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SYNTHESIS AND BIOLOGICAL ACTIVITIES OF SOME NEW N- AND S-MANNICH BASES OF 3-ARYL-2-THIOXO-2, 3-DIHYDROQUINAZOLIN-4(1H)-ONE

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ABSRACT
The Mannich reaction on 3-aryl-2-thioxo-2, 3-dihydroquinazolin-4(1H)-one, in neutral medium and in alkaline medium with different secondary amines yielded a single product in each case. The mannich bases obtained have been characterized as the corresponding 1-N-substituted aminomethyl-3-aryl-3, 4-dihydro-4-oxoquinazolin-2-thione **(II)** and 2-S-substituted amino methyl thio-3-aryl 4(3H) quinazolinone **(III)** on the basis of analytical spectral data. These N- and S-Substituted compounds have been screened for their Anti- bacterial, Anti -fungal, Anti-inflammatory and Analgesic activities.
Keywords: Quinazolinone, N-Mannich base, S-Mannich base, aqueous potassium carbonate, Secondary amines, Analgesic activity, Anti-inflammatory activity.

INTRODUCTION

Various 4(3H)-quinazolinones and their derivatives are known for their varied biological and pharmacological importance[1]. The N- and S-substituted amino alkyl moieties have been found to be associated with CNS, analgesic and anti-inflammatory activities. Therefore, in continuation of our investigations on quinazolinones and the Mannich bases.[2-4] The required 1-N-substituted aminomethyl-3-aryl-3,4-dihydro-4-oxoquinazolin-2-thione**(II)** and 2-S-substituted amino methyl thio-3-aryl-4(3H) quinazolinone **(III)** has been prepared from its different aromatic primary amines[5,6,7] and condensed with various secondary amines in the presence of ethanol and aqueous formaldehyde(Neutral medium) and aqueous potassium carbonate(Alkaline medium) (Scheme-1). Purification of the products yielded a single compound (TLC) in each case. They have been characterized by the analytical, IR and NMR Spectral data (Table-1).

EXPERIMENTAL

Melting points were recorded in open capillaries using Toshniwal melting point apparatus and are uncorrected.IR Spectra (Vmax in cm-1) were recorded on Perkin-Elmer infracord-283 spectro-photometer in nujal mull and NMR spectra on varian EM-360(90HMz) spectrophotometer using TMS as internal standard[8-10]. The 1-N-substituted aminomethyl-3-aryl-3, 4-dihydro-4-oxoquinazolin-2-thione **(II)** and 2-S-substituted amino methyl thio-3-aryl-4(3H)-quinazolinone **(III)** were prepared by known procedures.

