Synthesis and Antimicrobial Activity of Some compounds Containing Benzimidazole Nucleus

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Abstract: Reaction of ethyl 2-(quinolin-8-yloxy)acetate **1** with o-phenylenediamine afforded 8-[(1H –benzimidaz-ol-2-yl)methoxy]quinoline **2**.The benzimidazole derivative **2** was used as a key intermediate for the synthesis of other N-substituted benzimidazole derivative **3-14.**The structures of the new compounds confirmed by elemental analyses, spectroscopic measurements and chemical reactions. Some of the newly synthesized compounds showed interesting antibacterial and antifungal activity *in vitro*.
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1. Introduction

Benzimidazole are an important group of hetero-cyclic compounds have been a wide spectrum of biological activities[1-4].On the other hand, quinoline derivatives found useful application as chemotherapye-utic agents against malaria, parasites and microbes [5-8]. From this point of view it was very interesting to synthesis some new benzimidazole derivatives incorporated into quinoline.

2. Material and Methods

Experimental

All melting points were determined in open glass capillaries on a Gallenkamp apparatus and are uncorrected. IR spectra (cm^{-1}) were recorded on a Pye-Unicam spectrophotometer type 1200 using KBr discs.1H–NMR spectra were recorded on a Varian EM-390 (90 MHz) spectrometer using TMS as an internal standard and DMSO-d6 as a solvent. Chemical shifts were expressed in δ(ppm)values. Elemental analysis were determined using a Parkin–Elmer 240C Microanalyser. The microanalyses were performed at the Microanalytical Unit, Faculty of Science, Cairo University.The physicochemical properties and spectral data of the synthesized compounds were give in Tables 1and 2 .

8-(*1H*-Benzimidazol-2-ylmethoxy)quinoline 2.

To a solution of **1** (0.01mol) in abs. ethanol (30 ml),o-phenylenediamine (0.01 mol) was added.The reaction mixture was refluxed for 4 hrs, then allowed to cool.The solid that formed was filtered off, washed with water, dried and crystallized from mixture of DMF and xylene.

***N*-Phenyl-2-[(quinoline-8-yloxy)methyl]-1H-benzi-midazole -1-carbthioamide 3.**

A mixture of **2** (0.01mol) and phenylisothio-cyanate (0.01mol) in abs.ethanol (30 ml) was refluxed for 6 hrs. The solvent was evaporated under reduced pressure.The formed solid was filtered and crystallized from ethanol.

8-[(1-Acetyl-*1H*-benzimidazol-2-yl)methoxy]quinol-ine 4

Equimolar mixture of compound **2** and Ac_2O (0.01mol of both) was refluxed in dry pyridine (30 ml) for 6 hrs. The mixture was cooled and poured into ice/ HCl. The formed solid was filtered and crystallized from DMF.

8-[(N-(2-Chloroethyl)-*1H*-benzimidazol-2-yl) methoxy]quinoline 5.

A mixture of **2 (**0.01 mol) and 1,2-dichloroethane (0.01mol) in abs.ethanol (30 ml) was refluxed for 6 hrs. The excess of solvent was evaporated under reduced pressure and the obtained solid was crystallized from ethanol.

8-[(N-(2-Hydrazinoethyl)-*1H*-benzimidazol-2-yl) methoxy]quinoline 6.

A mixture of **5** (0.05) and hydrazine hydrate (0.01 mol,95 %) was refluxed for 6 hrs. After cooling the formed solid was filtered, washed with water and crystallized from methanol.

8-[(*N*-(2-(*p*-Nitrobenzylidene)hydrazinoethyl)-1H-benzimidazol-2-yl)methoxy]quinoline 7

A mixture of **6 (**0.01mol) and p-nitrobenzaldehyde (0.015 mol) in abs.ethanol (30 ml)was refluxed for 5 hrs.The excess of solvent was evaporated under reduced pressure and the obtained solid was crystall-ized from ethanol.

8-[(1-(Chloroacetyl)-*1H*-benzimidazol-2-yl)methoxy] quinoline 8.

