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Synthesis and Antimicrobial Screening of 3H-Quinazolin-4-Ones Containing 3-Methyl Pyrazolinone Moiety.

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Abstract

Aseries of 2- benzyl – 3 - {4- [N'- (3-substituted-5-oxo-1-substituted-1, 5-dihydropyrazole-4-ylidene) hydrazino] phenyl}-3H-quinazoline-4-one, derivative were synthesized. The synthesized compounds were characterized by UV, IR, NMR, Mass spectral data. The synthesized compounds were screened for their antibacterial and antifungal activity against pathogenic bacteria and fungus. Compounds Q7, 3-[4-(3, 5-dimethyl-1H-pyrazol-4-ylazo) phenyl]-2-benzyl-3H-quinazolin-4-one and Q3,2-benzyl-3-{4-[N'-(3-methyl-5-oxo-1-isonictinoylpyrazole-4-ylidene) hydrazino] phenyl} - 3H- quinazoline-4 one exhibited good antibacterial and antifungal activity against the tested microorganisms.

Key Words

Quinazolinone, pyrazole, minimum inhibitory concentration, fungi and bacteria.

Introduction

4(3H)-Quinazolinones compounds occupy an important position in medicinal chemistry, presenting a wide range of bioactivities[1-5] such as anti-microbial, anti-tubercular, anticancer, anti-HIV, anti-inflammatory, anticonvulsant, antidepressant, hypolipidemic, analgesic, immunotropic activities and known to act as thymidyalate synthase, poly (ADP-ribose) polymerase and protein tyrosine Kinase inhibitors. The prevalence of pyrazole cores in biologically active molecules has stimulated the need for elegant and efficient ways to make these heterocyclic lead. Pyrazoles are an important class of compounds for new drug development that attracted much attention. Several pyrazole derivatives have been synthesized as target structures and evaluated for their biological activities. The cytotoxicity of the reported compounds in the review indicate good safety associated with many of the pyrazole derivatives The purpose of the present work was to explore and develop the novel molecule with improved potential for treating microbial infections. In this paper we reported the design, synthesis and evaluation of antimicrobial activity of 4(3H)-quinazolinone derivatives.

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Materials and Methods

Synthesis of 2-benzyl-4H-benzo [1, 3] oxazine-4-one (Q2)[6]

A mixture of phenyl acetic acid (0.06 mol) and phosphorous pentachloride (0.06 mol) was triturated. To phenyl acetyl chloride thus formed, anthranilic acid (0.06 mol) was added with trituration followed by water. The resulting solid **(Q_1)** was washed with hot water and crystallized from ethanol.A mixture of Q1 (0.01 mol) and acetic anhydride (o.05 mol) was refluxed under anhydrous condition for 4-6 hrs. The excess of acetic anhydride was then distilled off under reduced pressure and cooled to room temperature. The solid mass was used up immediately to the next step. M.p-280°c,Yeild -78% , $C_{15}H_{11}NO_2$, M.Wt 237, R_f- 0.67, UV λ_{max} 266.5, IR(KBr,cm1) 1615 (O=C-O),1538 (O=C-N),853 (Ar C=C),MS (m/z) 236

Synthesis of 3-(4-aminophenyl)-2-benzylquinazolin-4(3H)-one (Q3)

Equimolar quantities (0.01 mol) of Q_2 and P-Phenylenediamine respectively were refluxed in glacial acetic acid for 6 hrs. After cooling, the contents are poured onto crushed ice. The resulting solids were washed with distilled water, dried and recrystallized from hot 95% ethanol. M.p-290°c, Yeild -73% , $C_{21}H_{17}N_3O$, Mol. Wt 327, R_f-0.73,UV λ_{max} 266.6,IR(KBr,cm1) 3372 (N-H amines),1617 (O=C-N),862 (Ar C=C),1287 (C-N),1248 (mono substituted phenyl ring, MS (m/z) 327

Diazotization of 3-(4-aminophenyl)-2-benzylquinazolin-4(3H)-one (Q4)

A mixture of Q3 (0.01 mol) in conc. HCl (3ml) was cooled to 0-5°C and cooled sodium nitrite solution (1.5g in 10 ml of water) added to it drop wise during 10 minutes. The reaction mixture was then stirred for 30 minutes.

