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Synthesis and Identification of some new Derivatives Oxazole, Thiazole and Imidazol from Acetyl Cysteine

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Abstract

Some fused heterocyclic oxazoles and imidazols rings were synthesized from reaction of N- acetyl cysteine with different treatment. After thiol group protection, N-acetyl-S-ethyl cysteine (2) had been esterified to give ester 3 which cyclized to oxazole 4 with phosphorus oxychloride. N-acetyl-S-ethyl cysteine 2 were converted to acid chloride 5 with thionyle chloride. Amide 6 were synthesized from 5 with ammonia solution. Amide 6 converted to substituted carbamide 7 by react with P2S5, then the product reacted with α-chloroacetophenone to give substituted thiazol ring 8 that converted to bicyclic thiazole – imidazole ring system 9. Cyclized benzoxazole derivative 10 had been synthesized then converted to 3-(ethylthio)-1-methyl-1,3a-dihydrobenzo[d]imidazo[5,1-b]oxazole (11). Structure of new synthesized compounds were confirms by IR, 1H-NMR, and UV spectra as well as physical constant.

Keywords: heterocyclic compounds, oxazole, thiazole, Imidazole , protective thiol group

1. Introduction

Oxazole ring system and its derivatives have been incorporated into large number of compounds of potential medicinal values and applications [1, 2], they attract attention of many research groups due to its biological applications [3]. Also, thiazole derivatives have therapeutic effects against several diseases [4, 5]. Both oxazole and thiazole have been synthesized and incorporated into potentially active compounds with biological application such as antimicrobial [6], anticancer [2], anti-inflammatory [7], analgesic [7], and antiproliferative activities [8]. Also, many imidazole derivatives were designed as antifungal drugs such as clotrimazole, miconazole, ketoconazole, and …etc. [9-11]. Substituted oxazoles were synthesized in literature [12, 13]. Microwave free solvent technique was applied in the synthesis of oxazoles [14]. Some oxazoles and benzooxazoles were synthesized by starting from the reaction of acid chloride of N-benzayl glycine with amonophenol followed by cyclization of the product with phosphorus oxychloride to give fused rings of oxazole and imidazole [15, 16]. Substituted 1,3- oxazole were converted to a new oxazoles [17]. Some naturally occurring oxazoles possess anti-bacterial activity[18-19].

Base on above survey, herein, we aim to synthesize some derivatives of oxazole, imidazole, benzooxazole, thiazole, and imidazo[5,1-b]thiazole as new derivatives of expected biological applications and evaluate their activity as antimicrobial agents against Gram (-ve, +ve) bacteria in comparison with Ciprofloxacin.

2. Experimental

All chemicals were supplied by either Flucka , Moleculea , Carloerba and BDH Chemical Ltd and were used without further purification. All melting points are uncorrected and were taken in open capillary tubes using Electrothermal 9300 Engineering LTD. FT-IR spectra were recorded with a Model Tensor 27, Bruker Co., Germany, using KBr discs. UV spectra were recorded on Shimadzu Double-Beam Spectrophotometer UV-210 A using ethanol as a solvent. Routine NMR spectra were recorded at room temperature on a Bruker Avance TM 300 spectrometer as solutions in dimethyl sulfoxide (DMSO). All

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chemical shifts are quoted in δ relative to the trace resonance of protonated dimethyl sulfoxide (δ2.50 ppm), DMSO (δ39.51 ppm). Follow up of the reactions and checking the purity of the compounds were made by TLC on silica gel-precoated aluminum sheets (Type 60, F 254, Merck, Darmstadt, Germany) and the spots were detected by exposure to UV lamp at λ254 nanometer for few seconds. The chemical names given for the prepared compounds are according to the IUPAC system. The reported yields are based upon pure materials isolated. Solvents were dried/purified according to conventional procedures. The physical properties of new compounds were cited in Table 1.

1.1. 2-Acetamido-2-(ethylthio)acetic acid (2)

A mixture of 2-acetamido-2-mercaptoacetic acid (1, 0.19g, 1 mmole) in (20 ml) ethanol and 10% potassium hydroxide (10 ml) was reflexed for 2 hr. Ethyl iodide was added dropwise to the mixture with stirring (TLC monitoring). Reaction mixture was evaporated under reduce pressure to afford compound 2 (ethanol).

