ISSN: 2321-3132

Research Article

International Journal of Chemistry and Pharmaceutical Sciences

www.pharmaresearchlibrary.com/ijcps

Antibacterial and antimycobacterial activities of 2,3-disubstituted quinazolin-4-ones

R.V. Sheorey[1], A. Thangathiruppathy[2], V. Alagarsamy[3]*

[1]Research Scholar, Department of Pharmacy, Karpagam University, Eachanari Post, Coimbatore–641021, India.
[2]Department of Pharmacology, SB College of Pharmacy, Sivakasi–626130, TN, India
[3]Medicinal Chemistry Research Laboratory, MNR College of Pharmacy, Sangareddy, Gr. Hyderabad-502294, A.P., India.

Abstract

A variety of novel 3-propyl-2-substituted amino-quinazolin-4(3*H*)-ones were synthesized from 3-propyl-2-hydrazino quinazolin-4(3*H*)-one with a variety of aldehydes and ketones. When tested for their *in vitro* antitubercular activity using H_{37}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-propyl-3*H*-quinazolin-4-one (SR6) and 2-(N-(4-nitro-benzylidene-hydrazino))-3-propyl-3*H*-quinazolin-4-one (SR7) 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 SR6 and SR7 showed the most potent activity (MIC in the range of 32-63 µg/ml) against the tested bacteria (Compound SR6 inhibited the growth of *P.aeruginosa*, *S.typhi* and *E.coli* at the MIC of 32 µg/ml and SR7 inhibited the growth of *K.pneumoniae*, *B.subtilis* and *P.aeruginosa* at the MIC of 32 µg/ml).

Key words: Antitubercular, Quinazolinone; Anti-bacterial; *M. tuberculosis*

Contents

Received 15 December 2013
Accepted 18 January 2014
Available Online 27 January 2014

***Corresponding author**
V. Alagarsamy
E-mail: drvalagarsamy@gmail.com
Manuscript ID: PRL2014-IJCPS1963

PAPER-QR CODE

1. Introduction

Tuberculosis (TB) is an infection, primarily in the lungs (a pneumonia), caused by bacteria called *Mycobacterium tuberculosis*[1,2]. 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[3]. Quinazolines and condensed quinazolines received the attention of medicinal chemists due to their potential biological activities. Among the biological activities exhibited by quinazolines the