Synthesis of hydrazono derivatives (Q5, Q9,)

To an ice cold mixture of the appropriate active methylene compound (ethyl acetoacetate, Ethyl cyanoacetate) (0.01 mole) and sodium acetate (4.10g ; 0.05mol) in ethanol (50ml) was added drop wise with stirring a solution of diazonium salt compound.

Q4- (0.01mol) over 15 minutes. The stirring was continued for 30 minutes and the reaction mixture then left for 2 hrs at room temperature. The solid product was collected recrystallized from ethanol to give the corresponding hydrazono derivatives.

Q5- M.p-300°c, Yeild -65% , $C_{27}H_{24}N_4O_4$, Mol. Wt .468, R_f- 0.68, UV λ_{max} 265, IR(KBr,cm1) 3300 (N-H amines),1533 (O=C-N),1189 (C-CH_3)835 (Ar C=C),1287 (C-N),1390 (mono substituted phenyl ring

Q9- M.p-300°c, Yeild -64% , $C_{26}H_{21}N_5O_3$, Mol. Wt. 451, R_f- 0.72 ,UV λ_{max} 336.6 , IR(KBr,cm1) 3169 (N-H amines) 1663 (O=C-N)1254 (C-CH_3) 835 (Ar C=C)1579 (N-N)1368 (C-N)1474 (mono substituted phenyl ring)

Synthesis of *2-benzyl-3-{4-[N'-(3-methyl-5-oxo-1,5-dihydropyrazole-4 ylidene) hydrazino] phenyl}-3H-quinazoline-4-one)* [Q6- Q8]

A mixture of the appropriate Q5 and hydrazines (0.32ml, 0.01mol) in ethanol (30ml) was heated under reflux for 4-6 hours. The solvent was concentrated and the reaction product was allowed to cool. The separated product was filtered off, washed with

water, dried and recrystallized from ethanol.

Q6- M.p-300°c, Yeild -71% , $C_{25}H_{20}N_6O_2$, Mol. Wt .436, R_f- 0.58, UVλ_{max}-265.5, 3302 (N-H amines), IR(KBr,cm1)1662 (O=C-N)1254 (C-CH_3)1514 (C=C ring)1573(N-N)1025 (C-N)1368 (mono substituted phenyl ring)

Q7-M.p-298-°c Yeild -83% , $C_{31}H_{24}N_6O_2$, M. Wt 512., R_f- 0.61, UVλ_{max}265.5 , IR(KBr,cm1) 3301 (N-H amines)1662 (O=C-N)1254 (C-CH_3)1475 (Ar C=C)1579(N-N)1318 (C-N)1368 (mono substituted phenyl ring)

Q8-M.p-302°c, Yeild -82% $C_{31}H_{23}N_7O_3$, M. Wt 541, Rf- 0.82, UV λ_{max} 265, IR(KBr,cm1) 3169 (N-H amines)1662 (O=C-N)1254 (C-CH_3)835 (Ar C=C)1571 (N-N)1368 (C-N)1401 (Pyridine CN)1401 (mono substituted phenyl ring

Synthesis of *3-{4-N'-(3-Amino-5-oxo-1, 5--dihydropyrazol-4ylidene) hydrazinophenyl}-2-benzyl-3H quinazolin-4-one* [Q10- Q12]

To a solution of the appropriate Q9 (0.01 mol) in glacial acetic acid (30ml) was added with hydrazines (1.30g, 0.012 mol) and anhydrous sodium acetate (0.82g, 0.01 mol). The reaction mixture was heated under reflux for 4 hours. The mixture was poured into ice-cooled water and stored in refrigerator. The crude product which separated was washed water, dried and recrystallized from methanol.

