Antimicrobial Activity and Characterization of Some Oxazole, Thiazol and Quinoline

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Abstract

New Heterocyclic compounds derivatives comprising 1,3-oxazole, chalcone ,thiazole, pyrimidine, quinolone moieties are reported. New derivatives of Quinazolin-4 (3H)-one ring comprising Schiff's bases,(1,3,4-Thiadiazole),(1,3,4-Oxadiazole) and (1,2,4-Triazole), Thiaurease moieties are reported. Compounds (1), (2) and (5) were synthesized by reaction of benzoyl chloride with urea , thiourea and anthranilic acid respectively , then compounds (1)and (2) were converted into(3a-c) and (4a-c) derivatives. While compound (5) reaction with urea to convert to compound (6) which was converted to (7a-c) . chalcone derivatives (9a,b) were readily obtained by reaction of compound (8) with different aldehydes, Compounds (9a , b) were converted into (10a,b) and (11a,b) The structure of these compounds has been established on the basis of their spectral data FTIR and ^{1}HNMR. These compounds were tested for invitro antibacterial activity against Escherichia coli, Sepidermidis, S.aureusand Klebseillastandard methods. These synthesized compounds have been shown moderate to good antibacterial activity.

Keywords:1,3 oxazole, chalcone, thiazole, pyrimidine, quinolone, antimicrobial activity.

Introduction

Heterocyclic compounds had been receiving considerable attention due to their pharmacological and pesticidalimportance[1] . The heterocyclic nitrogen compounds like quinazolinone derivatives has a vital role in synthetic drugs and biological processes. A Quinazolin-4-one derivative possessing broad spectrum of biological and pharmacological activities such as antifungal [2], antimicrobial [3], bronchodilator [4],antihistaminic [5], anti-inflammatory [6],1,3-Oxazole and thiazole derivatives possess a broad spectrum ofpharmacological activities such as antibacterial [(7-9)] antiviral, anti-inflammatory[(10,11)], antitumor [12]. The biological significance of the pyrimidine derivatives has led to the synthesis of substituted pyrimidineandtheir derivatives [13], pyrimidinederivatives have been important role in medical applications. One possible reason for their activity is the presence of a pyrimidine base in cytosine ,thymine and uracil ,which are essential building of nucleic acids ,RNA and DNA. Pyrimidine derivatives possess several interesting biologicalactivities such as antimicrobial [(14-15)], antitumor [16] ,and antifungal [17] ,antimalarial, [18] , anticancer [19] , antiallergic [20] , antitubercular activities [21] and anti-inflammatory activities [22] . Many Pyrimidinederivatives are used for thyroid drugs and leukemia [13] .

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Materials and Method

Apparatus

Melting point were determined in open capillary tubes and were uncorrected and the purity of the compounds were checked by TLC .The IR Spectra were recorded on a Perkin-Elmer 1600 series FTIR spectrometer, using KBr discs. ^{1}H NMR Spectra of prepared derivatives were recorded in DMSO with TMS as internal standard on aVarian-Mercury 300 MH_Z Spectrometer the reaction were followed .

Procedures

Synthesis of N-(aminocarbonyl)-benzamide (1)

A mixture of benzoyl chloride(1. 1 mole), and urea (1. 1 mole) in dry benzene(30ml) were

mixed in round bottom flask and refluxed for 15 hrs ,resulting mixture was poured in to crash ice and the solid filtered and recrystillazed fromappropriatesolvent table(1).

Synthesis ofN-(aminocarbonothioyl)-benzamide (2)

A mixture of thiourea (1mole) and(1mole) benzoyl chloride were dissolved in benzene (30 ml) then refluxed for (16hrs.), the mixture was cold and filtered to obtained the solid, and purified by recrystallization table(1).

Synthesis of N-substituted acetamide (General method)

In adry and clean conical flask (0.01mol) of substituted aromatic amine was dissolved in 15 ml dry benzene with continuous shaking and (0.015mol) of chloro acetyl chloride was added drop wise by dropping funnel,the mixture was heated in water bath for(1hr) after the reaction complete ,the product which separated were filtered and washed with sodium bicarbonate (5%) ,water ,dried and recrystallized from alcohol.

Procedure for Synthesis of derivatives(3a-c)

A mixture of compound (1) (0.01 mole) and (0.01 mole) of 2-chloro-N-(substituted phenyl)acetamide in ethanol were refluxed for 24 hrs and allowed to stand undisturbed over night,the product separated on cooling was filtered and purified byrecrystallization.

