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Incorporation of Fluorinated Pyridine in the Side Chain of 4-Aminoquinolines: Synthesis, Characterization and Antibacterial Activity

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ABSTRACT

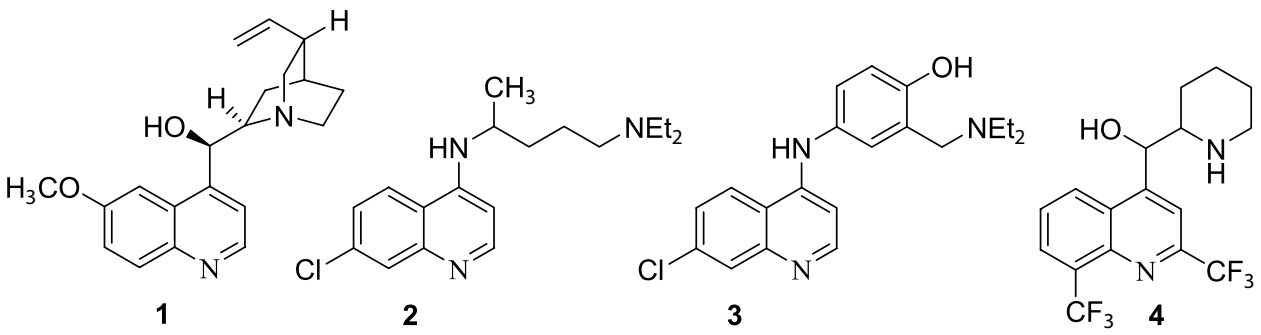
A series of hybrid of 4-aminoquinoline and fluorinated pyridine derivatives were synthesized and their chemical structure were confirmed by ^{19}F-NMR, ^{1}H-NMR, ^{13}C-NMR and FT-IR. All compounds were tested against one Gram-positive and one Gram-negative bacteria to assess their in vitro antibacterial activity. Compounds **10a**, **10b**, **11a** and **12b** showed moderate antibacterial activity against Gram-positive bacterium, Staphylococcus aureus.

Introduction

Quinolines are an important class of heterocycle, found in several natural products and numerous synthetic compounds [1–4]. Compounds with a quinoline nucleus have a wide range of pharmacological activities, such as anticancer [5], antibacterial [6], antiviral [7], anti-inflammatory [8], and antifungal [9], which is reflected in the large number of drugs on the market containing a quinoline template.

The most common use of quinoline nucleus is antimalarial activity that requires further investigation, mainly as a result of its cheap synthetic cost and diverse applications [10–12]. Structural modifications of natural product quinine **1** as an antimalarial drug led to synthesis of most effective antimalarial agents, namely chloroquine **2**, amodiaquine **3** and mefloquine **4** (▶ **Fig. 1**) [13, 14].

During the past six decades, chloroquine and other aminoquinolines were the pioneering antimalarial agents because of their therapeutic efficacy and cheap synthetic cost [15, 16]. Recent studies confirmed activity of 4-aminoquinoline classes against chloroquine-resistant of malaria parasite [17], the blood and sexual stages Plasmodium [18], and showed potential for the development of new drugs [19]. It has been shown that the length of alkyl groups with linking the basic nitrogen center to the quinoline ring is important for potency against chloroquine-resistant P. falciparum, the results suggested that both shortening and lengthening the carbon side chain in chloroquine leads to compounds that remain active against chloroquine-resistant strains of P. falciparum [17, 20]. It has been suggested that the chlorine atom at 7-position is important for antiplasmodial activity of 4-aminoquinoline compounds [21]. Stocks et al. have been shown that replacement of the diethylamino function with side chain t-butyl and heterocyclic rings such as piperidyl, pyrrolidinyl, and morpholinyl increase the antimalarial activity of chloroquine derivatives [22].



▶ **Fig. 1** Structures of some common quinoline antimalarial drugs.

Also, studies [23–25] have been shown potential activity of 7-Chloroquinolines with benzenesulfonamide moiety against breast cancer cells, chloroquinolinyl-chalcones against human prostate LNCaP tumor cells and chloroquine against MCF-7 human breast cancer cells. Chibale and co-workers synthesized a series of dihydroartemisinin derivatives with excellent antiplasmodial and antitumor activity via the conjugate addition of 7-chloro-4-aminoquinoline amines to a dihydroartemisinin-based acrylate [26]. In another study, Souza et al. have been synthesized quinoline derivatives with significant antitubercular activity [27].