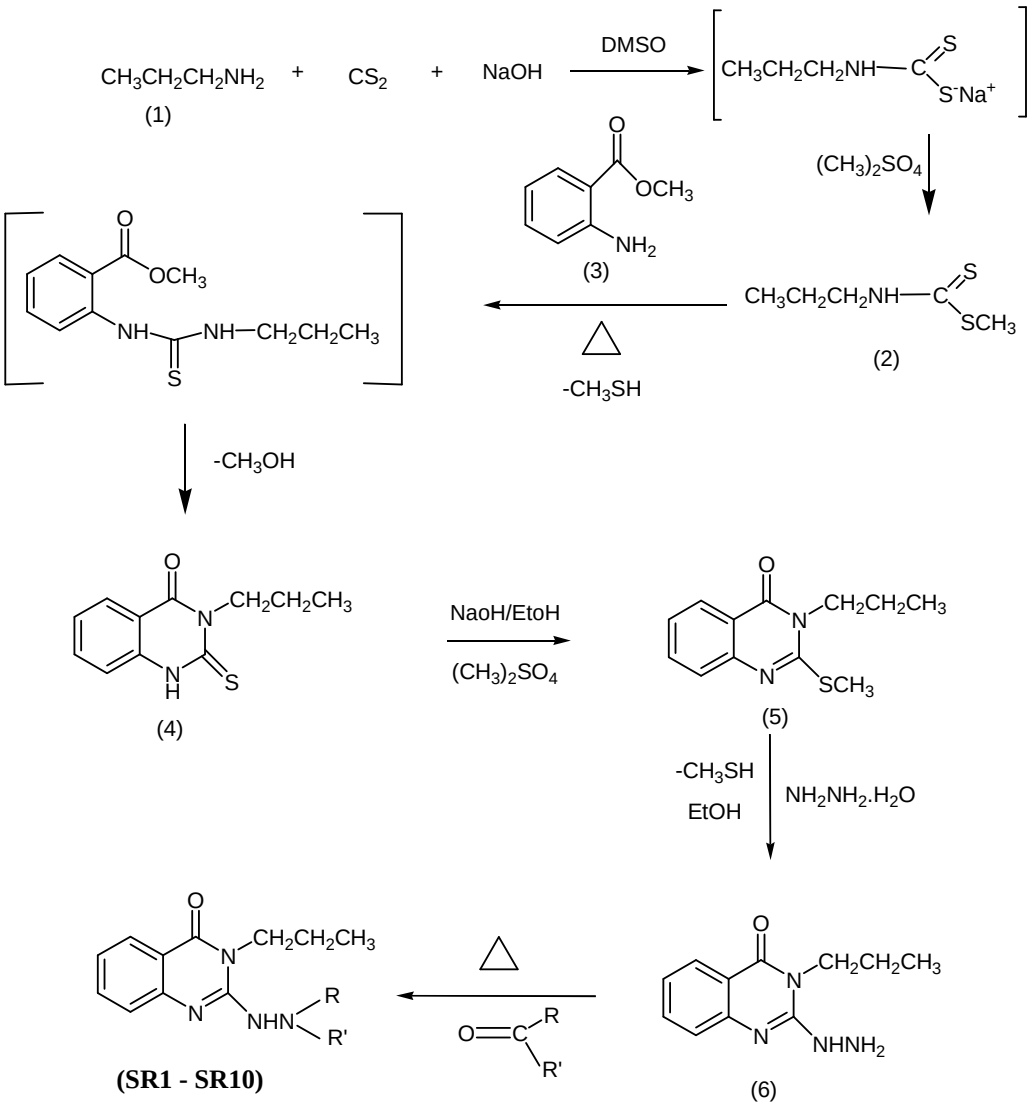
antimicrobial activities of 2,3-substituted quinazolines are interesting[4]. Literature survey indicates that the quinazoline nucleus substituted at 2,3-position showed significant antitubercular activity[5-13]. With this aim in the present study and in continuation of our efforts in developing potent antitubercular and other antimicrobial agents, we have placed the susbstituents 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.

2. Materials and Methods

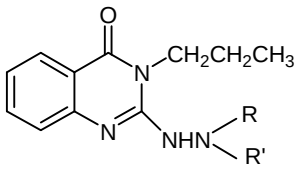
Chemistry:

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 (ν max in cm^{-1}). The NMR spectra of the synthesized compounds were recorded in $CDCl_3$ (unless specified) with TMS as internal reference (chemical shift in δ, 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.

The detailed synthetic plan for the synthesis of Series I *i.e.* 3-propyl-2-substitutedamino-3*H*-quinazolin-4-one derivatives (**SR1-SR10**) is described in scheme 1.

