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Research Article

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Synthesis and microbial activity of 3-[4-Benzylidene-5-oxo-2-phenyl-4,5-dihydro-imidazol-1-yl]-2-substituted-quinazolin-4(3*H*)-one and their derivatives

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ABSTRACT

Quinazolin-4(3H)-one based bis-azaheterocycles containing five or six membered heterocyclic ring at N-3 are medicinally important and majority of them are drug leads. Azlactones are also good pharmacophores and posses varied drug activity. Therefore a series of new compounds were prepared by condensation of 3-amino-2-substituted-4(3H)-quinazolinones with different substituted azlactones in glacial acetic acid. The structures of synthesized compounds were confirmed on the basis of IR, NMR and mass spectral data. The compounds are screened for anti-bacterial activity.

Key words: Quinazolinones, azlactones and anti-bacterial activity.

INTRODUCTION

Research programmes for the discovery of new compounds and evaluation of their therapeutic activity are under way in many laboratories. The heterocyclic nitrogen compounds especially quinazolinones when selectively functionalized act as building blocks for preparation of numerous biological active compounds. They play vital role in many biological processes and as synthetic drugs. Compounds containing quinazolinone-4(3H) ring system have been reported to possess different biological activities such as antibacterial [1], anti- fungal[2], anti- tubercular[3], anti viral, anticancer[4] and anti-convulsant activity depending on the substituent's in the ring system.

Azlactones(2-oxazolin-5-ones) are important synthons for the synthesis of several biologically active compounds[5]. The great biodiversity of oxazolone is reported in the medicinal field. They are known to exhibit anti-fungal [6], anti-bacterial [7] and anti-inflammatory activities.

These reports of interesting biological activities associated with quinazolin-4(3H)-one and azlactones prompted us to synthesize a series of compounds by condensing quinazolin-4(3H)-ones with azlactones.

EXPERIMENTAL SECTION

All the chemicals and solvents were of analytical grade and used without further purification. Melting points are determined using open capillaries in melting point apparatus and are uncorrected.

2.1.Synthesis of 3-amino-2-substituted(methyl/phenyl)-4(3H)-quinazolinones:
3-Amino-2-substituted(methyl/phenyl)-4(3H)-quinazolinones are prepared from anthranilic acid, benzoyl chloride, acetic anhydride and hydrazine hydrate.

2.2.Synthesis of 4-Benzylidene-2-phenyl oxazol-5(4H)-one.
4-Benzylidene-2-phenyl oxazol-5(4H)-ones(Azlactones) are prepared by following Erlenmeyer azlactone reaction. Azlactones are prepared by condensation of aromatic aldehydes with benzoyl derivative of glycine in presence of acetic anhydride and fused anhydrous sodium acetate.

2.3.Synthesis of 3-[4-Benzylidene-5-oxo-2-phenyl-4,5-dihydro-imidazol-1-yl]-2-phenyl-3H-quinazolin-4-one and their derivatives.
3-Amino-2-substituted(Me/Ph)-4(3H)-quinazolinone is condensed with 4-Benzylidene-2-phenyl oxazol-5(4H)-ones in presence of glacial acetic acid for 3hrs. The progress of the reaction was monitored by TLC. The product was precipitated by pouring the reaction mixture into ice cold water. The product was recrystallized from ethanol. The sequence of reaction is given in scheme-I.

