SYNTHESIS OF NOVEL 1,5 – BENZOTHIAZEPINES CONTAINING 2H(1) -QUINOLIN -2-ONE HETEROCYCLE±

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Abstract: New Heterocyclic systems namely 1,5-benzothiazepines derivatives **(4a-h)** have been synthesized via reaction of Chalcone(s) and 2-aminothio phenol in good yields. Some of the compounds have shown good anti-bacterial activity.

Introduction:

Many heterocyclic compounds containing nitrogen, oxygen and sulphur show wide variety of physiological activities. 1,5-benzothiazepine compounds have demonstrated interesting biological activity such as coronary vasodialatory[1], tranquiliser[2,3], anti depressant[4], anti spasmodic[6], neuroleptic[6], CNS[7] and anti-HIV[8] activity

Literature survey reveals that 1,5-benzothiazepines incorporating several alkyl, aryl groups and benzpopyranyl moiety on 4-postion of benzothiazepine skeleton. It is well known that 2H-(1)-benzopyran-2-one derivative exhibit wide range of biological activity and their isostere, 2H-(1)- quinolin-2-one are also endowed with activity[9].In continuation of our work on the sythesis of 1,5-benzothiazepines[10],we report here the synthesis of some,novel 1,5-benzothiazepines containing 2H-(1)-quinolin-2-one,utilizing (quinolin-2-one-3-yl)-2-propenones (Chalcones) and 2-amino thiophenol, guided mainly by the observation that many a times, the combination of two or more heterocyclic nuclei in a singular molecular framework enhances the biological profile many **a** fold.

Results and Discussion :

The requisite starting material 3-Acetyl- 4-hydroxy-1-methy 2H-(1)-quinolin-2-one[11] **(1)** has been prepared by the known literature method. Condensation of **(1)** with variety of aromatic, heteroaroamtic aldehydes **(2a-h)** in ethanol and sodium hydroxide resulted in 2H-(1)- qunolin-2-one-3-yl)-3-aryl-2-propenones **(3a-h)**. These compounds **(3a-h)** were characterised by spectroscopic means and are comparable with literature data.

2-propenone derivatives (chalcones) when treated with 2-amino thiophenol in ethyl alcohol medium with few drops of glacial acetic acid afforded 2-aryl-4- (4'-hydroxyl-1-methyl-2H-1-quinolin-2-one-3'-yl)-2,3-dihydro-1,5-benzothiazepines **(4a-h)** in very good yields. The compounds have been characterised by spectral means such as IR, NMR and Mass. In IR spectra, characteristic band at 1600-1616cm^{-1}is attributed to C=N bond for the 2,3-dihydro-1, 5-benzothiazepines. Further the structure was unequivocally proved by the NMR spectra of the protons attached to the carbons C-2 and C-3 which appeared as a typical ABX pattern [4a : δ 2.65($1H_A$,dd),4.45($1H_B$,dd),5.40($1H_X$,dd) with J_{AB} = 12.5 Hz, J_{BX} = 7.0 Hz and J_{AX} = 15.0 Hz). All the 1,5-benzothiazepines synthesised were characterised by mp's ,NMR ,IR and Mass.

Biological Testing :

The senstivity of bacteria to various substituted 1, 5-benzothiazepines was determined by " Cup-Diffusion Method"[12]. Known dilutions of the test solution and a standard solution of antibiotic drug pipetted into the cups, the plates are incubated, and the inhibitory zones resulting on the plates were noted and measured[12]. Among the compounds tested 4c,4d,4f,4g and 4h have shown very good anti-bacterial activity against Gram (+)ve bacteria, *B.subtilis* at a concentration of 100 μg/mm. Further testing is in progress for QSAR studies and the detailed results will be published elsewhere. The results are given in Table 2.