1.2. Ethyl 2-acetamido-2-(ethylthio)acetate (3) [20]

Thionyl chloride (130 ml, 11 mmole,) was added dropwise to 2-acetamido-2-(ethylthio)acetic acid (2) (1.7g, 10 mmole) in absolute ethanol (100 ml) with stirring at -5oC for 30min then heated at 50oC for 2h (TLC monitoring). Solvent was evaporated under reduced pressure to afford solid of compound 3 (ethanol-ether (50:50 v/v)).

1.3. 5-Ethoxy-4-(ethylthio)-2-methyloxazole (4)

Phosphorous oxychloride (100ml) was added dropwise to ethyl 2-acetamido-2-(ethylthio)acetate (3, 10 mmole) in 20 ml benzene then the reaction mixture refluxed with stiring for 2h, the mixture was cooled and neutralized with sodium bicarbonate to (weak basic media). Obtained product was filtered off and recrystallized from ethanol- water to afford product 4.

1.4. 2-Acetamido-2-(ethylthio)acetyl chloride (5)[21]

Thionyl chloride (10ml) was added to 2-acetamido-2-(ethylthio)acetic acid (2) (0.01 mole). The reaction mixture was heated on WB for 30 min with stirring. Reaction mixture poured on ice to get solid product, filtered off, was dried on suction to get compound 5.

1.5. 2-Acetamido-2-(ethylthio)acetamide (6)[22]

Acid chloride (0.01 mole) was mixed with ammonia solution with stirring for 10 minutes, the crystalline product 6 was separated by filtration and recrystallized from ethanol – water.

1.6. 2-Ethanethioamido-2-(ethylthio)ethanethioamide (7)[22]

2-Acetamido-2-(ethylthio)acetamide (6, 0.02 mole) in tetrahydrofuran (15ml) with phosphorus pentasulfide (0.04 mole) were heated with stirring for 1.5h at 50oC . The mixture after cooling was poured on crushed ice (50g) and left for 2h. Organic layer was separated via ethyl acetate (2 x 25 ml), evaporated under reduced pressure to give the product 7.

1.7. N-((ethylthio)(5-phenylthiazol-2-yl)methyl)ethanethioamide (8)

A mixture of ethanethioamido-2-(ethylthio) ethanethioamide (7, 0.01 mole) and α-chloroacetophenone (1.5 g , 0.01 mole) in absolute methanol was refluxed for 24h, the precipitate was formed on cooling filtered off, dried and recrystallized from ethanol to afford compound 8.

1.8. 7-(ethylthio)-5-methyl-2-phenyl-5,7a-dihydroimidazo[5,1-b]thiazole (9)

Compound (8, 0.01 mole) was dissolved in 25ml dry benzene then, phosphorus oxychloride (20ml) was added slowly. The mixture was refluxed for 4h then powered on crushed ice, extracted with methylene chloride (2 x 25 ml), the solvent, dried and evaporated to give a solid product which recrystallized from ether – pet. Ether.

1.9. N-(benzo[d]oxazol-2-yl(ethylthio)methyl)acetamide (10)[23]

2-Acetamido-2-(ethylthio)acetyl chloride (5, 0.01 mole) was added to o-aminophenol (0.01 mole, 1.1g) which was dissolved in methylene chloride (25ml). The mixture refluxed for 7h (TLC mentoring). Solvent was evaporated under reduced pressure and the product was filtered, dried and recrystallized from ether-pet.ether (60-80).

1.10. 3-(Ethylthio)-1-methyl-1,3a-dihydrobenzo[d]imidazo[5,1-b]oxazole (11)[23]

N-(benzo[d]oxazol-2-yl(ethylthio)methyl)acetamide (10, 0.01 mole) was dissolved in dry benzene (25ml), phosphorus oxychloride (20ml) was added slowly. The mixture was refluxed for 4h then powered on crushed ice, extracted with methylene chloride (2 x 25 ml), the solvent was evaporated to give a solid product which recrystallized from ether – pet. Ether.

