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Synthesis and Biological Activities of Some New C-Aminomethylation of 5*H*-5-Aryl-6,7,8,9-tetrahydrothiazolo[2,3-b]quinazolin-3(2*H*)-one and 6*H*-6-Aryl-2,3,7,8,9,10-hexahydrothiazino[2,3-b]quinazolin-4(3*H*)-one

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The synthesis of 5*H*-5-aryl-6,7,8,9-tetrahydrothiazolo[2,3-b]quinazolin-3(2*H*)-one and 6*H*-6-aryl-2,3,7,8,9,10-hexahydrothiazino[2,3-b]quinazolin-4(3*H*)-one, reaction between 4-aryl-3,4,5,6,7,8-hexahydroquinazolin-2-thione and methyl chloroacetate and ethyl β-bromo propionate. The Mannich reaction on 5*H*-5-aryl-6,7,8,9-tetrahydrothiazolo[2,3-b]quinazolin-3(2*H*)-one and 6*H*-6-aryl-2,3,7,8,9,10-hexahydrothiazino[2,3-b]quinazolin-4(3*H*)-one in ethanol, aqueous formaldehyde and different secondary amines yielded a single product C-Mannich base in each case. The obtained C-Mannich bases (compounds **VIII** and **X**) have been characterized on the basis of analytical spectral data. These C-Mannich bases have been screened for their antibacterial, antifungal, anti-inflammatory and analgesic activities.

Keywords: Quinazoline, Thiazino, Thiazolo, C-Mannich base.

