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ONE-POT SYNTHESIS OF *N*-SUBSTITUTED 2-AMINOTHIAZOLE DERIVATIVES AND *IN VITRO* ANTIBACTERIAL ACTIVITY

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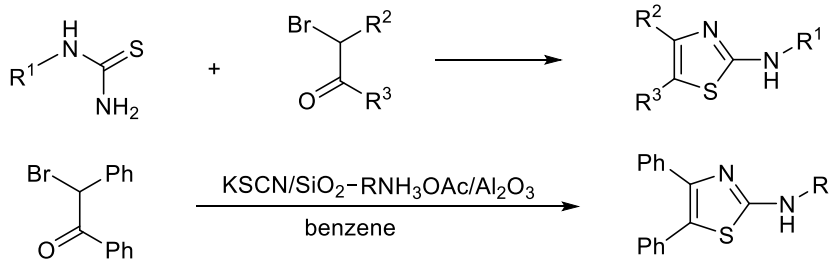
Abstract – A facile one-pot procedure for the synthesis of *N*-substituted 2-aminothiazoles under either conventional heating or microwave irradiation conditions is described. This approach efficiently produces *N*-substituted 2-aminothiazoles from 2-amino-4-arylthiazoles and aryl aldehydes in moderate to excellent yields. In general, the microwave-assisted method results in better yields (40–94%) compared to the conventional heating method (42–83%). The synthesized compounds are tested *in vitro* for the evaluation of antibacterial activity. Four compounds (**4g**, **4h**, **4i,** and **4j**) exhibit growth inhibitory activity against tested bacterial strains with minimum inhibitory concentration (MIC) values in the range of 1–44 μg/mL.

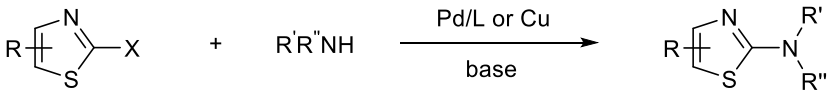
Thiazoles, versatile building blocks, have emerged as imperative and ubiquitous heterocycles in synthetic and medicinal chemistry. To this end, the 2-aminothiazole scaffold has played a function of a privileged structural subunit for the tailoring of various biologically and pharmaceutically active compounds.[1,2] It turns out that 2-aminothiazole-based derivatives possess broad biological features including antiviral, antibacterial, antifungal, antitubercular, antiprotozoal, anticancer, anti-inflammatory, antioxidant, anticonvulsant, antidiabetic, antileishmanial, antihypertensive activities.[1,3] In addition, this functionality has been utilized in many approved drugs of diverse pharmacological classes (e.g., dasatinib, cefcapene, talipexole, meloxicam, and famotidine).

The past decades have witnessed great efforts in the synthesis and discovery of bioactivities of compounds derived from the 2-aminothiazole scaffold.[4] The most common strategy for preparing substituted 2-aminothiazoles is the Hantzsch synthesis (Scheme 1a),[5] despite the arising limitations from using lachrymatory α-haloketone starting materials. The synthesis of 2-aminothiazoles starting from 2-halothiazoles with amines has been developed using palladium[6] or copper[7] as catalysts (Scheme 1b). Moreover, the preparation of 2-aminobenzothiazole derivatives can be achieved through copper(I)[8] or iron(III)-catalyzed[9] cross-coupling reactions of isothiocyanates with 2-haloanilines. Also, McGowan and co-workers reported the synthesis of *N*-aryl-2-aminothiazole derivatives by palladium-catalyzed coupling of 2-aminothiazoles with aryl bromides and triflates (Scheme 1c).[10] However, these methods have faced four primary bottlenecks: (i) the utilization of metal catalysts, (ii) large excess of supported reagents, (iii) tedious workup, and (iv) extra chemical waste. In trying to limit some of these drawbacks, we wish to develop an efficient one-pot synthesis as a green chemistry approach toward 2-aminothiazoles, further enriching the landscape of this fascinating scaffold.

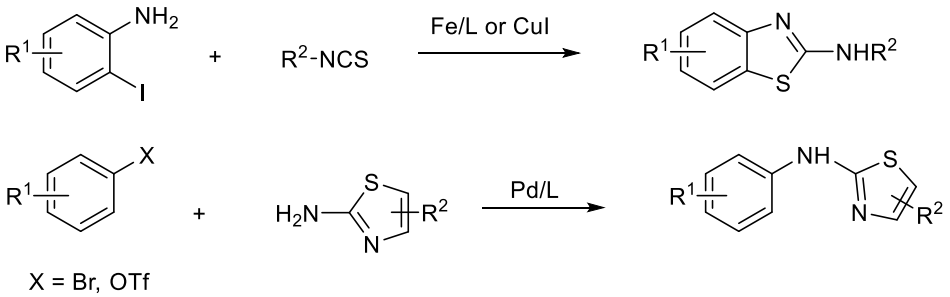
a) The Hantzsch synthesis approach



b) Amination approach



c) Cross-coupling approach

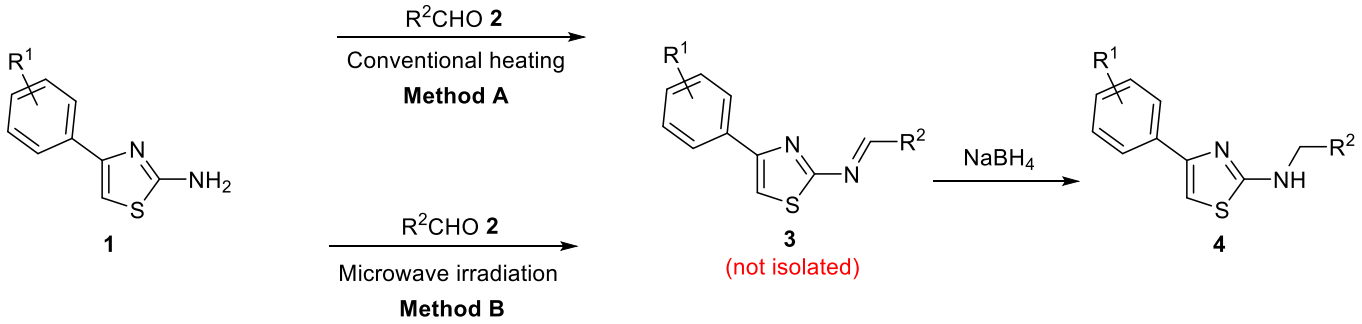


Scheme 1. Published synthetic routes to 2-aminothiazoles

Herein, we report the facile one-pot synthesis of *N*-substituted 2-aminothiazoles by reaction of 2-amino-4-phenylthiazole or 2-amino-4-arylthiazole with various aryl aldehydes under either conventional heating or microwave irradiation conditions. Furthermore, taking to account the pharmaceutical importance of 2-aminothiazole scaffold, the synthesized compounds are also tested *in vitro* for their antibacterial activity.