3. Results and Discussion

2-Acetamido-2-mercaptoacetic acid (1) was ethylated with ethyl iodide to afford 2-acetamido-2-(ethylthio)acetic acid (2) in a good yield (Scheme 1). Compound 2 was reacted with thionyl chloride under different conditions of neat or in the presence of ethanol to obtain ethyl 2-acetamido-2-(ethylthio)acetate (3) and 2-acetamido-2-(ethylthio)acetyl chloride (5), respectively (Scheme 1).

For instance, IR spectrum of compound 2 revealed strong absorption bands at ύ 1767 (C=O ester) 2878 (CH aliphatic), 1667 (C=O amide). 3270 (NH amide) cm-1 with disappearance of OH group stretch band for acid. Also, 1H-NMR spectra confirmed structure of compound 2 (Table 2). IR spectrum of compound 5 showed absorption bands at ύ: 3196, 3320 (NH2, NH), 1669 (C=O) 2960 (C-H alph) cm-1.

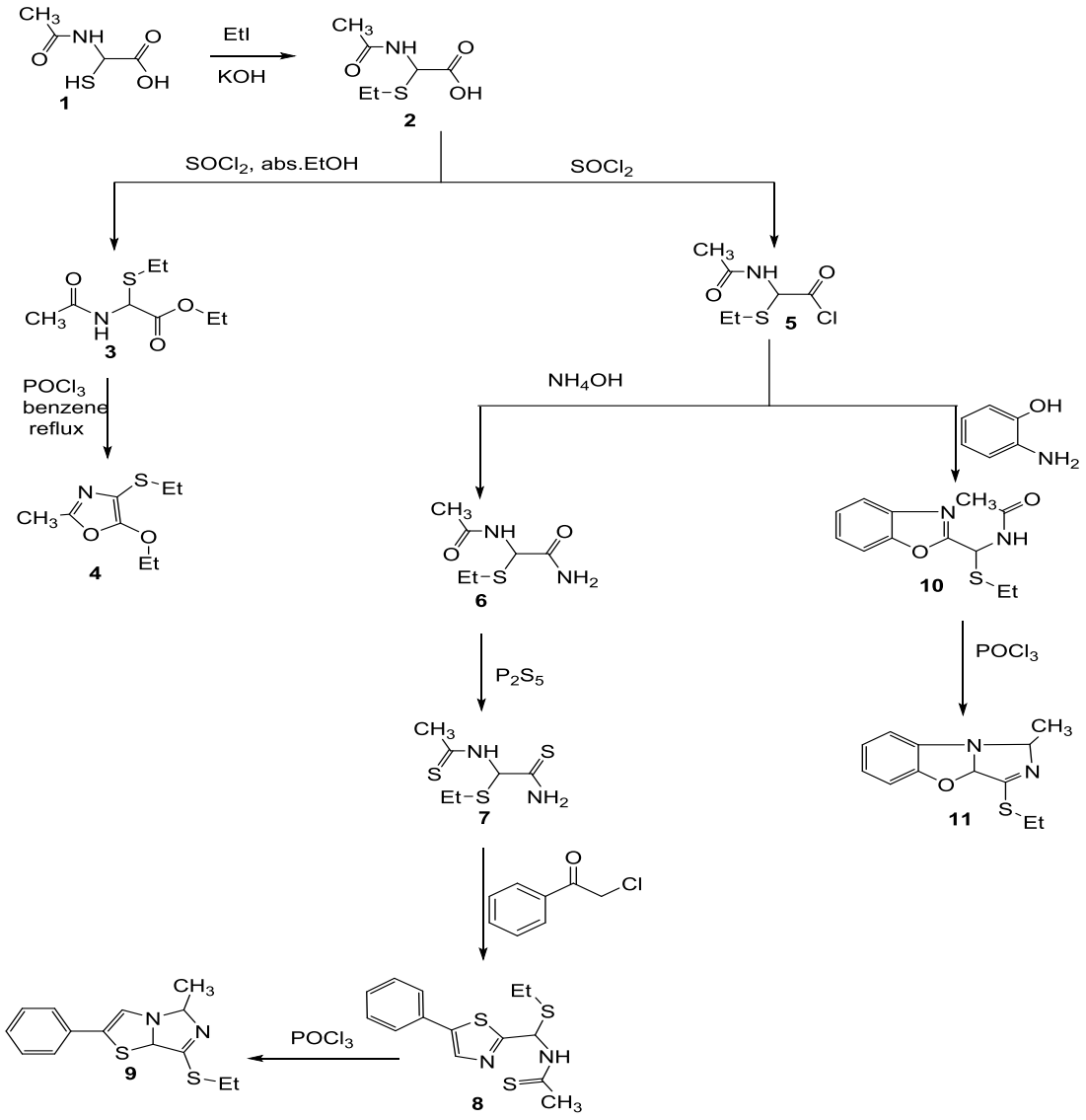
Compound **3** reacted with phosphorus oxychloride in benzene at reflux temperature to afford 5-Ethoxy-4-(ethylthio)-2-methyloxazole (**4**) in moderate yield (Scheme 1). Its IR spectrum revealed absorption bond at ύ= 1944 (C=O acid chloride), 1669 (C=O amide), 3352(NH) 2942, 2862 (CH aliphatic) cm^{-1}. Mechanism of formation of compound **4** was depicted in Scheme 2; phosphorus oxychloride with expulsion of hydrochloride acid molecule, is attacked by lone pair of carbonyl oxygen to give intermediates [A, B] to obtain compound **4** via cyclization. 2-Ethanethioamido-2-(ethylthio)ethanethioamide (**7**) was prepared via thiation process using phosphorus pentasulfide with compound **6**. IR spectrum of **7** showed absorption band at ύ = 1622 C=N, 1260 (C=S), 3300 NH cm^{-1}. The structure of compound **7** were confirmed by 1H-NMR spectra show in table (2). Also, compound **7** reacted with α-chloroacetophenone to afford *N*-((ethylthio)(5-phenylthiazol-2-yl)methyl)ethanethioamide (**8**) (Scheme 1).

