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RESEARCH ARTICLE

Piperidine Mediated Synthesis of Hetero Chalcones and 8-Substituted-2, 5-dihydro-2-(2-furanyl)-4-(2-thienyl)-1, 5-benzothiazepines as Antibacterial Agents

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Abstract: The reactions of 5-substituted-2-amino benzenethiols with hetero chalcones **3** have been carried out in dry toluene containing catalytic amount of piperidine, the products, 8-substituted-2,5-dihydro-2-(2-furanyl)-4-(2-thienyl)-1,5-benzo thiazepines **5** and hetero chalcones **3** were synthesized by piperidine mediated condensation of an ethanolic solution of a 1-thiophen-2-yl-ethanone **2** with corresponding furan-2-carbaldehyde **1.** The structures have been established on the basis of elemental (C, H, N) analysis, IR, ^{1}H NMR, Mass spectral data. The compounds **3** and **5** were screened for antimicrobial activities against a variety of bacterial agent.

Keywords: 8-Substituted-2, 5-dihydro-2-(2-furanyl)-4-(2-thienyl)-1, 5-benzothiaze pines, Hetero chalcones, Antibacterial activity

Introduction

1, 5-Benzothiazepines having different heterocyclic group at different positions having shown antiulcer[1,2], analgesic[3], vasodepressant[4], antihypertensive[5], anti-amnesia and anti-dementia[6], antibacterial and antifungal[7] and insecticidal[8], activity. 1, 5-Benzothiazepines having heterocyclic group at different position of ring have been found to be of psychopharmacological use. Various other useful properties[9-20] has been shown by 1, 5-benzothiazepines and different compounds having heterocyclic function have been synthesized.

The biodynamic nature of 1, 5-benzothiazepine derivatives led to the current synthesis of 1, 5-benzothiazepines having various substituents at positions 2, 4 and 8, which may prove to be medicinally potent. In this quest, the reactions of 5-substituted-2-aminobenzenethiols with compounds having α,β-unsaturation in conjugation with carbonyl system in acidic, basic and neutral media to give 2, 4-diaryl-2, 5-dihydro-1, 5-benzothiazepines[21], 2-carboxy-2, 3-dihydro-4-aryl-1,5-benzothiazepines[22], 2,5-dihydro-2-(4-pyridyl)-4-(2-thienyl)-1,5-

benzothiazepines[23] and tetra cyclic benzopyranobenzo thiazepines[24] have been reported. Herein is reported the synthesis of having various substituents at positions 2, 4 and 8. All the compounds have been tested for antibacterial activity. It was planned to use a weaker base like piperidine instead of using strong base to enhance the better yields.

Experimental

Melting points were determined in open capillary tubes and were not corrected. IR spectra (KBr, λ_{max} in cm^{-1}) were recorded on a Bruker IFS 66V spectrometer, ^1H NMR spectra (chemical shifts in δ, ppm) on a Gemini-400 MHz spectrometer in $CDCl_3$ using tetramethylsilane as the internal standard and MS spectra on a VG 7070H spectrometer. The purity of the compounds was verified by TLC (benzene/ethyl acetate, 9:1), using Merck brand Silica Gel-G plates and spotting was done using iodine.

Preparation of hetero chalcones 3

To a mixture of furan-2-carbaldehyde **1** (0.01 mol) and 1-thiophen-2-yl-ethanol **2** (0.01 mol) were dissolved in EtOH (50 mL). Piperidine (1 mL) was added and refluxed. After the completion of reaction, which was monitored by TLC, ethanol was distilled off and residue was poured on ice water (100 mL). It was kept overnight in the refrigerator. The resulting solid was collected by filtration, washed with distilled water and crystallized from methanol to give corresponding chalcones.

Preparation of 5-substituted -1,5-benzothiazepines 5

5-Substituted-2-amino-benzenethiol **4** (0.001 mol) and hetero chalcones **3** (3-furan-2-yl-1-thiophen-2-yl-propenone **3**) (0.001 mol) were refluxed in dry toluene containing catalytic amount of piperidine (1 mL) for 7 h. The crude solid obtained on removal of solvent gave a solid, which on purification by recrystallization from dry methanol gave 8-substituted-2-furan-2-yl-4-thiophen-2-yl-2, 3-dihydro, 1, 5-benzothiazepin **5.** Compounds **5a, 5d,** and **5g** were prepared by using similar procedures. However, the completion of reaction in case of **5c, 5h** required 8 h and **5b, 5e** and **5f** required 6 h heating with reflux. The total spectral data, physical data and analytical data of newly synthesized compounds have been given.