Polyfluorinated heteroaromatics systems have a wide application in bioorganic and medicinal chemistry [28–30]. Also, the present of fluorine atoms on heterocyclic molecules improved the chemical and biological properties of these systems [31, 32]. Perfluorinated heteroaromatic systems, and particularly polyfluorinated pyridine derivatives are highly susceptible towards nucleophilic attack that results of their electron-deficient nature [33, 34]. Perfluorinated pyridine derivatives such as pentafluoropyridine and 2,3,5,6-tetrafluoro-4-phenylsulphonylpyridine have been used as starting materials for synthesis of functionalized perhalopyridines [35, 36] and ring-fused perhalo compounds [37–40].

In continuation of our study on the synthesis of new substituted pefluoropyridines and 4-aminoquinoline compounds, we would like to report the synthesis and antibacterial activity of some new 4-alkylaminoquinoline derivatives from linking of quinoline ring to pentafluoropyridine and 2,3,5,6-tetrafluoro-4-phenylsulphonyl pyridine.

Materials and Methods

Chemical

All the solvents and starting materials were obtained commercially (Merck). ^{1}H NMR spectra were recorded at 300 MHz. ^{13}C NMR spectra were recorded at 75 MHz. ^{19}F NMR spectra were recorded at 282 MHz. IR spectra were recorded on a SHIMADZU-IR460 spectrometer in a KBr matrix. All melting points were obtained by Stuart Scientific apparatus. TLC monitored all reactions and all yields refer to overall isolated ones. TLC analysis was performed on silica gel TLC plates (Merck). Preparative Thin Layer Chromatography (Prep TLC) with plate dimensions: 20 cm × 20 cm, 2.5 mm SiO_2 thickness was carried out with mixed solvents (EtOH/ethyl acetate).

General procedure for Reaction of perfluoropyrines with amino- and hydroxy-functionalized quinolines

A mixture of perfluoropyrine (1 mmol) and hydroxy- or amine-functionalized quinoline (1 mmol) in the presence of K_2CO_3 (3 mmol) at CH_3CN (10 mL) were stirred at room temperature for the indicated time. After completion reaction, the reaction mixture was poured into 10 ml of water. In cases that precipitate formed, it filtered off and dried. In other cases, the mixture was extracted with $CHCl_3$ (3 × 10 ml), dried over $MgSO_4$ and solvent evaporated. The crude product was obtained after purification with preparative Thin Layer Chromatography (Prep TLC) with plate dimensions: 20 cm × 20 cm, 2.5 mm SiO_2 thickness or recrystallization with EtOH.

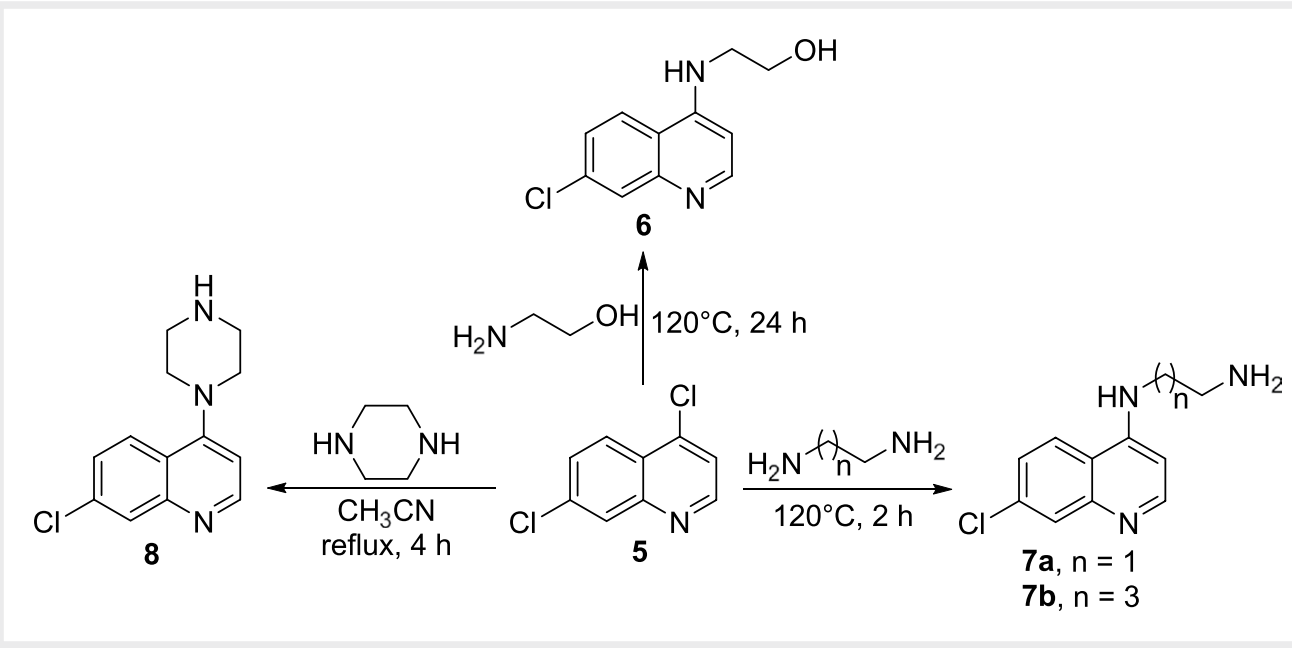
7-chloro-N-(2-((perfluoropyridin-4-yl)oxy)ethyl) quinolin-4-amine (10a)