± IICT Communication No: 020413

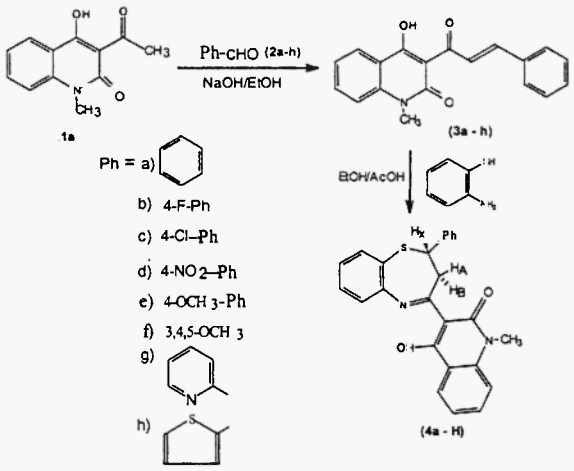
Table 1 : Physical and Spectral Data of 1,5-Benzothiazepines

Compound	Mp(°C)	Yield	^{1}H-NMR (200 MHz,$CDCl_3$), ppm
4a	225	75	δ 2.65 (1H,dd,J_{AB}= 12.5 Hz ; J_{Ax}=15.0 Hz ; H_A), 4.45 (1H,dd,J_{BA}= 12.5 Hz ; J_{BX}=7.0 Hz ; H_B) ; 5.40 (1H,dd,J_{XA}= 15.0 Hz ; J_{XB}=7.0 Hz ; H_X) , 7.00-8.25 (13H,m , Ar-H) & 3.62 (3H,s,N-CH_3)
4b	245	70	δ 2.65 (1H,dd,J_{AB}= 12.5 Hz ; J_{Ax}=15.0 Hz ; H_A), 4.48 (1H,dd,J_{BA}= 12.5 Hz ; J_{BX}=7.0 Hz ; H_B) ; 5.41 (1H,dd,J_{XA}= 15.0 Hz ; J_{XB}=7.0 Hz ; H_X) , 7.00-8.25 (12H, m , Ar-H) & 3.60 (3H,s,N-CH_3)
4c	250	70	δ 2.60 (1H,dd,J_{AB}= 12.5 Hz ; J_{Ax}=15.0 Hz ; H_A), 4.45 (1H,dd,J_{BA}= 12.5 Hz ; J_{BX}=7.0 Hz ; H_B) ; 5.40 (1H,dd,J_{XA}= 15.0 Hz ; J_{XB}=7.0 Hz ; H_X) , 6.80-8.20 (12H,m , Ar-H) & 3.60 (3H,s,N-CH_3)
4d	246	68	δ 2.61 (1H,dd,J_{AB}= 12.5 Hz ; J_{Ax}=15.0 Hz ; H_A), 4.45 (1H,dd,J_{BA}= 12.5 Hz ; J_{BX}=7.0 Hz ; H_B) ; 5.40 (1H,dd,J_{XA}= 15.0 Hz ; J_{XB}=7.0 Hz ; H_X) , 6.80-8.25 (12H, m , Ar-H) & 3.61 (3H,s,N-CH_3)
4e	256	70	δ 2.64 (1H,dd,J_{AB}= 12.5 Hz ; J_{Ax}=15.0 Hz ; H_A), 4.45 (1H,dd,J_{BA}= 12.5 Hz ; J_{BX}=7.0 Hz ; H_B) ; 5.40 (1H,dd,J_{XA}= 15.0 Hz ; J_{XB}=7.0 Hz ; H_X) , 6.90-8.20 (12H, m , Ar-H) & 3.61 (3H,s,N-CH_3), 3.80(3H,s, OCH_3)
4f	265	70	δ 2.61 (1H,dd,J_{AB}= 12.5 Hz ; J_{Ax}=15.0 Hz ; H_A), 4.45 (1H,dd,J_{BA}= 12.5 Hz ; J_{BX}=7.0 Hz ; H_B) ; 5.40 (1H,dd,J_{XA}= 15.0 Hz ; J_{XB}=7.0 Hz ; H_X) , 6.60-8.25 (10H, m , Ar-H) & 3.61 (3H,s,N-CH_3), 3.80(9H,S, OCH_3).
4g	250	72	δ 2.90 (1H,dd,J_{AB}= 12.5 Hz ; J_{Ax}=15.0 Hz ; H_A), 4.50 (1H,dd,J_{BA}= 12.5 Hz ; J_{BX}=7.0 Hz ; H_B) ; 5.40 (1H,dd,J_{XA}= 15.0 Hz ; J_{XB}=7.0 Hz ; H_X) , 7.20-8.10 (12H, m , Ar-H) & 3.61 (3H,s,N-CH_3)
4h	245	65	δ 2.70 (1H,dd,J_{AB}= 12.5 Hz ; J_{Ax}=15.0 Hz ; H_A), 4.60 (1H,dd,J_{BA}= 12.5 Hz ; J_{BX}=7.0 Hz ; H_B) ; 5.60 (1H,dd,J_{XA}= 15.0 Hz ; J_{XB}=7.0 Hz ; H_X) , 6.90-7.90 (11H, m , Ar-H) & 3.61 (3H,s,N-CH_3)

