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SYNTHESIS, ANTIBACTERIAL ACTIVITY STUDY OF NEW 3-((5-METHOXY-1H-BENZO[d]IMIDAZOLE-2-YLTHIO)METHYL)-2-CHLOROQUINOLINE DERIVATIVES

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ABSTRACT:
A new and convenient with high yielding method was developed for the synthesis of 3-((5-methoxy-1H-benzo[d]imidazol-2-ylthio)methyl)-2-chloroquinoline derivatives using 2-chloroquinolin-3-carbaldehydes and 5-methoxy-1H-benzo[d]imidazole-2-thiol. All the newly synthesized compounds were analyzed by spectroscopic data such as ^{1}HNMR, IR, Mass. The newly prepared compounds were screened for antimicrobial activity against bacterial strains *Staphylococcus aureas* (NCIM-2654), *Bacillus subtilis* (NCIM-2635), *Escherichia coli* (NCIM-2832) and *Pseudomonas aeruginosa* (NCIM-5032). These newly synthesized materials exhibit good to moderate antimicrobial activity against one Gram positive and one Gram negative pathogenic strains.

KEYWORDS:
2-chloroquinolin-3-carbaldehydes, 5-methoxy-1H-benzo[d]imidazole-2-thiol, antibacterial, 3-((5-methoxy-1H-benzo[d]imidazol-2-ylthio)methyl)-2-chloroquinoline, Spectroscopic.

INTRODUCTION:

The Quinoline ring system exhibits a major and very important class of heterocyclic compounds. It acts as a very important key intermediate for pharmacological compounds.[i-iii] The quinoline derivatives finds important biological and physiological activities like antimalarial,[iv-xi] antiinflammatory,[xii-xvii] antitumor,[xviii-xx] DNA binding capacity,[xxi-xxii] antibacterial,[xxiii-xxvi] antimicrobial,[xxvii-xxxiii] anticancer,[xxxiv-xxxv] antituberculosis,[xxxvi] antihistamine,[xxxvii] antifungal,[xxxviii] anti-HIV,[xxxix] antihypertensive[xl] and antiparasiticproperties.[xli] Quinoline also shows the study of processes like bioorganometallic and bioorganic.[xlii]

The benzimidazole ring system also exhibits a very important and major class of heterocyclic organic compounds. The benzimidazole class derivatives exhibits biological activities such as antimicrobial,[xliii-xliv] antiviral,[xlv-xlvi] antitumor,[xlvii] antimutagens,[xlviii] cardio-vascular,[xlix] anticamodulin,[l] antiparkinsons,[li] anticancer,[lii-liv] antiinflammatory,[lv] antiulcer[lvi] and other activities are well documented.[lvii] The benzimidazole ring system has been showed great

attention when it acts as the one of the component of vitamin B12.[lviii] on the other hand, mercaptobenzimidazoles are used in the synthesis of well known proton pump inhibitors such as pantoprazole,[lix] omeprazole,[lx] rabeprazole,[lxi] and lansoprazole[lxii] used in GRED as anti helicobacteragent.[lxiii] Therefore benzimidazole ring system acts as an important core structure for the drug design.[lxiv]

As like the biological importance, the quinolines nucleus particularly, 2-chloroquinolin-3-carbaldehyde has been used as a key intermediate structure for the synthesis of variety of medicinally valuable compounds. Meth-Cohn et al.[i] described the synthetic utility of 2-chloroquinolin-3-carbaldehydes. The 2-chloro-group of the title compounds has been replaced by H, I, OH, SR, Li, COOH, CHO, Ph, piperidine and N_3 groups. The aldehyde group has also been converted into oxime, hydrazone, acrylic acid derivatives. From these and related derivatives a variety of fused quinolines have been made including –thieno, - pyridazino, -tropono, -pyrano and fluro-quinolines.

Thus, the important role displayed by quinolines and benzimidazoles for various therapeutic and biological activities prompted us to synthesize some new derivatives of combining these two pharmacophores quinoline and benzimidazole in order to achieve compounds having better drug potentials.

In the literature search, it was observed that quinolines, tetrazole and mercaptobenzimidazole are the important pharmacophores, efforts has been made to combine these three moieties as a single molecule.[xlv]

Until now enough efforts have not been made to combine quinolines, mercaptobenzimidazole these two moieties as a single molecule. So our object was to synthesize and biological evaluation of a series of new compounds incorporating these two moieties quinolines and benzimidazole.