This compound was obtained as white solid after 24 h reaction time and purification with Prep TLC (EtOH/EtOAc, 1:4); 0.30 g (81 %); mp 179-182 °C; IR (KBr): ν_{max} 3250 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.41 (d, 1H, J = 4.9 Hz, Ar-H), 8.19 (d, 1H, J = 9.1 Hz, Ar-H), 7.78 (s, 1H, Ar-H), 7.49 (s, 1H, NH), 7.45 (d, 1H, J = 9.0 Hz, Ar-H), 6.60 (d, 1H, J = 5.4 Hz, Ar-H), 4.80 (m, 2H, CH_2), 3.73 (m, 2H, CH_2); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 151.8 (Ar-C), 149.8 (Ar-CH), 148.9 (Ar-C), 147.1 (m, C-4 py), 143.5 (dm, J = 236.3 Hz, C-2,6 py), 134.5 (dm, J = 253.0 Hz, C-3,5 py), 133.5 (Ar-CH), 127.5 (Ar-CH), 124.3 (Ar-C), 123.8 (Ar-C), 117.4 (Ar-CH), 99.0 (Ar-CH), 72.1 (CH_2), 42.2 (CH_2); ^{19}F NMR (DMSO-d_6, 282 MHz): δ -92.8 (m, 2F, F-2,6), -158.4 (m, 2F, F-3,5).