Table 2: Anti- Bacterial activity of 1,5-Benzothiazepienes (Results after 24 hr)

Test Organism	Conent µg/mm	Zone of inhibition(diamcter in mm) (100µg/cup) ——compounds——									
Gram+ve Bacteria		4a	4b	4c	4d	4e	4f	4g	4h	Positive control (PEN-G) 30µg/mm	Negative control ($CHCl_3$)
Bacillus.sph Aericsu	100	—								20	----
B.subtilis	100	9	8	18	16	---	40	35	20	19	
Staphylococ-cus.aureus	100									19	
Gram –ve										Streptomycin	
Pseudomonas .Auriginosa	100									29	
Klebsiella.aer-genues	100	9	7	8	7	9	11	10	10	30	
Ecsherichia.coli	100	12								28	

"----" represents no zone



Experimental :

All the melting points were carried out in an open capillary and are uncorrected. Proton NMR spectra were recorded on 200 MHz spectrometer in $CDCl_3$ and the chemical shift values were reported in δ (ppm) and J values are expressed in hertz.

3-acetyl-4-hydroxy-1-methyl-2H-(1) quinolin-2-one: (1a)
synthesised according to the reported procedure[11].

1-2H(1)-quinolin-2-one-3-yl)-3-aryl-2-propeonones: (3a-h)
To an ethanolic solution of **(1)**(0.01 mmole) was added 15% NaOH (10 ml) while stirring at room temperature,then the appropriate aldehyde (0.01mmole) was added and stirred10-12 hrs at R.T. At the end the reaction mixture was carefully neutralised with 5% aq.HCl to yield yellow colour solid,which was filtered,washed several times with cold EtOH and water, dried and recystallised with ethanol.

2-aryl-4-(4'-hydroxy-1-methyl-2H(1)-quinolin-2-one-3'-yl)-2,3-dihydro-1,5-benzothiazepines : (4a-h)
Propeonone **(3a-h)** (0.01mmole) was dissolved in ethanol (20ml),to this 2-thioamino phenol (0.01mmole) and few drops of acetic acid was added and the reaction mixture was refluxed on water bath. After 2hrs a yellow fluffy solid starts seperating out .The reaction mixture was further refluxed for one more hour, cooled and the seperated solid was filtered and washed several times with hot ethanol.The compound was dried and recrystallised using acetone to get pure 1,5-benzothiazepines. All other derivatives were prepared accordingly. The results are tabulated in table 1.

Acknowledgements : The authors are thankful to the Director,and the Head, Biology Division,IICT for providing the facilities and evaluating the bio efficacy respectively. One of the author SK is thankful to CSIR, New Delhi for the award of Research Associateship.

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Received on May 27, 2002