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SYNTHESIS AND BIOLOGICAL ACTIVITIES OF SOME NEW N- AND S-AMINOMETHYLATION OF 4-ARYL-3, 4, 5, 6, 7, 8-HEXAHYDROQUINAZOLIN-2-THIONES

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Abstract:

The Mannich reaction on 4-aryl-3, 4, 5, 6, 7, 8-hexahydroquinazolin-2-thione, 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 3-N-substituted aminomethyl 4-aryl-3, 4, 5, 6, 7, 8-hexahydroquinazolin-2-thiones **(V)** and 2-S-substituted aminomethyl 4-aryl-3, 4, 5, 6, 7, 8-hexahydroquinazolin-2-thiones **(VI)** 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: Quinazoline, N-Mannich base, S-Mannich base, aqueous potassium carbonate

Introduction:

Various 4(3H)-quinazolines 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 quinazolines and the Mannich bases [2-4]. The required 3-N-substituted aminomethyl-4-aryl-3, 4, 5, 6, 7, 8-hexahydroquinazolin-2-thiones **(V)** and 2-S-substituted aminomethyl 4-aryl-3, 4, 5, 6, 7, 8-hexahydroquinazolin-2-thiones **(VI)** has been prepared from its different aromatic aldehydes[5,6,7] and condensed with various secondary amines in the presence of dimethylformamide and aqueous formaldehyde(Neutral medium) and aqueous potassium carbonate(Alkaline medium)(Scheme II).

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).

Table-1: Physical data of 3-N-substituted aminomethyl-4-aryl-3, 4, 5, 6, 7, 8-hexahydroquinazolin-2-thiones (V) and 2-S-substituted aminomethyl 4-aryl-3, 4, 5, 6, 7, 8-hexahydroquinazolin-2-thiones (VI):

Compound	Substituent in V and VI at 4th position	-NR_1R_2 in V and VI at 2nd & 3rd position	Mol.form	Mol.wt	MP ^{0}C	%Yield
V A	Ar=C_6H_5	dimethyl amino	$C_{17}H_{22}N_3S$	204-206	300	78
V B	Ar=C_6H_5	diethyl amino	$C_{19}H_{26}N_3S$	210-212	328	75
V C	Ar=C_6H_5	4-morpholino	$C_{19}H_{24}N_3OS$	218-220	342	73
V D	Ar=C_6H_5	1-piperidino	$C_{20}H_{26}N_3S$	212-214	340	70
V E	Ar=C_6H_4-Cl(*p*)	dimethyl amino	$C_{17}H_{21}ClN_3S$	231-233	334	76
V F	Ar=C_6H_4-Cl(*p*)	diethyl amino	$C_{19}H_{25}ClN_3S$	238-240	362	73
V G	Ar=C_6H_4-Cl(*p*)	4-morpholino	$C_{19}H_{23}ClN_3OS$	241-243	376	68
V H	Ar=C_6H_4-Cl(*p*)	1-piperidino	$C_{20}H_{25}ClN_3S$	240-242	374	65
V I	Ar=C_6H_4-OCH_3(*o*)	dimethyl amino	$C_{18}H_{24}N_3OS$	219-221	330	78
V J	Ar=C_6H_4-OCH_3(*o*)	diethyl amino	$C_{20}H_{28}N_3OS$	226-228	358	76
V K	C_6H_4-OCH_3(*o*)	4-morpholino	$C_{20}H_{26}N_3O_2S$	231-233	372	73
V L	C_6H_4-OCH_3(*o*)	1-piperidino	$C_{21}H_{28}N_3OS$	229-231	370	69
VI B	C_6H_5	diethyl amino	$C_{19}H_{26}N_3S$	214-216	328	78
VI D	C_6H_5	1-piperidino	$C_{20}H_{26}N_3S$	225-227	340	65
VI F	C_6H_4-Cl(*p*)	diethyl amino	$C_{19}H_{25}ClN_3S$	234-236	362	76
VI H	C_6H_4-Cl(*p*)	1-piperidino	$C_{20}H_{25}ClN_3S$	237-239	374	58
VI J	C_6H_4-OCH_3(*o*)	diethyl amino	$C_{20}H_{28}N_3OS$	229-231	358	70
VI K	C_6H_4-OCH_3(*o*)	4-morpholino	$C_{20}H_{26}N_3O_2S$	232-234	372	68
VI L	C_6H_4-OCH_3(*o*)	1-piperidino	$C_{21}H_{28}N_3OS$	230-232	370	62