One-pot synthesis of *N*-substituted 2-aminothiazole derivatives

Previously, a stepwise approach for synthesis of *N*-benzyl-4-phenylthiazol-2-amines was reported in the literature.[11] 2-Amino-4-phenylthiazole was reacted with aromatic aldehydes to form Schiff bases. Then, the Schiff bases were reduced with sodium borohydride to give the corresponding amines. This two-pot procedure suffered from several problems, such as tedious work-up, the isolation of the generally unstable Schiff bases, and relatively low overall yields (50%–60%). We envisioned that the reduction of the formed Schiff bases could be performed in a one-pot fashion after completion of the condensation step as shown in Scheme 2 without isolation of imine product. The substrates 2-amino-4-arylthiazoles **1** could be readily prepared from available acetophenones and thiourea according to the method reported in the literature.[12]

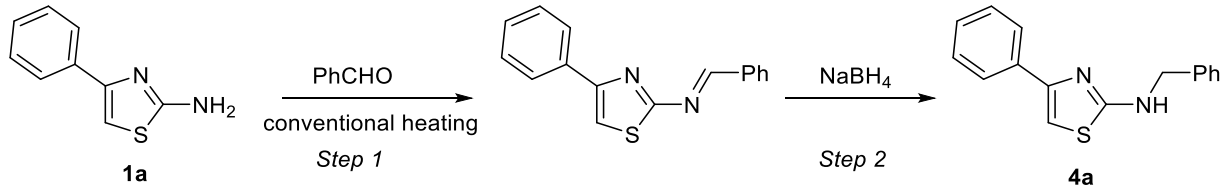


Scheme 2. The one-pot strategy for synthesizing *N*-substituted 2-amino-4-arylthiazoles

To begin our study, the reaction of 2-amino-4-phenylthiazole with benzaldehyde was conducted as a model reaction under conventional heating (method A) for optimization of reaction conditions. The results are tabulated in Table 1. We thus found that the proposed one-pot protocol was efficient and concise, leading to the desired molecule **4a** in satisfactory overall yield, 61% (entry 1). As shown in entries 2 and 3, the use of acids as additives was unpromising, giving significantly lower yields of **4a**. In such cases, side reaction forming (aryl)bis(thiazol-2-imine)methane dominated the formation of Schiff base.[13] In contrast, the addition of base additives promoted the formation of Schiff base; consequently, the yield of compound **4a** dramatically improved (entries 4–7). After screening common bases as a catalyst, piperidine was found to be superior, not only furnishing the final product with a higher yield but also shortening reaction time (entry 7). It should be noted that the formation of Schiff base was reversible; thus, the reverse conversion of this intermediate to starting thiazol-2-amine by hydrolysis process was observed when water was employed as

a solvent; consequently, giving a very low yield of **4a** (entry 10). Our investigations on solvents revealed that toluene was optimal for the first process, providing the best result, up to 83% overall yield (entry 11). Encouraged by this result, we further used 1.5 equivalents of piperidine, but a decrease in the yield of the target product was observed. Temperature screening indicated that the first step of the one-pot process conducted at reflux gave a higher product yield in a shorter reaction time (entries 11 and 13). Probably, a higher temperature might promote the water elimination in the whole condensation process to generate imine. After optimal conditions for condensation of 2-amino-4-phenylthiazole with benzaldehyde were established, we sought to find efficient conditions for the reduction of the formed Schiff base intermediate. It was found that the amount of reducing agent $NaBH_4$, ranging from 2–5 equivalents, did not significantly influence the yield of **4a**, giving relatively comparable yields (entries 11, 14–15).

Table 1. Optimization of conventional reaction conditions of reaction of 2-amino-4-phenylthiazole (1a) with benzaldehyde [a]



Entry	Conditions for step 1	Conditions for step 2	Yield (%)[b]
1	EtOH, reflux, 8 h	$NaBH_4$ (3 equiv.), EtOH, 40 ºC, 1 h	61%
2	HCl (0.1 equiv.), EtOH, reflux, 8 h	$NaBH_4$ (3 equiv.), EtOH, 40 ºC, 1 h	27%
3	AcOH (0.1 equiv.), EtOH, reflux, 8 h	$NaBH_4$ (3 equiv.), EtOH, 40 ºC, 1 h	33%
4	K_2CO_3 (1 equiv.), EtOH, reflux, 8 h	$NaBH_4$ (3 equiv.), EtOH, 40 ºC, 1 h	63%
5	pyridine (1 equiv.), EtOH, reflux, 8 h	$NaBH_4$ (3 equiv.), EtOH, 40 ºC, 1 h	67%
6	Et_3N (1 equiv.), EtOH, reflux, 8 h	$NaBH_4$ (3 equiv.), EtOH, 40 ºC, 1 h	65%
7	piperidine (1 equiv.), EtOH, reflux, 6 h	$NaBH_4$ (3 equiv.), EtOH, 40 ºC, 1 h	70%
8	piperidine (1 equiv.), MeCN, reflux, 8 h	$NaBH_4$ (3 equiv.), EtOH, 40 ºC, 1 h	55%
9	piperidine (1 equiv.), $CHCl_3$, reflux, 8 h	$NaBH_4$ (3 equiv.), EtOH, 40 ºC, 1 h	47%
10	piperidine (1 equiv.), H_2O, reflux, 8 h	$NaBH_4$ (3 equiv.), EtOH, 40 ºC, 1 h	20%
11	piperidine (1 equiv.), toluene, reflux, 4 h	$NaBH_4$ (3 equiv.), EtOH, 40 ºC, 1 h	83%
12	piperidine (1.5 equiv.), toluene, reflux, 4 h	$NaBH_4$ (3 equiv.), EtOH, 40 ºC, 1 h	76%
13	piperidine (1 equiv.), toluene, 80 ºC, 8 h	$NaBH_4$ (3 equiv.), EtOH, 40 ºC, 1 h	75%
14	piperidine (1.5 equiv.), toluene, reflux, 4 h	$NaBH_4$ (2 equiv.), EtOH, 40 ºC, 1 h	79%