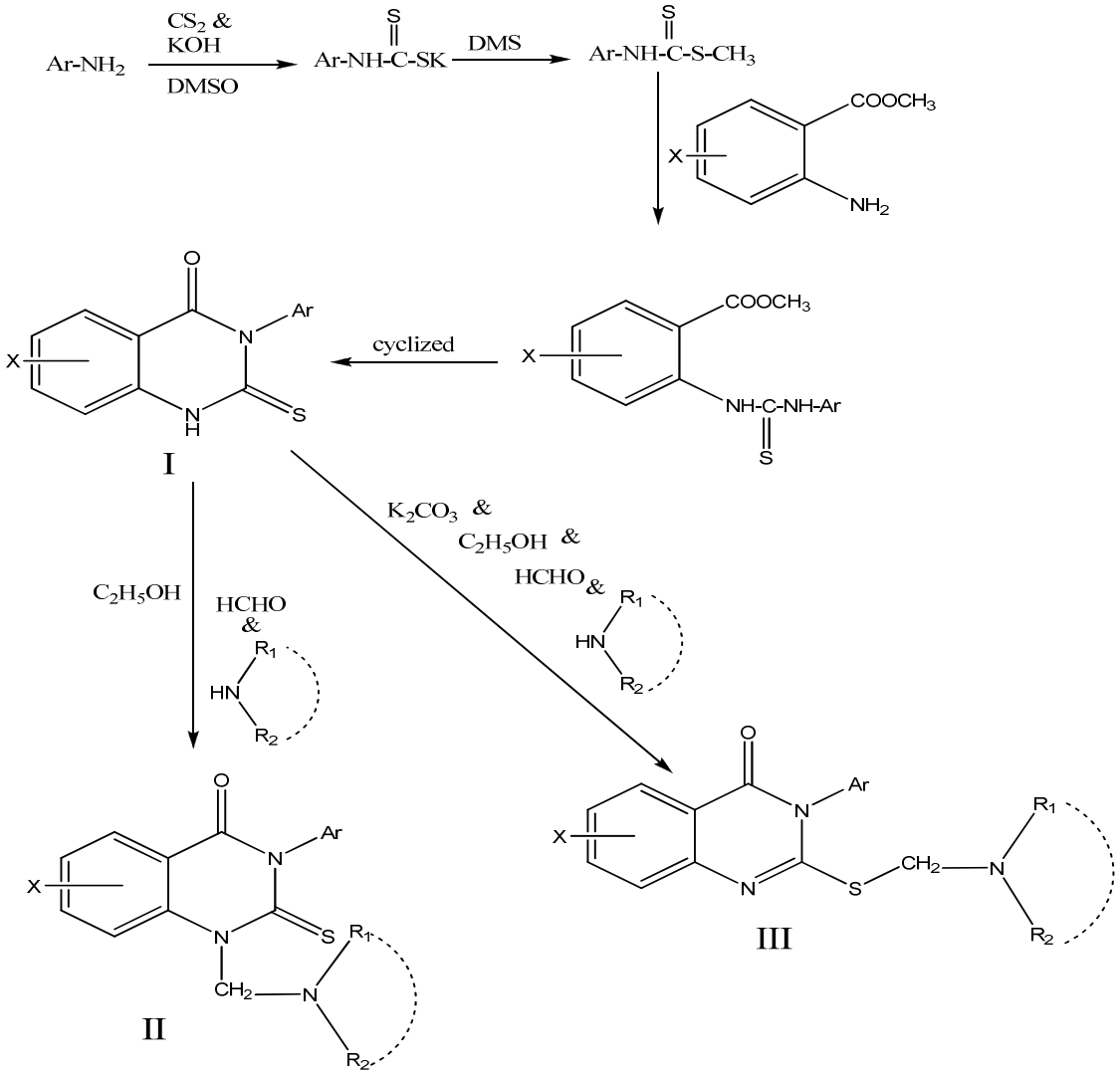
Procedure for the Synthesis of 1-N-substituted aminomethyl-3-aryl-3, 4-dihydro-4-oxoquinazolin-2-thione (II)

Different aromatic primary amines will be converted in to their dithiocarbamic acid salts, which will be methylated to obtain S-methyl derivatives for easy nucleophilic substitution.[11,12] Each of the S-methyl derivative will be then condensed with appropriate methyl anthranilates to get the respective diarylthioureas, which will be subsequently cyclized to their 3-aryl-3,4-dihydro-4-oxo-2(1H) thiones.[13-15]

Each of the thiones will be subjected to the Mannich condensation under neutral medium aqueous formaldehyde and ethanol, different acyclic or cyclic secondary amines, with a normal expectation of obtaining N- Mannich bases **(II)** respectively. Physical data of compounds showed in Table-1.

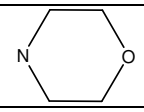
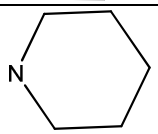
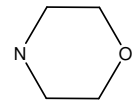
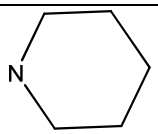
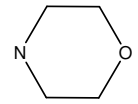
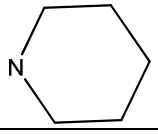
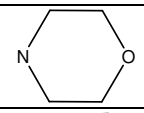
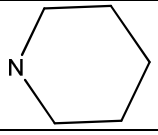
Procedure for the Synthesis of 2-S-substituted amino methyl thio-3-aryl-4(3H)-quinazolinone (III)

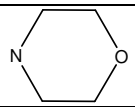
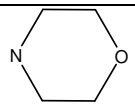
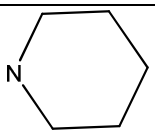
Different aromatic primary amines will be converted in to their dithiocarbamic acid salts, which will be methylated to obtain S-methyl derivatives for easy nucleophilic substitution. Each of the S-methyl derivative will be then condensed with appropriate methyl anthranilates to get the respective diarylthioureas, which will be subsequently cyclized to their 3-aryl-3,4-dihydro-4-oxo-2(1H) thiones[16-19]. Each of the thiones will be subjected to the Mannich condensation under basic conditions by using aqueous potassium carbonate and different acyclic or cyclic secondary amines, ethanol and aqueous formaldehyde with a normal expectation of obtaining S-Mannich bases **(III)** respectively[20-24]. Physical data of compounds showed in Table-1.



