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ISSN: 0975-7538

Research Article

## Antibacterial and antimycobacterial activities of 3-ethyl-2-substituted quinazolin-4-ones

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### ABSTRACT

A variety of novel 3-ethyl-2-substitutedamino-quinazolin-4(3H)-ones were synthesized from 3-ethyl-2-hydrazino quinazolin-4(3H)-one with a variety of aldehydes and ketones. When tested for their *in vitro* antitubercular activity using H<sub>37</sub>RV strain on Middle brook 7H11 agar slants with OADC growth supplement, all the test compounds inhibited the growth of *Mycobacterium tuberculosis* at micro gram concentration. Among the test compounds, 2-(N-(4-Chloro-benzylidene-hydrazino))-3-ethyl-3H-quinazolin-4-one (**S6**) and 2-(N-(4-Nitro-benzylidene-hydrazino))-3-ethyl-3H-quinazolin-4-one (**S7**) are found to be the most active compounds against *M.tuberculosis* with the MIC of 6µg/ml. The title compounds are also screened for the antimicrobial activity against some other gram positive and gram negative bacteria by agar dilution method, compounds **S6** and **S7** showed the most potent activity (MIC in the range of 32-63 µg/ml) against the tested bacteria.

**Keywords:** Antitubercular; Anti-bacterial; *M. tuberculosis*; Quinazolinone

### INTRODUCTION

Tuberculosis (TB) is an infection, primarily in the lungs (a pneumonia), caused by bacteria called *Mycobacterium tuberculosis* (Ang D et al., 2006; Houben E et al., 2001). Along with the recent increase in cases of tuberculosis, there is a progressive increase in multidrug resistant (MDR) tuberculosis. Some of the MDR isolates are resistant to as many as seven of the commonly employed antimycobacterial drugs (World Health Organization, 2007). Quinazolines and condensed quinazolines received the attention of medicinal chemists due to their potential biological activities. Among the biological activities exhibited by quinazolines the antimicrobial activities of 2, 3-substituted quinazolines are interesting. Literature survey indicates that the quinazoline nucleus substituted at 2,3-position showed significant antitubercular activity (Gursoy A et al., 2005; Pattan S.R et al., 2006; Nandy P et al., 2006; Kucukguzel G et al., 2006; Alagarsamy V et al., 2008; Krishan V et al., 2009; Sen A et al., 2009; Oniga O et al., 2010; Balasubramanian S et al., 2003). With this aim in the present study and in continuation of our efforts in developing potent antitubercular and other antimicrobial agents, we have placed the substituents at the C-2

and N-3 position of quinazoline ring and studied their antitubercular and other antimicrobial activity against different gram positive and negative bacteria.

### EXPERIMENTAL

#### Chemistry

Melting points (mp) were taken in open capillaries on a Thomas Hoover melting point apparatus and are uncorrected. IR spectra of the synthesized compounds were recorded by FT-IR (Shimadzu, Japan) using KBR pellet ( $\nu$  max in  $\text{cm}^{-1}$ ). The NMR spectra of the synthesized compounds were recorded in  $\text{CDCl}_3$  (unless specified) with TMS as internal reference (chemical shift in  $\delta$ , ppm) using Varian 300 MHz and Bruker 500 MHz (Washington, USA) spectrometers. The Mass spectra of the compounds were obtained on JEOL GC mate instrument (Masspec, Japan). Elemental analyses were performed in Perkin-Elmer 2400 CHN elemental analyzer (Waltham, USA). The progress of the reaction was monitored on readymade silica gel plates (Merck) using chloroform: methanol (9:1) as a solvent system. Iodine was used as a developing agent. Spectral data (IR, NMR and mass spectra) confirmed the structures of the synthesized compounds and the purity of these compounds was ascertained by microanalysis. Elemental (C, H, N) analyses indicated that the calculated and observed values were within the acceptable limits ( $\pm 0.4\%$ ). All chemicals and reagents were obtained from Aldrich (USA), Lancaster (UK) or Spectrochem Pvt. Ltd (India) and were used without further purification.