VI Q	C_6H_4-OH(*o*)	dimethyl amino	$C_{17}H_{22}N_3OS$	208-210	316	74
VI R	C_6H_4-OH(*o*)	diethyl amino	$C_{19}H_{26}N_3OS$	228-230	344	70
VI S	C_6H_4-OH(*o*)	4-morpholino	$C_{19}H_{24}N_3O_2S$	234-236	358	68

Spectral data (IR & ^{1}H NMR) of Test compounds of Scheme-II (V & VI):

4-(4-methoxyphenyl)-3-(piperidin-1-yl methyl)-3,4,5,6,7,8-hexahydroquinazoline-2(1H)-thione (V L)

IR (KBr, cm-1):

3220(NH Stretch) , 3010(C-H Stretch Aromatic) ,2850(-OCH_3 Stretch Aliphatic), 1496(C=C Stretch) , 1470(-N-CH_2 Stretch) , 1200(C=S Stretch).

^{1}H NMR Spectra ($CDCl_3$, δ ppm):

1.4(t , 6H , 3CH_2) 1.8(t, 4H , 2CH_2) 2.3(d ,4H ,2CH_2) 2.6(d ,4H ,2CH_2) 3.6(s, 3H, OCH_3) 4.4(s, 1H, CH) 4.6(s, 2H, CH_2) 6.8(d, 2H, Ar-H) 7.2(d, 2H, Ar-H) 9.7(s, 1H, NH)

(4-(4-chlorophenyl)-1,4,5,6,7,8-hexahydroquinazolin-2-yl thio)-N,N-diethylmethanamine (VI F)

IR (KBr ,cm-1):

3220(NH Stretch) , 3010(C-H Stretch Aromatic) , 2960(C-H Stretch Aliphatic) , 1496(C=C Stretch) , 1370(-S-CH_2 Stretch) , 682.15(-Cl Stretch).

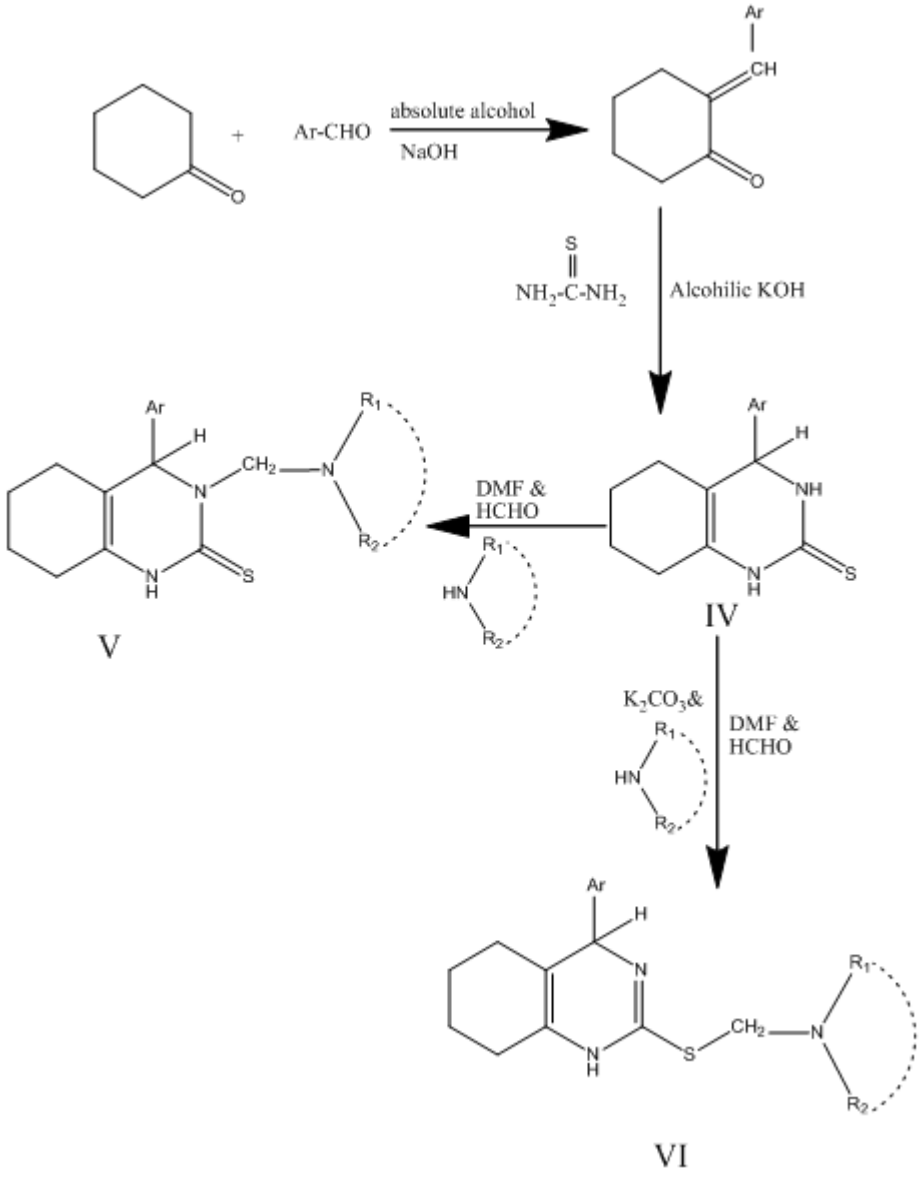
^{1}H NMR Spectra ($CDCl_3$, δ ppm):

