Int. J. Chem. Sci.: 12(3), 2014, 1001-1008
ISSN 0972-768X
www.sadgurupublications.com

NOVEL ANALOGUES OF 1, 5-BENZOTHIAZEPINE: SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL EVALUATION

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ABSTRACT

The chemistry and pharmacology of thiazoles and thiazolochromenones are of great interest to medicinal chemists nowadays, because they are known to possess a wide range of pharmacological properties. A series of novel 6-(3-((2 Z, 4E)-2-phenylbenzo[b][1,4]thiazepin-4-yl)pyridazin-3(2H)-one were prepared by the reaction of 6-(3-((E)-3-phenylacryloyl) phenyl amino)pyridazin-3(2H)-one with 2-aminobenzenethiol. All compounds were tested for their antimicrobial activity against bacteria and fungi. It is interesting to note that the in heterocyclic compounds containing substituent's at the 4th position of benzodiazepines system displayed notable antibacterial activity, almost equal to penicillin.

Key words: [1,5]-benzothiazepines, 2-aminobenzenethiol, Chalcone antimicrobial activity, Antibacterial activity.

INTRODUCTION

1, 5-Benzothiazepine is one of the three possible benzo-condensed derivatives, *viz.*, 1, 4-,4, 1- and 1, 5-benzothiazepines of the 1, 4-thiazepine[1]. Benzotiazepines are well known compounds for diverse therapeutically properties like antibacterial[2-3] and antifungal[4]. They also possess a wide range of pharmacological properties[5-6] including anti-HIV[7], anticoagulant[8] and anti-allergenic[9]. Owing to their bioactivities, the 1, 5-benzothiazepine is especially important nitrogen and sulphur containing heterocyclic compounds in drug research.

1, 5-benzotiazepines are gaining more attention due to their pharmacological significance. Diltiazem[10] is well explored as effective cardiovascular drugs and are found to

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contain [1,5]-benzotiazepines nucleus. Some of the benzotiazepines have been claimed to exhibit antimicrobial[11], anticonvulsant antispasmodic[12], neurolaptic[13] and antidepressant[14] activities. Synthesis of benzothiazepines has been intensely studied and numerous procedures are described in the literature[15] but [1,5]-benzothiazepines from chalcones containing pyridazines derivatives[16] have not been synthesized and documented yet. With these objectives, it was decided to prepare some novel [1,5]-benzothiazepines by using 6-(3-((E)-3-phenylacryloyl)phenyl amino)pyridazin-3(2H)-one earlier prepared biologically active chalcone and 2-aminobenzenethiol.

EXPERIMENTAL

All melting points reported are uncorrected. TLC was used to monitor the progress of reactions and to test the purity of the compounds on silica gel 'G' coated glass plates with solvent system, benzene: ethanol ammonia (7 : 2 : 1), upper layer). IR spectra (KBr) were recorded a Perkin-Elmer infracord-577 spectrophotometer, ^{1}H NMR an a Jeol FT 90 MHz spectrophotometer using TMS as internal standard and mass on a Varian Match-7 instrument at 70 eV.

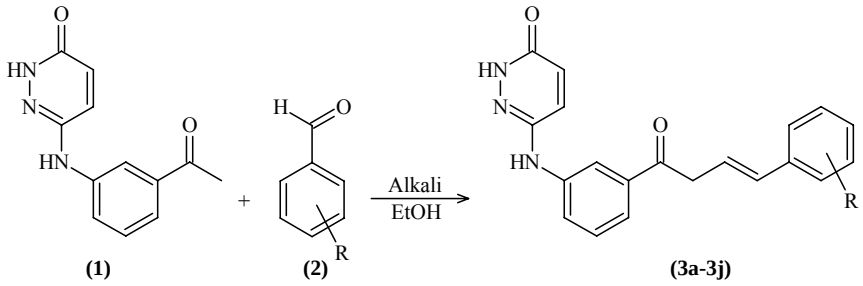
General procedure for the preparation of 6-(3-((2 Z,4E)-2-phenylbenzo[b][1,4] thiazepin-4-yl)pyridazin-3(2H)-one (4a-j)

Chalcones derivatives were synthesized by condensing 6-(3-((E)-4-phenylbut-3-enoyl) phenylamino) pyridazin-3(2H)-one with various aromatic substituted aldehydes according to the method in the literature to give corresponding Chalcones **(3a-j)**.

