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Synthesis and antimicrobial screening of some new N_3-substituted derivatives of quinazolin-4(3*H*)one

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ABSTRACT

*Quinazolin-4-one-3-yl-propan-2-one **(2)** was prepared by N-alkylation of Quinazolin-4(3H)one **1**. The treatment of compound **2** with hydrazine hydrate yielded hydrazine derivative **(3)**, which on condensation with variously substituted aryl aldehydes gave the corresponding hydrazones **(4)**. Compound **3** on reaction with phenyl isocyanate and phenyl isothiocyanate transformed into the corresponding carbamates and thiocarbamates **(5)** respectively. Compound **3** also gave a tricyclic compound **(6)** when refluxed in presence of ammonium acetate and acetic acid, while hydrazone derivative **(7)** when treated with dehydroacetic acid.*

Keywords: Quinazoline, chloroacetone, hydrazones.

INTRODUCTION

Quinazoline derivatives has attracted considerable attention due to their significant biological activities[1, 2], especially antiallergic[3], antifungal[4], anti-HIV[4], antihypertensive[6], anti-inflammatory[7], antibacterial[8], anticonvulsant[9, 10], antithrombotic[11], antitubercular[12], CNS depressant[13], antihistaminic[14]. In this paper, we report a new route for the synthesis of N3 substituted derivatives of quinazolinone.

EXPERIMENTAL SECTION

Compound **1** was synthesized by reported method[15].

Synthesis of 1-(Quinazolin-4-one-3-yl) propan-2-one (2)

The mixture of compound **1** (6 gm, 0.04 mole), chloroacetone (5.0 gm, 0.05 mole) and anhydrous potassium carbonate (1gm) in dry acetone (25 ml) was refluxed for 12 hours, cooled

and the separated solid extracted with ether. After removal of ether under reduced pressure gave solid which was recrystallised from ethanol to furnish **2**, yield 83%, m.p. 170^0C.

Elemental Analysis: Found : C, 65.44; H, 4.95; N, 13.87 %; $C_{11}H_{10}O_2N_2$; Required : C, 65.34; H, 4.98; N, 13.85 %; **IR(KBr) :** ν_{max}, 1722 (C=O), 1673 (cyclic amido C=O) cm^{-1}; **^{1}H NMR($CDCl_3$) :** δ, 2.3 (3H, s, $COCH_3$), 4.7 (2H, s, N-CH_2-CO), 7.2-8.1 (5H, m, Ar-H and –N=CH) ppm.

Synthesis of 1-(Quinazolin-4-one-yl)-2-hydrazonyl propane (3)
The mixture of compound **2** (2.2 gm, 0.01 mole), hydrazine hydrate (1.0 gm, 0.02 mole) and 5% methanolic NaOH (10 ml) was stirred for ½ hr. and the separated solid was filtered and recrystallised from ethanol to furnish compound **3**, yield 86%, m.p. 115^0C.

Elemental Analysis: Found : C, 61.12; H, 5.54; N, 25.89 %; $C_{11}H_{12}ON_4$; Required : C, 61.10; H, 5.59; N, 25.91 %; **IR(KBr) :** ν_{max}, 3467-3277(-NH_2), 1676 (cyclic amido C=O), 1613 cm^{-1}(C=N); **^{1}H NMR($CDCl_3$) :** δ, 2.2 (3H, s, =C-CH_3), 4.6 (2H, s, -CH_2). 7.2-8.1 (5H, m, Ar-H and N=CH) and 5.1 (2H, s, -NH_2) ppm.

Table No.1: Physical and analytical data of Hydrazones (4) and Carbamates (5)