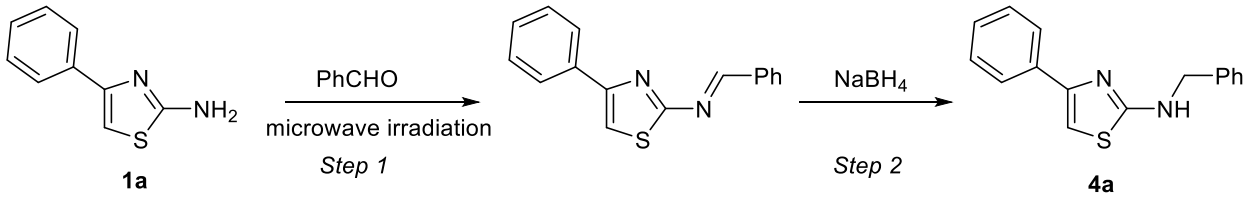
15	piperidine (1 equiv.), toluene, reflux, 4 h	$NaBH_4$ (5 equiv.), EtOH, 40 ºC, 1 h	83%

[a] General condition for step [1]: **1a** (1.0 mmol), benzaldehyde (1.1 equiv.), solvent (2 mL), for step [2]: $NaBH_4$ (3 equiv.), anhydrous EtOH (2 mL). [b] Isolated yield.

Notwithstanding, increasing the amount of sodium borohydride to 5 equivalents was not beneficial, leading to the formation of boron complex and thus causing a complicated work-up procedure (entry 15). Moreover, the use of 1.5 equivalents of $NaBH_4$ or less (not shown in Table 1) significantly reduced the yield. Based on the results of these screening experiments, the reaction conditions in entry 11 were identified as optimal conditions for the one-pot transformation under conventional heating, giving the target molecule a good yield of up to 83%. Notably, bypassing isolation of the unstable intermediate Schiff base enhanced synthetic economy and efficiency and, thus, reducing chemical waste as well.

Microwave mediated synthesis has attracted increasing attention over the last decades, stemming from its compelling advantages as better heating efficiency, high rate of reaction, high selectivity, and high purity of product. With the aim to accelerate the reaction rate and increase the yield of product, we tried carrying out the same one-pot protocol with the assistance of microwave activation (MW) as a green chemistry approach (method B). Microwave irradiation was conducted on CEM Discover SP-D (100 W) with sealed 10 mL vessel automated power control based on temperature feedback. The results are summarized in Table 2.

Table 2. Optimization of microwave-assisted reaction conditions of reaction of 2-amino-4-phenylthiazole (1a) with benzaldehyde [a]



Entry	Conditions for step 1	Conditions for step 2	Yield (%)[b]
1	toluene, piperidine, MW, 120 ºC, 10 min	$NaBH_4$, EtOH, 40 ºC, 1 h	83%
2	EtOH, piperidine, MW, 100 ºC, 10 min	$NaBH_4$, EtOH, 40 ºC, 1 h	87%
3	EtOH, piperidine, MW, 100 ºC, 20 min	$NaBH_4$, EtOH, 40 ºC, 1 h	92%
4	EtOH, piperidine, MW, 100 ºC, 30 min	$NaBH_4$, EtOH, 40 ºC, 1 h	92%
5	EtOH, piperidine, MW, 100 ºC, 20 min	$NaBH_4$, EtOH, MW, 40 ºC, 10 min	89%

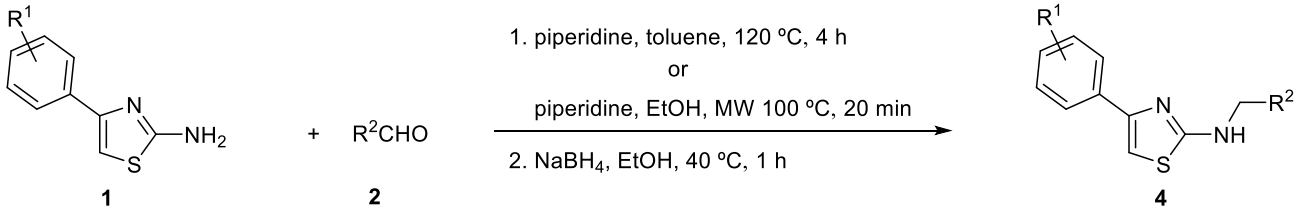
[a] General conditions for step [1]: **1a** (1.0 mmol), benzaldehyde (1.1 equiv.), piperidine (1 equiv.), anhydrous solvent (2 mL); for step [2]: $NaBH_4$ (3 equiv.), anhydrous EtOH (2 mL). [b] Isolated yield.

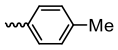
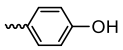
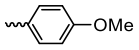
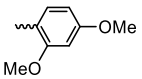
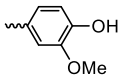
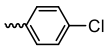
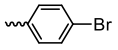
The condensation reaction of 2-amino-4-phenylthiazole with benzaldehyde using the optimal conditions of method A under microwave irradiation for 10 min led to the formation of thiazole **4a** in 83% yield (entry 1). It was found that the use of anhydrous EtOH as solvent for step 1 significantly increased the yield of product, and the maximum yield of **4a** (92%) was obtained by irradiating at 100 ºC for 20 min in EtOH (entries 2–4). It has been proved that microwave could smoothly accelerate reaction and considerably reduce reaction time.[14] In a further attempt, we also tried conducting the reduction of imine intermediate with sodium borohydride upon microwave irradiation. However, the yield of the desired compound **4a** was lower that obtained under conventional condition (entry 5). Generally, microwave-assisted one-pot synthesis method was superior to the conventional heating method, drastically decreasing the reaction time and giving a higher yield of the desired product.