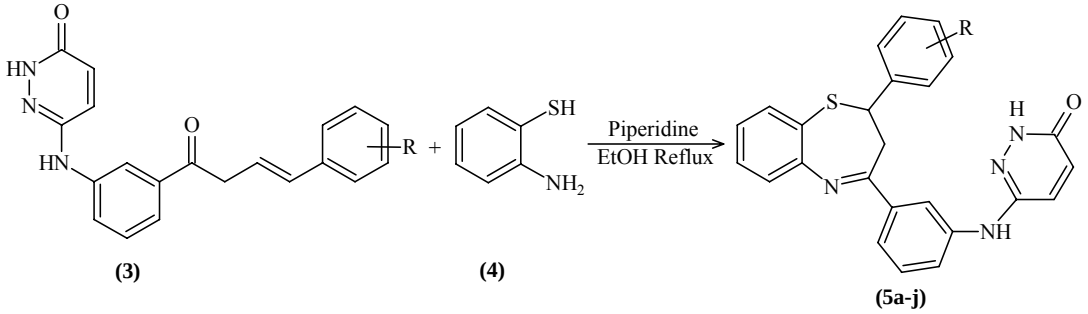
Equimolar quantities 2-aminobenzenethiols (1 mmol) and 6-(3-((E)-3-phenylacryloyl) phenyl amino) pyridazin-3(2H)-one(1 mmol) were dissolved in a minimum quantity of dry ethanol (10 mL) and few drops of piperidine. The reaction mixture was refluxed for a period of 5 hrs. Removal of the excess of solvent under reduced pressure gave crude solid, which on recrystallization from dry ethanol **(4a-j)**.

RESULTS AND DISCUSSION

Synthesis and chemical transformations of 2,3-dihydro-1,5-benzothiazepines have been intensely studied by several research groups and as a result numerous new 1,5-benzothiazepine derivatives have been described in the literature. 1, 5-benzothiazepines derivatives are very important and useful compounds in organic and pharmaceutical chemistry. Chalcones (**3a-j**) were obtained by using various aldehydes. Further, **(3a-j)** were treated with 2-aminobenzenethiol in presence of few drops of piperidine as a catalyst and ethanol as solvent by conventional method.



Scheme 1: Synthesis of chalcones



Scheme 2: Synthesis of 1, 5-benzothiazepines

Spectral analysis: Spectral analysis of selected compounds.

6-(3-((E)-2,3-dihydro-2-(3,4-dimethoxyphenyl)benzo[b][1,4]thiazepin-4-yl)phenylamino) pyridazin-3(2H)-one (4b)

Yield 82%, M. P. 190°C; IR (KBr): 3250 (Ar. C=C Stre.), 3200 (N-H Stre.), 1675, 1670, (2 C=O), 2840 (OCH_3); 1545 (NH), 630 (C-S) ^{1}H NMR (DMSO-d_6): δ 3.95 (s, 3H, -OCH_3), δ 3.98 (s, 3H, -OCH_3), 7.14-7.89 (m, 7H, Ar-H), 6.20 (s, 1H, -CH of thiazole), 5.259 s, 1H, -NH), 7. 26 (d, 1H, Jα, β = 16 Hz, H β), 6.90-7.30 (m, 5H, Ar-H), 6.63-7.95 (s, 1H, Ar-H), 6.83-6.90 (d. 1H J = 9.8 Hz, CH pyridazine), 7.17-7.22 (d. 1H. J = 9.9 Hz CH Pyridazine), 7.51-7.54 (t. 1H, NH pyridazine D_2O exchangeable); Mass; (m/z), 484 Analysis (% for) $C_{27}H_{24}N_4O_3S$ Calcd. C, 66.92; H, 4.99; N, 11.56; O, 9.91; S, 6.62 found. C, 67.00; H, 5.10; N, 11.98; O, 9.98; S, 6.66.

