ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Synthesis and Biological activities of some S-Mannich bases of 1,4,5,6,7,8-Hexahydro Quinazolines

Damerakonda Kumaraswamy*[1], Vanga mallareddy

Dept. of Pharmaceutical chemistry, Vaagdevi College of Pharmacy, Warangal, Andhra Pradesh, India.

ABSRACT

The Mannich reaction on 4-aryl-hexahydro quinazolin-2(1H) thione with different secondary amines yielded a single product in each case. The mannich bases obtained have been characterized as the corresponding S-Mannich bases of quinazolinones on the basis of analytical spectral data. These S-Substituted compounds have been screened for their Anti- bacterial, Anti fungal, Anti -inflammatory activities.

Keywords: Mannich reaction, 4- aryl-hexxahydro quinazolin-2(1H) thione, S-Mannich bases, Anti- bacterial, Anti fungal, Anti –inflammatory.

Corresponding author

ISSN: 0975-8585

INTRODUCTION

Various 4(3H)-quinazolinones and their derivatives are known for their varied biological and pharmacological importance [1]. 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 S-Mannich bases of 1,4,5,6,7,8-Hexahydro quinazolines has been prepared from its different aromatic aldehydes and condensed with various secondary amines in the presence of ethanol and aqueous potassium carbonate(Scheme I). Purification of the products yielded a single compound (TLC) in each case. They have been characterized by the analytical, IR and PMR 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 PMR spectra on varian EM-360(90HMz) spectrophotometer using TMS as internal standard [5-7]. S-Mannich bases of quinazolines has been prepared by known procedure.

Synthesis of S-Mannich bases of 1,4,5,6,7,8-Hexahydro quinazolines -General procedure

Different aromatic aldehydes reacted with cyclohexanone in the presence of absolute alcohol and sodium hydroxide to form 2-arylidene cyclohexanone[8]. After 2-arylidene cyclohexanone reacted with thiourea in the presence of alcoholicKOH to form 4-arylidene 3,4,5,6,7,8-hexahydro quinazolin-2-thione[9]. Each of the thrones will be subjected to the mannich condensation under basic conditions by using aqueous formaldehyde, different acyclic or cyclic secondary amines, ethanol and aqueous potassium carbonate with a normal expectation of obtaining S-Mannich bases respectively.

ISSN: 0975-8585

SCHEME-I

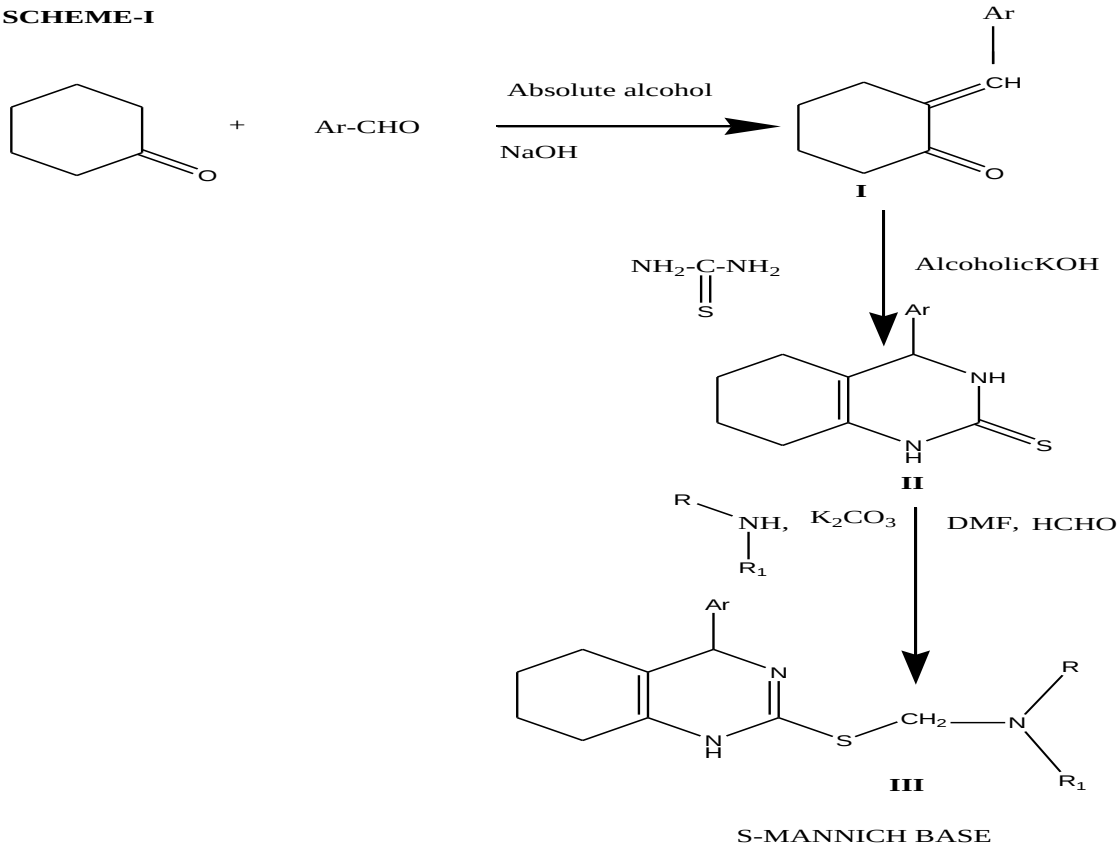
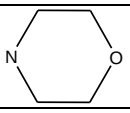
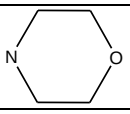


