



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-thiazepine¹. Benzothiazepines are well known compounds for diverse therapeutically properties like antibacterial²⁻³ and antifungal⁴. They also possess a wide range of pharmacological properties⁵⁻⁶ including anti-HIV⁷, anticoagulant⁸ and anti-allergenic⁹. Owing to their bioactivities, the 1, 5-benzothiazepine is especially important nitrogen and sulphur containing heterocyclic compounds in drug research.

1, 5-benzothiazepines are gaining more attention due to their pharmacological significance. Diltiazem¹⁰ is well explored as effective cardiovascular drugs and are found to

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contain [1,5]-benzothiazepines nucleus. Some of the benzothiazepines have been claimed to exhibit antimicrobial¹¹, anticonvulsant antispasmodic¹², neuroleptic¹³ and antidepressant¹⁴ activities. Synthesis of benzothiazepines has been intensely studied and numerous procedures are described in the literature¹⁵ but [1,5]-benzothiazepines from chalcones containing pyridazines derivatives¹⁶ 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, ¹H NMR an a Jeol FT 90 MHz spectrophotometer using TMS as internal standard and mass on a Varian Match-7 instrument at 70 eV.

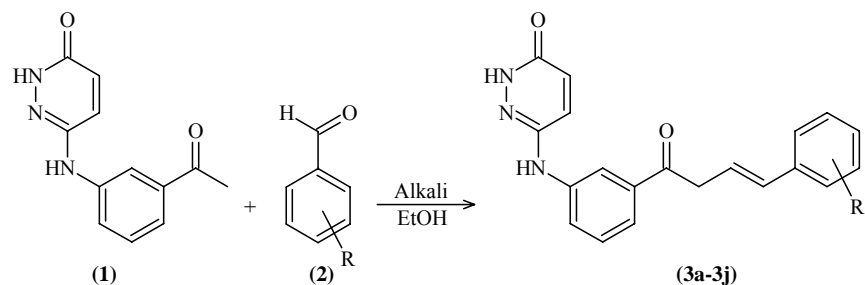
General procedure for the preparation of 6-(3-((2 Z,4E)-2-phenylbenzo[b][1,4]thiazepin-4-yl)pyridazin-3(2H)-one (4a-j)

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**).

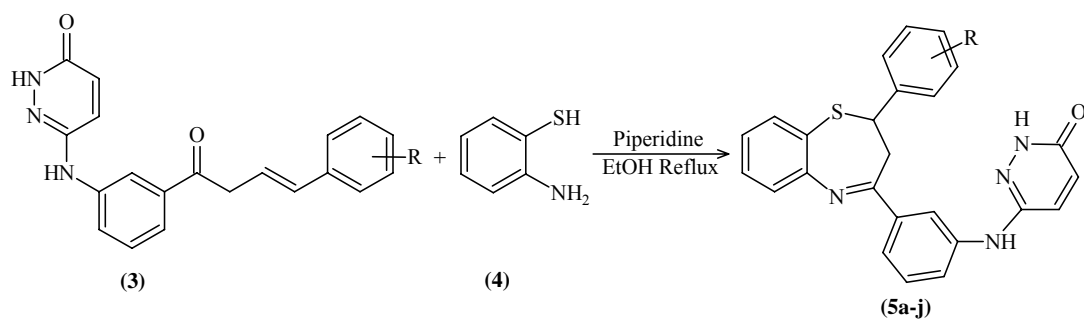
Equimolar quantities 2-aminobenzenethiols (1 mmol) and 6-(3-((E)-3-phenylacryloyl) phenyl amino) pyridazin-3(2H)-one(1 mmol) were dissolved in a minimum quantity of dry ethanol (10 mL) and few drops of piperidine. The reaction mixture was refluxed for a period of 5 hrs. Removal of the excess of solvent 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 (OCH₃); 1545 (NH), 630 (C-S) ¹H NMR (DMSO-d₆): δ 3.95 (s, 3H, -OCH₃), δ 3.98 (s, 3H, -OCH₃), 7.14-7.89 (m, 7H, Ar-H), 6.20 (s, 1H, -CH of thiazole), 5.259 s, 1H, -NH), 7.26 (d, 1H, J_{α, 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 D₂O exchangeable); Mass; (m/z), 484 Analysis (% for) C₂₇H₂₄N₄O₃S 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); ¹H NMR (DMSO-d₆): 7.14-7.89 (m, 7H, Ar-H), 6.20