Comp.	R	Mol. Formula	M.P. ^{o}C	Yield (%)	Elemental analysis Calcd / (Found)		
					C	H	N
4b	o-ClC_6H_4	$C_{18}H_{15}ON_4Cl$	143	68	63.81 (63.84)	4.46 (4.42)	16.54 (16.59)
4c	p-ClC_6H_4	$C_{18}H_{15}ON_4Cl$	214	68	63.81 (63.85)	4.46 (4.49)	16.54 (16.52)
4d	o-OHC_6H_4	$C_{18}H_{16}O_2N_4$	4.86	78	67.49 (67.44)	5.03 (5.07)	17.49 (17.44)
4e	p-OHC_6H_4	$C_{18}H_{16}O_2N_4$	185	72	67.49 (67.52)	5.03 (5.05)	17.49 (17.51)
4f	3,4,5$(OCH_3)_3C_6H_2$	$C_{21}H_{22}O_4N_4$	222	84	63.95 (63.91)	5.62 (5.58)	14.20 (14.25)
4g	C_6H_5CH=CH-	$C_{20}H_{18}ON_4$	226	61	72.71 (72.65)	5.49 (5.45)	16.96 (16.94)
4h	p-OH,m-$OCH_3C_6H_3$	$C_{29}H_{18}O_3N_4$	220	76	65.13 (65.11)	5.18 (5.15)	15.99 (15.95)
4i	o-$NO_2C_6H_4$	$C_{18}H_{15}O_3N_5$	219	79	61.89 (61.85)	4.33 (4.31)	20.05 (20.09)
4j	p-$N(CH_3)_2C_6H_4$	$C_{20}H_{21}ON_5$	256	74	69.14 (69.19)	6.09 (6.15)	20.16 (20.11)
4k	o-OH,m-$OCH_3C_6H_3$	$C_{19}H_{18}O_3N_4$	180	64	65.13 (65.19)	5.18 (5.25)	15.99 (15.85)
4l	o-$CH_3C_6H_5CH$=CH-	$C_{21}H_{20}ON_4$	210	61	73.23 (73.28)	5.85 (5.85)	16.27 (16.25)
4m	o-SHC_6H_4	$C_{18}H_{16}ON_4S$	228	59	64.26 (64.22)	4.79 (4.75)	16.65 (16.69)
4n	β-OH-naphthyl	$C_{22}H_{18}O_2N_4$	270	71	71.34 (71.39)	4.90 (4.96)	15.13 (15.16)

Synthesis of (Quinazolin-4-one-3-yl) 2-(arylidenehydrazono) propane (4a)
A mixture of equimolar quantities of **3** (0.2 gm, 0.0009 mole), p-methoxy benzaldehyde (0.12 gm, 0.0009 mole) in methanol (10 ml) and 2-3 drops of acetic acid was refluxed on a steam bath

for 15 minutes. Yellow solid obtained was filtered and recrystallised from ethanol, yield, 84 %, m.p. 196^0C.

Elemental Analysis: Found: C, 68.23; H, 5.44; N, 16.79 %; $C_{19}H_{18}O_2N_4$; Required: C, 68.25; H, 5.43; N, 16.76 %; **IR(KBr):** ν_{max}, 1675 (cyclic amido C=O), 1610 (C=N) cm^{-1}; **^{1}H NMR (DMSO-d_6):** δ, 2.3 (3H, s, =C-CH_3), 3.9 (3H, s, -OCH_3), 4.9 (2H, s, N-CH_2), 7.14-8.2 (9H, m, Ar-H and N=CH), 8.9 (1H, s, =CH) ppm.

All other hydrazones were prepared by same method employed for 4a and characterized by physical and analytical data included in Table No.1.

Synthesis of 1-(Quinazolin-4-one-3-yl) 2-(N-aryl carbamyl) propane (5a)
The mixture of compound **3** (0.2 gm, 0.0005 mole) and phenyl isothiocyanate (0.08 gm, 0.0005 mole) in THF was refluxed on a steam bath for 2 hours and the separated solid was filtered and recrystallised from DMF, yield 64%, m.p. 164^0C.

Elemental Analysis: Found: C, 61.56; H, 4.87; N, 19.89 %; $C_{18}H_{17}ON_5S$; Required: C, 61.52; H, 4.88; N, 19.93 %; **IR (KBr):** ν_{max}, 3260 (NH), 1675 (cyclic amido C=O), 1625 (C=S), 1615 cm^{-1} (C=N); **^{1}H NMR (DMSO-d_6):** δ, 2.15 (3H, s, =C-CH_3), 4.7 (2H, s, N-CH_2), 6.5 (1H, s, -NH), 6.8 (1H, s, -NH), 7.2-8.1 (10H, m, Ar-H and N=CH) ppm.

5b: (X = O), yield 78%, m.p. 182^0C; **Elemental Analysis**: Found: C, 64.49; H, 5.14; N, 20.89 %; $C_{18}H_{17}O_2N_5$; Required: C, 64.47; H, 5.11; N, 20.88 %