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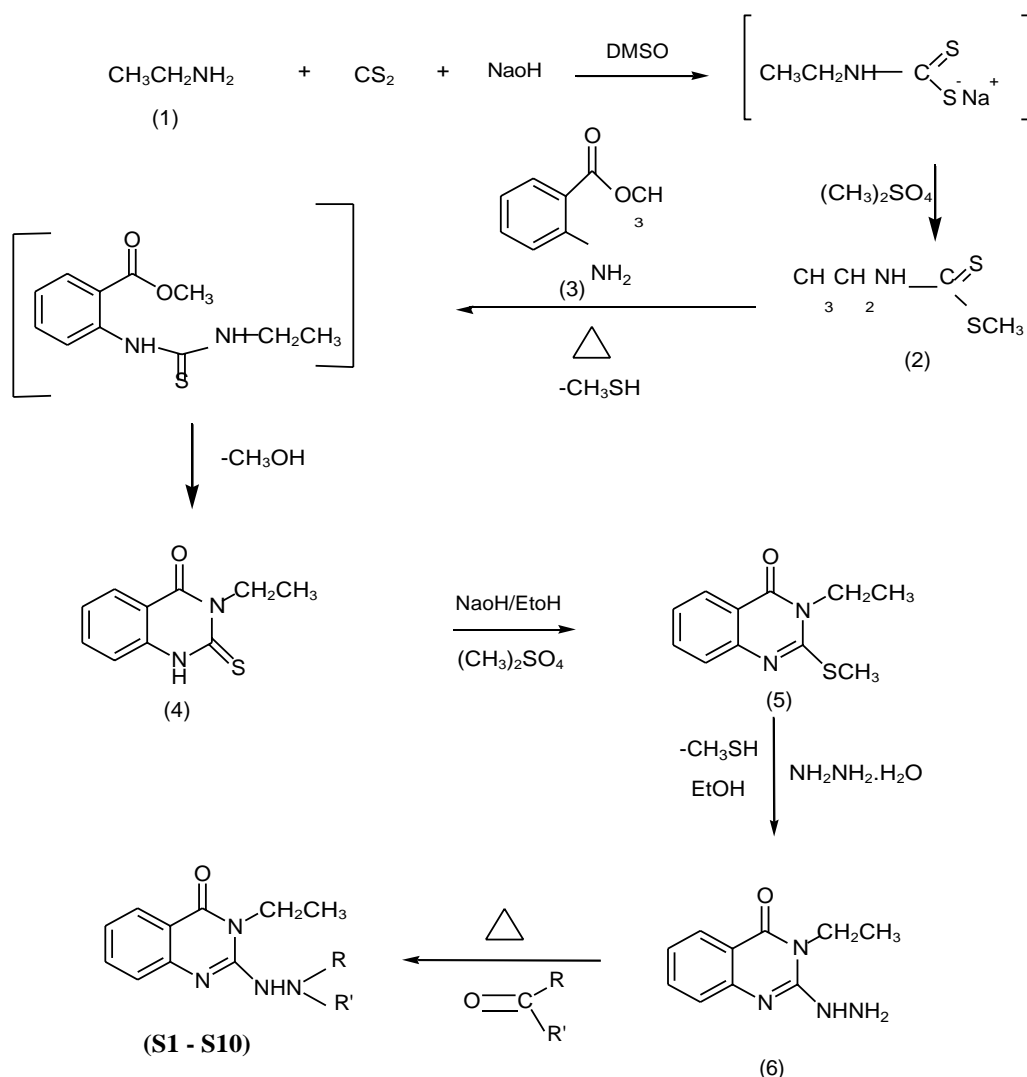
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Received on: 31-10-2012

Revised on: 01-01-2013

Accepted on: 05-01-2013



**Figure 1: Synthesis of 3-ethyl-2-substituted amino-3H-quinazolin-4-ones**

The detailed synthetic plan for the synthesis of Series I *i.e.* 3-Ethyl-2-substitutedamino-3H-quinazolin-4-one derivatives (S1-S10) is described above.

## PHARMACOLOGY

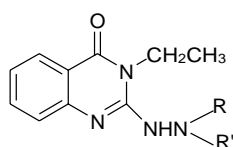
### Antimicrobial activity

Minimum Inhibitory Concentration (MIC) was determined to assess the antimicrobial potency of the compound by agar streak dilution method (Alagarsamy V et al., 2003; Pandya S.N et al., 1999). A stock solution of the synthesized compound (100  $\mu\text{g}/\text{ml}$ ) in dimethyl formamide was prepared and graded quantities of the test compounds were incorporated in specified quantity of molten sterile agar (nutrient agar for antibacterial activity and Sabouraud's dextrose agar medium for antifungal activity). A specified quantity of the medium at 40-50  $^\circ\text{C}$  containing the compound was poured into a petridish to give a depth of 3-4 mm, and allowed to solidify. Suspension of the microorganism were prepared to contain approximately  $5 \times 10^5$  cfu/ml, and applied to plates with serially diluted compounds in dimethyl formamide to be tested and incubated at 37 $^\circ\text{C}$  for 24 h. The MIC was considered to be the lowest

concentration of the test substance exhibiting no visible growth of bacteria or fungi on the plate.