EXPERIMENTAL

In the laboratory 2-chloroquinoline-carbaldehyde was prepared using reported method. Required solvents and reagents were purchased from spectrochem, Avra chemicals and S.D. fine chem. otherwise stated. Physical constants (melting point) were carried out in open capillaries at atmospheric pressure. Proton NMR was recorded on Bruker AVANCE in DMSO at 500 MHz using standard as TMS. Bruker FTIR was used for recording of IR spectra. Waters Q-TOF Micromass (E SIMS) used for mass spectra analysis, showing a molecular ion peak.

GENERAL PROCEDURE

Acetanilides (2a)

In 20 mL acetic acid was added 9.3 gm aniline (10 mmol) in a 100 mL RBF and slowly added 15 mL acetic anhydride (15 mmol) and heated the reaction mass to 120-130 ^{0}C for 24 hrs, progress of reaction was monitored on thin layer chromatography (TLC). After completion, reaction mixture was cooled to room temperature and poured on ice-cold water, solid obtained was filtered and washed with water (dry wt. 12.5 gm).

2-chloroquinoline-3-carbaldehyde (3a)

In a 100 mL RBF was taken 10.95 gm (15 mmol) Dimethylformamide (DMF) and cooled to 0-5 ^{0}C, maintaining this temperature slowly drop wise was added 53 gm $POCl_3$ (35 mmol) in 1 hr. After addition was added 6.75 gm (5 mmol) acetanilide and slowly heated the reaction mass to 85-90 ^{0}C and maintained temperature for 8-10 hrs. Progress of reaction was monitored on thin layer chromatography (TLC). After completion, reaction mixture was cooled to room temperature and poured on ice-cold water, solid obtained was filtered and washed with water. (dry wt. 6.5 gm, 69%). The crude product was recrystallized in ethylacetate to get the pure product.

(2-Chloroquinoline-3-yl)methanol (4a)

In methanol 15 mL was added 2-chloroquinoline-3-carbaldehyde 1.9 gm, 10 mmol stirred for five minute then slowly sodium borohydride 0.5 gm, 13 mmol was added at room temperature with constant stirring. Continued stirring for further 10 minute and the reaction progress was checked on thin layer chromatography (TLC). After completion, reaction mixture was concentrated on rotary evaporator. Residue taken in ice water, solid obtained was filtered and cold water was used for washing to afford wet compound which was further dried to afford titled compound (1.85 gm, 95%).

Compound (4c)

ESMS: 207.8 (m+1) m/z

2-chloro-3-(chloromethyl)quinolines (5a)

Thionyl chloride (2 mL) in dichloromethane 5 mL was added drop wise in stirred solution of 2-chloroquinolin-3-yl- methanol 1.75 gm, 9 mmol in 10 mL dichloromethane taken in a 50 mL RBF. The reaction mixture stirred further 1 hr at atmospheric temperature and reaction progress was checked by thin layer chromatography using hexane ethyl acetate solvent system. After complete conversion of starting material, the reaction mass was concentrated on rotary evaporator to obtain crude product 1.85 gm, 96%, which was enough pure and used directly for the next step.

Compound (5c)

^{1}H NMR ($CDCl_3$, δppm): 2.75 (s, 3H), 4.85 (s, 2H), 7.43– 7.68 (m, 3H), 8.22 (s, 1H);

E SIMS: 242.0 (m+1) m/z

Compound (5e)

^{1}H NMR ($CDCl_3$, δppm): 3.95 (s, 3H), 4.85 (s, 2H), 7.20– 7.72 (m, 3H), 8.18 (s, 1H);

3-((5-methoxy-1H-benzo[d]imidazol-2-ylthio)methyl)-2-chloroquinoline (6a)

To the solution of 5-methoxy-1H-benzo[d]imidazole-2-thiol 1.80 gm (10 mmol) in methanol 20 mL was added sodium hydroxide 0.6 gm, 15mmol. To this pre-stirred (10 min) solution 2-chloro-3-(chloromethyl)quinoline 1.75 gm, 9 mmol was added at room temperature and stirred for 1 hr. The reaction progress was checked on thin layer chromatography using Hexane and ethyl acetate as solvent system (8:2). After complete conversion of reaction mass, the solvent removed under vacuum on rota evaporator. To the obtained residue cold water 100 mL added, filtered solid and washed with water 50 mL to get product, which is dried. Dried compound purified in methanol water to get pure 3.15 gm, 89%.