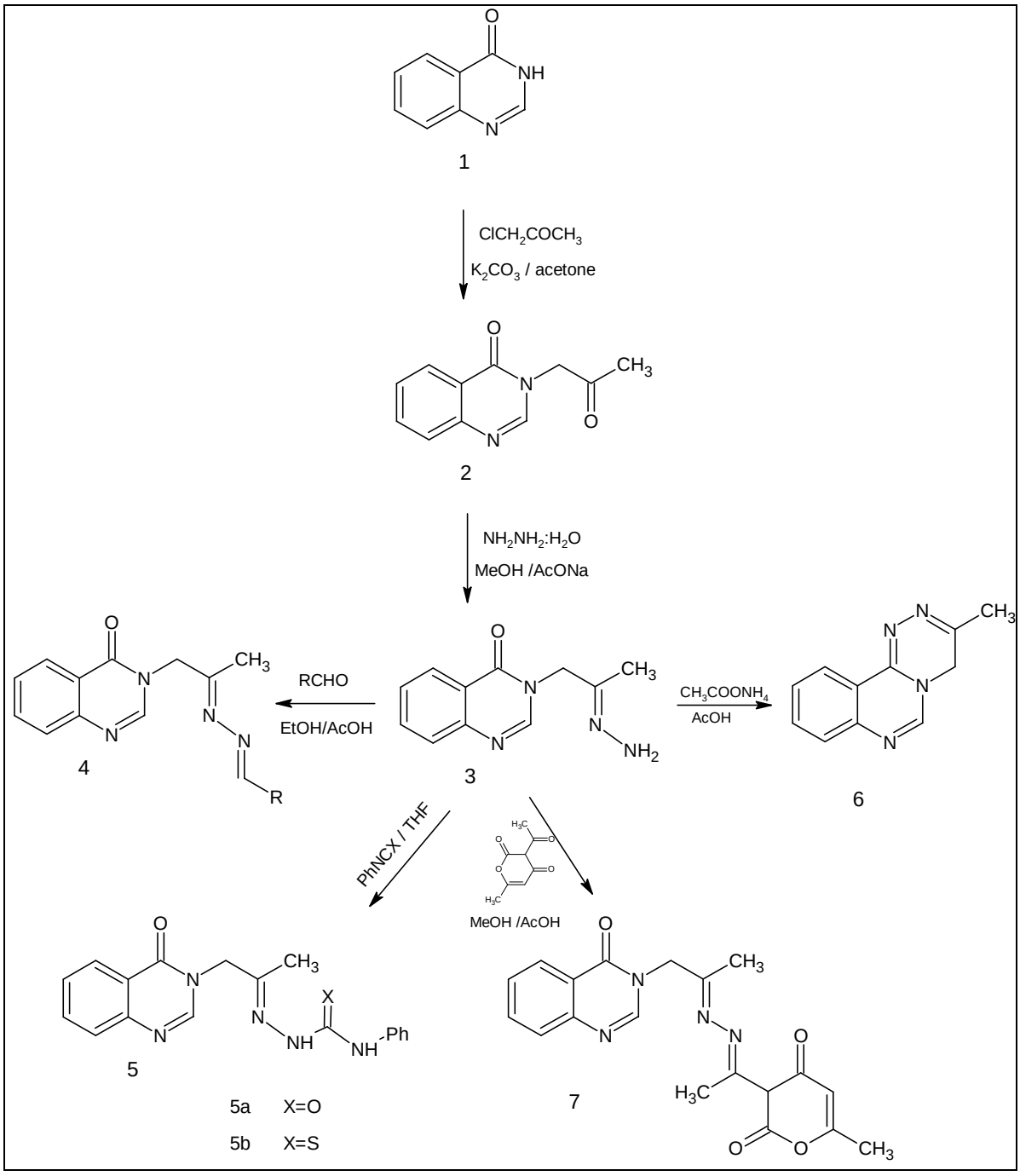
Synthesis of 3-Methyl 1,4,5-Triazino(3,4-c)quinazoline (6)
To compound **3** (0.2 gm, 0.0009 mole), ammonium acetate (0.1 gm) was added and refluxed in presence in glacial acetic acid (10ml) on an oil bath till yellow colour of reaction mixture changes to dark brown. The reaction mixture was then poured in ice-water mixture and neutralized with ammonia and kept overnight. The separated solid was filtered and recrystallised from ethanol, yield 76%, m.p. 171^0C.

Elemental Analysis: Found: C, 66.69; H, 5.11; N, 28.29 %; $C_{11}H_{10}N_4$; Required: C, 66.65; H, 5.08; N, 28.26 %; **IR (KBr):** ν_{max}, 1615 (C=N), 1602 (C=C) cm^{-1}; **^{1}H NMR ($CDCl_3$):** δ, 2.3 (3H, s, =C-CH_3), 5.0 (2H, s, N-CH_2), 7.3-8.2 (5H, m, Ar-H and N=CH) ppm.