6-(3-((E)-2, 3-dihydro-2-(4-hydroxyphenyl)benzo[b][1, 4]thiazepin-4-yl)phenylamino) pyridazin-3(2H)-one (4c)

Yield 55%, M. P. 182°C; IR (KBr): 3250 (Ar. C=C Stre.), 3215 (N-H Stre.), 1672, 1672, (2 C=O), 1545 (NH), 630 (C-S); ^{1}H NMR (DMSO-d_6): 7.14-7.89 (m, 7H, Ar-H), 6.20

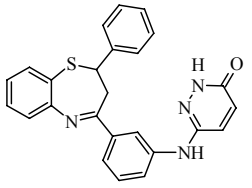
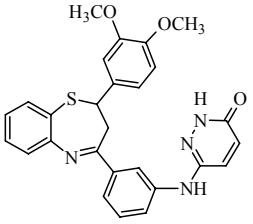
(s, 1H, -CH of thiazole), 5.259 s, 1H, -NH), 7.26 (d, 1H, Jα, β = 16 Hz, H β), 6.90-7.30 (m, 5H, Ar-H), 6.83-6.90 (d. 1H J = 9.8 Hz, CH pyridazine), 7.17-7.22 (d. 1H. J = 9.9 Hz CH Pyridazine), 7.51-7.54 (t. 1H, NH pyridazine D2O exchangeable); 4.17 (d, 1H, -OH). Mass; (m/z), 440 Analysis (% for) $C_{25}H_{20}N_4O_2S$ Calcd. C, 68.12; H, 4.59; N, 12.76; O, 7.21; S, 7.26; found. C, 68.10; H, 4.61; N, 12.78; O, 7.18; S, 7.24.

6-(3-((E)-2,3-dihydro-2-(4-chlorophenyl)benzo[b][1,4]thiazepin-4-yl)phenylamino) pyridazin-3(2H)-one (4g)

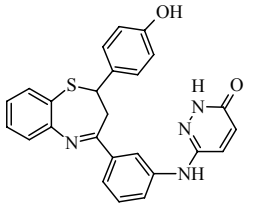
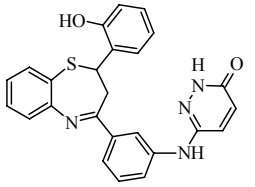
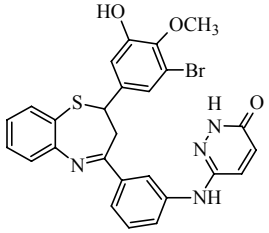
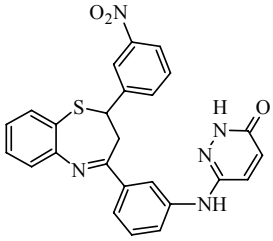
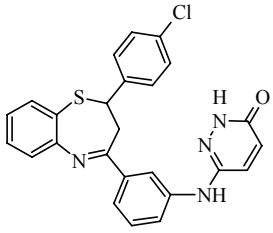
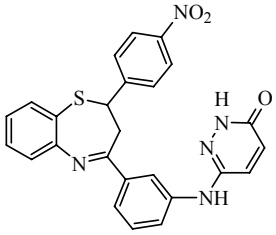
Yield 72%; M. P. 192ºC; IR (KBr): 3250 (Ar.C=C Stre.), 3200 (N-H Stre.), 1675 (C=O), 814 (C-Cl), 1543 (NH), 633 (C-S) ^{1}H NMR (DMSO-d_6): δ7.14-7.89 (m, 7H, Ar-H), δ 6.22 (s, 1H, -CH of thiazole), δ 5.262 (s, 1H, -NH), δ 7. 42 (d, 1H, Jα, β = 16 Hz, H β), δ 6.90-7.30 (m, 5H, Ar-H), δ 6.63-7.95 (s, 1H, Ar-H), δ 6.79-6.84 (d. 1H J = 9.8 Hz, CH pyridazine), δ 7.17-7.22 (d. 1H. J = 9.9 Hz CH Pyridazine), δ 7.49-7.52 (t. 1H, NH pyridazine D_2O exchangeable); Mass; (m/z), 484 Analysis (% for) $C_{25}H_{19}ClN_4O_4S$ Calcd. C, 65.92; H, 4.25; N, 12.56; O, 3.51; S,6.92 found. C, 65.60; H, 4.50; N, 12.98; O, 3.58; S, 6.65.

