm: δ 7.37 (d, 6H, Ar-H, *J* = 8 Hz), 7.44 (d, 6H, Ar-H, *J* = 8 Hz), 7.69 (d, 3H, Ar-CH=, *J* = 16 Hz), 7.78-7.85 (m, 9H, Ar-H, O=C-CH=), 8.13 (d, 6H, Ar-H, *J* = 8 Hz). ^{13}C NMR (DMSO-*d_6*) ppm: δ 187.6 (C=O), 156.2 (P-O-C-Ar), 142.1 (C=C), 135 (C-Ar), 133.6 (C-Ar), 132.8 (C-Ar), 130.5 (C-Ar), 128.9 (C-Ar), 122.7 (C-Ar), 119.9 (C=C), 119.8 (C-Ar).

***Tris*(4-(3-(3,4,5-fluoro-phenyl)acryloyl)phenyl)phosphate (5c):** IR (KBr, ν_{max}, cm^{-1}): 3160 broad (olefinic =C-H, Ar=C-H), 1670 (conj. C=O *str*.), 1600 (-C=C- *str*.), 1340 (P=O *str*.), 1130 (P-O-C- *str*.). ^{1}H NMR (DMSO-*d_6*) ppm: δ 6.88-6.91 (m, 12H, Ar-H), 7.55-7.63 (m, 3H, O=C-CH=), 7.76 (d, 6H , Ar-CH=, *J* = 8 Hz), 7.91 (d, 6H, Ar-H, *J* = 8 Hz), 7.95-8.10 (m, 6H, Ar-H).

***Tris*(4-(3-(3,4,5-OMe-phenyl)acryloyl)phenyl)phosphate (5d):** IR (KBr, ν_{max}, cm^{-1}): 3180-2900 broad (olefinic =C-H, Ar=C-H), 1660 (conj. C=O *str*.), 1597 (-C=C- *str.*), 1320 (P=O *str*.), 1125 (P-O-C *str*.). ^{1}H NMR (DMSO-*d_6*) ppm: δ 3.70 (s, 9H, Ar-OMe), 3.86 (s, 18H, Ar-OMe), 6.89-6.92 (d, 6H, Ar-H, *J* = 12 Hz), 7.20 (s, 6H, Ar-H), 7.60-7.65 (d, 3H, O=C-CH=, *J* = 20 Hz), 7.83-7.88 (d, 3H, Ar-CH=, *J* = 20 Hz), 8.06-8.09 (d, 6H, Ar-H, *J* = 12Hz).

***Tris*(4-(3-(4-Bromophenyl)acryloyl)phenyl)phosphate (5e):** IR (KBr, ν_{max}, cm^{-1}): 3135 broad (olefinic =C-H, Ar=C-H), 1670 (conj. C=O *str*.), 1596 (-C=C- *str.*), 1331 (P=O *str*.), 1109 (P-O-C- *str*.); ^{1}H NMR (DMSO-*d_6*) ppm: δ 6.88 (d, 6H, Ar-H, *J* = 8 Hz), 7.33-8.12 (m, 24H, Ar-H, Ar-CH=, O=C-CH=).

***Tris*(4-(3-(3-Chlorophenyl)acryloyl)phenyl)phosphate (5f):** IR (KBr, ν_{max}, cm^{-1}): 3150 (olefinic C-H, HC=Ar), 1665 (conj. C=O *str*.), 1560 (-C=C- *str*.), 1350 (P=O *str*.), 1160 (P-O-C- *str*.); ^{1}H NMR (DMSO-*d_6*) ppm: δ 6.89 (d, 6H, Ar-H, *J* = 9 Hz), 7.36-7.48 (m, 6H, Ar-H), 7.65 (d, 3H, O=C-CH=, *J* = 12 Hz), 7.78-7.81 (m, 3H, olefinic C-H), 7.97-8.11 (m 12H, Ar-CH).

***Tris*(4-(3-(4-Nitrophenyl)acryloyl)phenyl)phosphate (5h):** IR (KBr, cm^{-1}): 3160 broad (olefinic =C-H, Ar=C-H), 1670 (conj. C=O *str*.), 1336 (P=O *str*.), 1105 (P-O-C- *str*.), 1590 (-C=C- *str*.). ^{1}H NMR (DMSO-*d_6*) ppm: δ 6.91 (d, 6H, Ar-H, *J* = 9 Hz), 7.75 (d, 3H, Ar-CH=, *J* = 18 Hz), 8.08-8.16 (m, 15H, Ar-H, O=C-CH=), 8.27 (d, 9H, Ar-H, *J* = 9 Hz).