Data

*Compound **3a***

Dirty Yellow solid, mp 87-88 ^oC. IR (KBr, cm^{-1}): 1646 ($\nu_{C=O}$), 1625 ($\nu_{CH=CH}$): ^1H NMR ($CDCl_3$, 400 MHz): 7.92 (d, 1H, C_α H, J = 15.3 Hz), 8.12 (d, 1H, C_β H, J = 15.3 Hz), 7.23-7.56 (m, 6H). MS (*m/z*, %): 204 (M^+, 100), 188 (34), 176 (27), 172 (52), 112 (13), 93 (12). Anal. Calcd. for $C_{11}H_8O_2S$: C, 64.52; H, 3.86; O, 15.50. Found: C, 64.71; H, 3.95; O, 15.68.

*Compound **3b***

Yellow solid, mp 91-92 ^oC. IR (KBr, cm^{-1}): 1650 ($\nu_{C=O}$), 1630 ($\nu_{CH=CH}$); ^1H NMR ($CDCl_3$, 400 MHz): 6.92 (d, 1H, C_α H, J = 15.3 Hz), 7.82 (d, 1H, C_β H, J = 15.3 Hz), 7.13-7.26 (m, 6H):. MS (*m/z*, %): 220 (M^+); 220 (M^+, 100) 203 (37), 188 (72), 110 (28), 109 (42), 93 (12), 84 (14), 30 (18), 28 (15). Anal. Calcd. for $C_{11}H_8OS_2$: C, 59.82; H, 3.54; O, 7.21. Found: C, 59.97; H, 3.66; O, 7.26.

*Compound **3c***

Light yellow solid, mp 185-186 ^oC. IR (KBr, cm^{-1}): 1646 ($\nu_{C=O}$), 1625 ($\nu_{CH=CH}$): ^1H NMR ($CDCl_3$, 400 MHz); 6.82 (d, 1H, C_α H, J = 15.3 Hz), 7.64 (d, 1H, C_β H, J = 15.3 Hz), 7.03-7.29

(m, 6H,). MS (*m/z*, %): 204 (M^+, 88), 188 (100), 176 (36), 175 (27), 173 (13), 112 (11), 94 (22), 72 (8), 67 (48), 17 (10), 14 (12). Anal. Calcd for $C_{11}H_8O_2S$; C, 64.81; H, 3.82; O, 15.64. Found: C, 64.89; H, 3.95; O, 15.68.

*Compound **3d***

Dork yellow solid, mp 95-96 °C. IR (KBr, cm^{-1}): 1648 ($\nu_{C=O}$), 1627 ($\nu_{CH=CH}$); ^1H NMR ($CDCl_3$, 400 MHz); 6.92 (d, 1H, C_α H, J = 15.3 Hz), 7.82 (d, 1H, C_β H, J = 15.3 Hz), 7.13-7.26 (m, 6H). MS (*m/z*, %) 188 (M^+, 100), 172 (36), 112 (52), 88 (23), 64 (56), 30 (12), 18 (10). Anal. Calcd. for $C_{11}H_8O_3$: C, 70.20; H, 4.25; O, 25.46. Found: C, 70.21; H, 4.29; O, 25.51.

*Compound **5a***

Yellow solid, mp 92-94 °C. IR (KBr, cm^{-1}): 1608 ($V_{N=C}$); ^1H NMR ($CDCl_3$, 400 MHz): 3.83 (s, 3H,-OCH_3), 4.12 (br, 1H, -NH), 6.84 (d, 1H, J = 8 Hz, C-2-H), 6.92 (d, 1H, J = 8 Hz, C-3-H), 6.44 (s, 1H, C_9-H), 6.82-7.85 (m, 9H). MS (*m/z*, %): 341 (M^+, 67), 343 ($M+2^+$, 48), 310 (42), 274 (22), 258 (100), 243 (16), 227 (9), 154 (23), 109 (36), 83 (10), 80 (32), 67 (89), 31 (10). Anal. Calcd for $C_{18}H_{15}O_2S_2N$ (341): C 63.34; H, 4.43; N, 4.10; O, 9.37. Found: C, 63.45; H, 4.55; N, 4.12; O, 9.39.