To a solution of compound **2 (**0.05 mol) and anhydrous potassium carbonate (0.05 mole) in dry acetone (30 ml), chloroacetyl chloride (0.05 mol) was added dropwise. The mixture was stirred at room temperature for about 8 hrs. The mixture was then poured into water and extracted with ethyl acetate . The formed solid was filtered and crystallized from ethanol.

4-[(2-(Quinolin-8-yloxy)methyl)-1*H*-benzimidazol-1-yl)-1, 3-thiazol-2-amino 9

To a solution of **8** (0.01mol) in abs. ethanol (30 ml) was added thiourea(0.01 mol).The reaction mixture was refluxed for 6 hrs. Then after cool and treated with ammonium hydroxide solution till it became alkaline (pH 9) .The solid that formed was filtered off ,washed with water , dried and crystallized from ethanol .

Ethyl 2-[(quinolin-8-yloxy)methyl]-1*H*-benzimidazole-1-carboxylate 10

Mixture of compound **2** (0.01mol) and ethyl chloroformate (0.01mol) in abs. ethanol (30 ml) was refluxed for 6 hrs. The solvent was evaporated under reduced pressure.The formed solid was filtered and crystallized from mixture of ethanol and acetone.

2-[(Quinoline-8-yloxy)methyl]-1*H*-benzimidazole-1-carbohydrazide 11

Mixture of compound **10** (0.01mol) and hydrazine hydrate (0.012 mol) in abs. ethanol(30 ml)was refluxed for 6 hrs.The solvent was evaporated under reduced pressure.The formed solid was filtered and crystallized from dioxane.

***N*-Phenyl-4-[(2-(quinolin-8-yloxy)methyl)-1*H*-benzimidazol-1-yl)carbonyl]thiosemicarbazide 12.**

A mixture of **11** (0.01mol) and phenylisothiocyanate (0.01 mol) in abs. ethanol (30 ml) was refluxed for 6 hrs.The solvent was evaporated under reduced pressure. The formed solid was filtered and crystallized from ethanol.

N-(*p*-Chlorobenzylidene)-2-[(quinolin-8-yloxy)methyl]-1H-benzimidazol -1-carbohydrazide 13

A mixture of **11 (**0.015 mol) and p-chlorobenzaldehyde (0.015 mol) in abs. ethanol (30 ml) was refluxed for 5 hrs. The reaction mixture was cooled to room temperature .The precipitated solid was filtered and crystallized from ethanol.

5-[2-(quinolin-8-yloxy)methyl)-1H-benzimidazol-1-yl]-1,3,4-oxadiazole-2(3H)-thione 14

To a solution of **11** (0.01mol) in ethanolic KOH (0.01mol in 30 ml ethanol),was added carbon disulphid (0.02 mol) .The reaction mixture was refluxed for 8 hrs.The solvent was evaporated under reduced pressure. The residue was diluted with water and acidified with HCl. The formed solid was filtered and crystallized from ethanol.

Biological activity

The newly synthesized compounds **2,4,5,8** and **11** were tested *in vitro* for their anti-bacterial activity and their minimum inhibition (MIC) against Gram Positive bacteria (*Staphylococcus aureus* and *Bacillus subtilis*) and Gram Negative bacteria(*pseudomonas aeruginasa* and *Escherichia coli*) using diffusion agar technique ,at the 2.5 mg/ml,5 mg/ml and 1 mg/ml levels against the microorganisms used. The antifungal activity of same compounds were tested against *Aspergillus fumigatus, Penicillium italicum, Syncephalastrum racemosum ,and Candida albicans* using diffusion agar at 2.5 mg/ml ,5 mg/ml and 1 mg/ml levels again microorganisms used. Chloramphenicol was used as a standard antibacterial agent and Terbinafin was used as a standard antifungal agent (Table 3).

3. Results and Discussion

Condensation of ethyl 2-(quinolin-8-yloxy)acetate **1** with *o*-phenylenediamine in boiling abs.ethanol afforded the corresponding 8-[(*1H*-benzimidazol- 2-yl) methoxy]quinoline **2.** The structure of compound **2** was established on the basis of its elemental analysis and spectral data. Its ^{1}H-NMR spectrum revealed a broad signal at δ 10.8 ppm due to NH group. In addition, the mass spectrum revealed the peak at *m/z* 275 corresponding to its molecular ion.