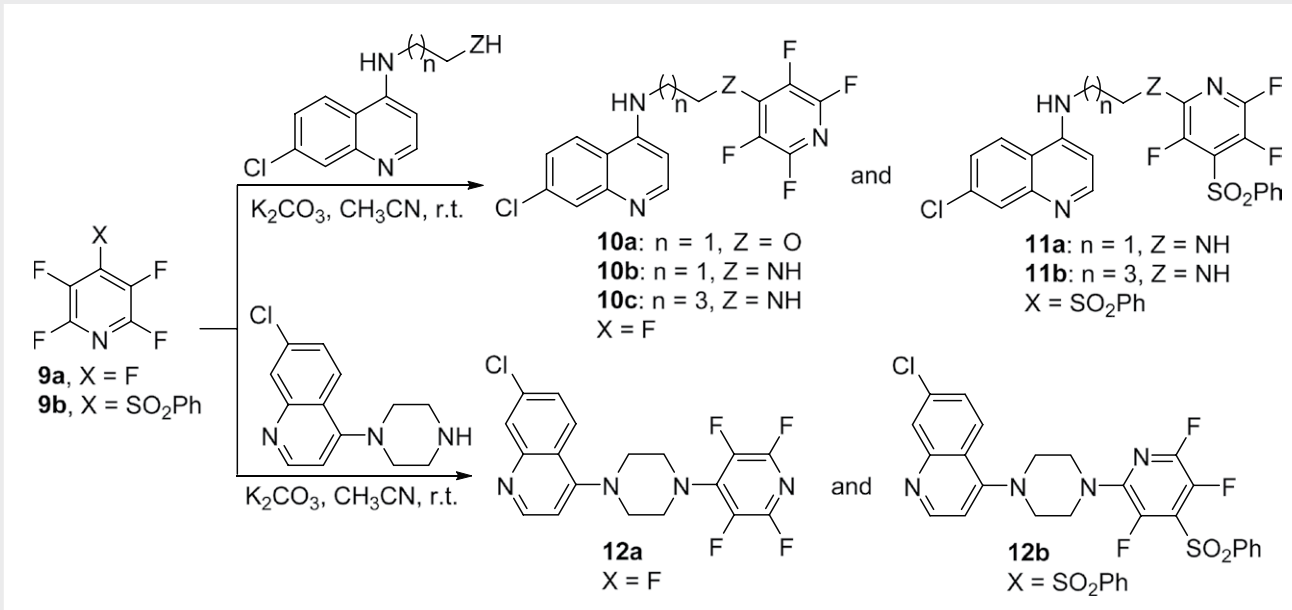
Result and discussion

Chemistry

The Amino- and hydroxyl-functionalized quinolines were synthesized by using reported method [41] from reaction of 4,7-dichloroquinoline with diaminoalkanes and aminoalcoholes (▶ **Fig. 2**).



▶ **Fig. 2** Synthesis of amino- and hydroxy-functionalized quinolines.

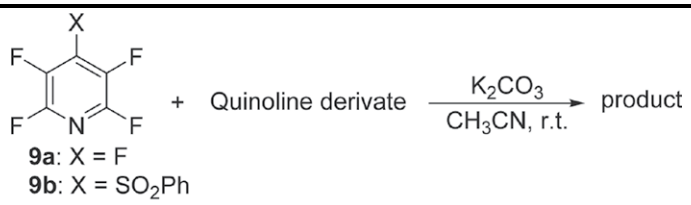


▶ **Fig. 3** Reaction of hydroxy- and amino-functionalized quinolines with **9a** and **9b**.

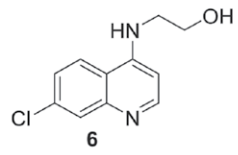
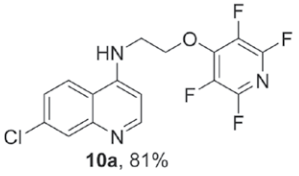
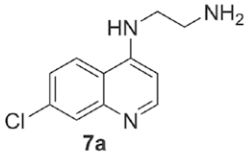
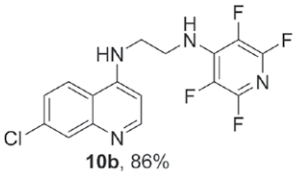
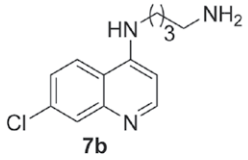
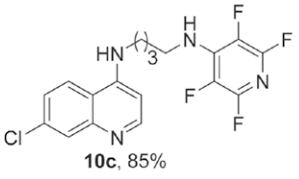
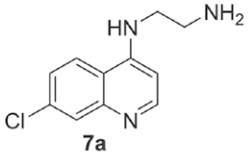
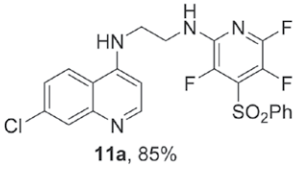
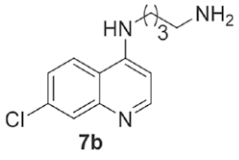
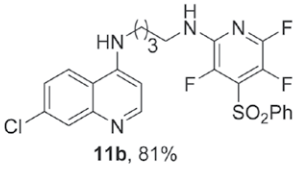
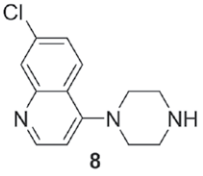
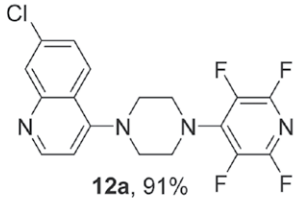
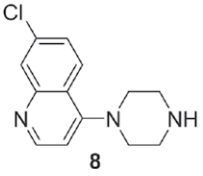
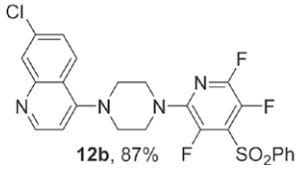
The reaction of pentafluoropyridine **9a** and 2,3,5,6-tetrafluoro-4-phenylsulphonyl pyridine **9b** with hydroxy-functionalized quinoline **6** and amino-functionalized quinolines **7a**,**b** and **8** were carried out in CH_3CN in the presence of potassium carbonate (▶ **Fig. 3**).