General Procedure for Synthesis of derivatives (4a-c)

A mixture of compound (2) (0.01 mole) and (0.01 mole) of 2-chloro-N-(substituted phenyl)acetamide in ethanol were refluxed for 24 hrs and allowed to stand undisturbed over night,the product separated on cooling was filtered and recrystallized from appropriatesolvent table(1).

Synthesis of (2-phenyl)-1,3-benzoxazin-4(H) ones(5)

A mixture of benzoyl chloride (1.4 gm,0.01 mole) and anthranilicacid(1.38 gm ,0.01 mole) in triethyl amine(30ml) were stirred at 0-5C for 1hr ,then further stirred for additional 1hr at room temperature . apasty mass obtained which was washed thoroughly with sodium carbonate(10%) to remove unreacted acid .the solid separated by cooling and was dried and purified by recrystallization.

Synthesis of (2-phenyl)-3 – carboxamidequinazoline-4- (3H)ones(6)

Compound (5) (2.23 ,0.02 mole) and urea (0.6gm,0.02 mole),) in pyridine 20ml,the reaction mixture was refluxed for (12hrs) in oil bath at(180-200C) ,then the reaction mixture was poured in to ice cold water containing conc .HCl.the separated solid was filtered ,washed and recrystallized fromappropriate solvent table(1).

General Procedure for synthesis of derivatives (7a-c)

2-chloro-N-(substituted phenyl)acetamide(0.01 mole)and(2-phenyl)-3–carboxamide quinazoline-4-(3H)ones[6] (0.01 mole) of in ethanol were refluxed for 24 hrs and kept the product over night,the solid separated on cooling was filtered and purified by recrystallization.

Synthesis of N-(4-acetylphenyl)benzamide(8)

To a mixture of 4-amino acetophenone (0.01 mole, 1.39g) in 25 ml of benzene and benzoyl chloride (0.01 mole,1.4g) was refluxed for 3 hrs according to literature procedure[12]. After that, mixture was kept overnight. The product thus obtained was recrystallized fromappropriate solvent table(1).

Synthesis of N-(4-(3-4-substituted aryl) acryloyl) phenyl)benzamide(9a9b)

Amixture of(substituted benzaldehyde) (0.01 mole) and compound (8) (0.01 mole) and (20%) 10ml NaOH in ethanol (30mL) was stirring for 24 hrs at room temperature .After that, mixture was poured onto crushed ice to get precipitate. The product thus obtained was purified byrecrystallization table(1).

Synthesis of N-(4-(2 mercapto-6-(substituted aryl)-1,6-dihydropyrimidin-4-yl)phenyl) benzamide(10a,b)

A mixture of required chalcone (9a,b) (0.01 mole) and thiourea (0.01 mole) in1,4 dioxan (10ml)and acatalytic amount of glacial acetic acid are taken in around bottom flask and heated under reflux for about 24 hrs . the reaction mixture was poured into cold water with stirring, the product was filtered and purified by recrystallization.

Synthesis of N-(4-(2-hydroxyl-6-(substituted aryl)-1,6-dihydropyrimidin-4-yl)phenyl)benzamid

(11a,b)

A mixture of N-(4-(3-4-substituted aryl)acryloyl) phenyl)benzamide(9a,b) (0.01 mole) and urea(0.01 mole) in the presence of KOH(1gm) in 20ml ethanol was heated under reflux for12 hrs ,then cooled and poured in ice cold water, the solid mass was obtained by filteration, recrystallization table(1).

Results and Discusion

All compounds were prepared according to the following scheme :