The benzimidazole derivative **2** was used as a key intermediate for the synthesis of other *N*-substituted benzimidazole derivatives. Thus, reaction benzimidazole derivative **2** with phenylisothiocyanate and acetic anhydride[9] afforded carbothioamide derivative **3** and *N*-acetyl benzimidazole derivative **4**.Compound **4** showed characteristic peak at 1688 cm^{-1} (C=O)(in its IR spectrum), and its ^{1}H-NMR spectrum revealed signal at δ 3.34 ppm characteristic of the $COCH_3$ proton. In addition, the mass spectrum revealed the peak at *m/z* 315 (M^+- 2 ,3.4%) .

Interaction of compound **2** with 1,2-dichloroethane afforded 8-[(N-(2-chloroethyl)-*1H*-benzimidazol-2-yl)methoxy]quinoline **5**. Reaction of **5** with hydrazine hydrate affoded 8-[(*N*-(2-hydrazinoethyl)-*1H*-benzimidazo-2-yl)methoxy]quinoline **6**.The chemical structure of **6** was established on the basis of its elemental analysis and spectral data. Its ^{1}H-NMR spectrum revealed a broad signal at δ 5.55 ppm and 8.89 ppm corresponding to NH_2 and NH protons. In IR spectrum of compound **6** showed absorption bands at 3325, 3228 cm^{-1} due to NH,NH_2 (Table 2).Next, compound **6** reacted with p-nitrobenzaldehyde[10]afforded the corresponding N-(p-nitrobenzylidene)-1H-benzimidazole derivatives **7.**The IR spectrum of the compound **7** showed the presence of NH absorption band at 3333 cm^{-1} and C=N absorption band at 1531 cm^{-1} .The ^{1}H-NMR spectrum of **7** were exhibited signal at δ 8.90 ppm and δ 8.38 ppm due to (NH) and N=CH protons. Treatment of benzimidazole derivative 2 with chloroacetyl chloride in acetone and anhydrous potassium carbonate[11] afforded N-chloroacetyl-1H-benzimidazole derivative **8**.Reaction **8** with thiourea [12] in absolute ethanol afforded the corresponding 1,3-thiazol-2-amine derivative **9** (Scheme 1). The formation of thiazole **9** was established on the basis of analytical and spectral data. The IR spectrum of **9** showed absorption bands at 3376,3272,1609 and 1084 cm^{-1}due to NH_2,C=N and C-S, respectively.

Treatment of benzimidazole derivative **2** with ethyl chloroformate afforded ethyl benzimidazole-1-

carboxylate **10.** ^{1}H-NMR spectrum of **10** revealed a triplet and quartet signals at δ1.26 ppm and δ 4.13 ppm due to methyl and methylene of the ester group . Reaction of **10** with hydrazine hydrate[13] in refluxing ethanol afforded benzimidazole-1-carbohydrazide **11**. ^{1}H- NMR spectrum of **11** revealed broad signal at δ 6.16 ppm and δ 8.89 ppm corresponding to the NH and NH_2 groups. Next, compound **11** reacted with phenyl-isothiocyanate[14], *p*-chlorobenzaldehyde and carbon disulphide[15]afforded thiosemicarbazide derivative **12** , N-(*p*-chlorobenzylidene**)**-1H-benzimidazol-1-carbohydrazide **13** and 1,3,4-oxadiazole-2(3H)- thione **14**.The chemical structure of **12,13** and **14** established on the basis of its elemental analysis and spectral data (Table 1 and 2).