The reaction of 2-((7-chloroquinolin-4-yl)amino)ethan-1-ol **6** with pentafluoropyridine **9a** in the presence of potassium carbonate in CH_3CN, gave 7-chloro-N-(2-((perfluoropyridin-4-yl)oxy) ethyl)-quinolin-4-amine **10a** (▶ **Table 1**, Entry 1) after purification using silica gel plate chromatography eluted by ethyl acetate/Ethanol. It is result of nucleophilic attack at more activated 4-position of pyridine ring. ^{19}F NMR spectrum of compound **10a**, showed two resonance peaks at -92.8 and -158.4 ppm related to ortho and meta fluorine atoms to nitrogen of pyridine ring, respectively. ^{1}H NMR spectrum of this compound showed four doublets at δ = 8.41, 8.19, 7.45 and 6.60 ppm and a singlet at δ = 7.78 ppm for quinoline hydrogens. It also indicated a broad singlet peak in δ = 7.49 ppm for NH. Chemical shifts of two methylene groups were located at δ = 4.80 and 3.73 ppm. In ^{13}C NMR spectrum of compound **10a**, aromatic carbons were located in the range of δ = 99.0–151.8 ppm.

▶ **Table 1** Reaction of perfluoropyrines **9a** and **9b** with amino- and hydroxyl-functionalized quinolines.



9a: X = F
9b: X = SO_2Ph

Entry	Quinoline derivate	X	Product	M.P(°C)
1	 **6**	F	 **10a**, 81%	179 – 182
2	 **7a**	F	 **10b**, 86%	237 – 240
3	 **7b**	F	 **10c**, 85%	170 – 173
4	 **7a**	F	 **11a**, 85%	230 – 233
5	 **7b**	SO_2Ph	 **11b**, 81%	114 – 117
6	 **8**	SO_2Ph	 **12a**, 91%	207 – 210
7	 **8**	SO_2Ph	 **12b**, 87%	168 – 171

▶ **Table 2** In vitro antibacterial activity ▶ **6, 7, 8**, **10**, **11** and **12** by disc diffusion method.

Compound	Diameter of growth of inhibition zone(mm)	
	Staphylococcus aureus	Escherichia coli
6	3	–
10a	12	–
7a	3	–
10b	14	–
7b	5	–
10c	–	–
11a	15	–
11b	–	–
8	–	–
12b	15	–
Gentamicin	22	20
Ciprofloxacin	31	26

▶ **Table 3** Minimum inhibitory concentration (MIC) (μg/ml) of **10a, 10b, 11a** and **12b.**

Compound	Staphylococcus aureus	Escherichia coli
10a	350	–
10b	350	–
11a	400	–
12b	400	–
Gentamicin	10	10
Ciprofloxacin	5	5

^{13}C NMR spectrum of this compound showed aliphatic carbons at δ = 72.1 and 42.2 ppm. A similar reaction occurred with quinoline derivatives **7a**, **7b** and **8** to give products **10b**, **10c** and **12a**, respectively.

