Available online at www.derpharmachemica.com

Scholars Research Library

Der Pharma Chemica, 2012, 4 (3): 1186-1190
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X
CODEN (USA): PCHHAX

Antitubercular, antibacterial and antifungal activity of some pyridoquinazolones derivatives

Rachna Rai* and S.P. Shrivastava

Department of Chemistry, (Heterocyclic Research Laboratory), Dr. H.S. Gour University Sagar (MP) India

---

ABSTRACT

To purpose this goal our research affords are directed to find new chemical classes of anti-tubercular active agents with different mode of action's. series of quinazoline IIIrd have been synthesized involving three synthetic steps and bioevaluated for their possible anti tubercular activity against H_{37} RV strain using Lowenstein Jenison medium and antimicrobial activity against E coli,staphylococcus Aures, Klebsidlla pneamoniar and also evaluated antifungal activity against Aspergillus Flavus,Aspergillus niger, and Trichoderma Viridae.

Key Words: Arylaldehyde, urea, P Aminobenzoic acid, PPA, Benzoin, Antitubercular, antibacterial, Antifungal.

INTRODUCTION

Tuberculosis (TB) is one of the oldest and mostpervasive diseases in history[1,2] . According to alarming,data from the World Health Organization (WHO), TB has spread to every corner of the globe. As much asone-third of the world's population is currently infectedand more than 5000 people die fromTB everyday[3.] It is estimated that between 2002 and 2020, approximately 1000 million people will be newly infected, over 150 millionpeople will develop diseases and 36 million will die of TB if proper control measures are not established[4].

From a theoretical perspective quinazolines are undoubtedly of interest for study as they are multipurpose heterocyclic systems with multiple reactive centres compounds such as fungicides bactericides, defoliants and plant growth stimulants,[5,7] various biological activities have been attributed to benzoxazin-4-ones as well as the corresponding quinazoline derivatives found to posses antipyretic,[8] antiinflamatory,[9] antimitotic, anticancer activity,[10] and also have a good storage stability in detergents[11].

Pyrido derivative constitute an important class of compounds possessing diverse type of biological properties including antibacterial, antidiabetic,[12-18] antifungal[19] and antiarrhythonic.[20]

The quinozolone skeleton which is present in a variety of biologically active compounds are pharmacologically active in various therapeutic areas in the wide range of biological activities are known including hypnotic, sedative, analgesic, anticonvulsant, antibacterial, antidiabetic, anti inflammatory and antitumor.[21] and antitubercular agent.[22]

MATERIALS AND METHODS

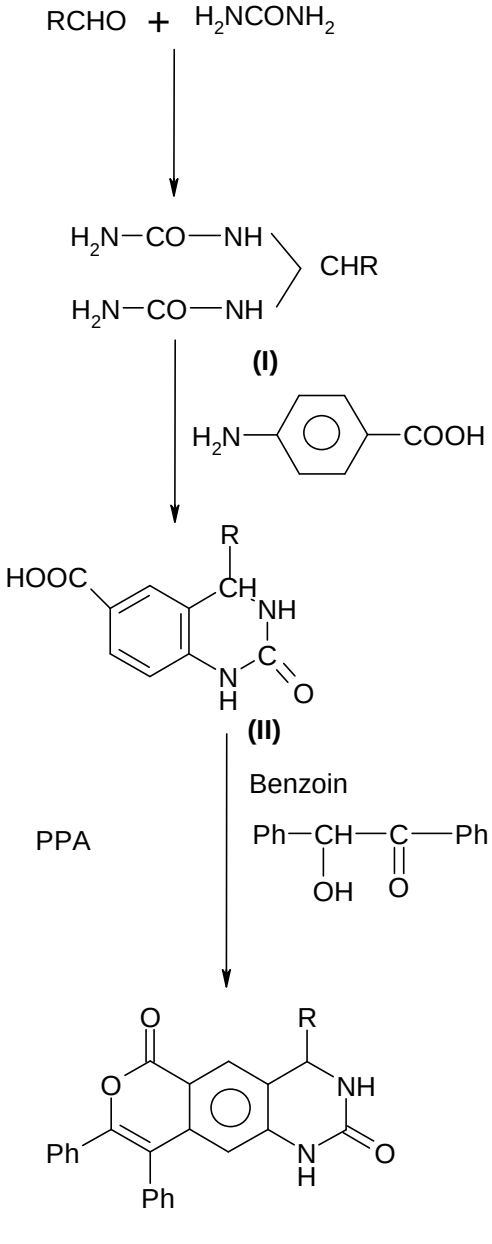
All the melting points have been determined in an open capillary and are uncorrected. IR spectra were recorded on perkin Elmer 377 spectrophotometer and H^1NMR spectra on Amx 400 MHz in DMSO using TMS an an internal standard. Elemental analysis of the newly synthesized heterocycles were carried out on a calro elba 1108 analyzer and results were found with in the range of the theoretical value.