With optimized conditions in hand, we proceeded to explore the scope of the microwave-assisted one-pot transformation. As shown in Table 3, a range of substituted benzaldehydes possessing diverse substituents (Me, OH, OMe, F, Cl, Br) on the phenyl moiety was well tolerated under the reaction conditions, providing the corresponding thiazole derivatives in moderate to excellent yields (40–94%). In general, aldehydes bearing electron-withdrawing substituents on phenyl rings tended to give lower yields in comparison with aldehydes with neural or electron-donating substituents. 4-Methylbenzaldehyde (entry 2), 4-methoxybenzaldehyde and 3,4-dimethoxybenzaldehyde (entries 4–5) reacted smoothly with 2-amino-4-phenylthiazole to afford good yields of *N*-substituted benzyl-2-amino-4-phenylthiazoles (86–89%). When *para*-hydroxybenzaldehyde and vanillin were employed, the low solubility of reactants in step 2 resulted in very low isolated yields. The solubility was enhanced in 80% aqueous EtOH as a solvent for step 2; therefore, the reduction reaction proceeded cleanly to corresponding products, and the yields of **4c** and **4f** were considerably promoted to 86% and 83%, respectively (entries 3 and 6). Halogenated benzaldehydes were also compatible with the optimized conditions, providing desired thiazoles in 72–83% yields (entries 7–10). It should be noted that chloro-substituted on *meta*-position of phenyl ring instead of on *para*-position slightly decreased the yield from 76% to 72% (entries 8 and 9). Unfortunately, in the case of heterocyclic aldehydes such as furan-2-carbaldehyde or picolinaldehyde, the product formation accomplished in moderate yields of corresponding 2-aminothiazoles **4k** and **4l** (entries 11 and 12). As shown in entries 13 and 14, thiazoles bearing 4-methyl-substituted and 2-bromo-substituted phenyl moiety were also treated with benzaldehyde to produce corresponding *N*-benzyl-2-amino-4-arylthiazole products in excellent yields, 94% and 90%, respectively. Interestingly, the same reactions carried out under conventional reflux conditions led to **4a-n** in lower yields, except for compound **4l** (Table 3). It is noteworthy that our one-pot approach compares favorably to the previous reports for the synthesis of *N*-substituted 2-aminothiazoles with respect to reaction time and overall yield.[15] For instance, a publication reported yields of compounds **4a**, **4b**, **4d** in 50–64% after required 24 h heating in an oil bath.[16] Using our approach, such compounds

were obtained in very good yields of 84–92% under microwave assisted method in less than 2 h and 72–83% upon conventional heating method in around 5 h.

Table 3. Synthesis of 2-aminothiazoles 4a-n by the one-pot reaction of 2-amino-4-phenylthiazole derivatives (1) and aryl aldehydes (2) [a]



Entry	R^1	R^2	Product	Yield (%) [b]	Yield (%) [c]
1	H		**4a**	92	83
2	H		**4b**	84	72
3[d]	H		**4c**	86	82
4	H		**4d**	89	80
5	H		**4e**	86	78
6[d]	H		**4f**	83	75
7	H		**4g**	79	67
8	H		**4h**	76	67
9	H		**4i**	72	60
10	H		**4j**	83	72
11	H		**4k**	64	55
12	H		**4l**	40	42
13	4'-Me		**4m**	94	84
14	2'-Br		**4n**	90	80

[a] General conditions for step [1]: **2** (1.0 mmol), aldehyde **3** (1.1 equiv.), piperidine (1 equiv.), anhydrous solvent (2 mL); for step [2]: $NaBH_4$ (3 equiv.), anhydrous EtOH (2 mL). [b] Isolated yields of microwave-assisted method. [c] Isolated yields of conventional heating method. [d] Using 2 mL of 80% aqueous EtOH as solvent for step [2].

Antibacterial activity of the synthesized 2-aminothiazoles

Fourteen *N*-substituted 2-aminothiazoles (five new compounds **4c**, **4f**, **4g**, **4k** and **4n**) synthesized via the present one-pot approach were screened *in vitro* for their antibacterial activity against two Gram-positive strains (*Staphylococcus aureus* (*S. aureus*), *Bacillus cereus* (*B. cereus*)), two Gram-negative strains (*Escherichia coli* (*E. coli*), *Vibrio alginolyticus* (*V. alginolyticus*)) using macrodilution method.[17]

Table 4. Minimum inhibitory concentrations (MIC, μg/mL) of synthesized compounds (4a-n) against selected microorganisms

Compound	Microorganisms			
	***E. coli* BL21 (DE3)**	***V. alginolyticus* PVSulx**	***S. aureus* ATCC 25923**	***B. cereus* AT3**
4a	>64	>64	>64	>64
4b	>64	>64	>64	>64
4c	>64	>64	>64	>64
4d	>64	>64	>64	>64
4e	>64	>64	>64	>64
4f	>64	>64	>64	>64
4g	>64	34 ± 4^{a}	44 ± 0^{a}	28 ± 2^{a}
4h	>64	18 ± 2^{b}	6.5 ± 0.5^{c}	7 ± 0.5^{c}
4i	>64	34 ± 0^{a}	34 ± 2^{b}	24 ± 2^{b}
4j	10 ± 2^{a}	1 ± 0.25^{c}	2.5 ± 0.5^{d}	2.5 ± 0.25^{d}
4k	>64	>64	>64	>64
4l	>64	>64	>64	>64
4m	>64	>64	>64	>64
4n	>64	>64	>64	>64
Ciprofloxacin	0.05 ± 0.01^{b}	0.75 ± 0.01^{c}	1 ± 0.25^{d}	1 ± 0.25^{d}

Data are the mean ± SD. Statistical analysis was performed by one-way ANOVA followed by Tukey's HSD test. Significance is indicated by different letters ($P < 0.05$). The average MIC values of the different compounds against the same tested microorganism not sharing subscripts differ significantly at $\alpha=0.05$ as indicated by Tukey's HSD.