Table 1: Physical data of the prepared compound 2-14

Compd .No.	Mol.Formula	Element Analyses Calcd./ Found					M.p./°C	Yield %
		C	H	N	S	Cl		
2	$C_{17}H_{13}N_3O$	74,17	4,76	15,26			164-168 .	85
	275,305	74,19	4,79	15,30				
3	$C_{24}H_{18}N_4OS$	70,22	4,42	13,65	7,81		214-216	60
	410,49	70,25	4,44	13,68	7,83			
4	$C_{19}H_{15}N_3O_2$	71,91	4,76	13,24			230-234	70
	317,34	71,94	4,79	13,29				
5	$C_{19}H_{16}Cl\ N_3O$	67,56	4,77	12,44		10,50	148-150	75
	337,8	67,60	4,73	12,41		10,46		
6	$C_{19}H_{19}N_5O$	68,45	5,74	21,01			80-82	50
	333,38	68,47	5,76	21,04				
7	$C_{26}H_{22}N_6O_3$	66,94	4,75	18,02			130-134	75
	466,49	66,99	4,79	18,05				
8	$C_{19}H_{14}Cl\ N_3O_2$	64,87	4,01	11,94		10,08	200-204	85
	351,8	64,83	4,04	11,90		10,03		
9	$C_{20}H_{15}N_5OS$	64,33	4,05	18,75	8,59		120-122	60
	373,43	64,35	4,07	18,77	8,61			
10	$C_{20}H_{17}N_3O_3$	69,15	4,93	12,10			200-204	80
	347,36	69,17	4,96	12,15				
11	$C_{18}H_{15}N_5O_2$	64,86	4,54	21,01			98-100	85
	333,34	64,88	4,56	21,05				
12	$C_{25}H_{20}N_6O_2\ S$	64,09	4,3	17,94	6,84		246-250	70
	468,53	64,11	4,32	17,96	6,88			
13	$C_{25}H_{18}\ Cl\ N_5O_2$	65,86	3,98	15,36		7,78	210-212	80
	455,89	65,89	4	15,39		7,81		
14	$C_{19}H_{13}\ N_5O_2\ S$	60,79	3,49	18,66	8,54		190-194	70
	375,4	60,8	3,51	18,67	8,52			

Table 2: Spectral Data of The Newly Prepared Compound 2-14

Compd .No.	Spectral Data
2	IR;*ν*(cm^{-1}):3279(NH),1605(C=N),3055,2922,2851(CH). ^{1}H-NMR(DMSO-d_6),δ:7.11(1H,d,Quinoline C_5-H), 7.44-7.54(3H,m,Quinoline $C_{3,6,7}$-H),8.29(1H,d, Quinoline C_4-H),8.86 (1H,d, Quinoline C_2-H),10.8(1H,br s,NH),4.92(2H,s,CH_2),6.38-6.56(4H, m,Benzimidazole). M.S:m/z(%):275(5.89),246(2.35),145(4.22),158(100),131(4.88),128(15.7).
3	IR;*ν*(cm^{-1}):3204(NH),1240(C=S),303,22953,2852(CH),1595(C=N). ^{1}H-NMR(DMSO-d_6),δ7.10(1H,d,Quinoline C_5-H), 7.43-7.55(8H,m,Quinoline$C_{3,6,7}$-H and Ar-H), 8.30 (1H, d,Quinoline C_4-H),8.84(1H,d,QuinolineC_2-H),12.54(1H,brs,NH),4.90(2H,s,CH_2),6.72-6.75(4H,m,Benzimidazole).
4	IR;*ν*(cm^{-1}):1688(C=O),3048,2923,2853(CH),1586(C=N). ^{1}H-NMR(DMSO-d_6),δ:7.21(1H,d,Quinoline C_5-H),7.45-7.69(3H,m,Quinoline $C_{3,6,7}$-H),8.32 (1H,d, Quinoline C_4-H), 8.83(1H,d,QuinolineC_2-H),4.81(2H,s,CH_2),3.34(3H,s,CH_3),6.38-6.82(4H, 4H,m, Benzimidazole). M.S:m/z(%):315(3.40),301.25(2.2),275(9.41),158(24.82),145(100)128(17).
5	IR;*ν*(cm^{-1}):3057,2955,2849(CH),1614(C=N). ^{1}H-NMR(DMSO-d_6),δ:7.05(1H,d,Quinoline C_5-H), 7.44-7.60(3H,m,Quinoline $C_{3,6,7}$-H),8.26(1H, d, Quinoline C_4-H), 8.33 (1H,d,QuinolineC_2-H), 4.91(2H,s,CH_2),6.35-6.54 (4H,m,Benzimidazole), 2.49-2.52 (4 H , m,CH_2-CH_2).