The structures of prepared compounds were identified by FTIR (table 2) and ^{1}H NMR spectra (table 3) . All results spectral data were in correspondence to expected values. The purity of prepared compounds were checked by using TLC chromatography . The physical properties of compounds are listed in (table 1) . Compound (1) was synthesized from benzoyl chloride and urea with dry benzene .The IR spectra of this compound , show the appearance of bands at 3360 , 3342 , 3225,3068 and 1674 cm^{-1} which could be due to v (NH_2 , NH) , v C-H aromatic and v C=O amide , respectively . The ^{1}H NMR spectram measured in DMSO-d_6 at 25 ^{o}C revealed a multiplet from 8.41 to 7.64 ppm for aromatic protons , a singlet at 11.58 ppm(N-H , 2H) and 3.7 ppm (NH_2). Also the reaction between benzoyl chloride and thiourea with dry benzene lead to the formation the compound (2).The spectroscopic observation of compound (2) is given show the appearance of (NH_2 , NH) bands at 3381 , 3320, 3257 cm^{-1} , (C-H aromatic) band at 3053 cm^{-1} and (C=C aromatic) bands at 1612-1523 cm^{-1} . The ^{1}H NMR spectra showed a singlet at 12.33 ppm (N-H , H) and 3.89 ppm (NH_2) , a multiplet from 8.2-7.7 ppm for aromatic protons.Compound (3a-c)were synthesized from compound (1) and 2-chloro-N-(substituted phenyl) acetamide with absolute ethanol as solvent. The FTIR spectra of derivative (3a) , observed the appearance of bands at 3232, 3076 , 1664 , 1610- 1515 and 1637 cm^{-1} which could be assigned to v N-H ,v C-H aromatic ,v C=O , C=C aromatic and v C=N ,respectively .^{1}H NMR spectra showed a singlet at 11.6 ppm(N-H , 2H) , a singlet at 7.1 ppm (C-H oxazole , H) , a multiplet from 8.4-7.84 ppm (ph-H , 9H) .Compounds (4a-c) were synthesized by the reaction of compound (2) with 2-chloro-N- (substituted phenyl) acetamide in ethanol to give 5- membered heterocyclic system (substituted 1,3 thiazol) .In compound (4a) , the transformation is confirmed by observed the appearance 3257 , 3088 , 1672 cm^{-1} which could be due to N-H , C-H aromatic and C=O as well as the appearance of C=N stretching band at 1626 cm^{-1}. The ^{1}H NMR spectra , the signal of (N-H , 2H) and (C-H thaizole ring , H) protons were appeared at 11.7 and 7.1 ppm , as well as the signal of (ph-H , 8H) protons were appeared between 8.6-7.8 ppm .The reaction of benzoyl chloride with anthranlic acid in basic media lead to the formation of compound

Antimicrobial activity

The activity of antibacterial and antifungal were studied by using cup-plate agardiffusion method () . The inhibition zones were measured in mm .amoxilline and mefenamicacide (500mg\ml) were used as astandard drugs for antimicrobial activity .the compounds were screened for antibacterial activity against klebsilliha,Escherichiacoli,Psreudomonasaeruginosa and Staphylococcus aureus in Mullar Hinton agar .and the results are shown in the tables 4a,4b,4c and 4d.The results of antibacterial screening , indicate that compounds(4b,7a,11b) show activity against S.aureus and Sepidermidis than E. coli and Klebseillaand compared these results with standard drugs(mefenamicacid and amoxicillin). While only the derivative 10b show good activity against Klebseillamore the activity for standard drugs .The results obtained by antifungal activity , it is found that the compounds (3a,4a,7a and 7b) show good activity against condid fungi and these results compared with standard drugs(mefenamic acid and Amoxicillin).

Table (1): FTIR spectra of the synthesized compounds

No.	*v* (N-H)	*v* (C-H) aromatic	*v* (C=O)	*v* (C=C)	*v* (C=N)	Others
1	3225	3068	1674	1618-1540	-	3360,3342(NH_2)
2	3257	3053	1665	1612-1523	-	3381-3320(NH_2)
3a	3232	3076	1664	1610-1515	1637	-
3b	3283	3092	1647	1600-1520	1626	-
3c	3225	3081	1651	1609-1519	1633	-
4a	3257	3088	1672	1610-1500	1626	-
4b	3274	3064	1658	1600-1518	1622	-
4c	3282	3094	1678	1611-1521	1630	-
5	-	-	1759	1600-1502	1608	1309(C-N) 1109(COC)
6	3100	3088	1632	1604-1527	1633	-
7a	3190	3058	1673	1584-1529	1641	-
7b	3213	3038	1682	1597-1517	1623	-
7c	3230	3064	1662	1600-1532	1635	-
8	3159	-	1602	1597-1539	-	-
9a	-	-	-	1597	-	1674(CH=CH) 1514,1336(NO_2)
9b	-	-	-	1598	-	1649(CH=CH)
10a	3270	-	-	1572-1536	1610	1518,1328(NO_2)
10b	3257	-	-	1575	1612	-
11a	3265	-	-	1576	1609	1504,1342(NO_2)
11b	3259	-	-	1557	1606	-