Compound (6a)

3-((5-methoxy-1H-benzo[d]imidazol-2-ylthio)methyl)-2-chloroquinoline (6a)

IR (cm^{-1}): 3342 (-NH); 2897 (-C-H); 1613, (-C=C); 748 (C-Cl);

^{1}H NMR (DMSO, δppm): 3.76 (s, 3H), 4.75 (s, 2H), 6.74 – 7.96 (m, 7H), 8.54 (s, 1H);

E SIMS: 356.2 (m+1) and 358.2 (m+3) m/z

Compound (6c)

3-((5-methoxy-1H-benzo[d]imidazol-2-ylthio)methyl)-2-chloro-7-methylquinoline (6c)

IR (cm^{-1}): 3391 (-NH), 2975 (-C-H), 1615 (-C=C), 752 (-C-Cl)

^{1}H NMR (DMSO, δppm): 2.64 (s, 3H), 3.75 (s, 3H), 4.74 (s, 2H), 6.72– 7.76 (m, 6H), 8.49 (s, 1H),

E SIMS: 370.2 (m+1) and 372.2 (m+3) m/z

Compound (6d)

3-((5-methoxy-1H-benzo[d]imidazol-2-ylthio)methyl)-2-chloro-6-methylquinoline (6d)

IR (cm^{-1}): 3379 (-NH), 2930 (-C-H), 1608 (-C=C), 748 (-C-Cl)

^{1}H NMR (DMSO, δppm): 2.64 (s, 3H), 3.75 (s, 3H), 4.74 (s, 2H), 6.72– 7.76 (m, 6H), 8.49 (s, 1H),

E SIMS: 370.2 (m+1) and 372.2 (m+3) m/z

Coinpound (6e)

3-((5-methoxy-1H-benzo[d]imidazol-2-ylthio)methyl)-2-chloro-7-methoxyquinoline 6e

IR (cm^{-1}): 3576 (-NH), 2973 (-C-H), 1621 (-C=C), 737 (-C-Cl)

^{1}H NMR (DMSO, δppm): 3.76 (s, 3H), 3.85 (s, 3H), 4.74 (s, 2H), 6.77– 7.85 (m, 6H), 8.40 (s, 1H),

E SIMS: 386.2 (m+1) and 388.2 (m+3) m/z

Compound (6f)

3-((5-methoxy-1H-benzo[d]imidazol-2-ylthio)methyl)-2-chloro-6-methoxyquinoline 6f

IR (cm^{-1}): 3409 (-NH), 2979 (-C-H), 1622 (-C=C), 741 (-C-Cl)

^{1}H NMR (DMSO, δppm): 3.76 (s, 3H), 3.85 (s, 3H), 4.74 (s, 2H), 6.77– 7.85 (m, 6H), 8.40 (s, 1H),

E SIMS: 386.2 (m+1) and 388.2 (m+3) m/z

RESULT AND DISCUSSION

A series of new 3-((5-methoxy-1H-benz0[d]imidazol-2-ylthio)methyl)-2-chloroquinoline derivatives were synthesized in high yield **(Scheme-1).** The process commences with acylation of aniline **1a-f** using acetic anhydride. In the second step acetanilides **2a–f** were converted to 2-chloroquinoline-3-carbaldehydes **3a–f** using $POCl_3$ and DMF (Vilsmeier Haack reagent). Followed by reduction of 2-chloroquinolin-3-carbaldehydes in the presence of sodium borohydride as reducing agent at room temperature in methanol solvent to obtain the (2-chloroquinolin-3-yl)methanol derivatives **4a-f** in 94-97% yields in very short time (10 min) entries 1-6 are mentioned in Table-2. These obtained (2chloroquinolin-3-yl)methanol derivatives **4a-f** reacted with thionyl chloride in dichloromethane as a solvent at room temperature to form 2-chloro-3-(chloromethyl)quinolines derivatives **5a-f** in 95-98% yield and are entered Table-1. These obtained 2-chloro-3-(chloromethyl)quinolines derivatives **5a-f** were reacted with 5-methoxy-1H-benz0[d]imidazole-2-thiol in methanol solvent in the presence of base like sodium hydroxide to give the target compounds 3-((5-methoxy-1H-benz0[d]imidazol-2-ylthio)methyl)-2-chloroquinoline **6a-f**. Progress of the reactions were monitored on TLC using mobile phase hexane: ethylacetate (8:2). The reaction proceeded smoothly under basic conditions and completed in 1 hr to obtain the corresponding titled compounds having entries 13-18 in Table-2 in high yields (85-95%).