Table 2:Continued

Compd .No.	Spectral Data
6	IR;ν(cm^{-1}):1614(C=N),3057,2955,2849(CH),3325,3228(NH_2,NH) ^{1}H-NMR(DMSO-d_6),δ:7.13(1H,d,Quinoline C_5-H),7.28-7.57(3H,m,Quinoline C3,6,7-H),8.34 (1H,d, QuinolineC_4-H),8.38(1H,d,QuinolineC_2-H),4.76(2H,s,CH_2),6.38-6.51(4H,m,Benzimidazole),2.49-2.51 (4H,m, CH_2-CH_2),8.89(1H,br s,NH),5.55(2H,br s,NH_2).
7	IR;ν(cm^{-1}):1531(C=N),3064,2919,2850(CH),3333(NH). ^{1}H-NMR(DMSO-d_6),δ7.14(1H,d,Quinoline C_5-H), 7.50-7.75(7H,m,Quinoline$C_{3,6,7}$-H and Ar-H), 8.19 (1H ,d,QuinolineC_4-H),8.34(1H,d,Quinoline C_2-H),4.59(2H,s,CH_2),6.38-6.49(4H,m, Benzimidazole), 2.49-2.51(4H,m,CH_2-CH_2),8.90(1H,br s, NH),8.83(1H,s,N=CH).
8	IR;ν(cm^{-1}):1674(C=O),3078,2998,2955(CH),1608(C=N). ^{1}H-NMR(DMSO-d6),δ:7.20(1H,d,Quinoline C_5-H), 7.43-7.28(3H,m,Quinoline $C_{3,6,7}$-H), 8.27 (1H, d,QuinolineC_4-H),8.85(1H,d,Quinoline C_2-H),4.55(2H,s,CH_2),6.42-6.53(4H,m,Benzimidazole),4.34 (2H,s , CH_2).
9	IR;ν (cm-1):3376,3272(NH_2),3063,2955(CH),1609(C=N),1084(C-S) ^{1}H-NMR(DMSO-d6),δ:7.11(1H,d,Quinoline C_5-H), 7.33-7.67(3H,m,Quinoline$C_{3,6,7}$-H),8.29(1H,d , Quinoline C_4-H),8.86(1H,d,Quinoline-C_2-H),5.12(2H,s,CH_2),6.64-6.94(6H,m,Benzimidazoleand NH_2) , 3.88(1H,s,C_5 Thiazole).
10	IR;ν(cm^{-1}):1728(C=O),3054,2922,2858(CH),1605(C=N). ^{1}H-NMR(DMSO-d_6),δ:7.09(1H,d,Quinoline C_5-H), 7.51-7.84(7H,m,Quinoline $C_{3,6,7}$-H and Benzimida-zole),8.85(1H,d,QuinolineC_4-H),8.99(1H,d,QuinolineC_2-H) ,5.12(2H,s,CH_2), 1.26(3H,t,CH_3-H_2),4.13 (2H,q,CH_2CH_3). M.S:m/z(%):344(10.01),252(0.53),222(12.8),206(100),192(55),184(5),173(8.7)185(80.7),131(6.4),117 (0.9).
11	IR;ν(cm^{-1}):1633(C=O),3049,2922,2853(CH),1600(C=N),3247,3173(NH_2,NH) ^{1}H-NMR(DMSO-d_6),δ:7.11(1H,d,Quinoline C_5-H), 7.54-7.64 (7H,m,Quinoline$C_{3,6,7}$-H and Benzimdaz-ole),8.42(1H,d,QuinolineC_4-H),8.50(1H,d,QuinolineC_2-H),4.76(2H,s,CH_2),6.16(2H,brs,NH_2),8.89(1H,brs, NH).
12	IR;ν(cm-1):3230(NH),1253(C=S),3029,2969,2853(CH),1603(C=N). ^{1}H-NMR(DMSO-d_6),δ:7.10(5 H,m,Quinoline C_5-H and Benzimidazol), 7.43-7.55(8H,m,Quinoline $C_{3,6,7}$-H and Ar-H), 8.30 (1H,d,QuinolineC_4-H),8.84(1H,d,QuinolineC_2-H),4.90(2H,s,CH_2),9.88 (2H,br s, NH–CS-NH),8.01(1H,br s,CONH).
13	IR;ν(cm^{-1}):1621(C=O),3046,2994,2805(CH),1588(C=N),3220(NH). ^{1}H-NMR(DMSO-d_6),δ:7.02-7.21(5H,m,Quinoline C_5-H and Benzimidazole), 7.53-7.597(7H,m,Quinoline $C_{3,6,7}$-H and Ar-H),8.24(1H,d,QuinolineC_4-H),8.38(1H,d,QuinolineC_2-H),4.76(2H,s ,CH_2),8.67(1H,s,N= CH),8.89(1H,br s,NH).
14	IR;ν(cm^{-1}):1251(C=S),3064,2954,2851(CH),1521(C=N),3176(NH). ^{1}H-NMR(DMSO-d_6),δ:7.03-7.23(5H,m,Quinoline C_5-H Benzimidazole),7.49-7.71(3H,m,Quinoline $C_{3,6,7}$-H),8.65(1H,d,QuinolineC_4-H),8.88(1H,d,QuinolineC_2-H),4.96 (2H,s, CH_2), 10.58 (1H,br s,NH).