### *In vitro* M. tuberculosis screening (Agar Dilution Method)

10 fold serial dilutions of each test compound/drug were incorporated into Middle brook 7H11 agar slants with OADC Growth Supplement. Inoculums of *M. tuberculosis* H<sub>37</sub>Rv were prepared from fresh Middle brook 7H11 agar slants with OADC Growth Supplement adjusted to 1mg/mL (wet weight) in Tween 80 (0.05%) saline diluted to  $10^{-2}$  to give a concentrate of approximately 107 cfu/mL. A 5 $\mu\text{L}$  amount of bacterial suspension was spotted into 7H11 agar tubes containing 10-fold serial dilutions of drug per mL. The tubes were incubated at 37 $^\circ\text{C}$ , and final readings were recorded after 28 days. Tubes having the compounds were compared with control tubes where medium alone was incubated with H<sub>37</sub>RV. The concentration at which complete inhibition of colonies occurred was taken as active concentration of test compound. The minimum inhibitory concentration (MIC) is defined as the minimum concentration of compound required to give complete inhibition of bacterial growth (National



Title compounds

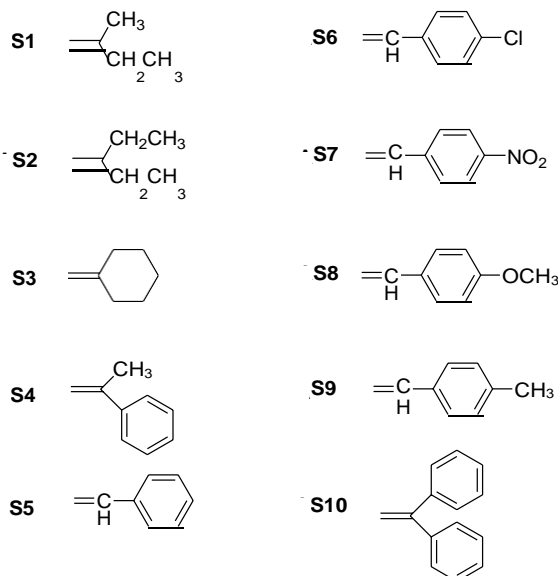


Figure 2: 3-Ethyl-2-substitutedamino-3H-quinazolin-4-one derivatives (S1-S10)

Table 1: Antibacterial activity (MIC in  $\mu\text{g/mL}$ ) of compounds S1-S10

Microorganisms	S1	S2	S3	S4	S5	S6	S7	S8	S9	S10	Standard*
<i>M. tuberculosis</i>	13	25	13	25	25	6	6	13	13	13	0.4
<i>P. vulgaris</i>	125	63	63	125	63	63	63	63	63	63	1
<i>Enterobacter spp.</i>	125	63	63	125	125	63	63	63	125	63	1
<i>K. pneumoniae</i>	63	63	63	125	125	63	32	63	63	63	1
<i>B. subtilis</i>	125	63	63	125	63	63	32	63	63	63	1
<i>S. flexneri</i>	63	63	125	63	125	63	63	125	63	63	1
<i>P. aeruginosa</i>	63	125	63	63	63	32	32	125	63	63	1
<i>S. enteritidis</i>	125	63	125	63	125	63	63	63	125	63	1
<i>S. typhi</i>	125	125	63	125	125	32	63	125	63	125	4
<i>E. coli</i>	63	63	125	125	125	32	63	125	63	63	2
<i>S. flexneri</i>	63	63	125	125	63	63	63	125	63	125	1

\*INH used as a reference standard against *M. Tuberculosis* whereas Ciprofloxacin used as a reference standard for other bacteria.

Committee for Clinical Laboratory Standards, 1995; Sriram D et al., 2007; Kunes J et al., 2000).

## RESULTS AND DISCUSSIONS

### Antibacterial activity

The title compounds are screened for their antibacterial activity against different gram positive and gram negative bacteria by agar dilution method, the results are depicted in Table 1. Among the different substituents on the aryl ring with electron withdrawing substituents (chloro and nitro) showed better activity over

the unsubstituted and electron donating substituent. Compounds **S6** and **S7** emerged as the most active compounds of the series. Compound **S6** shown most potent activity against *P. aeruginosa*, *S. Typhi* and *E. coli* while the compound **S7** showed most potent activity against *K. pneumoniae*, *S. Subtilis* and *P. aeruginosa*.