IR spectrum revealed presence of absorption band at ύ = 2960 C-H aliphatic, 1622 C=N, 1034-860 (C-S-C) cm^{-1}. Compound **8** has been cyclized to 7-(ethylthio)-5-methyl-2-phenyl-5,7a-dihydroimidazo[5,1-b]thiazole (**9**) upon treating with phosphorus oxychloride (Scheme 1). IR spectrum showed absorption bands at ύ 3375 (NH), 3052 (CH Aromatic), 2931 (CH aliphatic), 1661(C=O), 1632 (C=N), 1170, 1098, (C-O-C) cm^{-1}. Structure of compounds **2-9** were confirmed with IR and ^{1}H NMR (Table 1).

Compound **5** reacted with *o*-aminophenol to obtain N-(benzo[d]oxazol-2-yl(ethylthio)methyl)acetamide (**10**) in good yield which reacted with phosphorus oxychloride to cyclize to 3-(ethylthio)-1-methyl-1,3a-dihydrobenzo[d]imidazo[5,1-b]oxazole (**11**) (Scheme 1).

Table 1: The Physical constants for compounds (2-11)

Comp.	m.p (°C)	Color	Yield %	$\lambda_{Max\ (nm)}$	Molecule formula
2	112-115	White	60	278	$C_6H_{11}NSO_2$
3	91-93	Yellow	81	296	$C_8H_{15}NSO_3$
4	134-136	Gray	91	293	$C_8H_{13}NSO_2$
5	202-203	Pall Yellow	82	246	$C_6H_{10}ClNSO_2$
6	232-233	Brawn	87	312	$C_6H_{12}N_2SO_2$
7	191-192	Brawn	72	366	$C_6H_{12}N_2S_3$
8	178-180	Yellow	87	379	$C_{14}H_{16}N_2S_3$
9	211-213	Gray	92	332	$C_{14}H_{16}N_2S_2$
10	108-110	Black	74	411	$C_{12}H_{14}N_2SO_2$
11	77-78	Brawn-black	76	418	$C_{12}H_{14}N_2SO$