Initially, a set of reaction was carried out between 2-chloro-3-(chloromethyl)quinolines (1 mmol) and 5-methoxy-1H-benzo[d]imidazole-2-thiol (1.05mmol) in various solvents for the optimization of reaction condition at different temperature **(Table 1).**

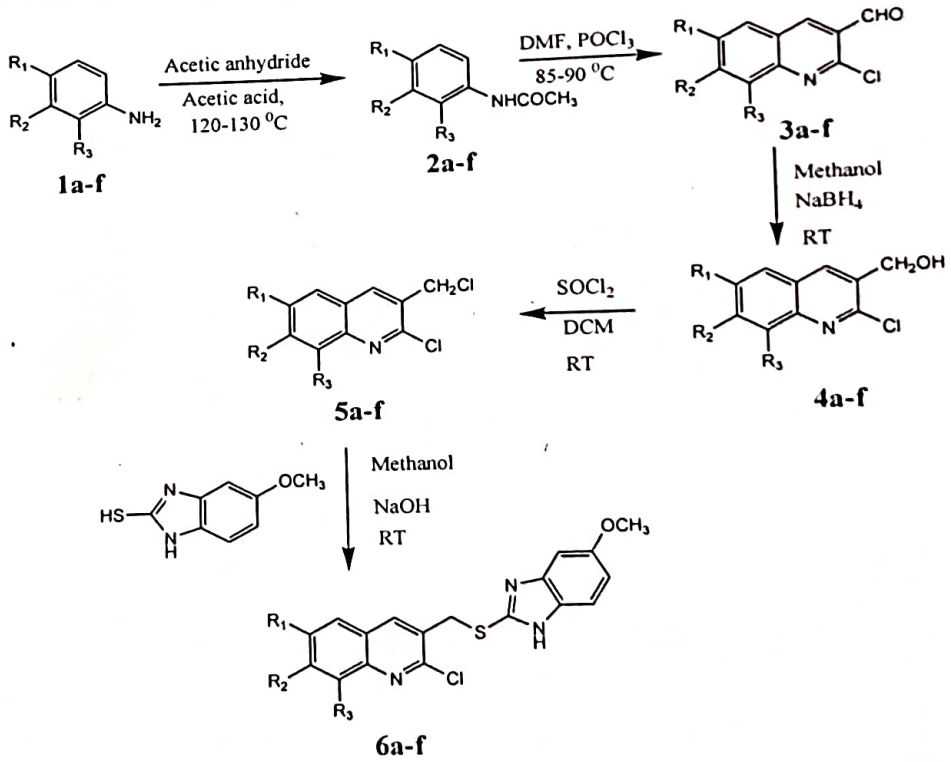
Table 1: Optimization of the reaction conditions

Entry	Solvent	Catalyst	Temperature (^{0}C)	Time (min.)	Yield (%)
1	CH_3COCH_3	K_2CO_3	RT	60	81
2	CH_3COCH_3	NaOH	RT	55	84
3	CH_3OH	K_2CO_3	RT	60	85
4	CH_3OH	NaOH	RT	60	89
5	C_2H_5OH	K_2CO_3	RT	55	78
6	C_2H_5OH	NaOH	RT	60	80
7	CH_3OH	K_2CO_3	40	50	76

8	CH_3OH	NaOH	40	55	70
9	C_2H_5OH	K_2CO_3	40	60	73
10	C_2H_5OH	NaOH	40	60	

In this optimization study, very good yield was obtained in methanol at room temperature using sodium hydroxide as base catalyst. Therefore, a series of reactions was carried out using different 2-chloro-3-(chloromethyl)quinolines (1 mmol) and 5-methoxy-1H-benzo[d]imidazole-2-thiol(1.05 mmol) in 20 mL methanol at room temperature using sodium hydroxide as base catalyst for the synthesis of 3-((5-methoxy-1H-benzo[d]imidazol-2-ylthio)methyl)-2-chloroquinoline derivatives as given in **Table 2.**

All the newly synthesized compounds were analyzed by spectroscopic data such as ^{1}HNMR, IR, Mass. The newly prepared compounds were screened for antimicrobial activity against bacterial strains *Staphylococcus aureas* (NCIM-2654), *Bacillus subtilis* (NCIM-2635), *Escherichia coli* (NCIM-2832) and *Pseudomonas aeruginosa* (NCIM-5032). These newly synthesized materials exhibit good to moderate antimicrobial activity against one Gram positive and one Gram negative pathogenic strains.