### Antitubercular activity

The synthesized compounds were screened for their *in vitro* antimycobacterial activity against *Mycobacterium tuberculosis* strain H<sub>37</sub>RV at the Tuberculosis Antimicrobial screening centre, Birla Institute of Technology

& Sciences, Hyderabad campus, Hyderabad. The results are expressed in terms of Minimum Inhibitory Concentration (MIC). The results of antimycobacterial activity depicted in Table 1 indicate that the test compounds inhibited the growth of *mycobacterium* in varying degree. Compounds with electron withdrawing substituents (chloro and nitro) on the aryl ring showed better activity over the unsubstituted or electron donating substituent on the aryl ring. Among the test compounds, 2-(N-(4-Chloro-benzylidene-hydrazino))-3-ethyl-3H-quinazolin-4-one (**S6**) and 2-(N-(4-Nitro-benzylidene-hydrazino))-3-ethyl-3H-quinazolin-4-one (**S7**) exhibited the antitubercular activity at the minimum micro gram concentration (6 µg/ml).

### SUMMARY AND CONCLUSION

In summary, series of novel quinazolin-4(3H)-one derivative have been tested for antimicrobial and antimycobacterial activities. These derivatives have exhibited significant antibacterial activity against the various gram positive and gram negative bacteria including *M. tuberculosis*. Among the series, 2-(N-(4-Chloro-benzylidene-hydrazino))-3-ethyl-3H-quinazolin-4-one (**S6**) and 2-(N-(4-Nitro-benzylidene-hydrazino))-3-ethyl-3H-quinazolin-4-one (**S7**) were found to be the most active antimicrobial agents, with the MIC of 32 µg/ml. Interestingly these compounds also showed significant antitubercular activity (Compound **S6** and **S7** showed activity at 6µg/ml), offering potential for further optimization and development to new antitubercular agents.

### REFERENCES

- Alagarsamy V, Pathak U.S, Venkateshperumal R, Meena S, Thirumurugan K, Rajasolomon V, and Clercq E, (2003) *Indian Journal of Pharmaceutical Sciences*, May-June.
- Alagarsamy V, Rajasolomon V, Parthiban P, Dhanabal K, Murugan S, Saravanan G, and Anjana G.V, (2008) *J. Heterocyclic Chem.*, 45, 709.
- Ang D, Hsu A.L, and Tan B.H, *Singapore Med. Journal.*, 47, 747 (2006).
- Aridoss G, Balasubramanian S, Parthiban P, and Kabilan S, (2006) *Eur. J. Med. Chem.*, 41, 268- 275.
- Balasubramanian S, Ramalingan C, and Kabilan S, (2003) *Synth. Commun.*, 33(17), 2979-2984 .
- Balasubramanian S, Ramalingan C, Aridoss G, and Kabilan S, (2005) *Eur. J. Med. Chem.*, 40, 694-700.
- Gursoy A, Unal B, Karali N, and Otuk G, (2005) *Turk J. Chem.*, 29, 233-245.
- Houben E, Nguyen L, and Pieters J, (2001) "Interaction of pathogenic mycobacterium with the most immune system" *Current Opin Microbiol*, 9, 76-85.
- Krishan V, Pandya S.N, Singh U.K, Gupta S, Prasanth P, and Bhardwaj G, (2009) *International Journal of Pharmaceutical Sciences and Nanotechnology*, 1(4).
- Kucukguzel G, Kocatepe A, De Clercq E, Sahin F, and Gulluce M, (2006) *Eur. J. Med. Chem.*, 41, 353-359.
- Kunes J, Bazant J, Pour M, Waisser K, Slosarek M, and Janota J, (2000) *Il Farmaco*, 55, 725-729.
- Nandy P, Vishalakshi M.T, and Bhat A.R, (2006) *Indian J. Heterocycl. Chem.*, 15, 293-294.
- National Committee for Clinical Laboratory Standards. (1995) Antimycobacterial susceptibility testing for *M. tuberculosis*. T. Villanova, PA: National Committee for Clinical Laboratory Standards.
- Oniga O, Moldovan C, Oniga S, Tipericiu B, Parnau A, Verite P, Crisan O, and Ionut I, (2010) *Farmacia*, 58, 6.
- Pandya S.N, Sriram D, Nath G, and Clercq E. (1999) *Il Farmaco*, 54, 624-628.
- Pattan S.R, Krishna Reddy V.V, Manvi F.V, Desai B.G, and Bhat A.R, (2006) *Indian J. Chem.*, 45B, 1778-1781.
- Ramalingan C, Balasubramanian S, and Kabilan S, (2004) *Synth. Commun.*, 34(36), 1105-1116.
- Rehman M, Choudary J, Ahmad S, and Siddiqui H, (2006) *Chem. Pharm. Bull.*, 54 (8), 1175-1178.
- Sen A, and Chaudhuri T.K, (2009) *Experimental Oncology*, 31(1), 22-26.
- Sriram D, Yogeeswari P, Dinakaran M, and Thirumurugan R, (2007) *Journal of Antimicrobial Chemotherapy*, 59, 1194-1196.
- World Health Organization, Tuberculosis fact sheet (2007).