Synthesis of alkylideno/arylideno bis ureas(l): A mixture of an aldehyde (0.1 mole) and urea (.2 mole) in ethanol was heated under reflux for 4h. Ethanol was distilled off and residual thick oily material was cooled to 0^0C. It solidified in about 1 h, After washing initially with 1% NaOH solution and finally with cold water. The crude material was dried at 100^0C and recrystallised from diluted methanol.

Synthesis of 4-Aryl,6-carboxylato–1,2,3,4-tetrahydroquinazolines(lI): Alkylideno/arylideno bis urea I (0.4 mole) and p-aminobenzoic acid (0.04 mole) were mixed together and heated at 145-150^0C for 4 hrs. A clear liquid was obtained on heating which on cooling to RT solidified, it was treated with diluted HCl (50 ml) and stirred very well. After filtering off the solid, it was washed with water and treated with an aqueos solution of $NaHCO_3$ (10%), when the effervescence completely ceased, the solid was filtered off. The solid was rejected and the filtrate was acidified with diluted HCl On complete neutralization a solid separated out which was filtered off and washed with water it was dried at 100^0C and recrystallized from glacial acidic acid.

Synthesis of 4-Aryl-8,9 diphenyl-1,4 dihydro,3H–7,Oxa-1,3 diazaonthracene (lll) 4-Aryl-8,9 diphenyl-1,4 dihydro,3H–7,Oxa-1,3 diazaonthracene (0.2 mole) and benzoin (0.2 mole) in polyphosphoric acid (10 ml) was heated at 100^0C for 5h. During heating the contents were occasionally stirred. Subsequently. The reaction mixture was poured into ice cold water (100 ml) and washed initially with 10% aqueous sodium bicarbonate solution (50 ml) and finally with water. The solid thus obtained was dried under vacuum and recrystalized from methanol.

Reaction sequence:



IR and H'NMR spectral data of the synthesized compounds:IR (ν_{max} in cm^{-1})III(a): 3061.13 Aro(C-H str), 2924.18 Ali(C-H str),3402.54(N-H str),1681.98 (C=0 str),1068.60(C-O-C str),3246.31(O-H str), 1558.54(C=C str),1361.79(bending in plane),756.12(out of plane bending).

III(b); 3419.9(N-H str),3030.27 Aro(C-H str), 2933.83 Ali(C-H str),1681.98(C=0 str),1068.6(C-O-C str),754.19 (Aro-Cl),1558.54(C=C str),1338.68(bending in plane),675.11(out of plane bending).

III(c); 3030.27 Aro(C-H str),3007.12 Ali(C-H str),3400.62(N-H str),1697.41(C=O str),3064.99(O-H str),1597.11(C=C str),1419.66(bending in plane),698.25(out of plane bending).

III(d); 3061.13 Aro(C-H str), 2933.83 Ali(C-H str), 3419.9(N-H str), 3296.46(O-H str), 1697.41 (C=O str), 1068.6(C-O-C), 754.19(Aro-Cl), 1577.82 (C=C str), 1386.64 (bending in plane), 673.18 (out of plane bending).

III(e); 3419.90 (N-H str), 3383.26 (O-H str), 3061.93 Aro(C-H str), 2933.83 Ali (C-H),1681.98 (C=O str),1068.80 (C-O-C str), 1417.73 (C-H bending in plane), 696.33 (C-H bending out of plane).

H'NMR ($CDCl_3$ in ppm), III(a);6.001 (Asym Multi, substituded benzene ring), 6.352 (Sym multi 4H, chloro subs benzen ring), 7.51 (s.2H, N-H)

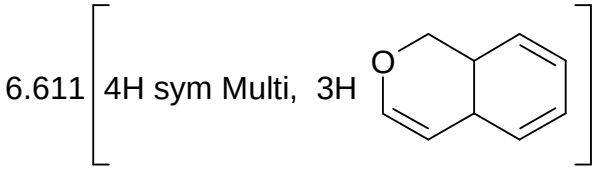


TABLE:1 Physical & Analytical data of the synthesized quinozoles derivative, (III_{a-f})