Q10- M.p-304°c, Yeild -75% , M. Wt .437, R_f- 0.55, UVλ_{max} 265, IR(KBr,cm1) 3170 (N-Hamines)1662 (O=C-N)1254 (C-CH_3)835 (Ar C=C)1571(N-N) 1317 (C-N)1512 (mono substituted phenyl ring)

Q11- M.p-292°c, Yeild -67%, M.Wt .513, R_f- 0.78, UVλ_{max} 264.8, IR(KBr,cm1) 3169 (N-H amines)1662 (O=C-N)1254 (C-CH_3)1571, 835 (Ar C=C)1512(N-N)1317 (C-N)1368 (mono substituted phenyl ring), 1HNMR(δppm): 7.60-7.55 (m, 6H, ArH) 2.8 (s, 2H, NH)2.7 (s, 2H, CH_2), MS (m/z):513

Q12-M.p-301°c, Yeild -73% , $C_{30}H_{22}N_8O_3$, M. Wt .542, R_f- 0.62, UV λ_{max} 164.6, IR(KBr,cm1) 3169 (N-H amines)1662 (O=C-N)1254 (C-CH_3)1571, 835 (Ar C=C)1368 (N-N)1317 (C-N)1402 (mono substituted phenyl ring)1571 (pyridine CN)

Biological activity

Sixteen compounds were screened for their anti-microbial activity against various bacteria like *Vibrio cholera, Escherchia coli, Bacillus subtilis, Bacillus linctus, Micrococcus luteus, Staphylococcus aureus, Klebsiella pneumonia, Coryne bacterium, Staphylococcus albus* and various fungal organisms like *Aspergillus niger, Aspergillus fumigatus, Aspergillus parasiticus, Candida albicans, Monascus ruber, Streptomyces griseus* .Among the 4(3H)-Quinazolinones derivatives **Q9, Q10** and compound **Q12** produce good anti-microbial activity with minimum inhibitory concentration of 25µg/ml. Rest of the compounds shows moderate activity. These antimicrobial data clearly shows that the presence of cyano substitution and pyrazolone substitution with NH2, phenyl group at 4(3H)-Quinazolinones causes remarkable

improvement in antimicrobial activity against both bacterial and fungal organisms.

Results and discussion

In the present study various 4(3H)-Quinazolinones derivatives were synthesized. The structure of the synthesized compounds was confirmed by IR, NMR, Mass spectral data. The IR spectrum of all the synthesized compound show bands in the region of 3150-3302 and 1533-1663 cm^{-1} corresponding to NH and C=O. The IR spectrum of Q7, Q11, Q12 shows band in the region of 1401, 1571, 1474 cm^{-1} showing the presence of C-N. All the synthesized compound shown bands in the region of 1189-1254, 835, 1317-1402 cm^{-1} Showing the presence of C-CH_3, Ar-C=C and mono substituted phenyl ring.The NMR spectrums of all the compound shows characteristic peak of for CH_2 at 2.8 δ ppm, the NH_2 protons appears at 3.8 δ ppm, for aromatic protons appears as multiplet from 1.3 to 7.6 δ ppm. All the Mass spectra of the synthesized compound were found to be corresponding with its m/z mass. The synthesized compounds were screened for their *in vitro* antimicrobial activity against various bacterias like *Vibrio cholera, Escherchia coli, Bacillus subtilis, Bacillus linctus, Micrococcus luteus, Staphylococcus aureus, Klebsiella pneumonia, Coryne bacterium, Staphylococcus albus* and various fungal organisms like *Aspergillus niger, Aspergillus fumigatus, Aspergillus parasiticus, Candida albicans, Monascus ruber, Streptomyces griseus*. Among the synthesized 2,3-disubstituted-3H-Quinazolin-4-one derivatives, compound Q9,Q10 and Q12 shown good activity against both bacterial and fungal organisms with MIC value of 25(µg/ml).

Conclusion

Some novel 2,3-disubstituted-3H-Quinazolin-4-one derivatives with the aim to get better yield and faster reaction and to get more potent drug for the treatment of microbial infectious diseases.The structure of the compounds was confirmed by spectral analysis. The synthesized 2, 3-disubstituted-3H-Quinazolin-4-one derivatives exhibited moderate to good anti-microbial activity. Further studies on its possible mechanism and *in vivo* trials in experimental animals to broaden their Pharmacological assessment, may provide a new analogue that can overcome drug resistance, prolonged treatment, complex drug regimen and side effects involved in the treatment of infectious diseases.