INTRODUCTION

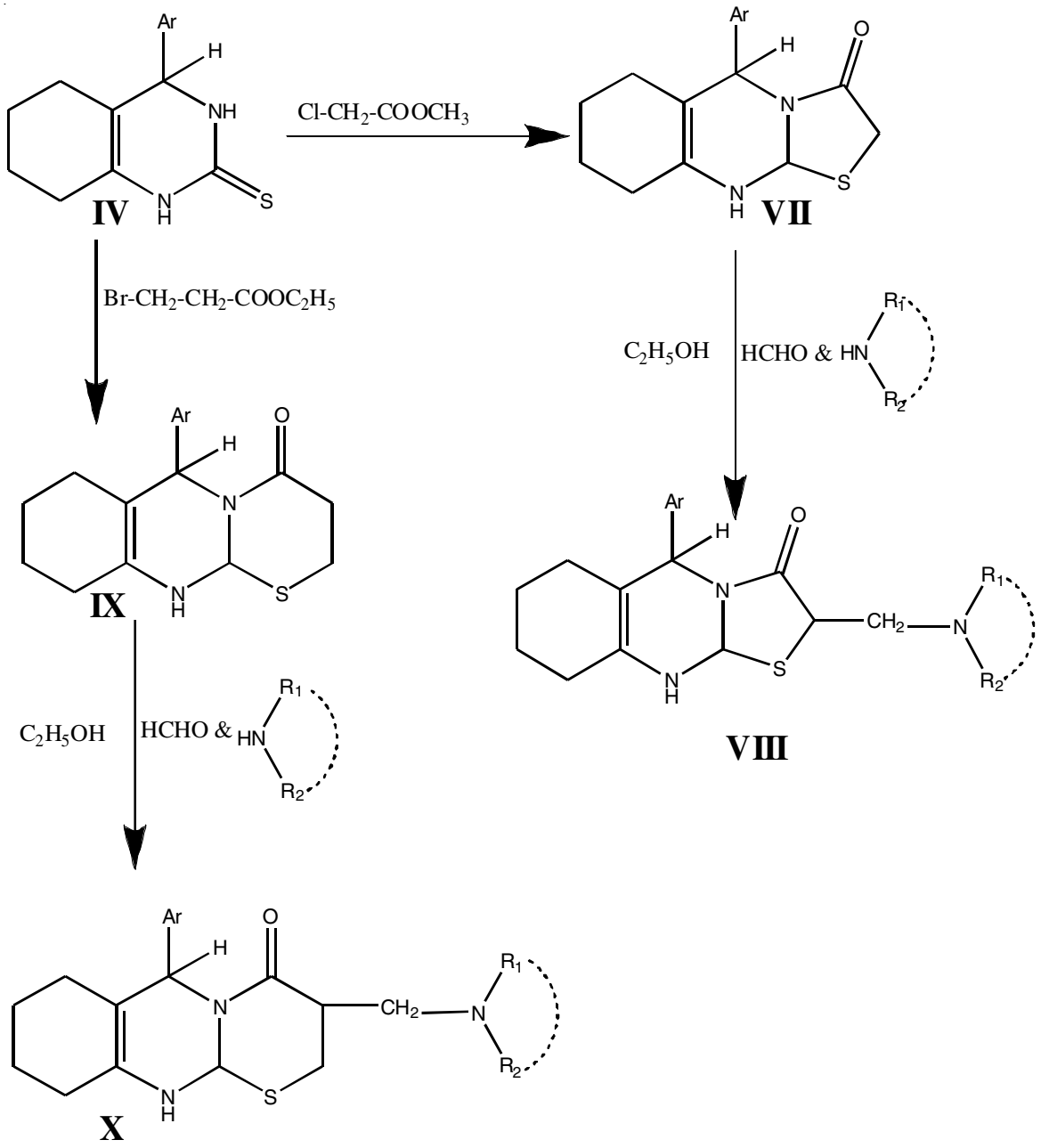
Various 4(3*H*)-quinazolines and their derivatives are known for their varied biological and pharmacological importance [1]. The C-substituted amino alkyl moieties have been found to be associated with CNS, analgesic and anti-inflammatory activities. Therefore, in continuation of our investigations on quinazolines and the Mannich bases [2-4]. The required C-Mannich bases (**VIII**) and (**X**) have been prepared from its different aromatic aldehydes [5], methyl chloroacetate, ethyl β-bromo propionate and condensed with various secondary amines in the presence of ethanol and aqueous formaldehyde (**Scheme-I**). Purification of the products yielded a single compound (TLC) in each case. These compounds 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 (ν_{max}, cm^{-1}) were recorded on Perkin-Elmer infracord-283 spectrophotometer in nujal mull and NMR spectra on varian EM-360 (90 MHz) spectrophotometer using TMS as internal standard [6-8]. The C-Mannich bases (**VIII**) and (**X**) were prepared by known procedures.

General procedure for synthesis of new C-Mannich bases (VIII): Different aromatic aldehydes reacted with cyclohexanone in the presence of absolute alcohol and sodium hydroxide to form 2-arylidene cyclohexanone [6,7,9,10]. After 2-arylidene cyclohexanone reacted with thiourea in the presence of alcoholic KOH to form 4-aryl-3,4,5,6,7,8-hexahydroquinazolin-2-thione. After the 4-aryl-3,4,5,6,7,8-hexahydroquinazolin-2-thione reacted with methyl chloroacetate to form 5*H*-5-aryl-6,7,8,9-tetrahydrothiazolo[2,3-b]quinazolin-3(2*H*)-one. Each of the thiazolo compounds will be subjected to the Mannich condensation in ethanol by using different acyclic or cyclic secondary amines and aqueous formaldehyde [10] with a normal expectation of obtaining C-Mannich bases (**VIII**), respectively. Physical data of compounds showed in Table-1.