Scheme 1

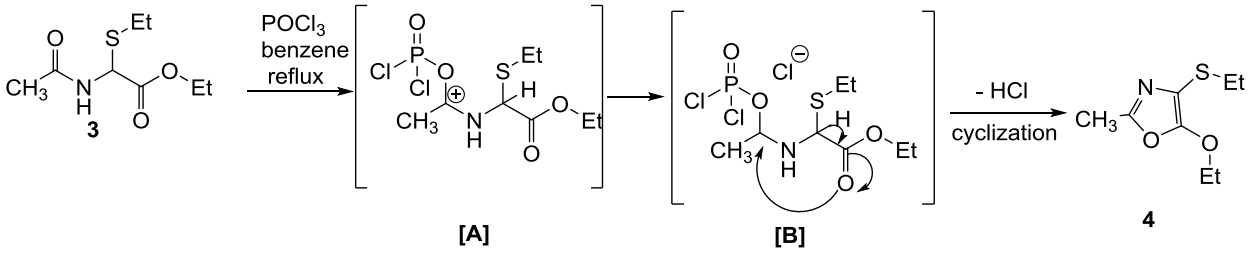
Formation of compounds **10** and **11** were depicted in scheme 3. Nucleophilic attack of amine group of *o*-aminophenol to carbonyl group of compound 5 to afford intermediate [B] via expulsion of HCl. Cyclization of intermediate [B] to intermediate [C] occurred with extrusion of water molecule to afford compound **10**. Upon reaction with phosphorus oxychloride, compound **10** cyclized to compound **11** via intermediates [D and E] with extrusion of HCl and phosphorodichloridic acid respectively (Scheme 3). IR spectrum of compound **11** showed absorption band at ύ = 3077(CH Aromatic), 2927 (CH aliphatic), 1673 (C=N), 1179, 1118 (C-O-C) cm^{-1}. Structures of compounds **10** and **11** were confirmed upon IR and ^1H NMR (Table 2).

Table (2) ^{1}H-NMR spectra

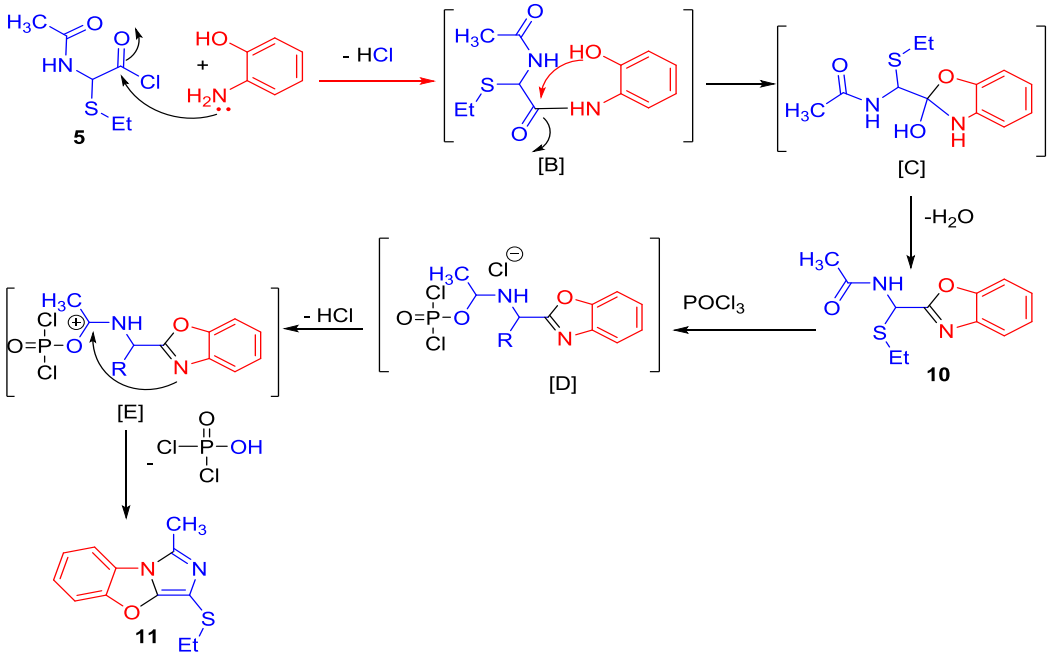
Compound	^{1}HNMR (δ , ppm)
2	1.10 δ , t , 3H (CH_3-CH_2-S-) , 2.503 δ, q , 2H for -CH_2-S-, 3.412 δ, s , 3H CH_3-C=O , 4.075 δ, s , 1H for S-CH-C=O, 8.578 δ, s , NH, 8.950 δ, s , 1H, COOH .
3	1.227 δ , t , 6H (2 group CH_3-CH_2) , 2.074 δ, q , 2H for -CH_2-S-, 2.894 δ, q , 2H for -CH_2-O-, 3.623 δ, s , 3H CH_3-C=O , 4.005 δ, s , 1H for S-CH-C=O, 8.323 δ, s , NH .
4	1.254 δ , t , 6H , 2 groups of CH_3 , 1.982 δ, q , 2H for CH_2-S-, 3.95 δ, q , 2H for CH_2-O- , 2.487 δ, s , 3H for CH_3-Ar. Heterocyclic ring .