Comp	R	m.p°c	Yield	Molecular Formula	Molucular weight	Elemental analysis					
						C%		H%		N%	
						Cal	Found	Cal	Found	Cal	Found
III(a)	$2C_6H_5Cl$	190^0	60%	$C_{29}H_{17}O_3N_2$	493.23	70	69.89	7	6.9	5	4.9
III(b)	$4C_6H_5Cl$	188^0	71%	$C_2H_{17}O_3N_2$	493.34	70	69.89	7	6.9	5	4.9
III(c)	C_6H_5	180^0	68%	$C_{29}H_{18}O_3H_2$	454.21	76.1	75.8	8	7.9	6	5.89
III(d)	$4C_6H_5NO2$	195^0	72%	$C_{29}H_{18}O_4N_2$	492.18	76	75.8	9	8.9	6	5.91
III(e)	$4C_6H_5OH$	185^0	75%	$C_{29}H_{19}O_4N_2$	465.68	75	74.81	8	7.84	6	5.92
III(f)	$4C_6H_5OH_3$	186^0	72%	$C_{29}H_{19}O_3N_2$	462.30	75	74.91	8	7.9	6	5.96

Biological Activity:
All the six compounds 3(a-f) were screened for their antibacterial activity against E. Coli, staphylococous aureus and klebsiella pneumonial. These compounds were also evaluated for their antifungal activity three different fungals viz Aspergillus flaves and Aspergilus niger and trichoderma viridae were used at two concentration level. Viz. 100 ppm & 500 ppm involving nutrient agar media, standard drug Streptomycin used for antibacterial and Griseofulvin used as a antifungal activity respectively.

Anti-tubercular activity:
Drug susceptibility of MIC of the test compounds against M. tuberculosis H_{37} RV were performed by L J Agar (MIC) method. where primary 500, 250, 125 and secondary 50, 25, 12.5, 6.250, 3.125, 1.3625 □g/ml dilutions of each test compounds were added liquid. A culture of M tuberculosis H_{37} RV growing on L.J medium was harvested in 0.85% saline in bigou bottles. All test compounds make first stock solution of 2000 □g/ml concentration of compounds were prepared in DMSO. These tubes were then incubated in 37ºC for 24h, followed by streaking of M tuberculosis H_{37}RV (5×104 acid fast bacilli per tube). These tubes were then incubated at 37ºC growth of bacilli was seen after 12 days. 22 days and finally 28 days of incubation. Tubes having the compounds were compared with control tubes where medium alone was incubated with M.tuberculosis H_{37}RV. The concentration at which no development of colonies occurred or <26 colonies was taken as MIC concentration of test compound. The standard strain M.tuberculosis H_{37}RV was tested with drug isoniazide.

TABLE:II Antitubercular activity table data of the synthesized compounds

Minimum inhibitory concentrations (MICS □g/ml)

Compound	MIC values (mg/ml) of M.tuberculosis H_{37} RV	% inhibition
III(a)	62.5	99%
III(b)	50	97%
III(c)	500	99%
III(d)	40	98%

Table III: Antibacterial activity table of the synthesized quinazolines derivatives Against Various bacteria at two different conc. (In ppm)

Comp code	E.Coli		Staphylococcus Aureus		Klebsidlla pneamoniae	
	100 ppm	500 ppm	100 ppm	500 ppm	100 ppm	500 ppm
III(a)	-	+	-	++	-	++
III(b)	++	+++	++	+++	++	+++
III(c)	-	++	+	++	+	+++
III(d)	++	+++	++	+++	++	+++
III(e)	+	++	+	+	-	+
III(f)	+	++	-	+	+	++
Std	++++	++++	+++	++++	+++	++++

Std: Streptomycin ;
inhibition diameter in mm : ++++ strongly active range>19;
+++ moderately active range<12-18;
++ weakly active range 8-12;
- inactive range>8;

Table IV: Antifungal activity table of synthesized quinazolines derivatives against Various fungus at two different conc. (In ppm)

Comp code	Aspergilus nigar		Aspergilus flavus		Trochoderma virdae	
	100 ppm	500 ppm	100 ppm	500 ppm	100 ppm	500 ppm
III(a)	-	+	-	+	+	++
III(b)	++	+++	+++	+++	+++	+++
III(c)	++	+++	++	+++	++	+++
III(d)	-	++	++	+++	+	+++
III(e)	+	++	+	+	+	+
III(f)	+	++	+	++	+	+
Std	+++	++++	+++	++++	++++	++++

inhibition diameter in mm : ++++ strongly active range>19;
+++ moderately active range<12-18;
++ weakly active range 8-12;
- inactive range>8;

RESULTS AND DISCUSSION

The compound (II) has been prepared from arylideno alkylideo/bis urea and p amino benzoic acid in the presence of ethanol.

The synthesized heacterocyclic compounds (III) have been prepared from compound (II) in benzoin & polyphosphoric acid was added & refluxed about 4h during heating.

The synthesized quinozoline derivatives have been screened for antibacterial activity against E coli, staphylococcus aureus, and Klebsidlla pneumonie, at two different concentration 100 ppm & 500 ppm respectively by nutrient agar media and antifungal activity against Aspergillus nigar, Aspergilus flavus and Tricoderma viridae by nutrient agar media at two different concentration, standard drug Streptomycin used for antibacterial and griseofulvin used as a antifungal activity and have also been screened under the similar condition for comparison.