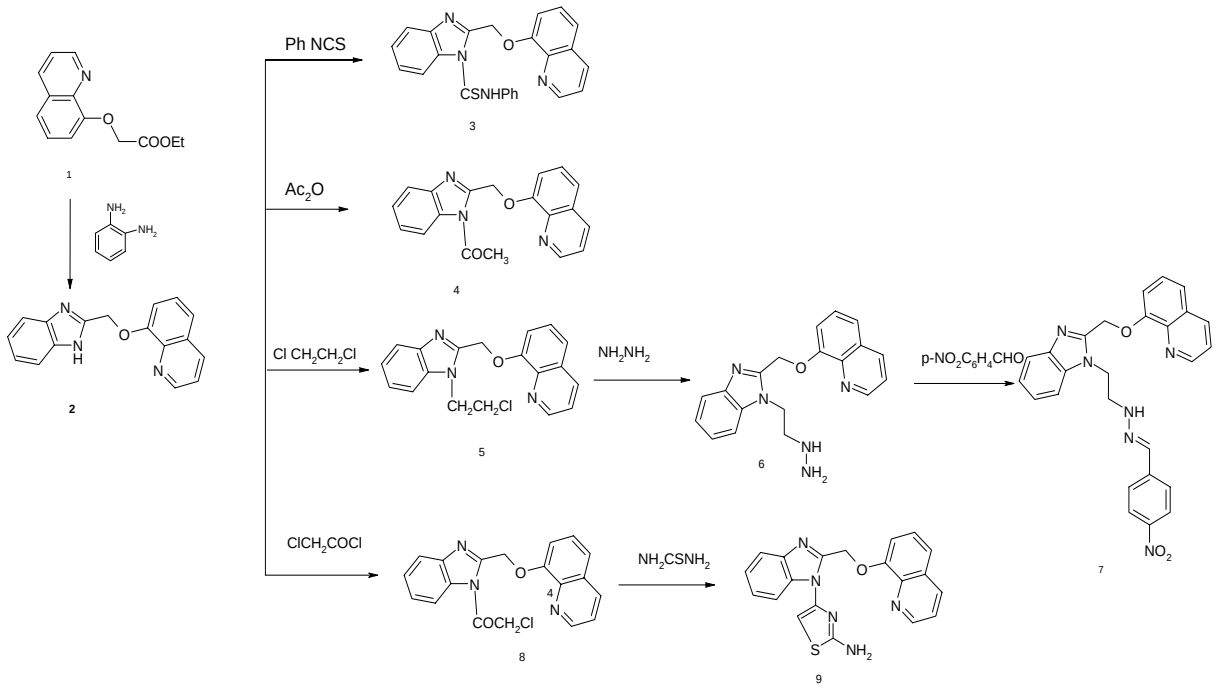
Table 3: Antimicrobial activity of tested compounds