1.0(d , 6H , $(CH_3)_2$) 1.6(t, 4H , $(CH_2)_2$) 1.9(d ,4H ,$(CH_2)_2$) 2.6(d ,4H , $(CH_2)_2$) 3.5(s, 1H, CH) 3.9(s, 2H, CH_2) 7.0(d, 2H, Ar-H) 7.5(d, 2H, Ar-H) 9.4(s, 1H, NH).

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 3-N-substituted aminomethyl-4-aryl-3, 4, 5, 6, 7, 8-hexahydroquinazolin-2-thiones **(V)** and 2-S-substituted aminomethyl 4-aryl-3, 4, 5, 6, 7, 8-hexahydroquinazolin-2-thiones **(VI)** were prepared by known procedures.



Scheme-II

Procedure for the Synthesis of 3-N-substituted aminomethyl-4-aryl-3, 4, 5, 6, 7, 8-hexahydroquinazolin-2-thiones (V):

Different aromatic aldehydes reacted with cyclohexanone in the presence of absolute alcohol and sodium hydroxide to form 2-arylidene cyclohexanone[11-14]. After 2-arylidene cyclohexanone reacted with thiourea in the presence of alcoholicKOH to form 4-aryl-3, 4, 5, 6, 7, 8-hexahydro quinazolin-2-thione. Each of the thiones will be subjected to the Mannich condensation under neutral conditions by using different acyclic or cyclic secondary amines, dimethylformamide and aqueous formaldehyde [15]with a normal expectation of obtaining N-Mannich bases **(V)** respectively. Physical data of compounds showed in Table-1.

Procedure for the Synthesis of 2-S-substituted aminomethyl 4-aryl-3, 4, 5, 6, 7, 8-hexahydroquinazolin-2-thiones (VI):

Different aromatic aldehydes reacted with cyclohexanone in the presence of absolute alcohol and sodium hydroxide to form 2-arylidene cyclohexanone[16]. After 2-arylidene cyclohexanone reacted with thiourea in the presence of alcoholicKOH to form 4-aryl-3, 4, 5, 6, 7, 8-hexahydro quinazolin-2-thione. 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, dimethylformamide and aqueous formaldehyde with a normal expectation of obtaining S-Mannich bases **(VI)** respectively. Physical data of compounds showed in Table-1.

Anti-bacterial and Anti-fungal screening:

The anti-bacterial activity[17] of the test compounds **(V & VI)** 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, Ciprofloxacin used as standard drug, the MIC results are represented in Table-2. Anti-fungal activity[18] was evaluated against two fungi*: Fusarium oxysporum* and *Dreschlera haloids*, the test compounds **(V & VI)** screened for antifungal activity using Sabouraud dextrose of czapexs dox agar medium, Flucanozole used as standard drug, the MIC results are represented in Table- 3.

