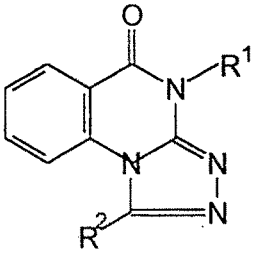
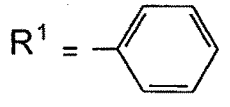
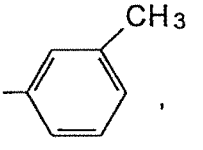
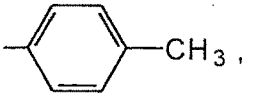
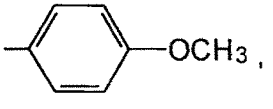
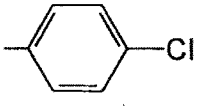
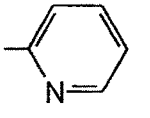
Summary

SUMMARY

The thesis presents the synthesis and biological activity of some 1,2,4-triazolo[4,3-*a*]quinazolin-5(4*H*)-ones containing aryl substitution at position 4 and alkyl substitutions at position 1. Although a large number of quinazolines and condensed quinazolines have been prepared and studied, the synthesis of 1,2,4-traizolo[4,3-*a*] quinazoline nucleus is relatively unexplored. The following types of compounds were therefore proposed to be synthesized:



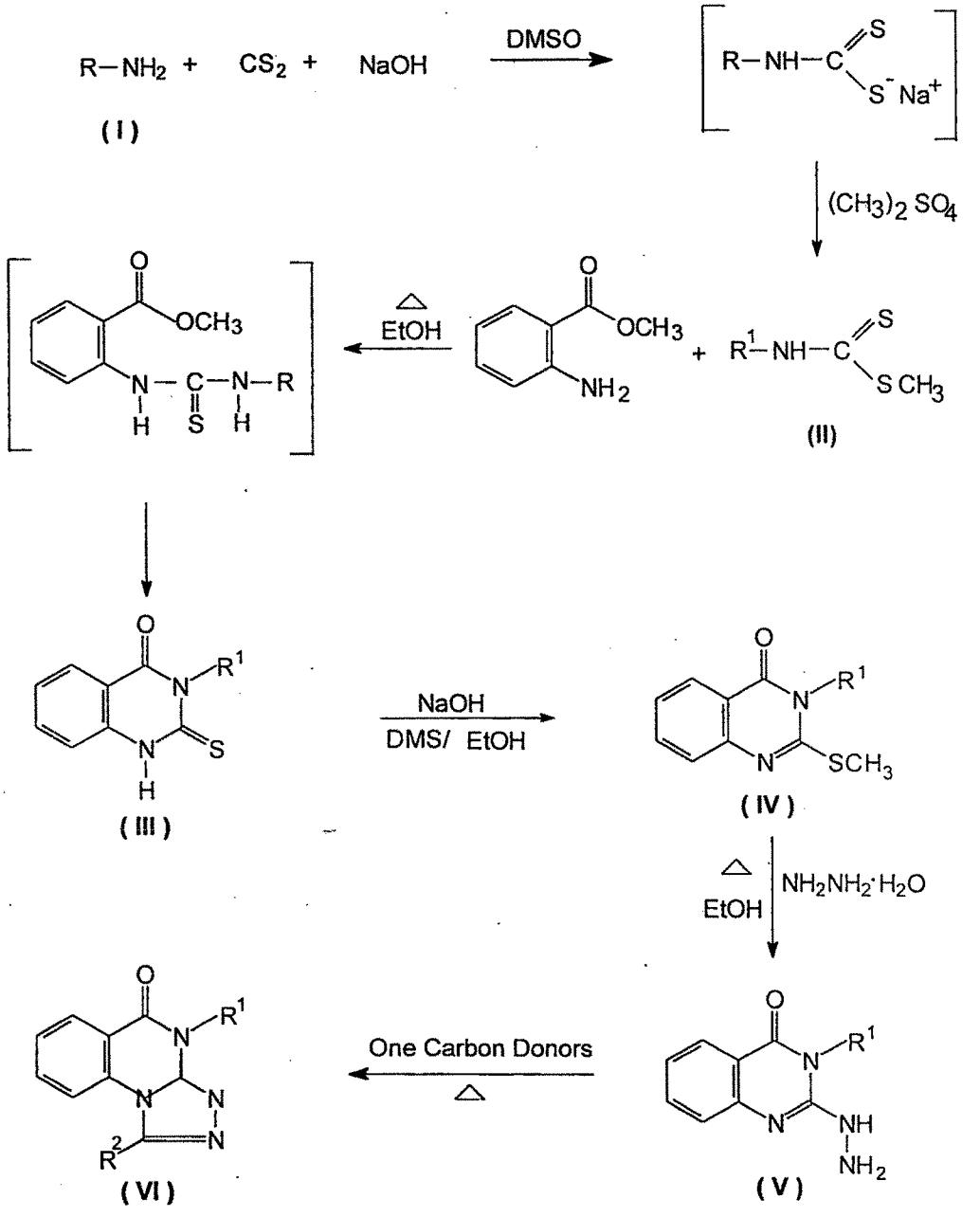
R^1 =  ,  ,  ,

 ,  and 

R^2 = —H, — CH_3, — CH_2CH_3, — $CH_2CH_2CH_3$ and — CH_2Cl

In all 30 title compounds were synthesized and studied for various biological activities.

The synthetic route depicted in Scheme-I was adopted for the synthesis of the title compounds.



(SCHEME-IV)

The synthesized compounds were characterized by UV, IR, NMR, Mass and elemental analysis. The data are presented under the respective compounds and are in accordance with the assigned structures.

The compounds synthesized were subjected to the following biological studies:

1. Alpha adrenergic blocking activity

In the present study it was found that the Triazolo quinazolone derivatives which have been synthesized showed α_1-adrenoceptor blocking activity. Out of fifteen compounds (**1, 2, 5, 6, 8, 11, 16, 17, 21, 22, 24, 25, 26, 27** and **29**) six compounds (**1, 8, 21, 24, 26** and **27**) were found to have good α_1-adrenoceptor blocking activity.

All compounds were given to rats by oral as well as i.p. route in the form of suspension using 0.5 % sodium CMC as suspending agent.

The compounds (**1, 6, 8, 26, 27** and **29**) were tested for preliminary α_1-adrenergic blocking activity by intraperitoneal (i.p.) route *in vivo*. Those, which showed some promising activity, were tested in detail and confirmed for α_1-adrenergic blocking activity by oral route also. α-adrenoceptor antagonistic activity of title compounds was confirmed by *in vitro* experiments using rat thoracic aortic strip.

The compounds **8, 26** and **27** showed α_1-adrenergic blocking activity in the initial screening by i.p. route (5 mg/kg). These compounds also showed α_1-adrenergic blocking activity by oral route (10 mg/kg). Apart from these three compounds, **1** and **21** (10 mg/kg) also showed α_1-adrenergic blocking activity when given by oral route.

From the study it was found that adrenaline reversal response was also produced by **1, 8, 21, 26** and **27** at the dose of 10 mg/kg by oral route giving the clear indication that these compounds have the ability to block the α_1-adrenoceptor mediated increase in blood pressure of adrenaline.

It has been found that test compounds (**1, 8, 26** and **27**) produced decrease in mean arterial pressure and increase in heart rate at the dose of 5 mg/kg by i.p. route and 10 mg/kg by oral route. Increase in heart rate may be because of reflex action. Also these compounds when given orally at the dose of 10 mg/kg, it reduced the mean arterial pressure of α_1-adrenoceptor agonist Phenylephrine (selective α_1-adrenoceptor agonist) when given by femoral vein.

There is a significant reduction in the Dose Response Curve of Phenylephrine to rat aorta in the animals treated with test compounds.

When all data were compared with the Prazosin taking as standard (selective α_1-adrenoceptor blocker), it has been found that α_1-adrenoceptor blocking potency of **1, 8, 26** and **27** was 20 X (twenty times) less as compared to Prazosin.

2. Antihistaminic activity

Thirty compounds containing 1,4-disubstituted-1,2,4-triazoloquinazoline ring system have been evaluated for their *in vivo* antihistaminic activity. Protection against histamine induced bronchospasm on conscious guinea pigs method was adopted to determine the antihistaminic potential of the test compounds. All of them have been found to exhibit good antihistaminic activity. Percentage protection data showed that all compounds of the series show significant protection in the range of 68-72%.

Among the series, 1-methyl-4-(4-chlorophenyl)-*s*-triazoloquinazolin-4(3*H*)-one (**22**) was the most potent with the percentage protection of 72.71 which is equipotent with that of standard chlorpheniramine maleate (percentage protection 71.00) but less potent than standard certirizine (percentage protection 78.95) and aminophylline (percentage protection 90.29).

As the test compounds could not be converted to water soluble form, *in vitro* evaluation for antihistaminic activity could not be performed.

3. Sedative-hypnotic activity

As sedation is one of the major side effects associated with antihistamines, the test compounds were also evaluated for their sedative potentials.