General procedure for synthesis of new C-Mannich bases (X): Different aromatic aldehydes reacted with cyclohexanone in the presence of absolute alcohol and sodium hydroxide to form 2-arylidene cyclohexanone [11]. Then 2-arylidene cyclohexanone reacted with thiourea in the presence of alcoholic KOH to form 4-aryl-3,4,5,6,7,8-hexahydroquinazolin-2-thione. After that the 4-aryl-3,4,5,6,7,8-hexahydroquinazolin-2-thione reacted with ethyl β-bromo propionate to form 6*H*-6-aryl-2,3,7,8,9,10-hexahydrothiazino-[2,3-b]quinazolin-4(3*H*)-one. Each of the thiazino compounds will be subjected to the Mannich condensation in ethanol by using different acyclic or cyclic secondary amines and aqueous formaldehyde [12] with an expectation of obtaining C-Mannich



Scheme-I

bases (**X**), respectively. Physical data of compounds showed in Table-1.

Spectral data (IR and ^{1}H NMR) of test compounds of VIII and X (Scheme-I)

5-(4-Chloro phenyl)-2-(morpholinomethyl)-6,7,8,9,10,10a-hexahydro-2*H*-thiazolo[2,3-b]quinazolin-3(5*H*)-one (VIII G): IR (KBr, ν_{max}, cm^{-1}): 3220 (NH stretch), 3010 (C-H stretch aromatic), 1658 (C=O stretch), 1496 (C=C stretch), 1470 (-N-CH_2 stretch), 682.15 (-Cl stretch). ^{1}H NMR spectra ($CDCl_3$, δ ppm): 1.7 (t, 4H, $2CH_2$), 1.9 (d, 4H, $2CH_2$), 2.6 (d, 4H, $2CH_2$), 3.1 (s, 2H, CH_2), 3.5 (d, 4H, $2CH_2$), 3.8 (s,1H, CH), 5.5 (s, 1H, CH), 5.8 (s, 1H, CH), 7.3 (d, 4H, Ar-H), 8.8 (s, 1H, NH).

6-(4-Methoxy phenyl)-3-(dimethyl amino methyl)-2,3,7,8,9,10,11,11a-octahydro-[1,3]-thiazino[2,3-b]quinazolin-4(6H)-one (X I): IR (KBr, ν_{max}, cm^{-1}): 3220 (NH stretch), 3010 (C-H stretch aromatic), 2850 (-OCH_3 stretch), 1658 (C=O stretch), 1496 (C=C stretch), 1470 (-N-CH_2 stretch). ^{1}H NMR spectra ($CDCl_3$, δ ppm): 1.6 (t, 4H, $2CH_2$), 1.9 (d, 4H, $2CH_2$), 2.5 (s, 6H, $2(CH_3)_2$), 2.7 (s, 2H, CH_2), 3.1 (s, 2H, CH_2), 3.5 (s, 1H, CH), 3.8 (s, 3H, OCH_3) 5.5 (s, 1H, CH), 5.7 (s, 1H, CH), 6.8 (d, 2H, Ar-H), 7.3 (d, 2H, Ar-H), 8.2(s, 1H, NH).

Antibacterial and antifungal screening: The antibacterial activity [13] of the test compounds (**VIII** and **X**) 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.

The antifungal activity [14] was evaluated against two fungi*: Fusarium oxysporum* and *Dreschlera haloids*, the test compounds (**VIII** and **X**) screened for antifungal activity using

TABLE-1
PHYSICAL DATA OF C-AMINOMETHYLATION OF 5*H*-5-ARYL-6,7,8,9-TETRAHYDROTHIAZOLO[2,3-b]QUINAZOLIN-3(2*H*)-ONE AND 6*H*-6-ARYL-2,3,7,8,9,10-HEXAHYDROTHIAZINO[2,3-b]QUINAZOLIN-4(3*H*)-ONE