Scheme-1

Table-1: Physical data of 1-N-substituted aminomethyl-3-aryl-3, 4-dihydro-4-oxoquinazolin-2-thione (II) and 2-S-substituted amino methyl thio-3-aryl-4(3H)-quinazolinones (III).

Compound	Substituent in II and III compounds at 6th position	Substituent in II and III compounds at 3rd position	-NR_1R_2 in II and III compounds at 2nd position	Mol.form	Mol .wt	MP^0 C	%Yield
II A	X=H	Ar=C_6H_5	-N-$(CH_3)_2$	$C_{17}H_{17}N_3OS$	311	112-114	74
II B	X=H	Ar=C_6H_5	-N-$(C_2H_5)_2$	$C_{19}H_{21}N_3OS$	339	117-119	78
II C	X=H	Ar=C_6H_5		$C_{19}H_{19}N_3O_2S$	353	124-126	70
II D	X=H	Ar=C_6H_5		$C_{19}H_{21}N_3OS$	339	120-122	68
II E	X=H	Ar=C_6H_4-CH_3(*p*)	-N-$(CH_3)_2$	$C_{18}H_{19}N_3OS$	325	119-121	72
II F	X=H	Ar=C_6H_4-CH_3(*p*)		$C_{20}H_{21}N_3O_2S$	367	129-131	65
II G	X=H	Ar=C_6H_4-CH_3(*p*)		$C_{21}H_{23}N_3OS$	365	123-125	62
II H	X=H	Ar=C_6H_4-OCH_3(*o*)	-N-$(CH_3)_2$	$C_{18}H_{19}N_3O_2S$	341	115-117	70
II I	X=Br	Ar=C_6H_5		$C_{19}H_{18}BrN_3O_2S$	432	174-176	63
II J	X=Br	Ar=C_6H_4-OCH_3(*o*)		$C_{21}H_{22}BrN_3O_2S$	460	175-177	56
III A	X=H	Ar=C_6H_5	-N-$(C_2H_5)_2$	$C_{19}H_{21}N_3OS$	339	124-126	72
III B	X=H	Ar=C_6H_5		$C_{19}H_{19}N_3O_2S$	353	133-135	68
III C	X=H	Ar=C_6H_5		$C_{20}H_{21}N_3OS$	351	131-133	64

III D	X=H	Ar=C_6H_4-CH_3(*p*)	-N-(C_2H_5)$_2$	$C_{20}H_{23}N_3OS$	353	134-136	72
III E	X=H	Ar=C_6H_4-CH_3(*p*)		$C_{20}H_{21}N_3O_2S$	367	138-140	65
III F	X=H	Ar=C_6H_4-OCH_3(*o*)	-N-(CH_3)$_2$	$C_{18}H_{19}N_3O_2S$	341	130-132	76
III G	X=H	Ar=C_6H_4-OCH_3(*o*)	-N-(C_2H_5)$_2$	$C_{20}H_{23}N_3O_2S$	369	139-141	73
III H	X=H	Ar=C_6H_4-OCH_3(*o*)		$C_{20}H_{21}N_3O_3S$	383	144-146	65
III I	X=H	Ar=C_6H_4-OCH_3(*o*)		$C_{21}H_{23}N_3O_2S$	381	142-144	60
III J	X=Br	Ar=C_6H_5	-N-(CH_3)$_2$	$C_{17}H_{16}BrN_3OS$	390	156-158	74

Spectral data (IR and ^{1}H NMR) of Test compounds of Scheme-1 (II and III)

1-((dimethyl amino) methyl)-3-phenyl-2-thioxo-2, 3-dihydroquinazolin-4(1H)-one (II A)

IR (KBr, cm-1): 3010(C-H Stretch Aromatic), 2960(C-H Stretch Aliphatic), 1658(C=O Stretch), 1496(C=C Stretch), 1198.96(C=S Stretch).