The minimum inhibitory concentration (MIC) shows the antibacterial effect of the synthesized compounds. Among all synthesized derivatives, four halogenated compounds (**4g**, **4h**, **4i** and **4j**) showed weak or moderate antibacterial activity against tested microorganisms (Table 4). Notably, compound **4j** displayed a broad spectrum antibacterial profile against all four tested organisms, including multi-antibiotic resistant *V. alginolyticus* PVSulx, with MIC values of 1–10 μg/mL, despite its lower inhibition compared to positive control drug ciprofloxacin.

In conclusion, a facile and efficient one-pot strategy has been developed for the synthesis of *N*-substituted 2-aminothiazole derivatives from easily accessible starting materials of 2-aminothiazoles and aldehydes under either conventional heating or microwave irradiation conditions. The microwave-assisted one-pot method was favored with respect to shorter reaction time and higher yield. This one-pot method presented fine functional group tolerance with moderate to excellent yields. The present strategy is expected to provide a new synthetic entry for the expedient construction of a highly functionalized thiazoles library, offering the advantages of a simple manipulation procedure, high yields and environmental sustainability. For exhibiting the biological value of the synthesized derivatives, the compounds were screened *in vitro* for their antibacterial activity. Four compounds (**4g**, **4h**, **4i**, and **4j**) showed inhibitory capability against tested microorganisms and might serve as promising candidates for chemotherapeutic armamentarium with the antibacterial application.

EXPERIMENTAL

Chemicals and apparatus

All chemical reagents and solvents were purchased from Acros Organics and Merck. IR spectra were recorded as KBr pellets on a JASCO FT/IR-4700 spectrometer. ^{1}H-NMR (400 MHz) and ^{13}C-NMR (100 MHz) spectra were acquired on a JEOL ECS 400 MHz NMR spectrometer. Microwave irradiation was conducted on CEM Discover SP-D utilizing sealed 10 mL vessel automated power control (100 W) based on the sensor feedback data. Chemical shifts (δ) are recorded in ppm relative to tetramethylsilane (TMS) as the internal standard; coupling constants (J) are shown in Hz. HR-ESI-MS spectra were recorded with 1100 series LC/MS/MS Trap Agilent spectrometer. Merck silica gel 60 F_{254} aluminum backed plate and Merck silica gel 60N (0.040-0.063 mm) were used for thin-layer chromatography (TLC) and flash column chromatography, respectively.

Typical procedure for the preparation of 2-amino-4-phenylthiazoles (1)

2-Amino-4-phenylthiazoles (**1a**) was prepared by the reported method.[12] In a 25 mL flask, 2 mL of Et_3N (0.01 mmol) was added to a solution of the acetophenone (2.40 g, 20 mmol), thiourea (2.28 g, 30 mmol) and iodine (5.58 g, 22 mmol) dissolved in isopropanol (20 mL). The reaction mixture was stirred under reflux for 4 h. After reaction completion (monitored by TLC), the reaction mixture was evaporated to

remove the solvent. The crude was dissolved in boiling water and then extracted with Et_2O. The organic phase was adjusted to pH = 8 with an amount of NH_3 to give the solid which was then recrystallized from EtOH-water to afford a pure corresponding 2-aminothiazole product (2.89 g, 82% yield).

4-Phenylthiazol-2-amine (1a): off-white solid; FT-IR (KBr) ν_{max} (cm^{-1}): 3437 , 3255, 3157, 3115, 1598, 1524, 1482, 1439, 1336, 1199, 1032, 909, 844, 770, 714; ^{1}H-NMR (DMSO-d_6, 400 MHz): δ (ppm) 7.79 (dd, *J* = 7.4, 1.2 Hz, 2H), 7.35 (t, *J* = 7.7 Hz, 2H), 7.24 (dd, *J* = 7.2, 1.2 Hz, 1H), 7.06 (brs, 2H), 7.00 (s, 1H); ^{13}C-NMR (DMSO-d_6, 100 MHz): δ (ppm) 168.2, 149.9, 135.0, 128.5, 127.2, 125.6, 101.5; (+)-HRESI-MS *m/z* $[M+H]^+$ 177.0478 (calcd for $C_9H_9N_2S$, 177.0486).[12]

In a similar manner, substrates **1b** and **1c** were obtained from the corresponding 4'-methylacetophenone and 2'-bromoacetophenone, respectively.

4-(*p*-Tolyl)thiazol-2-amine (1b): off-white solid; FT-IR (KBr) ν_{max} (cm^{-1}): 3385, 3125, 2917, 1626, 1536, 1515, 1492, 1338, 1289, 1194, 1115, 1038, 821, 729; ^{1}H-NMR (DMSO-d_6, 400 MHz): δ (ppm) 7.67 (d, *J* = 7.9 Hz, 2H), 7.16 (d, *J* = 7.9 Hz, 2H), 7.02 (brs, 2H), 6.91 (s, 1H), 2.29 (s, 3H); ^{13}C-NMR (DMSO-d_6, 100 MHz): δ (ppm) 168.1, 149.9, 136.4, 132.3, 129.1, 125.5, 100.6, 20.8; (+)-HRESI-MS *m/z* $[M+H]^+$ 191.0641 (calcd for $C_{10}H_{11}N_2S$, 191.0643).[18]

4-(2-Bromophenyl)thiazol-2-amine (1c): pale yellow solid; FT-IR (KBr) ν_{max} (cm^{-1}): 3437, 3263, 3107, 1621, 1514, 1465, 1425, 1330, 1117, 1055, 1025, 909, 832, 762, 724; ^{1}H-NMR (DMSO-d_6, 400 MHz): δ (ppm) 7.76 – 7.59 (m, 2H), 7.40 (t, *J* = 7.5 Hz, 1H), 7.23 (t, *J* = 7.0 Hz, 1H), 7.09 – 6.88 (m, 3H); ^{13}C-NMR (DMSO-d_6, 100 MHz): δ (ppm) 167.4, 148.0, 135.8, 133.5, 131.5, 129.1, 127.6, 120.7, 105.8; (+)-HRESI-MS *m/z* $[M+H]^+$ 254.9585 (calcd for $C_9H_8N_2SBr$, 254.9592).[18]