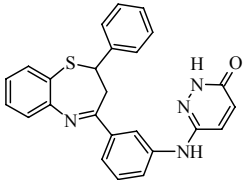
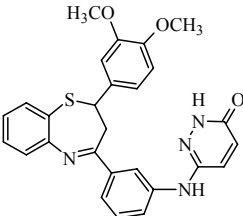
(s, 1H, -CH of thiazole), 5.259 s, 1H, -NH), 7.26 (d, 1H, $J_{\alpha, \beta} = 16$ Hz, H β), 6.90-7.30 (m, 5H, Ar-H), 6.83-6.90 (d, 1H $J = 9.8$ Hz, CH pyridazine), 7.17-7.22 (d, 1H. $J = 9.9$ Hz CH Pyridazine), 7.51-7.54 (t, 1H, NH pyridazine D₂O exchangeable); 4.17 (d, 1H, -OH). Mass; (m/z), 440 Analysis (% for) C₂₅H₂₀N₄O₂S 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)

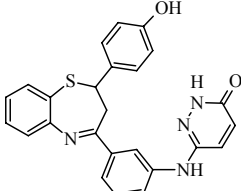
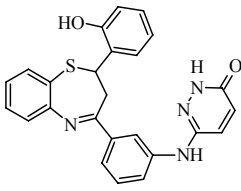
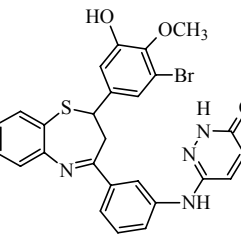
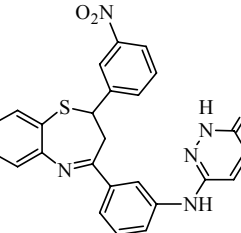
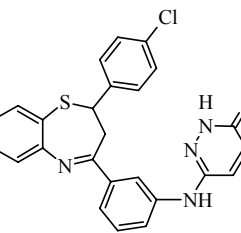
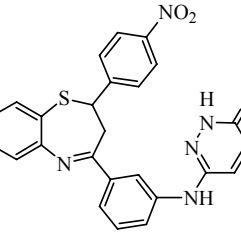
Yield 72%; M. P. 192°C; IR (KBr): 3250 (Ar.C=C Stre.), 3200 (N-H Stre.), 1675 (C=O), 814 (C-Cl), 1543 (NH), 633 (C-S) ¹H NMR (DMSO-d₆): δ 7.14-7.89 (m, 7H, Ar-H), δ 6.22 (s, 1H, -CH of thiazole), δ 5.262 (s, 1H, -NH), δ 7.42 (d, 1H, $J_{\alpha, \beta} = 16$ Hz, H β), δ 6.90-7.30 (m, 5H, Ar-H), δ 6.63-7.95 (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 D₂O exchangeable); Mass; (m/z), 484 Analysis (% for) C₂₅H₁₉ClN₄O₄S 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-benzothiazepines from such bioactive chalcones and study their antibacterial and antifungal activities.

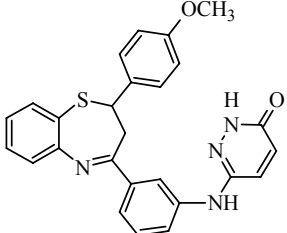
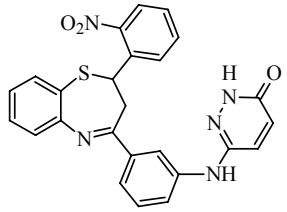
Table 1: Physical constants and analysis data of substituted-1,5-benzothiazepines (5a-j)

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

^aIsolated yield after column chromatography

Under this reaction system, a series of experiments for synthesis of 1, 5-benzothiazepines 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	
		<i>E. coli</i> ATCC 8739	<i>S. auranus</i> ATCC6538	<i>A. niger</i> ATCC16404	<i>C. A.</i> 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	
		<i>E. coli</i> ATCC 8739	<i>S. aureus</i> ATCC6538	<i>A. niger</i> 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-benzothiazepine derivatives are reported herein. These simple and conventional method, which gives moderate percentage of yield. Novel 1,5-benzothiazepines shows bacterial as well as fungal activities.