Compound	Substituent in **VIII** and **X** at 4th position	-NR_1R_2 in **VIII** and **X** at 2nd and 3rdposition	m.f.	m.w.	m.p. (°C)	Yield (%)
VIII A	Ar = C_6H_5	Dimethyl amino	$C_{19}H_{23}N_3OS$	341	236-238	72
VIII B	Ar = C_6H_5	Diethyl amino	$C_{21}H_{27}N_3OS$	369	242-244	75
VIII C	Ar = C_6H_5	4-Morpholino	$C_{21}H_{25}N_3O_2S$	383	249-251	70
VIII D	Ar = C_6H_5	1-Piperidino	$C_{22}H_{27}N_3OS$	381	246-248	62
VIII E	Ar = C_6H_4-Cl(*p*)	Dimethyl amino	$C_{19}H_{22}N_3OSCl$	375	234-236	74
VIII F	Ar = C_6H_4-Cl(*p*)	Diethyl amino	$C_{21}H_{26}N_3OSCl$	403	240-242	72
VIII G	Ar = C_6H_4-Cl(*p*)	4-Morpholino	$C_{21}H_{24}N_3O_2SCl$	417	246-248	68
VIII H	Ar = C_6H_4-Cl(*p*)	1-Piperidino	$C_{22}H_{26}N_3OSCl$	415	244-246	56
VIII I	Ar = C_6H_4-OCH_3(*o*)	Dimethyl amino	$C_{20}H_{25}N_3O_2S$	371	233-235	72
VIII J	Ar = C_6H_4-OCH_3(*o*)	Diethyl amino	$C_{22}H_{29}N_3O_2S$	399	239-241	76
VIII M	Ar = C_6H_5-CH=CH	Dimethyl amino	$C_{21}H_{25}N_3OS$	367	230-232	74
VIII N	Ar = C_6H_5-CH=CH	Diethyl amino	$C_{23}H_{29}N_3OS$	395	240-242	72
VIII Q	Ar = C_6H_4-OH(*o*)	Dimethyl amino	$C_{19}H_{23}N_3O_2S$	357	228-230	72
VIII R	Ar = C_6H_4-OH(*o*)	Diethyl amino	$C_{21}H_{27}N_3O_2S$	385	241-243	76
X A	Ar = C_6H_5	Dimethyl amino	$C_{20}H_{25}N_3OS$	355	224-226	74
X B	Ar = C_6H_5	Diethyl amino	$C_{22}H_{29}N_3OS$	383	232-234	78
X C	Ar = C_6H_5	4-Morpholino	$C_{22}H_{27}N_3O_2S$	397	238-240	72
X D	Ar = C_6H_5	1-Piperidino	$C_{23}H_{29}N_3OS$	395	236-238	65
X E	Ar = C_6H_4-Cl(*p*)	Dimethyl amino	$C_{20}H_{24}N_3OSCl$	389	244-246	72
X F	Ar = C_6H_4-Cl(*p*)	Diethyl amino	$C_{22}H_{28}N_3OSCl$	417	246-248	76
X G	Ar = C_6H_4-Cl(*p*)	4-Morpholino	$C_{22}H_{26}N_3O_2SCl$	431	249-251	62
X H	Ar = C_6H_4-Cl(*p*)	1-Piperidino	$C_{23}H_{28}N_3OSCl$	429	247-249	58
X I	Ar = C_6H_4-OCH_3(*o*)	Dimethyl amino	$C_{21}H_{27}N_3O_2S$	385	235-237	75
X J	Ar = C_6H_4-OCH_3(*o*)	Diethyl amino	$C_{23}H_{31}N_3O_2S$	413	240-242	70
X M	Ar = C_6H_5-CH=CH	Dimethyl amino	$C_{22}H_{27}N_3OS$	381	233-246	72
X N	Ar = C_6H_5-CH=CH	Diethyl amino	$C_{24}H_{31}N_3OS$	409	238-240	70
X Q	Ar = C_6H_4-OH(*o*)	Dimethyl amino	$C_{20}H_{25}N_3O_2S$	371	232-234	74
X R	Ar = C_6H_4-OH(*o*)	Diethyl amino	$C_{22}H_{29}N_3O_2S$	399	234-236	70

Sabouraud dextrose of czapexs dox agar medium, flucanozole used as standard drug, the MIC results are represented in Table-3.

Analgesic and anti-inflammatory testing: The analgesic and anti-inflammatory [15] activities of the Mannich bases (**VIII** and **X**) 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 Tables 4 and 5.