General procedure for conventional one-pot synthesis of 2-aminothiazole derivatives (4)

A solution of 2-amino-4-arylthiazole (**1**) (1.0 mmol) and aryl aldehyde (1.1 mmol) in toluene (2 mL) was charged into a 4 mL vial. For this mixture, 99 μL of piperidine (1 mmol) was added, and the reaction vial was heated at 120 ºC for 4 h. Upon completion, as indicated by TLC, the reaction was cooled to ambient temperature and concentrated under reduced pressure to give the residue used directly for the next step without any purification. The resulting residue was redissolved in 2 mL of EtOH, and $NaBH_4$ (113.5 mg, 3 mmol) was added and then stirred at 40 ºC for an additional 1 h. After that, 1 mL of water was added, and then the mixture was neutralized by the addition of saturated aqueous NH_4Cl solution. The aqueous mixture was extracted with EtOAc (3 x 2 mL). The combined organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by silica gel column chromatography (hexane: EtOAc as eluent) to give corresponding *N*-aryl-2-amino-4-arylthiazole derivatives (**4**).

General procedure for microwave-assisted one-pot synthesis of 2-aminothiazole derivatives (4)

A solution of 2-amino-4-arylthiazole (**1**) (1.0 mmol) and aryl aldehyde (1.1 mmol) in EtOH (2 mL) was charged into a 10 mL microwave vessel. For this mixture, 99 μL of piperidine (1 mmol) was added, and the capped reaction vessel was irradiated by microwaves with a power of 100 W to reach a reaction temperature of 100 ºC under autogenerated pressure for 20 min. Upon completion, the reaction was cooled to ambient temperature and adjusted the volume of solvent by adding EtOH to 2 mL. After that, $NaBH_4$ (113.5 mg, 3 mmol) was added, and the mixture was stirred at 40 ºC for 1 h. Then, 1 mL of water was added, and the mixture was neutralized by the addition of saturated aqueous NH_4Cl solution. The aqueous mixture was extracted with EtOAc (3 x 2 mL). The combined organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by silica gel column chromatography (hexane: EtOAc as eluent) to give corresponding *N*-aryl-2-amino-4-arylthiazole derivatives (**4**).

***N*-Benzyl-4-phenylthiazol-2-amine (4a):** off-white solid; FT-IR (KBr) ν_{max} (cm^{-1}): 3238, 3115, 3051, 2887, 1587, 1480, 1445, 1335, 1232, 1108, 1072, 1047, 973, 714; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.84 – 7.74 (m, 2H), 7.41 – 7.32 (m, 6H), 7.31 – 7.26 (m, 2H), 6.69 (s, 1H), 5.93 (s, 1H), 4.49 (d, *J* = 2.6 Hz, 2H); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) 169.4, 151.5, 137.7, 134.9, 128.7, 128.5, 127.7, 127.6, 126.0, 101.1, 49.8; (+)-HRESI-MS *m*/*z* $[M+H]^+$ 267.0958 (calcd for $C_{16}H_{15}N_2S$, 267.0956).[16]

***N*-(4-Methoxybenzyl)-4-phenylthiazol-2-amine (4b):** off-white solid; FT-IR (KBr) ν_{max} (cm^{-1}): 3241, 2931, 1614, 1548, 1511, 1249, 1177, 1031, 822, 700; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.79 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.37 – 7.31 (m, 2H), 7.29 – 7.25 (m, 3H), 6.85 (d, *J* = 8.7 Hz, 2H), 6.67 (s, 1H), 6.22 (brs, 1H), 4.38 (s, 2H), 3.78 (s, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) 169.6, 159.2, 151.3, 134.9, 129.7, 129.1, 128.7, 127.8, 126.1, 114.1, 101.0, 55.4, 49.4; (+)-HRESI-MS *m*/*z* $[M+H]^+$ 297.1057 (calcd for $C_{17}H_{17}N_2OS$, 297.1062).[16]

***N*-(2,4-Dimethoxybenzyl)-4-phenylthiazol-2-amine (4c):** off-white solid; FT-IR (KBr) ν_{max} (cm^{-1}): 3393, 3221, 3000, 2935, 2834, 1614, 1549, 1463, 1337, 1289, 1208, 1156, 1130, 1036, 834, 772, 702; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.78 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.38 – 7.31 (m, 2H), 7.30 – 7.22 (m, 2H), 6.65 (s, 1H), 6.45 (d, *J* = 2.3 Hz, 1H), 6.41 (dd, *J* = 8.2, 2.4 Hz, 1H), 6.01 (brs, 1H), 4.39 (d, *J* = 3.3 Hz, 2H), 3.79 (s, 3H), 3.78 (s, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) 169.8, 160.8, 158.7, 151.6, 135.1, 130.3, 128.6, 127.6, 126.2, 118.4, 103.8, 100.8, 98.7, 55.5, 55.4, 45.5; (+)-HRESI-MS *m*/*z* $[M+H]^+$ 327.1164 (calcd for $C_{18}H_{19}N_2O_2S$, 327.1167).[19]

4-(((4-Phenylthiazol-2-yl)amino)methyl)phenol (4d): off-white solid; FT-IR (KBr) ν_{max} (cm^{-1}): 3390, 3212, 3116, 3081, 1605, 1550, 1516, 1238, 1172, 826, 770, 704; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.79 – 7.73 (m, 2H), 7.37 (t, *J* = 7.5 Hz, 2H), 7.29 (dd, *J* = 7.3, 1.0 Hz, 1H), 7.07 (d, *J* = 8.1 Hz, 2H), 6.73 (d, *J* = 8.5 Hz, 2H), 6.70 (s, 1H), 5.59 (s, 1H), 4.24 (s, 2H); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) 170.4,

156.2, 151.2, 134.4, 129.5, 128.8, 128.5, 128.1, 126.2, 116.1, 101.1, 49.9; (+)-HRESI-MS *m*/*z* $[M+H]^+$ 283.0912 (calcd for $C_{16}H_{15}N_2OS$, 283.0905).