Table: 1 Physical, analytical and Some Spectral data of S-Mannich bases of 1,4,5,6,7,8-Hexahydro quinazolines.

compound	Substituent In III at 4th position	-NRR1 InIII at 2nd position	Mol.form	MP 0c	Elemental analysis Found (%) (calc) C H N	IR SPECTRA(KBr,cm-1)
IIIA	Ar=C_6H_5		$C_{19}H_{25}N_3OS$	198 to 200	65.70 5.71 13.66(65.56 5.50 13.49)	1496.4(C=C Stretch),3510.1(NH Stretch),1296.4(C-S Stretch).
IIIB	Ar=C_6H_5	-N-$(CH_3)_2$	$C_{17}H_{23}N_3S$	204 to 206	68.01 6.71 11.97 (67.91 6.56 11.89)	1496.2(C=C Stretch),3510.2(NH Stretch),1296.3(C-S Stretch).
IIIC	Ar=Cl-C_6H_4	-N-$(CH_3)_2$	$C_{17}H_{22}N_3SCl$	202 to 205	61.89 5.24 11.44 (61.78 5.21 11.38)	1496.3(C=C Stretch),3510.4(NH Stretch),1296.2(C-S Stretch),650.5(C-Cl Stretch).
IIID	Ar=Cl-C_6H_4		$C_{19}H_{24}N_3OSCl$	195 to 198	52.24 4.29 10.87 (52.31 4.31 10.77)	1496.1(C=C Stretch),3510.3(NH Stretch),1296.1(C-S Stretch),652.2(C-Cl Stretch).
IIIE	Ar=CH=CH_2-C_6H_4	-N-$(CH_3)_2$	$C_{19}H_{25}N_3S$	203 to 206	55.41 5.24 9.79 (55.52 5.17 9.71)	1496.5(C=C Stretch),3510.1(NH Stretch),1296.2(C-S Stretch).
IIIF	Ar=2-OCH_3-C_6H_4	-N-$(CH_3)_2$	$C_{20}H_{27}N_3OS$	208 to 210	50.81 4.14 9.23 (50.89 4.07 9.37)	1496.4(C=C Stretch),3510.1(NH Stretch),1296.4(C-S Stretch),1730.3(C-O Stretch).

ISSN: 0975-8585

BIO ASSAY

ANTI-BACTERIAL AND ANTI-FUNGAL SCREENING

The anti-bacterial activity of the compounds (VI) was assayed against the following bacteria: *Staphylococcus aureus* , *Bacillus subtilis, Klebsiella pneumoniae a*nd *Escheresia coli* employing agar diffusion method. The method adopted in the present investigation was Filter paper strip method[10]. Measurement of the diameter of zone of inhibition, simultaneously controls were maintained employing Dimethylsulphoxide to observe the solvent effects. The IC50 Values of Anti-bacterial activities are represented in Table2.

The Anti-fungal activity was evaluated against the organism is Candida albicans. The test compounds were screened for anti fungal activity using Sabouraud Dextrose Agar medium[10]. Solutions of the test compounds at the concentrations of 250ug/ml,500ug/ml,1000ug/ml and1500ug/ml were prepared in DMSO and sterile filter paper strips/disk was impregnated in the respective concentrations for about 15 mins. Strips of respective test compounds as well as Standard drug(fluconazole 100ug/ml) were placed on the petri plates by means of sterile forceps in laminar air flow cabinet. The zone of inhibition(in mm) was measured after 24 hrs of incubation at 250C.The IC50 Values of anti fungal activity are represented in Table 3.

Table: 2 IC50 Values of Anti- bacterial activity of S-Mannich bases of 1,4,5,6,7,8-Hexahydro quinazolines.