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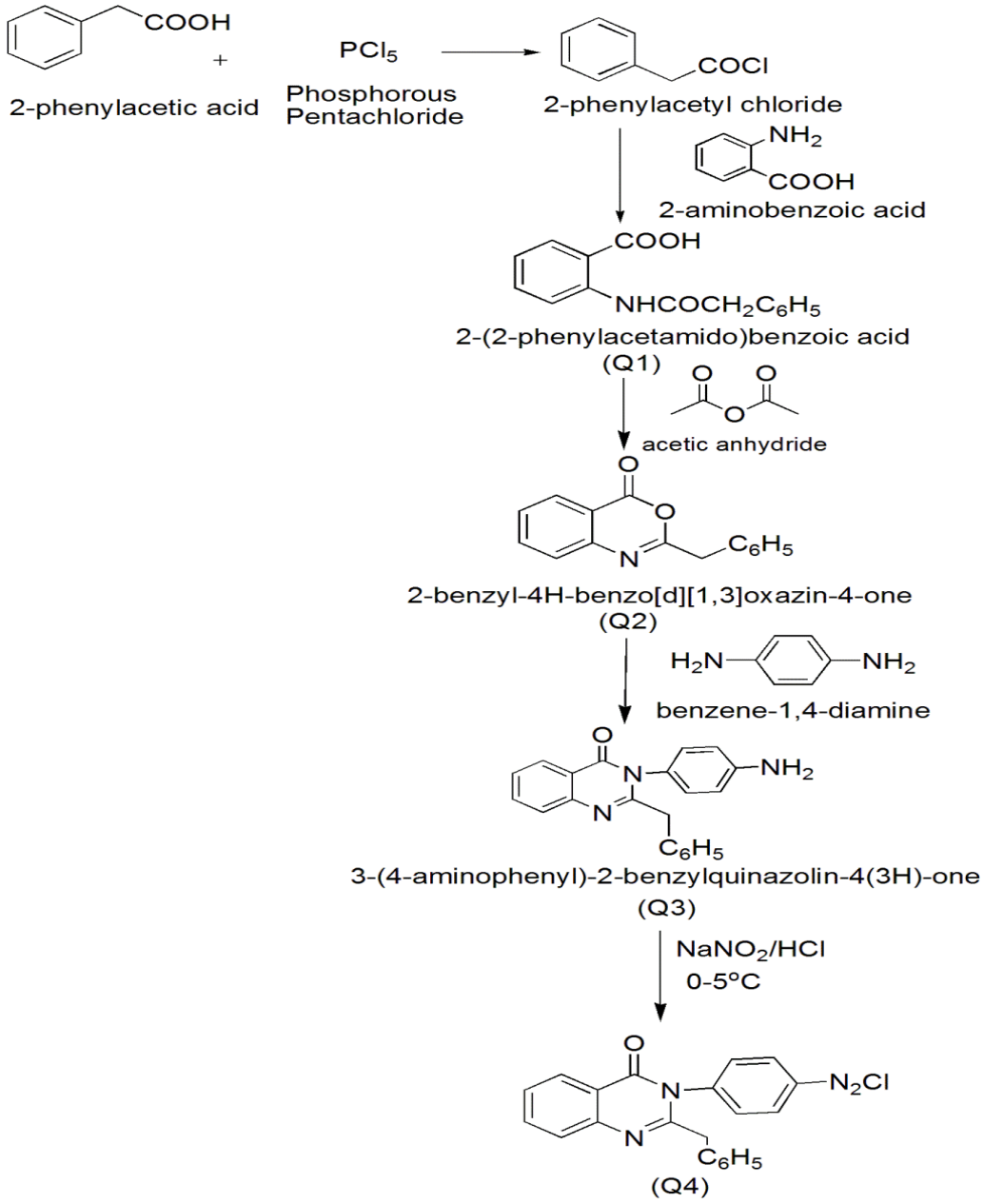