The advantage of this approach through 6-(3-propionylphenylamino) pyridazin-3(2H)-one are rapid reaction rates, enhancement in chemical yield and synthesis on preparative scale. Hence, in the present studies, it was thought to be fruitful to synthesize 1, 5-benzothaizepines from such bioactive chalcones and study their antibacterial and antifungal activities.

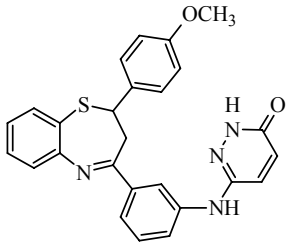
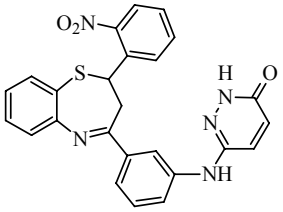
Table 1: Physical constants and analysis data of substituted-1,5-benzothiazepines (5a-j)

Entry	Structure of compound	Yield[a] (%)	Time (hrs)	M.P. (°C)
5a		72	5-6	185
5b		82	5-6	190

Cont…

Entry	Structure of compound	Yield[a] (%)	Time (hrs)	M.P. (°C)
5c		55	5-6	182
5d		70	5-6	175
5e		65	5-6	188
5f		68	5-6	165
5g		72	5-6	192
5h		85	5-6	165

Cont…

Entry	Structure of compound	Yield[a] (%)	Time (hrs)	M.P. (°C)
5i		87	5-6	190
5j		50	5-6	170

[a]Isolated yield after column chromatography

Under this reaction system, a series of experiments for synthesis of 1, 5-benzothiazipines were performed.

Microbial activity

The antimicrobial activity of these [1,5]-benzothiazepines **(5a-j)** was tested by "paper disc diffusion plate method"[17]. Activity of standard antibacterial drug, penicillin & antifungal drug, gresiofulvin were also checked under the same conditions and concentration. Solvent DMSO also tested for their antimicrobial activity and has shown no activity.

The experiments were performed in duplicate and average zones of inhibition in mm (including the size of the discs have been recorded and tabulated in Table 2).

Table 2: Microbial activity of synthesized [1, 5]-benzothiazepines

Entry	Compounds	Bacteria		Fungi	
		E. coli **ATCC 8739**	***S. auranus*** **ATCC6538**	***A. niger*** **ATCC16404**	**C. A. ATCC10231**
1	**5a**	**12 mm**	**10 mm**	-ve	10 mm
2	**5b**	7 mm	8 mm	-ve	8 mm
3	**5c**	**11 mm**	**10 mm**	-ve	-ve

Cont…

Entry	Compounds	Bacteria		Fungi	
		E. coli **ATCC 8739**	***S. auranus*** **ATCC6538**	***A. niger*** **ATCC16404**	**C. A. ATCC10231**
4	**5d**	8 mm	-ve	-ve	**11 mm**
5	**5e**	10 mm	6 mm	-ve	9 mm
6	**5f**	9 mm	7 mm	10 mm	10 mm
7	**5g**	8 mm	**9 mm**	**11 mm**	8 mm
8	**5h**	**11 mm**	7 mm	**12 mm**	9 mm
9	**5i**	**11.5 mm**	**9 mm**	-ve	**11 mm**
10	**5j**	10 mm	**9 mm**	-ve	**13**
16	**Penicillin**	10.5 mm	8.5 mm	-	-
17	**Grysofulvin**	-	-	10.5 mm	10 mm

Legends –ve indicates No activity

CONCLUSION

Synthesis of newer 1,5-benzothiazipine derivatives are reported herein. These simple and conventional method, which gives moderate percentage of yield. Novel 1,5-benzothaizepines shows bacterial as well as fungal activities.

ACKNOWLEDGEMENT

The authors are thankful to the Principal Dr. S. N. Thore, Deogiri College, Aurangabad & Principal Dr. Sandesh Gurav, K. E. S. Anandibai Pradhan Science College, Nagothane, Dist. Raigad for encouragement during the process of this work.

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Revised : 04.04.2014 *Accepted : 07.04.2014*