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REFERENCES

1. A. Levai, Synthesis of Optically Active 1,5-benzothiazepines Trends Heterocyclic Chem., **4**, 51 (1995).
2. G. R. Subbanwad, M. A. Baseer and Y. B. Vibhute, Synthesis and Antibacterial Activity of some Isoxazolines Ind. J. Pharm. Sci., **2**, 264 (2002).
3. V. M. Barot, M. R. Patel and H. B. Naik, Synthesis, Characterization and Microbial Screening of Isoxazole Derivatives Asian J. Chem., **13(1)**, 347 (2001).

4. M. Gurav and S. V. Agarkar, Chalcones, 3-chlorochromones, 1,5-benzothiazepines *Ind. J. Chem.*, **37B**, 161 (1998).
5. F. Bigi, Clean Synthesis in Water, Part 2: Uncatalysed Condensation Reaction of Meldrums Acid Aldehydes *Tetrahedron Lett.*, **42**, 5203 (2001).
6. D. U. Warad, C. D. Satish, V. H. Kulkarni and C. S. Bajgur, Antifungal Active Tetra Aza Macrocyclic Transition Metal Complexes: Designing, Template Synthesis, and Spectral Characterization, *Indian J. Chem.*, **39A**, 415 (2000).
7. L. Xie, Y. Tukeuchi, L. M. Consetino, K. J. Lee, Antiaids Agents, 37, Synthesis and Structure Activity Relationship of (3'R4R')ciskhellactone Derivatives as Novel Potent Anti HIV Agents, *Med. Chem.*, **42**, 2662 (1999).
8. H. K. Desai, D. H. Gawad and B. S. Joshi, *Indian J. Chem.*, **15B**, 291 (1977).
9. D. R. Bukel and H. Smith, *J. Med. Chem.*, **18**, 391 (1975).
10. H. Kugita, H. Inone, M. Ikezaki and S. Takeo, *Chem. Pharm. Bull. Jpn.*, **18**, 2028 (1970). K. Kinoshita, J. D. Harse, V. M. Braimridge and S. A. Mannig, *Can. J. Cardiol.*, **4(1)**, 37 (1998).
11. K. Aoki, K. Sato, S. Kondo and M. Vamamoto, *Eur. J. Clin. Pharmacol.*, **25**, 47 (1990).
12. Krapcho, J. US Pat (1968); *Chem. Abstr.*, **69**, 36194 (1968).
13. J. B. Renz, P. Jean and H. Winkler, *Fr Pat*, (1998), 1535, 533 (Cl. C07d, A, 61K).
14. J. Bernstein, *Brit. Pat.*, 1, 198, 825 (1970), (Cl. C07d); *Chem. Abstr.*, **73**, 77294 (1970).
15. J. Burris, M. Weir, S. Oparil, S. Weber, W. Cady and W. Stewart, *JAMA, J. Aam. Med. Assoc.*, **263**, 1507 (1990).
16. K. Weiss, P. Fitscha, A. Gazso, D. Gludovacz and H. Sinzinger, *Prog. Clin. Biol. Res.*, **301**, 353 (1989).
17. D. Alonzo, J. Allert, H. Thomas, A. Darbenzio, R. Raymond and Joseph, Syntheses of 1,5-benzothiazepines, Part Synthesis of 8-substituted-2,5-dihydro-2-(4-N-dimethylaminophenyl)-4-(4-methoxyphenyl)-1,5-benzothiazepines, *S. C. J. Cardivasc. Pharmacol.*, **3**, 159 (1998).

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