Table (2): Proton NMR signals of the synthesized compounds in DMSO-d_6

No.	δ ppm
1	11.58 (s,2H,NH), 3.7 (NH2), 7.64-8.41 (m, 5H, phH)
2	12. 33(s, H,NH), 3.89 (s,NH2), 7.7-8.2(m, 5H, phH)
3a	11.6(s ,2H,NH), 7.84-8.4 (m, 10H, oxa- Hand ph- H)
3b	12.1(s, 2H,NH), 7.92-8.31 (m, 10H,oxa-Handph-H), 2.1 (s,3H,CH_3)
3c	11.4(s, 2H,NH), 7.7-8.2(m, 9H,oxa-H, ph-H and pyrmi-H)
4a	11.6(s ,2H,NH), 7.6-8.6(m, 10H ,Thaiz-Handph-H)
4b	12.1 (s,2H,NH), 7.5-8.4 (m, 10H, Thaiz-Hand ph-H) 2.23 (s,3H,CH3)
4c	11. 7(s,2H,NH), 7.8 -8.6 (m, 9H, Thaiz H, ph-H and pyrmi-H)
5	7.55 -8.61 (m, 9H, Aromatic protons)
6	6. 1 (s,2H,NH2), 7.4-8.56 (m, 9H, Aromatic protons)
7a	9.33 (s, H,NH), 7.7-8.21 (m, 14H oxa-Handph-H)
7b	7.6 (s, H,NH), 7.5-8.1 (m, 14H, oxa-Handph-H), 2.1(s,3H,CH_3)
7c	9.4 (s, H,NH), 7.7-8.50 (m, 13H, oxa-H, ph-H and pyrmi-H)
8	11.98 (NH),2.3(s,3H ,CH3) 7.7-8.50 (m, 9H, Aromatic protons)
9a	10.8 (NH),7.8-8.6(m,13H, Aromatic protons) 6.3-6.7(d,2H,CH=CH)
9b	11.04 (NH), 7.4-8.8(m,13H, Aromatic protons) 6.5-6.8(d,2H,CH=CH)
10a	11.06 (NH),5.3(s,1H,OH) ,7.6-8.4(m,14H,pyrmi-H and ph-H)
10b	11.08 (NH), 5.1(s,1H,OH) ,7.7-8.9(m,14H, pyrmi-H and ph-H)
11a	11.1 (s,H,NH), 12.4(s,1H,SH) ,7.4-8.8(m,14H,) pyrmi-H and ph-H)
11b	11.98 (s,H,NH), 12.6(s,1H,SH) ,7.55-8.90(m,14H, pyrmi-Hand ph-H)

Table 3. Antimicrobial activity of oxazole derivatives represented by% inhabitation against different bacterial and fungl species

Compound	Inhi.bition Zone against(in mm)				Candida albicans
	Gram negative		Gram positive		
	E.Coil	klebsiella	S.aureus	S.epidermidis	
3a	-	-	17	17	15
3b	11	-	12	12	-
3c	8	-	-	11	12
Mefanamic	12	14	17	8	20
Amoixillin	36	9	15	28	12

Table 4. antimicrobaial activity of thiazol derivatives represented by% inhabitation against different bacterial and fungl species

Compound	Inhi.bition Zone against(in mm)				candida albicans
	Gram negative		Gram positive		
	E.Coil	klebsiella	S.aureus	S.epidermidis	
4a	-	-	13	11	17
4b	11	-	22	12	-
4c	-	-	14	11	12
Mefanamic	12	14	17	8	20
Amoixillin	36	9	15	28	12

Table 5. antimicrobaial activity of quinazoline 4-one derivatives represented by% inhabitation against different bacterial and fungl species

Compound	Inhi.bition Zone against(in mm)				Candida albicans
	Gram negative		Gram positive		
	E.Coil	klebsiella	S.aureus	S.epidermidis	
7a	20	11	21	13	15
7b	14	11	18	-	14
7c	-	12	14	11	-
Mefanamic	12	14	17	8	20
Amoixillin	36	9	15	28	12

Conclusion

Defferent heterocyclic derivatives containing thiazole, quinazolin -4-one, oxazol and pyrmidine in structure were prepared and characterized using spectroscopy techniques. four route in the synthesis, the first synthesis of oxazolderivaties 3a-3c by reaction of benzoyl chlorid with urea ,after that cycliztion product with (substituted phenyl) acetamids.in the same method prepared thiazole derivatives 4a-4c but with thiourea . the third route include preparation of quinazolin 4-one derivatives 7a-7b by reaction of benzoyl chloride with anthranilic acid and reaction product with urea a ndcyclizclizationby (substituted phenyl) acetamids .inthe final scheme synthesis was prepared pyrmidine derivatives 10a-11b.these derivatives have been evaluated in vitro for their antimicrobial activities against several microbes likeklebsilliha, Escherichiacoli,Psreudomonasaeruginosa and Staphylococcus aureus, addation of antifungl activity .

Financial Disclosure: There is no financial disclosure.

Conflict of Interest: None to declare.

Ethical Clearance: All experimental protocols were approved under the Department of Chemistry, College of Science-University of AL-Mustansiriyah- Baghdad-Iraq and all experiments were carried out in accordance with approved guidelines.

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