5	1.584 δ , t , 3H , 1.909 δ, q , 2H for CH_2-S-, 3.780 δ, s , 3H CH_3-C=O , 4.073 δ, s , 1H for S-CH-C=O, 8.578 δ, s , NH, 8.944 δ, s, NH_2 .
6	1.22 δ, t , 3H , 2.074 δ, q , 2H CH_2-S-, 2.494 δ, s , 3H for CH_3-C=S , 3.623 δ, s , 1H for CH , 7.66 δ, s , 1H for NH , 8.232 δ , s , 2H for NH_2
7	1.223 δ, t , 3H CH_3- , 1.38 δ, q , 2H -CH_2-S , 2.5 δ, s , 3H CH_3-C=S , 4.35 δ, s , 1H -CH-substituted on thiazole ring , 6.37 δ, s , thiazole proton C_4. 7.40-8.10 δ, dd, 5H phenyl ring , 10.1 δ, s , NH thio-amide .
8	1.979 δ, t, 3H CH_3-CH_2- , 2.004 δ, q , 2H for CH_2 , 2.48 δ, d , CH_3 substituted in position 3 , 3.31 δ, s & 3.931 δ, s & 4.54 δ, q, 3H heterocyclic fuse ring , 6.799-7.457 δ, d:d , 5H phenyl ring .
9	1.065 δ, t , 3H CH_3- , 1.254 δ, q , 2H -CH_2-S , 3.35 δ, s , 3H CH_3-C=O, 3.953 δ, 1H substituted on benzoxazole ring, 6.803-7.949 δ, d.d , 4H phenyl ring , 9.751 δ, s , NH amide .
10	1.335 δ, t, 3H CH_3-CH_2- , 2.03 δ, q , 2H for CH_2 , 2.45 δ, d , CH_3 substituted in position 3 , 3.91 δ, s & 4.54 δ, q, 2H heterocyclic fuse ring , 7.30-8.09 δ, s , 4H phenyl ring .

s: singlet , d : doublet , dd : doublet of doublet , t : treblet , q: quartet , m : multiple



Scheme 2



Scheme 3

4. BIOLOGICAL ACTIVITY

The biological activity of compounds **8-10** as antibacterial agents were tested against *Staphylococcus aureus (Gram-positive), Staphylococcus epidermidis (Gram-positive),. Escherichia coli (Gram-negative), Proteus vagaries (Gram-negative).* The results depicted in table **3** via using diffusion method [24,25] in comparison with Ciprofloxacin.

The results revealed that compounds **8** and **10** have higher activity than Ciprofloxacin against Gram-positive and Gram-negative, while compound **9** gave higher activity with *Staphylococcus epidermidis & Proteus Vagaries* bacteria and lower activity with *Staphylococcus aureus* and *Escherichia coli* in comparison with Ciprofloxacin (Table 3).

Table (3): Antibacterial activity of compounds 8-10

Compounds	Compounds zone of inhibition in mm			
	Gram-positive		*Gram-negative*	
	Staphylococcus aureus	*Staphylococcus epidermidis*	*Escherichia coli*	*Proteus vagaries*
8	19	22	18	18
9	18	16	15	11
10	27	19	22	21
Ciprofloxacin	19	18	16	14

5.CONCLUSION

In conclusion, new oxazole, imidazole, thiazole heterocyclic compounds (**8-10**) were prepared from cysteine derivative via protective SH group, as the thiol group is easily oxidized so it was converted to ethyl thiol.

All the prepared compounds were identified and elucidated using IR and ^{1}H NMR. Antibacterial activity of synthesized compound were studied and revealed that these derivatives are good antimicrobial agents.

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