***Tris*(4-(3-(4-Methoxyphenyl)acryloyl)phenyl)phos-phate (5g):** IR (KBr, ν_{max}, cm^{-1}): 3160-2900 broad (olefinic =C-H, Ar=C-H), 1660 (conj. C=O *str*.), 1560 (-C=C- *str*.), 1340 (P=O *str*.), 1080 (P-O-C- *str*.). ^{1}H NMR (DMSO-*d_6*) ppm: δ 3.81 (s, 9H, Ar-OCH_3), 6.88 (d, 6H, Ar-H, *J* = 9 Hz), 7.01 (d, 6H, Ar-H, *J* = 9 Hz), 7.65 (d, 3H, O=C-CH=), 7.74-7.84 (m, 9H Ar-H, olefinic CH), 8.05 (d, 6H, Ar-H, *J* = 9 Hz). ^{13}C NMR (DMSO-*d_6*) ppm: δ 187 (C=O), 161.9 (C-Ar-OMe), 156 (P-O-C-Ar), 145.1 (=C-Ar), 131.3 (C-Ar), 130.5 (C-Ar), 130.2 (C-Ar), 127.5 (C-Ar), 121.3 (C=C), 116.4 (C-Ar), 114.2 (C-Ar), 55.8 (O-CH_3).

Biological activity

Amylase activity determination: α-Amylase activity was determined according to the method as described by Ishimoto *et al*. [40]. The reaction mixture contain purified insect amylase solution (0.02 mL) in a test tube with 1 % starch solution (1 mL) and 0.02 M phosphate buffer (1 mL). This mixture was incubated at 40 ºC for 10 min. To a mixture, 3,5-dinitrosalicylic acid (DNSA) reagent (1mL) was added and incubated in a boiling water bath for 5 min. The contents were cooled and diluted with volume (3 mL) by distilled water. Absorbance was read at 540 nm. All the spectrophotometric measurements were performed on a UV-visible recording spectrophotometer (Shimadzu, Model-UV-1800). One unit (U/mL) of α-amylase activity is defined as the amount of protein (α-amylase) required for liberating 1 µmol of reducing sugar (maltose) from starch/min under assay conditions.

α-Amylase inhibitor assay: α-Amylase inhibitory activity was determined according to the method described in the literature [39]. With some modifications, 20 µL of enzyme (*Tribolium castaneum* amylase) and the synthetic compounds 100 µL were mixed and incubated for 30 min at room temperature followed by addition of 1 mL of 0.02 M sodium phosphate buffer and1 mL of 1 % starch solution in all the test tubes. After 10 min the reaction was terminated with addition of 1 mL of DNSA colour reagent followed by boiling in water bath for 5 min. The mixture was cooled to room temperature and diluted with 3 mL of distilled water and the absorbance measured at 540 nm (Shimadzu-UV-VIS Spectrophotometer). The control samples were also prepared accordingly without any synthetic compound and compared with the test samples. The results were expressed as % inhibition calculated using the formula:

$$\text{Inhibition activity (\%)} = \frac{\text{Abs (control)} - \text{Abs (compound)}}{\text{Abs (control)}} \times 100$$

Antimicrobial activity: Antimicrobial activities of the synthesized trichalcones (**5a-h**) were determined by disc diffusion method. The compounds were evaluated for antibacterial

activity against *E. coli* (Gram-negative), *Bacillus megaterium* (Gram-positive). The test compounds **5a-h** was dissolved in DMSO at a concentration of 500 µg/mL. The bacterial (24 h) cultures from the slants were diluted with sterile distilled water and mixed thoroughly to prepare a clear homogeneous suspension. These suspensions were spread on solidified agar (nutrient agar for bacteria) medium. The filter paper disks prepared by only DMSO (as a negative control) and with solutions of test compounds **5a-h** as well as standard compounds (penicillin as positive control) were carefully placed over the spread cultures and incubated at 37 ºC for 24 h for bacteria. After the incubation, period, the plates were examined for the zone of inhibition. The diameters for the zone of inhibitions were measured (in mm) including the diameter of the disc also.

RESULTS AND DISCUSSION

The synthetic strategy used for the synthesis of organophosphorus trichalcones (**5a-h**) is illustrated in **Scheme-I**. A key intermediate *tris*(4-acetylphenyl)phosphate (**3**) for the proposed synthesis was achieved by stirring a mixture of $POCl_3$ and sodium salt of *p*-hydroxy benzaldehyde in toluene at 25 ºC for 24 h using catalytic amount of TBAB as a phase transfer catalyst. The condensation between compound **3** and substituted benzaldehydes in DMSO at 25 ºC for 12 h afforded organophosphorus trichalcones (**5a-h**) in 70-90 % yields.