^{1}H NMR Spectra ($CDCl_3$, δ ppm): 2.4(s ,6H , -$(CH_3)_2$) 4.5(s ,2H , -CH_2) 6.4(d ,1H ,Ar-H) 6.7(t ,1H ,Ar-H) 6.9(t, 1H, Ar-H) 7.1(t, 1H, Ar-H) 7.3(m, 4H, Ar-H) 7.7(d, 1H, Ar-H).

6-Bromo-1-(morpholinomethyl)-3-phenyl-2-thioxo-2, 3-dihydroquinazolin-4(1H)-one (IIE)

IR (KBr, cm-1): 3010(C-H Stretch Aromatic), 1658(C=O Stretch), 1500(-N-CH_2 Stretch), 1496(C=C Stretch), 1198.96(C=S Stretch).

^{1}H NMR Spectra ($CDCl_3$, δ ppm): 2.5(t , 2H , -$(CH_2)_2$ morpholino) 3.4(t, 2H , -$(CH_2)_2$ morpholino) 4.5(s ,2H ,CH_2) 6.6(d ,1H ,Ar-H) 6.9(t, 1H, Ar-H) 7.3(m, 4H, Ar-H) 7.4(d, 1H, Ar-H) 7.9(d, 1H, Ar-H).

6-Bromo-3-(4-methoxyphenyl)-1-(piperidin-1-yl methyl)-2-thioxo-2, 3-dihydroquinazolin-4(1H)-one (II F)

IR (KBr, cm-1): 3010(C-H Stretch Aromatic), 2850(-OCH_3 Stretch), 1658(C=O Stretch), 1496(C=C Stretch), 1470(-N-CH_2 Stretch), 1198.96(C=S Stretch).

^{1}H NMR Spectra ($CDCl_3$, δ ppm): 1.5(t , 6H , -$(CH_2)_3$ piperidino) 2.5(t, 4H , -$(CH_2)_2$ piperidino) 3.8(s ,3H ,OCH_3) 4.5(s ,2H ,CH_2) 6.7(d, 1H, Ar-H) 7.0(d, 2H, Ar-H) 7.4(d, 2H, Ar-H) 7.8(d, 1H, Ar-H) 8.0(s, 1H, Ar-H).

2-((diethyl amino) methyl thio)-3-p-tolyl quinazolin-4(3H)-one (III E)

IR (KBr, cm-1): 3010(C-H Stretch Aromatic), 2960(C-H Stretch Aliphatic), 1658(C=O Stretch), 1496(C=C Stretch), 1370(S-CH_2 Stretch), 1340(-CH_3 Stretch).

^{1}H NMR Spectra ($CDCl_3$, δ ppm): 1.0(d ,6H , -$(CH_3)_2$) 2.1(s ,3H , -CH_3) 2.6(d ,4H ,$(CH_2)_2$) 3.9(s ,2H ,CH_2) 7.2(m, 4H, Ar-H) 7.5(t, 3H, Ar-H) 8.0(s, 1H, Ar-H).

6-Bromo-2-((dimethylamino) methylthio)-3-phenyl quinazolin-4(3H)-one (III F)

IR (KBr, cm-1): 3010(C-H Stretch Aromatic), 2960(C-H Stretch Aliphatic), 1658(C=O Stretch), 1496(C=C Stretch), 1370(-S-CH_2 Stretch).

^{1}H NMR Spectra ($CDCl_3$, δ ppm): 2.3(s, 6H, $(CH_3)_2$) 2.8(s, 2H, CH_2) 7.1(t, 1H, Ar-H) 7.7(d, 1H, Ar-H) 7.9(d, 4H, Ar-H) 8.2(d, 1H, Ar-H) 8.4(s, 1H, Ar-H).