2.3.a. 3-[4-Benzylidene-5-oxo-2-phenyl-4,5-dihydro-imidazol-1-yl]-2-methyl-3H-quinazolin-4-one
Yield 70%, m.p 185˚C
IR(KBr): 3062cm^{-1} (Ar C-H), 2925-2856cm^{-1} (C=C-H), 1794cm^{-1} (C=O of imidazolinone ring), 1672cm^{-1} (C=O of quinazolinone), 1552cm^{-1} (C=N), 1509cm $^{-1}$ (Ar C=C), 1469-1275cm^{-1} (Ar C-H bending); ^{1}H-NMR(d_6 - DMSO): 2.1δ (s,3H,CH_3), 7.3 δ (s , 1H, C=C-H), 7.4-8.3 δ (m,14H, Ar -H); ^{13}C-NMR(d_6-DMSO): 20.68δ(CH_3 carbon), 120-134δ(Ar-C), 152(carbonyl carbon of quinazolinone ring), 165 δ (carbonyl carbon of imidazolinone ring); Mass: m/z 407 (M+1) peak

2.3.b. 3-[4-(4-Methyl)-benzylidene-5-oxo-2-phenyl-4,5-dihydro-imidazol-1-yl]-2-methyl-3H-quinazolin-4-one.
Yield 65% , m.p 160˚C; IR(KBr): 3059cm^{-1} (Ar C-H), 1794cm^{-1} (C=O of imidazolinone ring), 1653cm^{-1} (C=O of quinazolinone), 1597cm^{-1} (C=N), 1554cm^{-1}, 1489cm^{-1} (Ar C=C), 1448-1232cm^{-1} (Ar C-H bending), 1165cm^{-1} (C-H bending of CH_3); ^{1}H-NMR(DMSO): 2.1 δ (s,3H,CH_3), 7.3 δ (s, 1H, C=C-H), 7.5-8.3 δ (m,13H,Ar-H); Mass: m/z 421(M+1) peak

2.3.c.3-[4-(4-Methoxy)-benzylidene-5-oxo-2-phenyl-4,5-dihydro-imidazol-1-yl]-2-methyl-3H-quinazolin-4-one.
Yield 75%, m.p 138˚C; IR(KBr): 3015cm^{-1} (Ar C-H),2842cm^{-1} (C=C-H), 1789cm^{-1} (C=O of imidazolinone ring), 1654cm^{-1} (C=O of quinazolinone), 1601cm^{-1} (C=N), 1552cm $^{-1}$, 1490cm^{-1} (Ar C=C), 1448-1311cm^{-1} (Ar C-H bending), 1163cm^{-1} (C-H bending of CH_3); ^{1}H-NMR(d_6 -DMSO): 2.1 δ (s,3H,CH_3), 3.6 δ (s,3H,OCH_3), 7.3 δ (s, 1H, C=C-HH), 7.1-8.3 δ (m,12 Ar-H); Mass: m/z 437(M+1) peak

2.3.d. 3-[4-(4-chloro)-benzylidene-5-oxo-2-phenyl-4,5-dihydro-imidazol-1-yl]-2-methyl-3H-quinazolin-4-one.
Yield 55%, m.p 206˚C; IR(KBr): 3059cm^{-1} (Ar C-H), 1797cm $^{-1}$ (C=O of imidazolinone ring), 1654cm $^{-1}$ (C=O of quinazolinone), 1588cm^{-1} (C=N), 1554cm^{-1} , 1487cm^{-1} (ArC=C), 1450-1235cm^{-1} (Ar C-H bending), 777cm^{-1} (C-Cl); ^{1}H-NMR(d_6 -DMSO): 2.1 δ (s,3H,CH_3), 7.3 δ (s,C=C-H, 1H), 7.6-7.7 δ (m,9Ar-H), 8.1 δ (d,2H,Ar-Cl ring), 8.3 δ (d,2H,Ar-Cl ring); Mass: m/z 441 (M+1) peak

2.3.e. 3-[4-Benzylidene-5-oxo-2-phenyl-4,5-dihydro-imidazol-1-yl]-2-phenyl-3H-quinazolin-4-one.
Yield 50%, m.p 125˚C; IR(KBr): 3060 cm^{-1} (Ar C-H), 2924 cm^{-1} (C=C-H), 1794cm $^{-1}$ (C=O of imidazolinone ring), 1654 cm^{-1} (C=O of quinazolinone ring), 1597 cm^{-1} (C=N), 1554cm^{-1},1491cm $^{-1}$ (Ar C=C), 1450-1200cm^{-1} (C-H bending); ^{1}H-NMR(d_6 -DMSO) : 7.3 δ (s, 1H, C=C-H), 7.5 δ (m,19H,Ar-H); ^{13}C-NMR(d_6 -DMSO) : 127-135 δ (Ar-C and benzylidene carbon), 164 δ (carbonyl carbon of quinazolinone ring), 169 δ (carbonyl carbon of imidazolinone ring); Mass: 469 (M+1) peak.