As can be seen from present results, aldehydes such as halo, alkoxy and nitro substituted benzaldehydes underwent condensation successfully to afford good to high yields of the corresponding organophosphorus trichalcones. The products were obtained in high purity by simple aqueous workup followed recrystallization saving the much more isolation time. No substantial influence of the electronic properties of substituents on benzaldehyde (**4**) to the yield of transformation was observed. The structure of all the products was established by ^{1}H, ^{13}C, ^{31}P NMR and IR spectral analysis.

In the IR spectrum of intermediate **3**, the appearance of sharp peak at 1681 cm^{-1} signifies the ketonic C=O group, the frequency in the 1294-1265 cm^{-1} range represents the presence of P=O group at the core and the formation of P-O-C(phenyl) bond is supported by the appearance of band in the 1197-1168 cm^{-1} range.

The ^{1}H NMR spectrum of compound **3** shows the singlet peak at 2.6 ppm for (9H) of ketonic methyl group and ^{13}C peak value at 196.5 ppm for C=O group indicates the substitution of all the chlorine atoms of $POCl_3$ placed by (-O-Ph-$COCH_3$) group, validating the formation of intermediate **3**. The mass spectrum *m/z* [M+1] = 453 is also supports the formation of intermediate **3**.

In the IR spectra of compounds (**5a-h**), sharp peak observed in between 1600-1560 cm^{-1} is for conjugated olefinic double C=C-C=O bond, confirms the formation of intermediate **3** to desired trichalcones. In ^{1}H NMR spectra of compounds (**5a-h**), the upfield peak 2.6 ppm for 9(H) methyl group as seen in the ^{1}H NMR spectrum of intermediate **3** is absent and appearance of downfield doublet peak around 8 ppm with *J* value between 15-20 Hz and the ^{13}C peak value around 121 and 142 ppm for the conjugated olefinic carbons (C=C-C=O) confirms the formation of compounds (**5a-h**).

Having optimized different variety of organophosphorus trichalcones (**5a-h**), next in order to explore the potential of these newly synthesized organophosphorus trichalcones derivatives, compounds (**5a-h**) were comprehensively evaluated for their insecticidal activity against α-amylase of insect pest, *Tribolium castaneum* (Herbst) (Coleoptera: Tenebrionadeae) using method described by Ishimoto *et al*. [40] and antibacterial activity against *Escherichia coli* (Gram-negative) and *Bacillus megaterium* (Gram-positive) bacterial strains using disc diffusion method.

The outcome of insecticidal activity has been represented in Table-2. It is found that all the compounds are active against amylase of insect pest, *Tribolium castaneum* (Herbst) (Coleoptera: Tenebrionadeae). Among the compounds (**5a-h**), compound **5g** showed the highest (63.4 %) insecticidal activity while other compounds **5c**, **5d**, **5f** and **5h** exhibited moderate (46-50 % inhibition) activity at the same level of concentration. It is also observed that among all the newly synthesized organophosphorus trichalcones, **5a**, **5b**, **5d**, **5e**, **5h** exhibited no antibacterial activity and compounds **5g**, **5f** and **5c** showed very poor antibacterial activity even at higher concentration of 500 µg/mL, which could indicate low toxicity associated and should be considered as ideal insecticidal agents (Table-2).

TABLE-2
ANTIBACTERIAL ACTIVITY OF COMPOUNDS (**5a-h**) AND ITS % INHIBITION OF α-AMYLASE ENZYME

Compd.	*E. coli*	*B. megaterium*	% Inhibition of α-amylase enzyme
5a	N.A.	N.A.	40.62
5b	N.A.	10 mm	25.50
5c	N.A.	N.A.	52.37
5d	N.A.	N.A.	60.82
5e	12 mm	13 mm	40.30
5f	N.A.	N.A.	62.21
5g	N.A.	N.A.	66.38
5h	N.A.	10 mm	55.21

N.A.: no activity; Compound concentration: 500 µg; Penicillin: 50 µg

Conclusion

A novel series of organophosphorus trichalcones (**5a-h**) using a key intermediate *tris*(4-acetylphenyl)phosphate (**3**), which is prepared by using tetrabutylammonium bromide (TBAB) as a phase transfer catalyst at very mild conditions were synthesized. The synthesized compounds were evaluated for their insecticidal and antibacterial activity. The enzyme inhibition activity data of newly synthesized compounds suggested that the compound **5g** exhibits the promising insecticidal activity. Interestingly, the compounds **5a-h** showed insignificant antibacterial activity.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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