2-Methoxy-4-(((4-phenylthiazol-2-yl)amino)methyl)phenol (4e): off-white solid; FT-IR (KBr) ν_{max} (cm^{-1}): 3517, 3386, 3209, 3113, 3060, 1602, 1555, 1514, 1432, 1338, 1273, 1152, 1030, 772, 704. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.81 – 7.77 (m, 2H), 7.37 – 7.32 (m, 2H), 7.26 (dt, *J* = 7.5, 1.2 Hz, 1H), 6.87 – 6.81 (m, 3H), 6.69 (s, 1H), 6.04 (s, 1H), 4.36 (s, 2H), 3.77 (s, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) 169.5, 151.4, 146.8, 145.3, 134.9, 129.5, 128.6, 127.7, 126.0, 120.8, 114.4, 110.3, 101.0, 55.8, 49.8; (+)-HRESI-MS *m*/*z* $[M+H]^+$ 313.1005 (calcd for $C_{17}H_{17}N_2O_2S$, 313.1011).

***N*-(4-Methylbenzyl)-4-phenylthiazol-2-amine (4f):** off-white solid; FT-IR (KBr) ν_{max} (cm^{-1}): 3400, 3208, 3107, 3025, 1575, 1550, 1481, 1446, 1334, 1216, 1080, 1023, 969, 803, 770, 703; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.81 – 7.77 (m, 2H), 7.34 (d, *J* = 7.2 Hz, 2H), 7.29 – 7.23 (m, 3H), 7.14 (d, *J* = 7.8 Hz, 2H), 6.68 (s, 1H), 6.01 (s, 1H), 4.42 (s, 2H), 2.34 (s, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) 169.5, 151.4, 137.4, 134.9, 134.6, 129.4, 128.5, 127.6, 126.0, 101.0, 49.6, 21.1; (+)-HRESI-MS *m*/*z* $[M+H]^+$ 281.1114 (calcd for $C_{17}H_{17}N_2S$, 281.1112).[16]

***N*-(3-Fluorobenzyl)-4-phenylthiazol-2-amine (4g):** off-white solid; FT-IR (KBr) ν_{max} (cm^{-1}): 3242, 3122, 3096, 2969, 2888, 1589, 1483, 1443, 1334, 1232, 1051, 976, 918, 781, 716. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.78 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.34 (dm, *J* = 8.1 Hz, 2H), 7.31 – 7.24 (m, 2H), 7.14 (d, *J* = 7.6 Hz, 1H), 7.08 (dt, *J* = 9.7, 2.1 Hz, 1H), 6.97 (td, *J* = 8.4, 2.5 Hz, 1H), 6.69 (s, 1H), 6.13 (s, 1H), 4.49 (s, 2H); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) 169.4, 164.4, 161.9, 151.7, 140.6, 140.6, 135.0, 130.4, 130.3, 128.7, 127.8, 126.2, 123.2, 123.2, 114.8, 114.7, 114.6, 114.5, 101.4, 49.3; (+)-HRESI-MS *m*/*z* $[M+H]^+$ 285.0866 (calcd for $C_{16}H_{14}N_2SF$, 285.0862).

***N*-(4-Chlorobenzyl)-4-phenylthiazol-2-amine (4h):** off-white solid; FT-IR (KBr) ν_{max} (cm^{-1}): 3406, 3207, 3072, 2970, 1548, 1487, 1091, 1018, 803, 771, 703; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.80 – 7.75 (m, 2H), 7.34 (t, *J* = 7.4 Hz, 2H), 7.30 – 7.24 (m, 5H), 6.68 (s, 1H), 6.26 (brs, 1H), 4.44 (s, 2H); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) 169.5, 151.6, 136.4, 135.0, 133.5, 129.0, 128.9, 128.7, 127.9, 126.2, 101.3, 49.2; (+)-HRESI-MS *m*/*z* $[M+H]^+$ 301.0567 (calcd for $C_{16}H_{14}N_2SCl$, 301.0566).[20]

***N*-(3-Chlorobenzyl)-4-phenylthiazol-2-amine (4i):** off-white solid; FT-IR (KBr) ν_{max} (cm^{-1}): 3402, 3232, 3118, 2969, 2891, 1577, 1479, 1426, 1335, 1232, 1075, 974, 774, 709; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.79 (d, *J* = 7.9 Hz, 2H), 7.39 – 7.32 (m, 3H), 7.30 – 7.25 (m, 4H), 6.71 – 6.70 (m, 1H), 5.98 (brs, 1H), 4.49 (s, 2H); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) 169.2, 151.7, 140.0, 134.9, 134.7, 130.1, 128.7, 128.0, 127.9, 127.8, 126.2, 125.8, 101.4, 49.3; (+)-HRESI-MS *m*/*z* $[M+H]^+$ 301.0555 (calcd for $C_{16}H_{14}N_2SCl$, 301.0566).[21]

***N*-(4-Bromobenzyl)-4-phenylthiazol-2-amine (4j):** pale yellow solid. FT-IR (KBr) ν_{max} (cm^{-1}): 3403, 3209, 3064, 2966, 1548, 1483, 1334, 1219, 1072, 1011, 771, 704; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.79 – 7.74 (m, 2H), 7.43 (d, *J* = 8.3 Hz, 2H), 7.33 (tm, *J* = 7.6 Hz, 2H), 7.29 – 7.24 (m, 1H), 7.21 (d, *J* = 8.3 Hz, 2H), 6.68 (s, 1H), 6.46 (brs, 1H), 4.40 (s, 2H); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) 169.4, 151.4, 136.8, 134.8, 131.7, 129.2, 128.5, 127.7, 126.0, 121.5, 101.1, 49.1; (+)-HRESI-MS *m*/*z* $[M+H]^+$ 345.0060 (calcd for $C_{16}H_{14}N_2SBr$, 345.0061).[15]