Synthesis of Hydrazone derivative of 3 with 3-acetylpyrone-3,4-dione (7)
The compound **3** (0.2 gm, 0.0009 mole) and dehydroacetic acid (0.15 gm, 0.0009 mole) in ethanol was refluxed for 4 hours in presence of 2-3 drops of acetic acid. The separated solid was then cooled, filtered and recrystallised from ethanol, yield 65%, m.p. 205^0C.

Elemental Analysis: Found: C, 62.34; H, 4.99; N, 15.27 %; $C_{19}H_{18}O_4N_4$; Required: C, 62.29; H, 4.95; N, 15.29 %; **IR (KBr):** ν_{max}, 1725 (cyclic ester C=O), 1710 (cyclic C=O), 1685 (cyclic amido C=O), 1635 (C=N) cm^{-1}; **^{1}H NMR (DMSO-d_6) :** δ, 2.1 (3H, s, =C-CH_3), 2.3 (3H, s, -N=C-CH_3), 2.4 (3H, s, -N=C-CH_3), 4.8 (2H, s, N-CH_2), 6.2 (1H, s, -CH), 7.2-8.3 (6H, m, Ar-H, N=CH and =CH) ppm.

Scheme



RESULTS AND DISCUSSION

Quinazolin-4(3H)one **1** was N-alkylated with chloroacetone to form quinazolin-4-one-3-yl-propan-2-one **(2)**. The formation of **2** was explained by the appearance of two singlets encountered at δ, 2.3 and 4.7 due to the $COCH_3$ and N-CH_2-CO respectively in its PMR spectrum. The appearance of IR band at 1722 cm^{-1} and 1673 cm^{-1} due to acyclic C=O and cyclic amide C=O respectively supports its formation. The treatment of compound **2** with hydrazine hydrate yielded hydrazine derivative **(3)**. The appearance of IR band at 3467-3277cm^{-1} and 1613 cm^{-1} due to NH_2 and C=N respectively and disappearance of IR band at 1722 cm^{-1} due to acyclic C=O supports its formation. Further, the compound **3** on condensation with variously substituted aryl aldehydes in methanol under acidic condition gave the corresponding hydrazones **(4)**. The

appearance of additional signal due to =CH protons at δ, 8.9 for arylidene derivatives in the PMR spectrum and the disappearance of IR band at 3467-3277 cm^{-1} due to NH_2 indicated their formation. Further, compound **3** was transformed into the corresponding carbamates and thiocarbamates **(5)** by treating with phenyl isocyanate and phenyl isothiocyanate respectively. The formation of compounds **5** were established by their correct IR and NMR spectral data. The compound **3** on cyclization with ammonium acetate gave tricyclic compound **(6)**. The disappearance of IR band at 1676 cm^{-1} due to cyclic amide C=O and another at 3467-3277 cm^{-1} due to $–NH_2$ in **3** indicated formation of compound **(6)**. The condensation of compounds **3** with dehydroacetic acid gave the corresponding hydrazone derivative **(7)**. The absence of IR band between 3437-3277cm^{-1} due to NH_2 in compound **3** and appearance of IR band at 1725, 1720 due to cyclic ester and cyclic C=O in compound **3** supports the formation of compound **(7)**.

CONCLUSION

The antimicrobial testing results indicate that the compounds 4b, 4j, 4m and 5b exhibited good antimicrobial activity against above bacterial and fungal species, while the compounds 4g, 4i and 5a has exhibited moderate antimicrobial activity against gram +ve and –ve both bacteria and fungal species.

The generalization can be made from above result is that the compounds with substituent group like R = -Cl, $-N(CH_3)_2$, -SH enhance the antimicrobial activity than the other substituents. It is observed that all the carbamates are equally active and have the considerable value as pesticides.

Table No.2: Antimicrobial screening data of the compounds 4 & 5

(Diameter of the zones of inhibition in mm.)

Comp.	R	Bacteria				Fungi	
		E. Coli	***P. valgaris***	***B. subtilis***	***S. aureus***	***A. niger***	***Phytophora spp.***
4a	p-$OCH_3C_6H_4$	14	15	14	16	13	14
4b	o-ClC_6H_4	22	21	21	22	20	19
4d	o-OHC_6H_4	11	12	14	15	12	13
4g	C_6H_5CH=CH-	17	18	17	18	17	19
4h	p-OH,m-$OCH_3C_6H_3$	13	16	14	13	14	15
4i	o-$NO_2C_6H_4$	17	18	19	17	18	16
4j	p-$N(CH_3)_2C_6H_4$	20	21	21	20	23	23
4m	o-SHC_6H_4	22	24	15	18	21	23
	X						
5a	O	17	18	19	20	22	18
5b	S	20	22	21	19	20	20

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