Anti-Bacterial and Anti-Fungal Screening

The anti-bacterial activity of the test compounds **(II and III)** were assayed against the following bacteria: *Staphylococcus aureus* and *Bacillus subtilis* (gram-positive); *Klebsella pneumonia* and *Escherchia coli* (gram-negative), employing filter-paper strip method[25], Ciprofloxacin used as standard drug, the MIC results are represented in Table-2. Anti-fungal activity was evaluated against two fungi*: Fusarium oxysporum* and *Dreschlera haloids*, the test compounds **(II and III)** screened for antifungal activity using Sabouraud dextrose of czapexs dox agar medium[26], Flucanozole used as standard drug, the MIC results are represented in Table-3.

Table-2: Anti- bacterial activities of 1-N-substituted aminomethyl-3-aryl-3, 4-dihydro-4-oxoquinazolin-2-thione (II) and 2-S-substituted amino methyl thio-3-aryl-4(3H)-quinazolinones (III).

Compound	Antibaterial activity MIC (µg/ml)			
	B.subtilis	*S.aureus*	*E.coli*	*K. pneumonia*
Ciproflaxocin	3.12	3.12	6.25	6.25
II A	6.25	12.5	50	100
II B	50	50	100	200
II C	50	100	200	400
II D	50	50	100	200
II E	25	50	200	400
II F	50	50	100	200
II G	50	100	100	400
II H	50	50	25	100
II I	50	50	100	200
II J	50	50	100	200
III A	50	50	100	200
III B	50	100	200	400
III C	50	50	100	100
III D	50	100	50	25
III E	50	50	100	200
III F	50	50	100	100
III G	50	50	100	200
III H	50	100	200	400
III I	50	50	100	100
III J	50	50	100	200

Table-3: Anti-fungal activities of 1-N-substituted aminomethyl-3-aryl-3, 4-dihydro-4-oxoquinazolin-2-thione (II) and 2-S-substituted amino methyl thio-3-aryl-4(3H)-quinazolinones (III).

Compound	Antifungal activity MIC (µg/ml)	
	Dreschlera haloids	*Fusarium oxysporum*
Flucanozole	3.12	6.25
II A	12.5	100
II B	100	200
II C	200	400
II D	100	100
II E	50	25
II F	100	200
II G	200	400

II H	100	100
II I	100	100
II J	100	100
III A	100	200
III B	200	400
III C	100	100
III D	50	50
III E	100	200
III F	100	100
III G	100	200
III H	200	400
III I	100	100
III J	100	25

Analgesic and Anti-Inflammatory Testing

The analgesic and anti-inflammatory activities of the Mannich bases **(II and III)** were determined by standard methods using albino mice and albino rats respectively as experimental animals[27]. Aspirin and Diclofenac sodium were employed as standard drugs. The screening of anti-inflammatory of test compounds by carrageenan induced rat paw edema method is used; Diclofenac sodium was used as standard. The screening of analgesic activity of test compounds by Eddy's hot plate method, Haffneris tail clip and writhing methods were used, Aspirin was used as standard drug. The results are represented in Table-4 and 5.

Table-4: Anti-inflammatory activities of 1-N-substituted aminomethyl-3-aryl-3, 4-dihydro-4-oxoquinazolin-2-thione (II) and 2-S-substituted amino methyl thio-3-aryl-4(3H)-quinazolinones (III).

	Time (Percentage inhibition of the paw volume)			
Compound	1hr	2 hr	3hr	4hr
Carraggenan	NA	NA	NA	NA
Diclofenacsodium	32.84***	54.00***	66.34***	80.31***
II A	8.75	19.86**	41.34***	68.25***
II B	0.36	17.77**	33.97***	58.73***
II C	6.56	14.98*	29.80***	56.82***
II D	0	10.80*	29.16***	32.06***
II E	2.91	14.98*	34.61***	46.98***
II F	10.94	18.46**	33.01***	53.33***
II G	12.77	24.39***	32.37***	56.19***
II H	18.97*	27.17***	33.33***	38.09***
II I	9.12	22.64**	43.58***	45.23***
II J	3.64	15.67	50.64***	40.00***
III A	5.47	23.69*	48.07***	66.66***
III B	7.66	17.77	40.70***	68.88***
III C	9.85	22.29*	43.58***	67.93***
III D	10.94	26.13**	44.23***	51.58***
III E	7.29	17.77**	34.93***	47.93***
III F	5.47	27.87**	41.98***	55.23***
III G	7.29	19.16	41.02***	46.34***
III H	4.37	13.58	33.01***	35.39***
III I	5.47	23.69*	48.07***	56.66***
III J	4.01	17.77	40.70***	58.88***

*** = p<0.0 01; ** = p<0.01; * = p<0.05

Table-5: Analgesic activities of 1-N-substituted aminomethyl-3-aryl-3, 4-dihydro-4-oxoquinazolin-2-thione (II) and 2-S-substituted amino methyl thio-3-aryl-4(3H)-quinazolinones (III).