Table-2: Anti- bacterial activities of 3-N-substituted aminomethyl-4-aryl-3, 4, 5, 6, 7, 8-hexahydroquinazolin-2-thiones (V) and 2-S-substituted aminomethyl 4-aryl-3, 4, 5, 6, 7, 8-hexahydroquinazolin-2-thiones (VI):

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

V H	50	100	200	400
V I	50	50	100	100
V J	50	100	200	400
V K	50	50	100	100
V L	100	50	100	200
VI B	50	50	100	200
VI D	50	50	100	200
VI F	50	50	25	200
VI H	25	100	100	400
VI J	50	50	100	200
VI K	50	50	100	200
VI L	50	100	100	400
VI Q	50	50	100	200
VI R	50	50	100	200
VI S	50	50	100	200

Table-3: Anti-fungal activities of 3-N-substituted aminomethyl-4-aryl-3, 4, 5, 6, 7, 8-hexahydroquinazolin-2-thiones (V) and 2-S-substituted aminomethyl 4-aryl-3, 4, 5, 6, 7, 8-hexahydroquinazolin-2-thiones (VI):

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

V K	100	100
V L	100	200
VI B	100	200
VI D	100	200
VI F	25	200
VI H	100	400
VI J	100	200
VI K	100	200
VI L	100	400
VI Q	100	200
VI R	100	200
VI S	100	200

Analgesic and Anti-inflammatory testing:

The analgesic and anti-inflammatory[19] activities of the Mannich bases **(V & VI)** were determined by standard methods using albino mice and albino rats respectively as experimental animals. 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 & 5.

Table-4: Anti-inflammatory activities of 3-N-substituted aminomethyl-4-aryl-3, 4, 5, 6, 7, 8-hexahydroquinazolin-2-thiones (V) and 2-S-substituted aminomethyl 4-aryl-3, 4, 5, 6, 7, 8-hexahydroquinazolin-2-thiones (VI):

	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***
V A	8.75	19.86**	41.34***	68.25***
V B	0.36	17.77**	33.97***	58.73***
V C	6.56	14.98*	29.80***	56.82***
V D	0	10.80*	29.16***	52.06***
V E	2.91	14.98*	34.61***	46.98***

V F	7.29	22.64***	37.50***	57.77***
V G	10.94	18.46**	33.01***	53.33***
V H	12.77	24.39***	32.37***	56.19***
V I	18.97*	27.17***	33.33***	48.09***
V J	4.01	13.58*	35.57***	46.50***
V K	6.56	19.51*	35.57***	50.15***
V L	3.64	15.67*	36.53***	38.41***
VI B	7.66	19.51	57.05***	70.15***
VI D	3.64	15.67	50.64***	62.00***
VI F	5.47	23.69*	48.07***	66.66***
VI H	9.85	22.29*	43.58***	57.93***
VI J	10.94	26.13**	44.23***	61.58***
VI K	7.29	17.77**	34.93***	47.93***
VI L	6.20	26.48**	44.23***	53.80***
VI Q	4.01	17.77	40.70***	58.88***
VI R	2.55	29.26**	50.00***	57.46***
VI S	5.83	25.43**	51.28***	58.73***

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

Table-5: Analgesic activities of 3-N-substituted aminomethyl-4-aryl-3, 4, 5, 6, 7, 8-hexahydroquinazolin-2-thiones (V) and 2-S-substituted aminomethyl 4-aryl-3, 4, 5, 6, 7, 8-hexahydroquinazolin-2-thiones (VI):

	Analgesic activity(% protection)		
Test compound	***Tail clip***	***Hotplate***	***Writhing***
Aspirin	68	64	68
V A	40	44	42
V B	36	40	42
V C	30	34	36
V D	32	34	38
V E	50	48	50
V F	48	46	48
V G	60	56	58
V H	62	60	62
V I	32	34	36

V J	40	42	44
V K	42	44	40
V L	34	36	38
VI B	43	45	42
VI D	42	44	43
VI F	50	52	54
VI H	66	62	64
VI J	35	37	33
VI K	42	44	43
VI L	44	46	42
VI Q	42	45	43
VI R	36	38	40
VI S	34	32	38