The phenylsulfonyl group is strong electron withdrawing group that helps to maintain the reactivity of pyridine ring toward further nucleophilic substitution processes. The reaction of N^1-(7-chloroquinolin-4-yl)ethane-1,2-diamine **7a** with 2,3,5,6-tetrafluoro-4-phenylsulphonyl pyridine **9b** in the presence of potassium carbonate in CH_3CN, gave N^1-(7-chloroquinolin-4-yl)-N^2-(3,5,6-trifluoro-4-(phenylsulfonyl)pyridin-2-yl)ethane-1,2-diamine **11a** in high yield (▶ **Table 1**, Entry 4), arising nucleophilic attack at 2-position of pyridine ring. ^{1}H NMR and ^{13}C NMR analysis as well as ^{19}F NMR analysis confirmed structure of product **11a**. ^{1}H NMR spectrum of compound **11a** showed five doublets at δ = 8.37, 8.14, 8.03, 7.41 and 6.60 ppm and a triple at δ = 7.41 ppm for aromatic hydrogens and some signals in the range of δ = 7.71–7.76 ppm for aromatic hydrogens and NH. It also indicated a multiplet peak at δ = 3.47 ppm for two methylene groups. ^{19}F NMR analysis of compound **11a** indicated three resonances at δ = − 91.6, − 137.9 and − 161.8 for fluorine atoms located at 6-, 3- and 5-positions of pyridine ring, respectively. ^{13}C NMR spectrum of this compound showed aromatic carbons in the range of δ = 124-151.6 ppm and aliphatic carbons at δ = 41.0 ppm. A similar reaction occurred with quinoline derivatives **7b** and **8** to give products **11b** and **12b**, respectively.

Biological assay

Medium used for the antibacterial testing was nutrient agar media (NAM) of the following composition: peptone 10 g; beef extract 6 g; sodium chloride 10 g; agar 3 % and final volume of the media was adjusted to 1 l with distilled water and autoclave at 15 lbs/in^2.

The starting material and newly synthesized compounds **6, 7, 8**, **10a–c**, **11a**, **11b** and **12b** were screened for their antibacterial activity against Gram-positive bacteria i. e. Staphylococcus aureus (MTCC 96) and Gram-negative bacteria i. e. Escherichia coli (MTCC 1652) using disc diffusion assay technique and minimum inhibition concentration (MIC) method (Bauer et al., 1966; Shinde et al., 2008). Standard antibiotics Gentamicin and Ciprofloxacin were used for the comparison against the antibacterial activities shown by the compounds (▶ **Table 2**, **3**). Compounds **10a**, **10b**, **11a** and **12b** were found more active against S. aureus at 4 μg/ml concentration than other compounds. However, no compound showed any activity against E. coli at this concentration. The zone of inhibition of compounds **10a**, **10b**, **11a** and **12b** against S. aureus were 12, 14, 15 and 15 mm, respectively and the zone of inhibition of standard antibiotics Gentamicin and Ciprofloxacin were 32 and 31 mm, respectively against S. aureus and 20 mm and 26 mm against E. coli. The MIC of compounds **10a**, **10b**, **11a** and **12b** was found to be 350, 350, 400 and 400 μg/ml, respectively against the S. aureus whereas no zone of inhibition was appeared unless a concentration of 4 μg/ml was used against in case of E. coli, similar to reported values for analogue compounds [42]. However, compounds **10c** and **11b** did not show any zone of inhibition against either of bacteria at 4 μg/ml concentration. The MIC of Gentamicin and Ciprofloxacin was 10 μg/ml and 5 μg/ml, respectively against both S. aureus and E. coli. According to the results, we can conclude that replacement of one fluorine atom of pentafluoropyridine by hydroxy-functionalized quinoline and amino-functionalized quinolines (with three atoms likage) increases the antibacterial activity of compounds **10a** and **10b**. Also, we selected 2,3,5,6-tetrafluoro-4-phenylsulphonylpyridine as a link to amino-functionalized quinolines (with three atoms likage) in order to improve of biological activity. Presence of the trifluoro-4-phenylsulphonylpyridine as nucleus increased antibacterial activity of compound **11a.** Also, in these reaction, replacement of one fluorine atom of 2,3,5,6-tetrafluoro-4-phenylsulphonyl pyridine by piperazine attached to quinoline increases the antibacterial activity (compound **12b**).

Conclusion

In conclusion, a series of hybrid of 4-aminoquinoline and fluorinated pyridine derivatives were designed and synthesized by the reaction of pentafluoropyridine and 2,3,5,6-tetrafluoro-4-phenylsulphonyl pyridine with hydroxy-functionalized quinoline **6** and amino-functionalized quinolines under mild conditions. Synthesized compounds were evaluated against one Gram-positive and one Gram-negative bacteria to assess their in vitro antibacterial activity. Compounds **10a**, **10b**, **11a** and **12b** showed moderate antibacterial activity against Gram-positive bacterium, Staphylococcus aureus.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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