Sedative-hypnotic activity was determined by measuring the reduction in motor activity. The results of this study presented in Table 2 & 3 of the thesis showed that almost all the test compounds were found to exhibit mild activity (less than 10 %), except for the compounds **3**, **4**, **6**, **7**, **8**, **9**, **12**, **13**, **14**, **19**, **28** and **29** which exhibited moderate activity (10-15 %). Cetirizine and Chlorpheniramine maleate as references showed 9% and 26% sedation, respectively.

Considering that quinazolines have been reported in the literature to possess a wide variety of biological activities, it was further planned to evaluate the synthesized compounds for other types of biological activities as given below:

- Anticancer activity.
- Anti HIV activity
- Antibacterial activity
- Antitubercular activity
- Analgesic activity and
- Antiinflammatory activity

4. Anticancer activity

Selected compounds (**1**, **4**, **IVb**, **6** and **9**) were screened for anticancer activity in drug–screening programme at the National Cancer Institute (NCI, USA).

Among the compounds tested for primary anticancer assay against a panel of 3 cell line i.e. lung, breast and CNS cancer, the compounds **IVb** shown 31%, 9% and 43% inhibition of growth against lung, breast and CNS cancer respectively, where as the other compounds shown less than 62% growth inhibition in all the 3 cell lines tested. Hence, the compound **IVb** was evaluated against the full panel of 60 human tumor cell lines, at a minimum of 5 concentrations at 10 fold dilutions. The results are expressed as GI_{50} values (Concentration required to inhibit the growth of 50 % cells) at micromolar concentration. The results are presented in.

The compound **IVb** has shown good cytotoxiciy against HL-60 (TB), leukemia (GI_{50} 2.58 μm), and strong cytotoxicity against UO-31 renal cancer (GI_{50} 0.364 μm).

5. AntiHIV activity

The synthesized compounds were evaluated for their inhibitory effect of the replication of HIV-1 and HIV-2 in human MT-4 cells.

The results of anti HIV activity (Table 6) shows that the compound **Vb** exhibited maximum 113 % protection against HIV-1 (IIIB) [EC_{50} 10.1 μg/ml] and 136 % protection against HIV-2 (ROD) [EC_{50} 7.85 μg/ml]; The compound **26** exhibited maximum 50% protection against HIV-1 (IIIB) [EC_{50} 4.94μg/ml] and 25% protection against HIV- 2 (ROD) [EC50 > 19.9 μg/ml]; The compound **Vf** exhibited maximum 23% protection against HIV-1 (IIIB) [EC_{50} >125 μg/ml] and 47% protection against HIV-2 (ROD) [EC_{50} >125 μg/ml]. While the rest of compounds exhibited mild protection at its subtoxic concentration.

6. Antibacterial activity

The antibacterial activity of title compounds was studied by agar cup-plate method, the results are expressed in the terms of zone of inhibition in mm..

Almost all the compounds exhibited mild antibacterial activity against *S.typhi*, however the test compounds did not inhibits the growth of *E.coli* (except **25** and **28**) at the concentration tested, while the rest of compounds showed mild to moderate antibacterial activity against some of the bacteria tested. none of the compounds was equipotent to ciprofloxacin, a standard drug employed in the investigation.

7. Antitubercular activity :

The synthesized compounds were screened for their *in vitro* antimycobacterial activity against *Mycobacterium tuberculosis* strain H_{37} Rv at the Tuberculosis Antimicrobial Acquisition & Coordinating Facility (TAACF, USA). The results are expressed in terms of Minimum Inhibitory Concentration (MIC) and percentage inhibition of growth.

The compound **27** was found to be the most potent agent and it showed 72% inhibition ; compound **IVa** exhibited 61% inhibition; compound **IVc** exhibited 60% inhibition while, the rest of compounds exhibited less than 60% inhibition. The test compounds exhibited their antimycobacterial activity at the concentration of 6.25 μg/ml (MIC 6.25 μg/ml). Some of the comounds did not exhibited antimycobacterial activity at this concentration.

8. Analgesic activity

The analgesic activity of selected title compounds was tested in mice by tail-flick technique.

The results of analgesic activity of title compounds indicate that the test compounds exhibited moderate activity while none of the test compounds was equiptent to pentazocine, a standard drug employed in the investigation.

9. Antiinflammatory activity

The antiinflammatory activity of selected title compounds was carried in rats by carrageenan-induced rat paw oedema method.

The results of antiinflammatory activity indicate that all test compounds exhibited mild to moderate activity, however none of the test compounds showed equipotent activity with diclofenac sodium, a standard drug employed in the investigation.