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 eight compounds tested, exhibit a mild to moderate antibacterial activity. Among this series, the test compounds **VIII A** (Ar = C_6H_5, -NR_1R_2 = dimethyl amino) and **VIII E** (Ar = C_6H_4–Cl (*p*), -NR_1R_2 = dimethyl amino) and **X A** (Ar = C_6H_5, -NR_1R_2 = dimethyl amino), **X E** (Ar = C_6H_4–Cl (*p*), -NR_1R_2 = dimethyl amino) exhibited most potent antibacterial towards *B. subtilis* and *S. aureus* with MIC values 6.25 and 12.5 µg/mL, respectively. The compounds **VIII F** (Ar = C_6H_4–Cl (*p*) -NR_1R_2 = diethyl amino) **VIII G** (Ar =

TABLE-2
ANTIBACTERIAL ACTIVITIES OF C-AMINOMETHYLATION OF 5*H*-5-ARYL-6,7,8,9-TETRAHYDROTHIAZOLO[2,3-b] QUINAZOLIN-3(2*H*)-ONE AND 6*H*-6-ARYL-2,3,7,8,9,10-HEXAHYDROTHIAZINO[2,3-b]QUINAZOLIN-4(3*H*)-ONE

Compound	Antibaterial activity MIC (µg/mL)			
	B. subtilis	*S. aureus*	*E. coli*	*K. pneumonia*
Ciproflaxocin	3.12	3.12	6.25	6.25
VIII A	6.25	12.5	50	100
VIII B	50	50	100	200
VIII C	50	100	200	400
VIII D	50	50	100	100
VIII E	6.25	12.5	50	100
VIII F	25	100	50	50
VIII G	50	25	100	200
VIII H	50	100	25	400
VIII I	50	50	100	100
VIII J	50	50	100	200
VIII M	50	50	100	200
VIII N	50	100	200	400
VIII Q	50	100	200	400
VIII R	50	50	50	100
X A	6.25	12.5	100	50
X B	100	50	200	50
X C	100	100	50	200
X D	50	100	100	50
X E	6.25	12.5	50	100
X F	25	50	100	200
X G	50	25	100	200
X H	50	100	25	400
X I	50	50	100	100
X J	50	100	200	400
X M	50	100	200	400
X N	50	50	100	200
X Q	50	100	50	100
X R	50	50	100	200

C_6H_4–Cl (*p*), -NR_1R_2 = morpholino) **VIII H** (Ar = C_6H_4–Cl (*p*), -NR_1R_2 = piperidino) and **X F** (Ar = C_6H_4–Cl(*p*), -NR_1R_2 = diethylamino) **XG** (Ar = C_6H_4–Cl (*p*), -NR_1R_2 = morpholino) **X H** (Ar = C_6H_4–Cl (*p*), -NR_1R_2 = piperidino) showed moderate antibacterial activity towards *B. subtilis*, *S. aureus* and *E. coli* with MIC values 25 µg/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* and *Fusarium oxysporum.* Among all the compounds tested, the test compounds **VIII E** (Ar = C_6H_4–Cl (*p*), -NR_1R_2 = dimethyl amino) and **VIII F** (Ar = C_6H_4–Cl (*p*) -NR_1R_2 = diethyl amino) and **X E** (Ar = C_6H_4–Cl (*p*), -NR_1R_2 = dimethyl amino) exhibited most potent antifungal towards *D. halodis*, *F. oxysporum* and *D. halodis* with MIC values 12.5 µg/mL, respectively. The compounds **VIIIG** (Ar = C_6H_4–Cl (*p*), -NR_1R_2 = morpholino) **VIII H** (Ar = C_6H_4–Cl (*p*), -NR_1R_2 = piperidino) and **X F** (Ar = C_6H_4–Cl (*p*) -NR_1R_2 = diethyl amino) **X G** (Ar = C_6H_4–Cl (*p*), -NR_1R_2 = morpholino) **X H** (Ar = C_6H_4–Cl (*p*), -NR_1R_2 = piperidino) showed moderate antifungal activity towards *D. halodis*, *F. oxysporum*, *D. halodis*, *F. oxysporum* and *D. halodis* with MIC values 25 µg/mL, respectively. Remaining all the test compounds showed lower antifungal activity than the standard drug (flucanozole) show in Table-3.