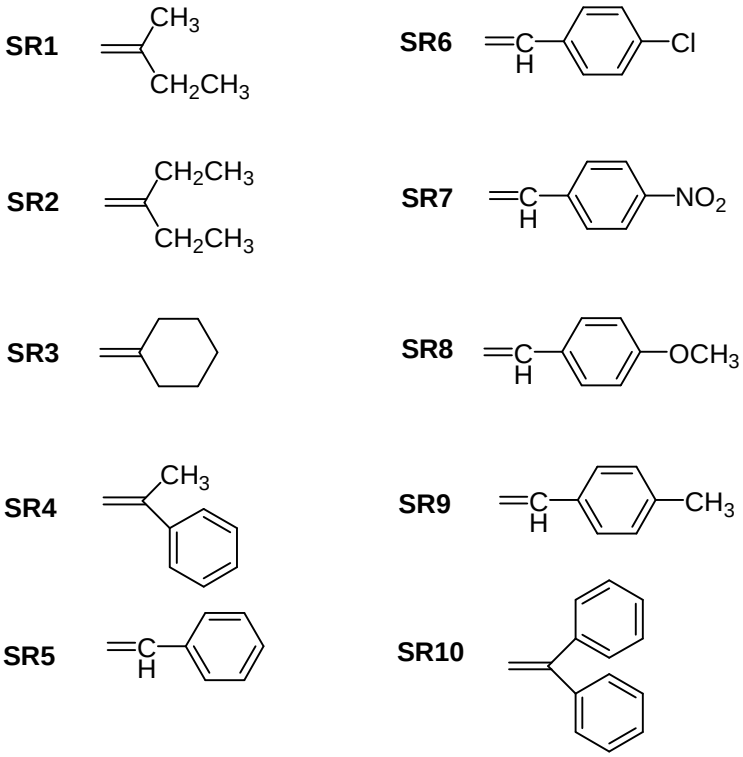


Scheme 1. Synthesis of 3-propyl-2-substituted amino-3*H*-quinazolin-4-ones



(SR1 - SR10)

Title compounds



Pharmacology

Antibacterial activity

Minimum Inhibitory Concentration (MIC) was determined to assess the antimicrobial potency of the compounds by agar streak dilution method.[17-18] A stock solution of the synthesized compound (100 µg/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. A specified quantity of the medium at 40-50 °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 x 10^{-5} cfu/ml, and applied to plates with serially diluted compounds in dimethyl formamide to be tested and incubated at 37 °C for 24 h. The MIC was considered to be the lowest concentration of the test substance exhibiting no visible growth of bacteria on the plate.

***In vitro M. tuberculosis* screening**[19-21]

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* $H_{37}Rv$ 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 5µL 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 ºC, and final readings were recorded after 28 days. Tubes having the compounds were compared with control tubes where medium alone was incubated with $H_{37}RV$. 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.

3. 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 substituents on the aryl ring with electron withdrawing substituents (chloro and nitro) showed better activity over the unsubstituted and electron donating substituent. Compounds **SR6** and **SR7** showed the most potent activity (MIC in the range of 32-63 µg/ml) against the tested bacteria (Compound **SR6** inhibited the growth of *P.aeruginosa*, *S.typhi* and *E.coli* at the MIC of 32 µg/ml and **SR7** inhibited the growth of *K.pneumoniae*, *B.subtilis* and *P.aeruginosa* at the MIC of 32 µg/ml).

Antitubercular activity

The synthesized compounds were screened for their *in vitro* antimycobacterial activity against *Mycobacterium tuberculosis* strain $H_{37}RV$ 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-propyl-3*H*-quinazolin-4-one **(SR6)** and 2-(N-(4-Nitro-benzylidene-hydrazino))-3-propyl-3*H*-quinazolin-4-one **(SR7)** exhibited the antitubercular activity at the minimum micro gram concentration (6 µg/ml).

Table 15: Antibacterial activity (MIC in µg/mL) of compounds SR1-SR10

Microorganisms	SR1	SR2	SR3	SR4	SR5	SR6	SR7	SR8	SR9	SR10	Standard*
M. tuberculosis	13	13	13	13	13	6	6	13	25	25	0.4
P.vulgaris	63	63	125	125	63	63	63	63	63	125	1
Enterobacter spp.	63	63	63	63	125	63	63	63	63	63	1
K.pneumoniae	125	63	63	125	63	63	**32**	63	125	63	1
B.subtilis	63	63	63	63	125	63	**32**	63	125	125	1
S.flexneri	63	125	125	63	63	125	63	63	63	125	1
P.aeruginosa	63	63	63	125	63	**32**	**32**	125	63	125	1
S.enteritidis	63	63	125	63	63	125	63	125	125	125	1
S.typhi	125	63	63	63	125	**32**	63	63	63	63	4
E.coli	63	125	63	125	63	**32**	63	63	63	63	2
S.flexneri	63	125	63	63	63	63	125	63	63	63	1

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

4. Summary and Conclusion

In summary, series of novel quinazolin-4(3*H*)-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-propyl 3*H*-quinazolin-4-one (**SR6**) & 2-(N-(4-nitro-benzylidene-hydrazino))-3-propyl-3*H*-quinazolin-4-one (**SR7**) 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 **SR6** and **SR7** showed activity at 6µg/ml), offering potential for further optimization and development to new antitubercular agents.