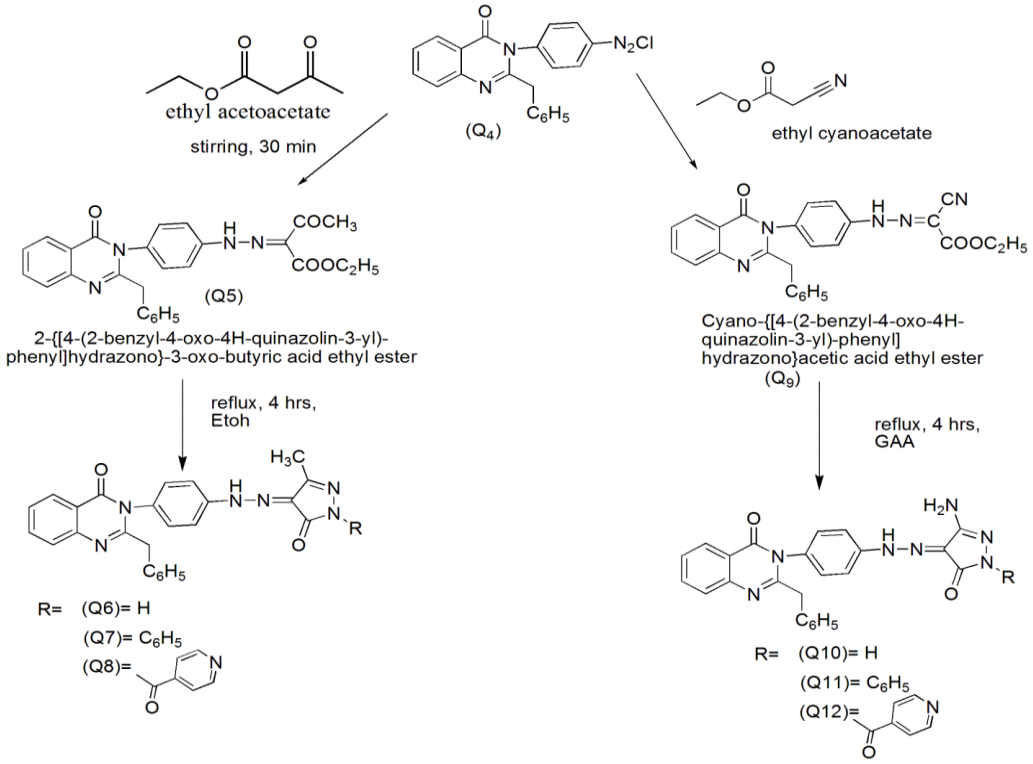

Scheme

Table 1: The *In vitro* antibacterial activity of 4(3H)-Quinazolinones derivatives.

Sr.no	**Micro organisms**	**Zone of inhibition(in mm)**							
		Compounds(10 µg/disc)							
		Q6	Q7	Q8	Q9	Q10	Q11	Q12	STD ciprofloxacin 10µg/disc
1	*Vibrio cholerae*	10	15	09	10	19	11	10	31
2	*Escherichia coli*	10	16	10	11	10	13	-	31
3	*Staphylococcus albus*	09	15	10	09	10	12	-	34
4	*Salmonella paratyphii*	-	11	09	10	08	10	11	20
5	*Klebsiella pneumonia*	-	11	08	09	10	09	09	20
6	*Micrococcus luteus*	-	-	-	-	-	10	-	20
7	*Cornybacterium*	09	-	12	-	10	11	14	26
8	*Bacillus subtilis*	10	-	-	14	10	10	13	30

Table 2: Antifungal activity of synthesized compound.

Sr.no	Microorganisms	Zone of inhibition(in mm)							
		Compounds(10 µg/disc)							
		Q6	**Q7**	**Q8**	**Q9**	**Q10**	**Q11**	**Q12**	**STD Clotrimazole10µg/disc**
1	*Aspergillus fumigatus*	-	14	14	09	14	18	15	30
2	*Candida albicans*	12	10	10	10	14	-	08	28
3	*Streptomyces griseus*	10	13	13	12	13	22	-	28
4	*Monascus ruber*	12	-	-	11	15	-	10	30
5	*Aspergillus parasiticus*	12	-	-	10	12	09	-	20
6	*Aspergillus niger*	11	7	09	-	09	09	09	23

Table 3: Antifungal activity of synthesized compound.

Sr.no	microorganisms	MIC VALUES (µg/ml)						
		1 Q6	**2 Q7**	**3 Q8**	**4 Q9**	**5 Q10**	**6 Q11**	**7 Q12**
1	*Aspergillus fumigatus*	50	25	50	25	25	25	12.5
2	*Candida albicans*	25	25	25	25	25	25	20
3	*Streptomyces griseus*	25	50	25	25	25	25	25
4	*Monascus ruber*	25	25	50	25	50	25	25
5	*Aspergillus parasiticus*	25	25	50	25	50	25	20
6	*Aspergillus niger*	25	50	25	25	25	25	12.5

Coflict of Interest: Not Declared

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