Compd .No.	Staphylococcus aureus			Bacillus subtilis			pseudomonas aeruginosa			Escherichia coil			Aspergillus fumigatus			Penicillium italicum			Syncephatastrum racemosum			Candida albicans		
	2,5	5	1	2,5		1	2,5	5	1	2,5	5	1	2,5	5	1	2,5	5	1	2,5	5	1	2,5	5	1
	mg/ml			mg/ml			mg/ml			mg/ml			mg/ml			mg/ml			mg/ml			mg/ml		
2	0	+	0	+	+	+	0	0	0	+	+	+	0	0	0	+	++	+	++	+	+	++	++	++
4	0	+	0	+	+	+	0	0	0	+	+	0	0	0	0	0	+	0	+	++	0	0	0	0
5	0	+	0	0	0	0	0	0	0	+	+	0	+	++	+	0	+	0	+	++	0	0	0	0
8	+	+	+	+	+	+	0	0	0	+	+	+	0	0	0	0	0	0	++	++	++	0	0	0
11	+	+	0	0	+	0	0	0	0	+	+	0	0	0	0	0	0	0	+	+	+	+	0	0
St	++	++	++	+++	+++	++	+++	+++	++	++	++	++	+++	+++	++	+++	+++	++	+++	+++	+++	++	++	++

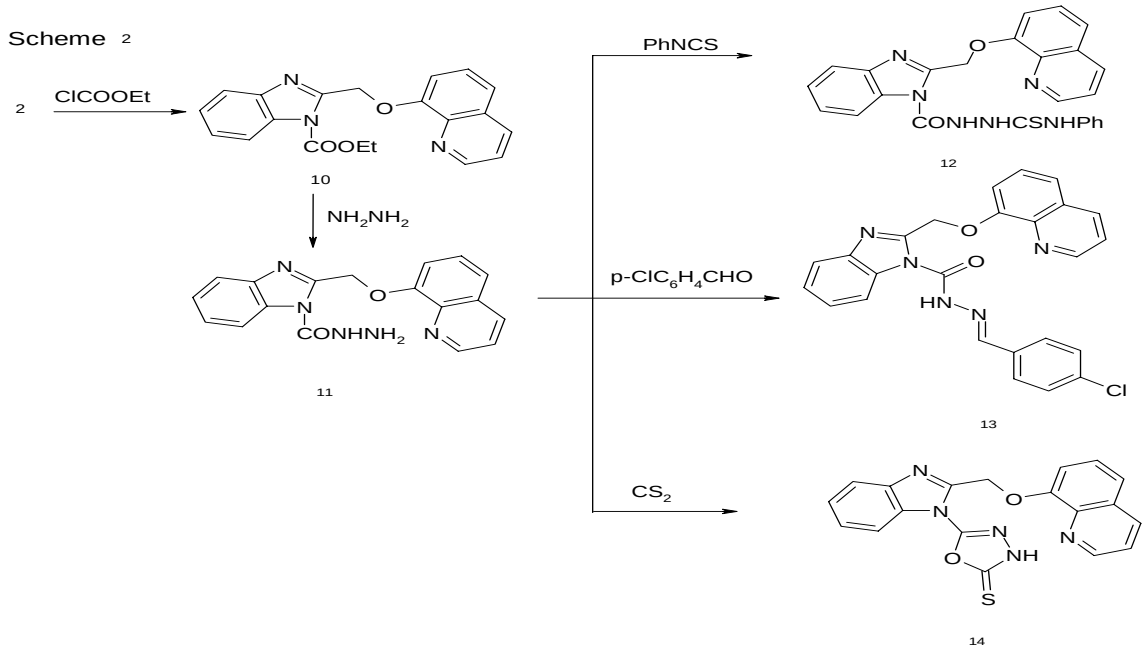
St= Reference standard; Chloramphenicol was used as a standard antibacterial agent and Terbinafin was used as a standard antifungal agent .

Diameter of the zone of inhibition :+ = 0.1-0.5cm; ++ =0.6-1.0; +++ = 1.1-1.5; 0 = not detected

Scheme 1



Scheme 2



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