5. References

1. D. Ang, A.L. Hsu, and B.H. Tan, Singapore *Med. Journal*., 47, 747 (**2006**).
2. E. Houben, L. Nguyen, and J. Pieters, "Interaction of pathogenic mycobacterium with the most immune system" *Current Opin Microbiol*, 9, 76-85 (**2001**).
3. World Health Organization, Tuberculosis fact sheet (**2007**).
4. M. Rehman, J. Choudary, S. Ahmad, and H. Siddiqui, *Chem. Pharm. Bull.*, 54(8), 1175-1178 (**2006**)
5. A. Gursoy, B. Unal, N. Karali, and G. Otuk, *Turk J. Chem.*, 29, 233-245 (**2005**).
6. S.R. Pattan, V.V. Krishna Reddy, F.V. Manvi, B.G. Desai, and A.R.Bhat, *Indian J. Chem.*, 45B, 1778-1781 (**2006**).
7. P. Nandy, M.T. Vishalakshi, and A.R.Bhat, *Indian J. Heterocycl. Chem.*, 15, 293-294 (**2006**).

8. G. Kucukguzel, A. Kocatepe, E. De Clercq, F. Sahin, and M. Gulluce, *Eur. J. Med. Chem.*, 41, 353–359 (2006).
9. V. Alagarsamy, V. Rajasolomon, P. Parthiban, K. Dhanabal, S. Murugan, G. Saravanan, and G.V. Anjana, *J. Heterocyclic Chem.*, 45, 709 (**2008**).
10. V. Krishan, S.N. Pandya, U.K. Singh, S. Gupta, P. Prasanth, and G. Bhardwaj, *International Journal of Pharmaceutical Sciences and Nanotechnology*, 1(4), (**2009**).
11. A. Sen, and T.K. Chaudhuri, *Experimental Oncology*, 31(1), 22-26 (**2009**).
12. O. Oniga, C. Moldovan, S. oniga, B. Tiperciuc, A. Parnau, P. Verite, O. Crisan, and I. Ionut, *Farmacia*, 58, 6 (**2010**).
13. S. Balasubramanian, C. Ramalingan, and S.Kabilan, *Synth. Commun.*, 33(17), 2979-2984 (**2003**).
14. C. Ramalingan, S. Balasubramanian, and S.Kabilan, *Synth. Commun.*, 34(36), 1105-1116 (**2004**).
15. G. Aridoss, S. Balasubramanian, P. Parthiban, and S. Kabilan, *Eur. J. Med. Chem.*, 41, 268- 275 (**2006**).
16. S. Balasubramanian, C. Ramalingan, G. Aridoss, and S.Kabilan, *Eur. J. Med. Chem.*, 40, 694-700 (**2005**).
17. V. Alagarsamy, U.S. Pathak, R. Venkateshperumal, S. Meena, K. Thirumurugan, V. Rajasolomon, and E. Clercq, *Indian Journal of Pharmaceutical Sciences,* May-June (**2003**).
18. S.N. Pandya, D. Sriram, G. Nath, and E. Clercq. II Farmaco, 54, 624-628 (**1999**).
19. National Committee for Clinical Laboratory Standards. Antimycobacterial susceptibility testing for *M. tuberculosis*. T. Villanova, PA: National Committee for Clinical Laboratory Standards, (**1995**).
20. D. Sriram, P. Yogeeswari, M. Dinakaran, and R. Thirumurugan, *Journal of Antimicrobial Chemotherapy*, 59, 1194-1196 (**2007**).
21. J. Kunes, J. Bazant, M. Pour, K.Waisser, M.Slosarek, and J. Janota, *II Farmaco*, 55, 725-729 (**2000**).