TABLE-3
ANTIFUNGAL ACTIVITIES OF C-AMINOMETHYLATION OF 5*H*-5-ARYL-6,7,8,9-TETRAHYDROTHIAZOLO[2,3-b] QUINAZOLIN-3(2*H*)-ONE AND 6*H*-6-ARYL-2,3,7,8,9,10-HEXAHYDROTHIAZINO[2,3-b]QUINAZOLIN-4(3*H*)-ONE

Compound	Antifungal activity MIC (µg/mL)	
	Dreschlera haloids	*Fusarium oxysporum*
Fluconazole	3.12	6.25
VIII A	50	100
VIII B	100	200
VIII C	200	400
VIII D	100	100
VIII E	12.5	100
VIII F	50	12.5
VIII G	25	200
VIII H	100	25
VIII I	100	100
VIII J	100	200
VIII M	100	200
VIII N	200	400
VIII Q	200	400
VIII R	50	100
X A	100	200
X B	200	50
X C	50	200
X D	100	50
X E	12.5	100
X F	25	50
X G	100	25
X H	25	400
X I	100	100
X J	200	400
X M	50	400
X N	100	200
X Q	50	100
X R	100	200

The test compounds showed mild to moderate anti-inflammatory activity in the range of 36.19 to 79.67 % inhibition of Carrageenan induced rat paw edema, show in Table-4. Comparatively more activity with 79.67 and 75.23 % of inhibition was observed for compounds **VIIIA** (Ar =C_6H_5, -NR_1R_2 = dimethylamino) and **XA** (Ar = C_6H_5, -NR_1R_2 = dimethylamino) at 4th h among all the test compounds. Moderate activity was observed for compounds **VIIIC** (Ar = C_6H_5, -NR_1R_2 = morpholino), **VIIIE** (Ar = C_6H_5-Cl (*p*),-NR_1R_2 = dimethylamino) and **VIII I** (Ar = C_6H_5-OCH_3 (*o*), -NR_1R_2 = dimethylamino) **X M** (Ar = C_6H_5- CH=CH, -NR_1R_2 = dimethyl amino), **X N** (Ar = C_6H_5- CH=CH, -NR_1R_2 = diethyl amino) with percentage inhibition of 71.61, 70.96, 68.25, 67.61and 66.66, respectively. Compound **X Q** (Ar = C_6H_4-OH (*o*), -NR_1R_2 = dimethylmino) showed lowest inhibition with 36.19 % among all the test compounds.

TABLE-4
ANTI-INFLAMMATORY ACTIVITIES OF C-AMINOMETHYLATION OF 5*H*-5-ARYL-6,7,8,9-TETRAHYDROTHIAZOLO[2,3-b] QUINAZOLIN-3(2*H*)-ONE AND 6*H*-6-ARYL-2,3,7,8,9,10-HEXAHYDROTHIAZINO[2,3-b] QUINAZOLIN-4(3*H*)-ONE