	Analgesic activity(% protection)		
Test compound	Tail clip	Hotplate	Writhing
Aspirin	68	64	68
II A	52	48	50
II B	50	46	44
II C	41	36	38
II D	33	35	43
II E	42	40	46
II F	34	36	32
II G	43	46	41
II H	45	47	43
II I	30	34	32
II J	41	44	40
III A	46	48	44
III B	40	38	40
III C	43	40	42
III D	31	30	35
III E	35	38	32
III F	34	40	36
III G	42	34	42
III H	34	36	40
III I	40	40	42
III J	38	35	32

RESULTS AND DISCUSSION

All the compounds of present investigation were found to be nontoxic as experimental animals were found to be safe. Among the Twenty compounds tested, exhibit a mild to moderate antibacterial activity, Among this series compound II A (X=H, Ar=C_6H_5, -N-$(CH_3)_2$) is a potent anti bacterial agent against B.subtilis and S.aureus with MIC values 6.25 and 12.5µg/ml and compounds II E and II H were also exhibit moderate antibacterial activity against B.subtilis and E.coli with MIC value 25µg/ml, compared with standard drug Ciproflaxocin show in Table-2. The same test compounds were also found to exhibit a mild to moderate fungicidal activity. These compounds effectively inhibit the spore germination of both the fungi *Dreschlera halodis* and *Fusarium oxysporum.* The anti-fungal action of the compound II A (X=H, Ar=C_6H_5, N-$(CH_3)_2$) show potent antifungal activity against D.halodis with MIC value is 12.5µg/ml, compounds II E (X=H, Ar=C_6H_4-CH_3(*p*),-N-$(CH_3)_2$) and III J (X=Br, Ar=C_6H_5, -N-$(CH_3)_2$) show moderate antifungal activity against F.oxysporum with MIC value is 25µg/ml compared with standard drug Flucanozole show in Table-3.

The test compounds showed mild to moderate anti-inflammatory activity in the range of 32.06 to 68.88 percentage inhibition of Carrageenan induced rat paw edema, show in Table--4. Comparatively more activity with 68.88 percentage of inhibition was observed for compound III B (X=H, Ar=C_6H_5, morpholine) and compounds IIA (X=H, Ar=C_6H_5, -N-$(CH_3)_2$), III C (X=H, Ar=C_6H_5, piperidine) and III A (X=H, Ar=C_6H_5, -N-$(CH_3)_2$) with percentages 68.25, 67.93, 66.66 at 4th hour among all the test compounds of this series compared with standard drug Diclofenac sodium.

All the test compounds showed mild to moderate analgesic activities compared with the standard drug, Aspirin. Percentage protection of analgesic activity in the range of 32-52, show in Table--5. Comparatively moderate analgesic activity exhibit compounds **IIA** (X=H, Ar=C_6H_5, -N-$(CH_3)_2$) and **IIB** (X=H, Ar=C_6H_5, N-$(C_2H_5)_2$) with 52 and 50 percentage protection, compared with standard drug, Aspirin.

CONCLUSION

In the present investigation the new N- and S- Mannich bases of quinazolinone derivatives were synthesized by using appropriate synthetic procedures. Scheme-1 (1-N-substituted aminomethyl-3-aryl-2-thioxo-2, 3-dihydroquinazolin-4(1H)-one **(II)** and Scheme-1 (2-S-substituted aminomethylthio-3-aryl-4(3H)-quinazolinones **(III)**. All the new derivatives were characterized by physical and spectral data. It was noted that the most of the derivatives were show mild to moderate antibacterial, antifungal, anti-inflammatory and analgesic activities.

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