Compound	IC50 VALUE(ug/ml)			
	E.coli	*K.pneumoniae*	*S.aureus*	*B.subtilis*
IIIA	268.4	300.4	332.5	230.5
IIIB	331.7	437.3	496.2	470.4
IIIC	419.1	346.1	278.1	340.7
IIID	433.8	397.9	470.3	292.1
IIIE	470.0	300.5	562.4	406.4
IIIF	457.0	514.4	348.8	368.8

Table:3 IC50 Values of Anti-fungal activity of S-Mannich bases of 1,4,5,6,7,8-Hexahydro quinazolines.

Compound	IC50 VALUE CANDIDA ALBICANS
IIIA	372
IIIB	315
IIIC	445
IIID	362.6
IIIE	488.6
IIIF	420.0

ISSN: 0975-8585

ANTI-INFLAMMATORY ACTIVITY

The Anti-inflammatory screened by carrageenan induced rat paw edema method [11].

Procedure

Young adult male wistar rats weighing 150-200 gm were used which are acclimatized to the laboratory rat feed and clean water. Rats were fasted for 12 hrs prior to experiment, while allowing access to water throughout the experiment. Rats were divided into 12 groups with each group containing 3 animals. One group of animals received 1% CMC saline solution which served as control. Second group of animals received 50mg/kg diclofenac sodium solution which serves as standard. The remaining 10 groups of animals received 50mg/kg and 100mg/kg of the synthesized compounds. A mark was made on both the hind paws just beyond the tibiotarsal junction, so that every time the paw is dipped in the mercury column up to the marked level to ensure constant paw volume. After 1hr of administration of the test and standard samples, 0.1 ml of 1% carrageenan suspension (in normal saline) was injected into dorsal region of the sub plantar surface of hind paw of rat subcutaneously with the help of 26G needle. The initial paw volume of each rat was recorded before drug administration. The paw volumes were measured at the end of 1, 2, 3, 4hrs using plethysmometer. Any change in paw volume of rats was obtained by subtracting initial paw volume from the paw volume at different time intervals. The average value of edema was calculated by taking the average of each group at different hours. Percentage inhibition of edema was calculated for each group with respect to its control group.

$$\text{Percentage inhibition} = (A-B) *100/A.$$

Where A is the mean increase paw volume in rats treated with control and B is the mean increase in paw volume in rats treated with test drug.

TABLE – 4: Mean Edema volume of Anti-inflammatory activity of S-Mannich bases of 1,4,5,6,7,8-Hexahydro quinazolines.

Treatment	Dose mg/kg	Mean Edema Volume (ml)				
		30 min	1hr	2hr	3hr	4hr
Control	-	0.30±0.02	0.42±0.02	0.50±0.02	0.60±0.02**	0.40±0.02
Standard	100	0.22±0.15	0.18±0.04	0.20±0.07	0.20±0.05**	0.30±0.03
IIIA	50	0.25±0.02	0.25±0.03	0.32±0.03	0.26±0.02**	0.22±0.02
	100	0.26±0.01	0.27±0.02	0.31±0.05	0.29±0.04**	0.25±0.02
IIIB	50	0.22±0.01	0.27±0.02	0.30±0.03	0.25±0.03**	0.24±0.02
	100	0.25±0.01	0.28±0.02	0.32±0.03	0.25±0.03**	0.21±0.02
IIIC	50	0.26±0.02	0.23±0.03	0.30±0.04	0.27±0.03**	0.25±0.02
	100	0.25±0.01	0.28±0.02	0.28±0.05	0.29±0.02**	0.22±0.01
IIID	50	0.21±0.02	0.25±0.03	0.32±0.05	0.26±0.04**	0.23±0.02
	100	0.25±0.02	0.24±0.03	0.27±0.05	0.27±0.04**	0.22±0.02
IIIE	50	0.25±0.02	0.29±0.03	0.31±0.04	0.27±0.03**	0.24±0.02

ISSN: 0975-8585

	100	0.25±0.02	0.28±0.03	0.30±0.04	0.28±0.03**	0.25±0.01
IIIF	**50**	0.22±0.01	0.27±0.02	0.32±0.03	0.25±0.03**	0.23±0.02
	100	0.23±0.02	0.25±0.03	0.26±0.04	0.24±0.03**	0.20±0.01

** showed very significant in relation with control

TABLE -5: Percentage inhibition against edema formation of S-Mannich bases of 1,4,5,6,7,8-Hexahydro quinazolines.