***N*-(Furan-2-ylmethyl)-4-phenylthiazol-2-amine (4k):** pale yellow solid. FT-IR (KBr) ν_{max} (cm^{-1}): 3396, 3211, 3115, 3046, 2926, 1548, 1334, 1191, 1147, 1011, 704; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.81 (d, *J* = 8.5 Hz, 2H), 7.43 – 7.34 (m, 3H), 7.28 (s, 1H), 6.73 (s, 1H), 6.33 (s, 2H), 5.53 (s, 1H), 4.53 (s, 2H); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) 168.6, 151.6, 151.2, 142.5, 135.0, 128.7, 127.8, 126.2, 110.6, 108.1, 101.6, 42.7; (+)-HRESI-MS *m*/*z* $[M+H]^+$ 257.0744 (calcd for $C_{14}H_{13}N_2OS$, 257.0749). [22]

4-Phenyl-*N*-(pyridin-2-ylmethyl)thiazol-2-amine (4l): pale yellow solid. FT-IR (KBr) ν_{max} (cm^{-1}): 3402, 3218, 3060, 3011, 1593, 1548, 1479, 1442, 1331, 1210, 755, 703; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.58 (d, *J* = 4.9 Hz, 1H), 7.85 – 7.80 (m, 2H), 7.67 (td, *J* = 7.7, 1.8 Hz, 1H), 7.40 – 7.34 (m, 3H), 7.31 – 7.24 (m, 1H), 7.21 (dd, *J* = 7.5, 4.9 Hz, 1H), 6.71 (s, 1H), 6.49 (brs, 1H), 4.70 (d, *J* = 4.6 Hz, 2H); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) 168.8, 156.7, 151.7, 149.3, 136.9, 135.1, 128.7, 127.7, 126.2, 122.6, 121.9, 101.3, 50.2; (+)-HRESI-MS *m*/*z* $[M+H]^+$ 268.0897 (calcd for $C_{15}H_{14}N_3S$, 268.0908).

***N*-Benzyl-4-(2-bromophenyl)thiazol-2-amine (4m):** off-white solid; FT-IR (KBr) ν_{max} (cm^{-1}): 3404, 3207, 3061, 2971, 1577, 1550, 1459, 1425, 1328, 1223, 1070, 1025, 760, 729, 699; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.72 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.61 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.36 – 7.24 (m, 6H), 7.12 (td, *J* = 7.7, 1.7 Hz, 1H), 6.90 (s, 1H), 6.11 (s, 1H), 4.44 (s, 2H); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) 168.7, 149.4, 137.8, 136.1, 133.7, 131.7, 129.0, 128.8, 127.8, 127.8, 127.4, 121.9, 106.0, 50.0; (+)-HRESI-MS *m*/*z* $[M+H]^+$ 345.0048 (calcd for $C_{16}H_{14}N_2SBr$, 345.0061).

***N*-Benzyl-4-(*p*-tolyl)thiazol-2-amine (4n):** off-white solid; FT-IR (KBr) ν_{max} (cm^{-1}): 3401, 3210, 3028, 2972, 2921, 1577, 1550, 1491, 1452, 1330, 1220, 1048, 821, 728, 698; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.68 (d, *J* = 8.2 Hz, 2H), 7.38 – 7.25 (m, 5H), 7.14 (d, *J* = 8.0 Hz, 2H), 6.62 (s, 1H), 6.05 (brs, 1H), 4.47 (s, 2H), 2.34 (s, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) 169.6, 151.7, 137.9, 137.5, 132.4, 129.3, 128.8, 127.8, 126.1, 100.4, 50.0, 21.4; (+)-HRESI-MS *m*/*z* $[M+H]^+$ 281.1110 (calcd for $C_{17}H_{17}N_2S$, 281.1112).[23]

Antibacterial activity assay

The antibacterial activity of synthesized compounds was evaluated by the macrodilution method and expressed as minimum inhibitory concentrations (MICs), in accordance with the standards of the Clinical

and Laboratory Standards Institute, USA.[17] The tested microorganisms are (a) Gram-positive bacteria: *Staphylococcus aureus* (*S. aureus*) ATCC 25923 obtained from American Type Culture Collection (ATCC) (Manassas, VA, USA), *Bacillus cereus* AT3 (*B. cereus* AT3) isolated from soil in Thua Thien Hue, Vietnam; (b) Gram-negative bacteria: *Escherichia coli* (*E. coli*) BL21 (DE3) obtained from Clontech, (Mountain View, CA, USA), *Vibrio alginolyticus* (*V. alginolyticus*) PVSulx isolated from shrimp pond in Thua Thien Hue, Vietnam. All the bacteria trains used in this assay were provided by Laboratory of Biotechnology, Faculty of Chemical Engineering, University of Science and Technology, the University of Danang, Vietnam. The *E. coli* BL21 (DE3), *S. aureus* ATCC 25923, *B. cereus* AT3 strains were grown in Luria-Bertani broth, and *V. alginolyticus* PVSulx were grown in alkaline peptone water (10 g/L peptone, 10 g/L NaCl) at 37 ºC with shaking. *V. alginolyticus* PVSulx exhibited multi-drug resistance to three antibiotics: tetracycline, erythromycin, sulfamethoxazole and trimethoprim combination.

Briefly, a 16-hour culture of approximately 5×10^5 CFU/mL was inoculated into tubes containing test compound dilutions with varying concentrations from 1 μg/mL to 64 μg/mL in sterile DMSO and made the final volume to 5 mL by the Mueller Hinton Broth medium. The medium (blank sample) without bacterial cells was included as the sterility control. Ciprofloxacin (LGC, USA) was used as a positive control. The inocula were grown in an incubator at 37 ºC, with shaking at 140 rpm. The optical density at 595 nm (OD595) of the inocula was recorded after 18–20 h in culture. The lowest concentration of antimicrobial agents that completely inhibits the growth of the microorganism in tubes was recorded as MICs. All experiments were performed in triplicate.

For results of antibacterial activity assay, data were analyzed by one-way analysis of variance (ANOVA) followed by Tukey's honest significant difference test. $P < 0.05$ was considered significant. Statistical analysis was carried out by using the windows program SPSS version 10.0 (Chicago, IL). The results were shown as the means and standard deviation obtained by three independent experiments.

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