Results and discussion:

All the test compounds of present investigation were found to be nontoxic as experimental animals were found to be safe. Among the Twenty two compounds tested, exhibit a mild to moderate antibacterial activity, Among this series, the test compounds **V E** (Ar=C_6H_4 –Cl (p), -NR_1R_2=dimethyl amino) and **V F** (Ar= C_6H_4 –Cl (p), -NR_1R_2=diethyl amino) exhibited most potent antibacterial towards B.subtilis with MIC values 6.25 and 12.5µg/ml respectively. The compounds **V A** (Ar=C_6H_5, -NR_1R_2=dimethyl amino) **VI F** (Ar= C_6H_5-Cl (p), -NR_1R_2=diethyl amino) **VI H** (Ar= C_6H_5-Cl (p), -NR_1R_2=piperidino) showed moderate antibacterial activity towards E.coli and B.subtilis with MIC values 25µg/ml respectively. Remaining all the test compounds showed lower antibacterial activity than the standard drug, Ciprofloxacin 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* & *Fusarium oxysporum.* Among all the compounds tested, the test compounds **VA** (Ar=C_6H_5, -NR_1R_2=dimethyl amino) **V E** (Ar=C_6H_4 –Cl (p), -NR_1R_2=dimethyl amino) and exhibited most potent antifungal towards F.oxysporum, D.halodis with MIC values 12.5µg/ml respectively. The compounds **V F** (Ar= C_6H_4 –Cl (p), -NR_1R_2=diethyl amino), **V G** (Ar= C_6H_4 –Cl (p), -NR_1R_2=morpholino) **V H** (Ar= C_6H_4 –Cl (p), -NR_1R_2=piperidino) and compound **VI F** (Ar= C_6H_5-Cl (p), -NR_1R_2= diethylamino) showed moderate

antifungal activity towards D.hlodis, F.oxysporum, D.halodis, D.halodis with MIC values 25µg/ml respectively. Remaining all the test compounds showed lower antifungal activity than the standard drug, Flucanozole, show in Table-3.

The test compounds showed mild to moderate anti-inflammatory activity in the range of 38.41 to 70.15 percentage inhibition of Carrageenan induced rat paw edema, show in Table-4. Comparatively more activity with 70.15 percentage of inhibition was observed for compound **VIB** (Ar=C_6H_5, -NR_1R_2=diethyl amino) at 4^{th} hour among all the test compounds. Moderate activity was observed for compounds **VA** (Ar=C_6H_5, -NR_1R_2=dimethyl amino), **VID** (Ar=C_6H_5,-NR_1R_2=piperidino) **VIF** (Ar= C_6H_5-Cl (p),-NR_1R_2=diethylamino) and **VIJ** (Ar= C_6H_5-OCH_3 (o), -NR_1R_2= diethyl amino) with percentage inhibition of 68.25, 62.00, 66.66and 61.58 respectively.Compound **VL** (Ar=C_6H_4-OCH_3 (o),-NR_1R_2= piperidino,) showed lowest inhibition with 38.41 percentage among all the test compounds.

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 32-66, show in Table-5. Comparatively superior analgesic activity exhibit **VIH** (Ar= C_6H_5-Cl (p), -NR_1R_2=piperidino) with 66 percentage protection, compared with standard drug, Aspirin. Compounds **VH** (Ar= C_6H_5-Cl (p), -NR_1R_2=piperidino) and **VG** (Ar= C_6H_5-Cl (p), -NR_1R_2=morpholino) exhibit moderate analgesic activity with 62 and 60 percentage protection against standard Aspirin. Remaining all the test compounds showed lower analgesic activity than the standard drug, Aspirin.

Conclusion:

In the present investigation the new N- and S- Mannich bases of quinazoline derivatives were synthesized by using appropriate synthetic procedures. In Scheme-II, to synthesise the 3-N-substituted aminomethyl-4-aryl-3, 4, 5, 6, 7, 8-hexahydroquinazolin-2-thiones **(V)** and 2-S-substituted aminomethyl 4-aryl-3, 4, 5, 6, 7, 8-hexahydroquinazolin-2-thiones **(VI).** 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-inflammatiory and analgesic activities.

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