Treatment	Dose Mg/kg	% Inhibition				
		30 min	1hr	2hr	3hr	4hr
Standard	**100**	**26.6**	**57.14**	**60.0**	**66.6**	**25.0**
IIIA	**50**	**16.6**	**40.07**	**36.0**	**56.0**	**45.0**
	100	**13.3**	**35.71**	**38.0**	**51.0**	**37.5**
IIIB	**50**	**26.6**	**35.71**	**40.0**	**58.33**	**40.0**
	100	**16.6**	**33.33**	**48.0**	**58.33**	**37.5**
IIIC	**50**	**13.3**	**45.23**	**40.0**	**55.0**	**37.5**
	100	**16.6**	**33.33**	**38.0**	**51.6**	**45.0**
IIID	**50**	**30.0**	**40.07**	**36.0**	**55.0**	**42.5**
	100	**16.6**	**42.85**	**46.0**	**56.0**	**45.0**
IIIE	**50**	**16.6**	**30.95**	**38.0**	**55.0**	**40.0**
	100	**16.6**	**33.33**	**40.0**	**53.3**	**37.5**
IIIF	**50**	**26.6**	**35.71**	**36.0**	**58.0**	**42.5**
	100	**23.3**	**40.07**	**46.0**	**60.0**	**50.0**

RESULTS AND DISCUSSION

All the compounds of present investigation were found to be nontoxic as experimental animals were found to be safe.

Antibacterial activity

- It could be evidenced from the results of present investigation that irrespective of their nature, none of the test compounds are comparable with the standard i.e., Gatifloxin in their antibacterial activity.
- Antibacterial activity among the test compounds is presented in **Table 2**. All the test Compounds showed a varied degree of antibacterial activity against the test organisms employed.
- However, among this series of compounds IIIE showed high activity against *E.Coli*, *B .subtilis* and *S.aureus,* whereas the test compounds IIIF exhibited more activity against K.pneumoniae.
- The antibacterial activity of test compounds showed that the newly synthesized S-Mannich bases of quinazoline derivatives (IIIA-F) exhibited mild to moderate antibacterial activity against the test organisms employed in the present investigation.

However, the degree of inhibition varied with the test compound and the test bacterium.

- Among the test compounds employed **IIIA** exhibited relatively mild activity.
- The test compounds **IIIE and IIIF** exhibited good antibacterial activity against *K.pneumoniae, E.coli, S.aureus* and *B.subtilis* at tested concentrations when compared to standard.
- The compounds **IIIE and IIIF** were found to be more potent.

Anti fungal activity

- It could be evidenced from the results of present investigation that irrespective of their nature, none of the test compounds are comparable with the standard i.e., fluconazole in their antifungal activity.
- Antifungal activity among the test compounds was represented in **Table 3**. The antifungal activity of test compounds showed that among the newly synthesized S-mannich bases of quinazoline the compounds **IIIC ,IIIE** exhibited high activity against ***Candida albicans.***
- Among the test compounds employed **IIIB** exhibited relatively mild activity.
- The compounds **IIIE** were found to be more potent.

Anti- inflammatory activity

- It could be evidenced from the results of present investigation that irrespective of their nature, none of the test compounds are comparable with the standard i.e.,diclofenac sodium in their anti-inflammatory activity.
- Anti-inflammatory activity among the test compounds is presented in **Table 4.** All the test compounds showed a varied degree of anti-inflammatory activity against the test organisms employed.
- The anti-inflammatory activity of test compounds showed that among the newly synthesized S- mannich bases of quinazolines , the compounds **IIIB, IIIF** showed very significant activity in relation with control.
- Among the test compounds employed **IIID** exhibited relatively mild activity.
  The compounds **IIIB, IIIF** were found to be more potent.

REFERENCES

[1] Vijaya Kumar B, Rathore HGS and Malla Reddy V. Indian J Chem1982; 21B: 1126.
[2] BVajaya Kumar, A Bhaskar Rao and V Malla Reddy. Indian J Chem 1985; 24 B: 889 - 892.
[3] Vajaya Kumar B, Bhaskar Rao A and Malla Reddy V. Indian Drugs 1985; 22: 373.
[4] B Vijaya Kumar and V Malla Reddy. Indian Drugs 1985; 23(2): 98-101.
[5] Ram Lakhan and Om Prakash Sing. Arch Pharm 1985; 318: 228-238.
[6] B Vajaya Kumar, A Bhaskar Rao and V Malla Reddy. J Indian Chem Soc 1985; 62: 257-259.

[7] Madhusudhan Rao V, Ph.D. Thesis submitted to Kakatiya University, 1986, Warangal, AP.
[8] BS Furniss, AJ Hannaford, PWG Smith and AR Tatchell; VOGEL'S Text book of Practical Organic Chemistry, Fifth Edition; 1260.
[9] Kalyan Chakravarthy A, Suresh T and Reddy VM. Heterocyclic Commun 2006; 12:389.
[10] Microbiological Assays and Tests. I.P. 1996; II: 100.
[11] Microbiological Assays. B.P. 1953; II: 796.