Synthesized quinazoline derivatives III(b), III(d), III(c) are highly active against selected bacteria and fungi and rest of the quinazoline derivatives have shown good to moderate activity. it was also observed that the promising antimicrobials have proved to be better ant tubercular, Specially compound III(d), III(b), and III(a) due to their better activity against H_{37} RV strain are the west choice for the preparation of new derivative in order to improve anti tubercular activity in future.

Acknowledgement
The authors are thankful to the Head Department of Chemistry, Dr H.S. Gour (A Central) University Sagar (MP) for providing laboratory and IR spectra facilities, we are also thankful to CDRI Lucknow for providing H^1NMR spectral datas of our compounds. I also thankfull to CSIR New Dehli for their financial support.

We are also greatful to Prof. Smt Smita Banarjee for her kind assistance for performing antimicrobial efficacy in Biotechnology Deptt.

REFERENCES

[1] A. L. Okunade, M. P. F. Elvin-Lewis and W. H. Lewis, **2004**. Natural Antimycobacterial metabolites: a new group of antimycobacterial status. Phytochemistry, **2004**, 65, 1017-1032.
[2] L. J Yves,. Antituberculosis drugs: Ten years of research. *Bioorg. Med. Chem.*, **2007** 15, 2479-2513.
[3] J. Imramovsky., S. Polanc, J. Vinsova, M. Kocevar, J. Jampilex, Z. Reckova and J. Kaustova,. A new modification of antitubercular active molecules. *Bioorg. Med. Chem*., **2007** 15: 2551-2559.
[4] E. L. Corbett, C.J. Watt, N. Walker, D. Maher, B.G. Williams, M.C. Raviglione and C. Dye,. The growing burden of tuberculosis: global trends and interactions with the HIV epidemic. *Arch. Intern. Med*., **2003** 163(9),1009-1021.
[5] D. K Dodiya, S. J Vaghasia, A. R Trivedi H. K Ram and U H Shah. *Ind. J. Chem***., 2010.802**, 49B
[6] J P Michael, *Nat. Prod. Rep* **2002**., 742**,**19
[7] K. M Shakhidoyatov, A Irisbaeu and N. P Abdullaev, Growth regulators of plants and herbicides (Fan. Tashkent),**1978,** 16.
[8] M S Amine, H A Aly and R. EI Syed, *Ind. J. Chem***. 2006,** 1020**,** 45B.
[9] J. B Jiang, D. P Hesson, B. A Dusak, D. L Dexter, G. J Kang and E Hamel. *J. Med. Chem.***1990,** 1721**.**, 33.
[10] B. Pramella, E. Rajanarender and A. K Murty, *Indian J. Het. Chem.***1992**, 115, 2.
[11] M. S Amin, A. M. F Eissa, A A El-Sawy, A F Shaaban and E L Sayed, *Olaj Szappan Kozmetika.*, 52, 6.
[12] K. Kamed, S. Ono, J. Kayama and Y. Abiko, *Acta, Endocrinol.* **1982,** 410**,** 99.
[13] E. Knaus, L. A Corleto & S. Redda, *Canadian Patent*,**1982** 1, 20, Mar**,** 120. Chem Abstr., 37**,** 38859c (**1982**).
[14] B. Palameta, T Bogri and J Bagh, *US Patent*, 4, 382**,** 088, 03 Mar**;** (**1983)** *Chem Abstr.*, 99 **,** 282091(**1983**).
[15] M. Kossayama, F Ischikawa, Y Waternable, Y Abiko & K Kamed, Ger. often, 2 Jan., 5, 728(**1976**). *Chem. Abstr.***1978** 89**,** 676 .
[16] S. K Pathak, in "Synthesis of potential hypoglycemic compounds" Ph.D. Thesis, Chemistry Department, Lucknow University, Lucknow.**1999** .15**.**.
[17] U. K. Pandey & S. Jindal, *Indian Drugs.***1995**, 317, 32.
[18] A. M. Katz, W. D Hagar, F.C Messinco & A. J Pappanbo, *Am J. Med.*, **1985,** 79 (Supl. 4A), 2**.**
[19] A Swartz, *J. Mol. Cell Cardiology***.,1987,** 19 (Suppl II)**,** 49.
[20] A. Monnschreck, H. Kollar, G. Stunoer, M. A. Davies & Truber, *Eur J. Med Chem.*,**1984** 381**,**26.
[21] S. Gouri, K. anjani, V. Tiwari, K. Vinay, K. Mishre, *Chemical Biology & Drug design.*,**2008,** 533 4,.
[22] A. Omar,AI. Deeb and Ahmed M.Alafeefy,*World Applied Sciences Journal* ,**2008,**5(1), 94-99,.