Scheme-1:

Synthesis of 3-((5-methoxy-1H-benzo[d]imidazol-2-ylthio)methyl)-2-chloroquinoline

ANTIBACTERIAL ACTIVITY:

The microbial cultures inoculums were prepared into sterile saline water. The nutrient agar plates were used as a medium for the bacterial growth. The *S. aureus, B. subtilis, E. coli* and *P. aeruginosa* cultures were spread on a sterile nutrient agar plates, wells are prepared in these plates using sterile cork borer having size 5mm. 100ug/ml synthesized material were dispersed in the sterile Dimethyl sulfoxide (DMSO) with the help of micropipette. The plates were incubated at 37°C for 24 hr to test antibacterial activity.

The antimicrobial activity of chemically synthesized materials was checked along with blank Dimethyl sulfoxide (DMSO) as negative control. The antimicrobial potential of synthesized material was studied using agar well gel diffusion method against bacterial strains *S. aureus*,

B. subtilis gram-positive, *E. coli*, *P. aeruginosa* gram-negative bacteria using streptomycin as the standard drug. These antibacterial studies revealed synthesized new derivatives present in the well which inhibits the growth of *S. aureus, B. subtilis, E. coli and P. aeruginosa bacterial strains*, Indicates that synthesized material has been use for antimicrobial activity. The above data represent the mean ± standard error of three replicates in table- 3.

Table-2: Data of newly synthesized compounds

Entry	Compound	R_1	R_2	R_3	Reaction Time (min)	Yield (%)	Melting Point (^{0}C)
1	4a	H	H	H	10	95	166-168
2	4b	H	H	CH_3	10	95	160-162
3	4c	H	CH_3	H	10	96	131-133
4	4d	CH_3	H	H	10	95	144-146
5	4e	H	OCH_3	H	10	95	122-124
6	4f	OCH_3	H	H	10	97	129-131
7	5a	H	H	H	30	96	----
8	5b	H	H	CH_3	30	95	----
9	5c	H	CH_3	H	30	96	----
10	5d	CH_3	H	H	30	97	----
11	5e	H	OCH_3	H	30	96	----
12	5f	OCH_3	H	H	30	95	----
13	6a	H	H	H	60	89	210-212
14	6b	H	H	CH_3	60	90	222-224
15	6c	H	CH_3	H	55	91	241-243
16	6d	CH_3	H	H	60	90	233-235
17	6e	H	OCH_3	H	55	91	225-227
18	6f	OCH_3	H	H	60	90	235-237

Table-3: Zone of inhibition of sample code- 1-6a, 2-6b, 3-6f, 4-6d, 5-6c, Antibiotic code- 6-F, Control code- 7 antimicrobial activity against human pathogens

Entry	Antibacterial activity			
	Gram + Ve		Gram -Ve	
	Staphylococcus aureus	*Bacillus subtilis*	*Escherichia coli*	*Pseudomonas aeruginosa*
1-6a	13.33 ± 0.57	16.00 ± 1.00	11.66 ± 0.57	11.66 ± 0.57
2-6b	11.00 ± 1.00	13.66 ± 0.57	11.33 ± 0.57	10.33 ± 1.15
3-6f	10.66 ± 1.15	15.33 ± 1.15	12.33 ± 0.57	11.00 ± 1.00
4-6d	14.00 ± 1.00	17.66 ± 0.57	13.66 ± 0.57	11.66 ± 0.57
5-6c	11.66 ± 0.57	13.00 ± 1.00	12.00 ± 1.00	12.00 ± 1.00
6-F	20.00 ± 0.57	25.00 ± 1.00	15.00 ± 1.00	11.33 ± 1.15

Figure caption:

Fig. 1 Antimicrobial activity on the *Staphylococcus aureus* (NCIM -2654), *Bacillus subtilis* (NCIM 2635), *Escherichia coli (NCIM-2832) and Pseudomonas aeruginosa* (NCIM - 5032) zone of inhibition for 6a-f type material *sample code- 1-6a, 2-6b, 3-6f, 4-6d, 5-6c, Antibiotic code- 6-F, Control code- 7 antimicrobial activity against human pathogens*

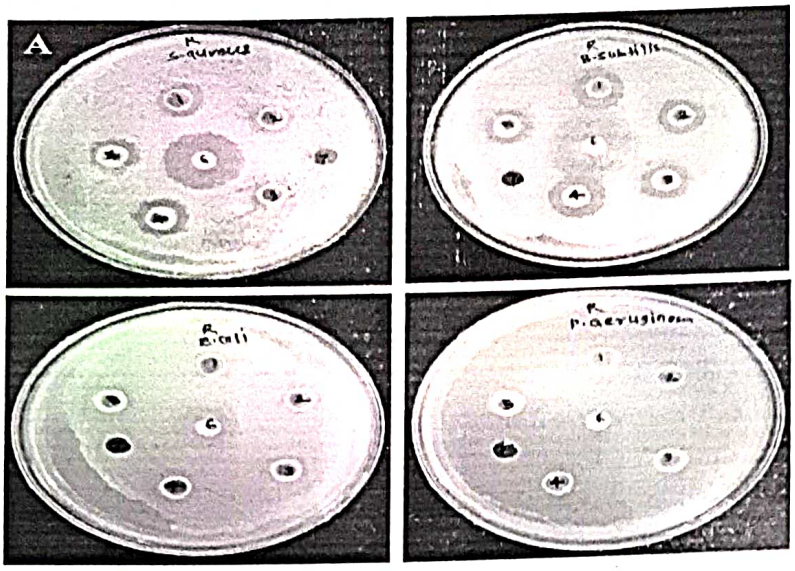
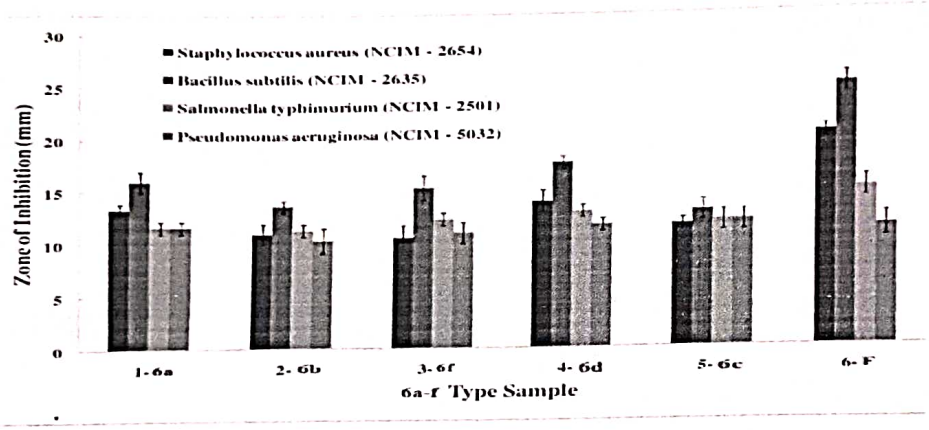


Fig. 2 The statistical analysis of **6a-f** type material against bacterial human pathogens



CONCLUSION

A new and convenient method was developed for the synthesis of 3-(1H-benzo(d)imidazole-2-yithio) methyl-2-chloroquinoline using 2-chloroquinolin-3-carbaldehydes and 5-methoxy-1H-benzo[d]imidazole-2-thiol in quantitative yield. All the reactions were performed under mild reaction conditions, shorter reaction time and in quantitative yields (Table 2). The methodology developed will be much use to combinatorial chemist. The newly prepared compounds were characterized by ^{1}HNMR, IR and Mass spectroscopy. The newly synthesized compounds were screened for antimicrobial activity against bacterial strains *Staphylococcus aureus* (NCIM-2654), *Bacillus subtilis* (NCIM-2635), *Escherichia coli* (NCIM-2832) and *Pseudomonas aeruginosa* (NCIM-5032). Chemically synthesized type materials exhibit excellent antimicrobial activity against one Gram positive and one Gram negative pathogenic strains.

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