Compound	Time (h, percentage inhibition of the paw volume)			
	1	2	3	4
Carraggenan	NA	NA	NA	NA
Diclofenac sodium	32.84***	54.00***	66.34***	80.31***
VIII A	11.49	26.33***	47.68***	79.67***
VIII B	3.44	22.41***	39.73***	63.22***
VIII C	20.68*	28.46***	40.39***	71.61***
VIII D	7.27	25.62***	41.05***	55.48***
VIII E	6.51	19.57***	48.67***	70.96***
VIII F	17.24	27.40***	39.73***	49.67***
VIII G	8.42	25.97***	43.04***	57.09***
VIII H	4.98	24.91***	35.76***	60.64***
VIII I	8.75	19.86**	41.34***	68.25***
VIII J	0.36	17.77**	33.97***	58.73***
VIII M	2.91	14.98*	34.61***	46.98***
VIII N	7.29	22.64***	37.50***	57.77***
VIII Q	18.97*	27.17***	33.33***	38.09***
VIII R	4.01	13.58*	35.57***	36.50***
X A	5.47	28.57***	48.39***	75.23***
X B	5.83	21.95*	43.91***	61.26***
X C	9.12	22.64**	43.58***	60.23***
X D	7.29	27.87***	47.11***	54.92***
X E	3.64	19.16*	45.19***	57.61***
X F	6.56	18.46*	47.43***	58.09***
X G	13.13	23.69**	42.94***	44.76***
X H	14.59	26.13*	41.02***	54.76***
X I	7.29	18.81	44.55***	56.98***
X J	7.66	19.51	57.05***	60.15***
X M	8.02	14.63	49.03***	67.61***
X N	5.47	23.69*	48.07***	66.66***
X Q	13.13	28.91**	35.25***	36.19***
X R	10.94	26.13**	44.23***	60.58***

$^{***}p < 0.0\,01$; $^{**}p < 0.01$; $^{*}p < 0.05$

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 36-66, show in Table-5. Comparatively superior analgesic activity exhibit compounds **VIII H** (Ar = C_6H_5-Cl (*p*), -NR_1R_2 = piperidino) and **X H** (Ar = C_6H_5-Cl (*p*), -NR_1R_2 = piperidino) with 66

TABLE-5
ANALGESIC ACTIVITIES OF C-AMINOMETHYLATION OF 5*H*-5-ARYL-6,7,8,9-TETRAHYDROTHIAZOLO[2,3-b] QUINAZOLIN-3(2*H*)-ONE AND 6*H*-6-ARYL-2,3,7,8,9,10-HEXAHYDROTHIAZINO[2,3-b] QUINAZOLIN-4(3*H*)-ONE

Test compound	Analgesic activity (% protection)		
	Tail clip method	Hotplate method	Writhing method
Aspirin	68	64	68
VIII A	40	42	44
VIII B	44	40	42
VIII C	42	42	44
VIII D	32	34	36
VIII E	50	52	50
VIII F	48	46	48
VIII G	62	60	58
VIII H	64	62	64
VIII I	34	37	40
VIII J	40	42	44
VIII M	42	44	40
VIII N	40	43	40
VIII Q	40	43	36
VIII R	45	41	43
X A	40	46	42
X B	48	44	40
X C	40	48	42
X D	42	44	46
X E	56	52	54
X F	50	52	54
X G	58	60	56
X H	66	62	60
X I	40	42	44
X J	44	40	40
X M	32	30	48
X N	40	44	48
X Q	48	46	40
X R	45	40	46

and 64 % protection, compared with standard drug, aspirin. Compounds **VIII G** (Ar = C_6H_5-Cl (*p*), -NR_1R_2 = morpholino) and **X H** (Ar = C_6H_5-Cl (*p*), -NR_1R_2 = piperidino) exhibit moderate analgesic activity with 62 and 60 % protection against standard aspirin. Remaining all the test compounds showed lower analgesic activity than the aspirin.

Conclusion

In the present investigations, the new C-Mannich bases of quinazolinone derivatives were synthesized by using appropriate synthetic procedures. **Scheme-I** showed the reaction of C-aminomethylation of 5*H*-5-aryl-6,7,8,9-tetrahydrothiazolo[2,3-b]quinazolin-3(2*H*)-one (**VIII**) and 6*H*-6-aryl-2,3,7,8,9,10-hexahydrothiazino[2,3-b] quinazolin-4(3*H*)-one (**X**). 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, anti-fungal, anti-inflammatiory and analgesic activities.

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