2.3.f .3-[4-(4-Methyl)-benzylidene-5-oxo-2-phenyl-4,5-dihydro-imidazol-1-yl]-2-phenyl-3H-quinazolin-4-one.
Yield 50%, m.p 130˚C; IR(KBr): 3061cm^{-1} (Ar C-H), 2923-2855cm^{-1} (C=C-H), 1794cm^{-1} (C=O of imidazolinone ring ring), 1654cm $^{-1}$ (C=O of quinazolinone ring), 1606cm^{-1} (C=N), 1492cm^{-1} (Ar C=C), 1449-1297 cm^{-1} (C-H bending), 1161cm^{-1} (Aliphatic C-H bending of CH_3); ^{1}H-NMR(d_6 -DMSO): 3.8 δ (s, 3H, CH_3), 7.1 δ (d,4H,Ar-H), 7.35 δ (s, 1H C=C-H), 7.6-8.8 δ (m, 14H,Ar-H); Mass: m/z 483 (M+1) peak.

2.3.g. 3-[4-(4-Methoxy)-benzylidene-5-oxo-2-phenyl-4,5-dihydro-imidazol-1-yl]-2-phenyl-3H-quinazolin-4-one.

Yield 45%, m.p 142-145˚C; IR(KBr): 3010 cm^{-1} (Ar C-H), 2800cm^{-1} (C=C-H), 1770 cm^{-1} (C=O of imidazolinone ring), 1640cm^{-1} (C=O of quinazolinone ring), 1600cm^{-1} (C=N), 1500cm^{-1}- 1480 cm^{-1} (Ar C=C), 1440-1300cm^{-1} (Ar C-H bending), 1260cm^{-1} (C-O of OCH_3), 1155cm^{-1} (C-H bending of CH_3); ^{1}H-NMR(d_6 -DMSO): 3.8 δ (s,3H, OCH_3), 7.35 δ (s, 1H, C=C-H), 7.1-8.3 δ (m,14H,Ar-H).; Mass: m/z 499 (M+1) peak

2.3.h. 3-[4-(4-Chloro)-benzylidene-5-oxo-2-phenyl-4,5-dihydro-imidazol-1-yl]-2-phenyl-3H-quinazolin-4-one.

Yield 45%, m.p 100˚C; IR(KBr): 3059cm^{-1} (Ar C-H), 2925-2856 (C=C-H), 1794cm^{-1} (C=O of imidazolinone ring), 1660cm^{-1} (C=O of quinazolinone), 1588cm^{-1} (C=N), 1557cm^{-1} (C-N), 1509cm^{-1} (ArC=C), 1469-1329cm^{-1} (Ar C-H bending), 766cm^{-1} (C-Cl); ^{1}H-NMR(d_6 -DMSO): 7.38 δ (s, 1H,C=C-H), 7.5-7.7 δ (m,10H,Ar-H), 7.8 δ (d, 2H,Ar-H), 8.1 δ (d, 4H,Ar-H), 8.3 δ (d, 2H,Ar-H); Mass: m/z-502

2.4 Biological activity

The anti bacterial activity of all synthesized compounds 1-8 were tested against seven pathogenic bacteria, viz; Bacillus subtilis, Pseudomonas fluorescence, Pseudomonas aerogenosa, Kleibsella pneumonia, streptococcus pneumonia, E.coli and Staphylococcus aureus, by disc diffusion technique. Compounds 1-7 were dissolved in DMSO and the discs were dipped in the respective compounds and placed on the petri dishes which were inoculated with the specific organisms against a control of DMSO. After 24hours the zone of inhibition was measured. The details of the activity are furnished in table-1

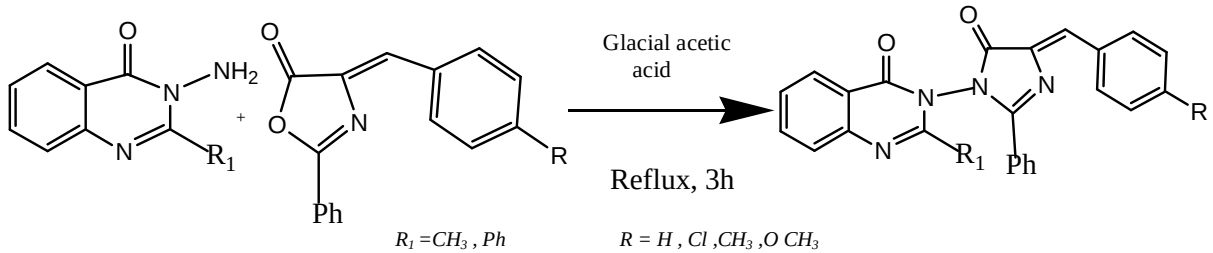
Table 1.Antibacterial activity of the title compounds (1-8)

	Bacillus subtilis	*Pseudomonas fluorescence*	*Pseudomonas aerogenosa*	*Kleibsella pneumonia*	*streptococcus pneumonia*	*E.coli*	*Staphylococcus aureus*
1	-	-	-	+	+	-	+
2	+	-	-	+	++	-	+
3	-	-	+	+	-	-	+
4	++	+	+	++	+	++	+
5	+	++	+++	+++	+++	+	+
6	+	-	-	+	+	-	-
7	+	+	-	++	+	-	+
8	+	++	+	-		+	++

+ indicates weak activity. ++ indicates moderate activity. +++ indicates good activity.

RESULTS AND DISCUSSION

Scheme-I



R_1 =CH_3 , Ph *R = H , Cl ,CH_3 ,O CH_3*

	2.3a	2.3b	2.3c	2.3d	2.3e	2.3f	2.3g	2.3h
R_1	CH_3	CH	CH_3	CH_3	Ph	Ph	Ph	Ph
R	H	CH_3	OCH_3	Cl	H	CH_3	O CH_3	Cl

All the compounds were synthesized as given in the scheme-III starting from 3-Amino-2-substituted (Me/Ph)-4(3H)-quinazolinones and 4-Benzylidene-2-phenyl oxazol-5(4H)-ones. The synthesized compounds were characterized based on IR, ^{1}H- NMR, ^{13}C- NMR, and mass spectral data. All the compounds showed characteristic C=O str frequency for imidazolinone and quinazolinone rings at 1794cm^{-1} and 1660cm^{-1} respectively. In the ^{1}H-NMR spectrum around 7.3 δ sharp singlet is observed for benzylidene proton (Ar-CH=). ^{13}C- NMR spectra recorded

signals corresponding to carbonyls of both imidazolinone, quinazolinone rings and other aromatic carbons. Molecular mass of the compounds was confirmed from mass spectral data.

Introduction of substituents such as chloro, methyl and methoxy showed considerable variation in activity against the organisms.

CONCLUSION

In summary, the presented new method of preparation of 3-[4-Benzylidene-5-oxo-2-phenyl-4,5-dihydro-imidazol-1-yl]-2-Substituted-3H-quinazolin-4-one and their derivatives from appropriate 3-amino-2-substituted-4(3H)-Quinazolinones and substituted azlactones in glacial acetic acid is very convenient, rapid and gives good yields. It was also found that the title compounds displayed good to moderate antibacterial activity against wide range of microorganisms.

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