*Compound **5b***

Yellow solid, mp 97-98 °C. IR (KBr, cm^{-1}): 1605 ($V_{N=C}$). ^1H NMR ($CDCl_3$, 400 MHz,); 2.41 (s, 3H), 4.00 (br, 1H), 6.86 (d, 1H, J = 8 Hz), 6.91 (d, 1H, J = 8 Hz), 6.36 (s, 1H, C_9-H), 6.82-7.91 (m, 9H). MS (*m/z*, %): 325 (M^+, 50), 310 (58), 258 (100), 253 (42), 201 (16), 156 (9), 154 (23), 109 (36), 89 (18), 82 (23), 67 (46), 28 (10). Anal. Calcd. for $C_{18}H_{15}OS_2N$: C 66.43; H, 4.65; N, 4.30; O, 4.92, S, 19.71. Found: C, 66.55; H, 4.73; N, 4.42; O, 5.03; S, 19.82.

*Compound **5c***

Yellow solid, mp 85-87 °C. IR (KBr, cm^{-1}): 1605 ($V_{C=N}$). ^1H NMR ($CDCl_3$, 400 MHz,); 3.83 (s, 3H), 4.12 (br, 1H), 6.84 (d, 1H, J = 8 Hz), 6.92 (d, 1H, J = 8 Hz), 6.42 (s, 1H, C_9–H), 6.82-8.85 (m, 9H). MS (*m/z*, %): 357 (M^+, 63), 343 (48), 326 (100) 310 (22), 290 (12), 284 (32), 240 (16), 225 (9), 152 (23), 109 (36), 83 (10), 80 (32), 47 (89), 27 (10). Anal. Calcd. for $C_{18}H_{15}OS_3N$: C, 60.47; H, 4.23; N, 3.97; O, 4.48; S, 26.91. Found: C, 60.55; H, 4.33; N, 4.02; O, 4.57; S, 27.05.

*Compound **5d***

Bright yellow solid, mp 95-96 °C. IR (KBr, cm^{-1}): 1608 ($V_{N=C}$). ^1H NMR ($CDCl_3$, 400 MHz): 2.43 (s, 3H), 4.12 (br, 1H), 6.84 (d, 1H, J = 8 Hz), 6.92 (d, 1H, J = 8 Hz), 6.48 (s, 1H, C_9-H), 6.82-8.85 (m, 9H). MS (*m/z*, %): 341 (M^+, 65), 343 ($M+2^+$, 48), 326 (100), 274 (22), 253 (89), 240 (10), 227 (9), 154 (23), 109 (36), 73 (10), 67 (32), 47 (28), 27 (23). Anal. Calcd. for $C_{18}H_{15}S_3N$: C 63.34; H, 4.43; N, 4.10; S, 28.17. Found: C, 63.45; H, 4.52; N, 4.12; S, 28.26.

*Compound **5e***

Yellow solid, mp 85-86 °C. IR (KBr, cm^{-1}): 1610 ($V_{N=C}$).^1H NMR ($CDCl_3$, 400 MHz): 3.83 (s, 3H), 4.12 (br, 1H), 6.84 (d, 1H, J = 8 Hz), 6.92 (d, 1H, J = 8 Hz), 6.52 (s, 1H, C_9-H), 6.82-8.85 (m, 9H). MS (*m/z*, %): 325 (M^+, 45), 310 (58), 258 (100), 253 (42), 201 (16), 156 (9), 154 (13), 109 (43), 89 (18), 73 (20), 67 (52), 27(16). Anal. Calcd. for $C_{18}H_{15}O_3S$ N: C 66.43; H, 4.65; N, 4.30; O, 4.92, S, 19.71. Found: C, 66.50; H, 4.73; N, 4.39; O, 4.98, S, 19.86.

Compound ***5f***

Dark yellow solid, mp 89-90 ^{o}C. IR (KBr, cm^{-1}): 1606 (($V_{N=C}$). ^{1}H NMR ($CDCl_3$, 400 MHz,): 2.40 (s, 3H), 4.12 (br, 1H), 6.84 (d, 1H, *J* = 8 Hz), 6.92 (d, 1H, *J* = 8 Hz), 6.32 (s, 1H, C_9-H), 6.82-8.85 (m, 9H). MS (*m/z*, %): 309 (M^+, 56), 294 (58), 242 (100), 227 (67), 206 (40), 160 (45), 134 (16), 122 (23), 67 (46), 48 (10). Anal. Calcd. for $C_{18}H_{15}O_2SN$: C 69.88; H, 4.85; N, 4.53; O, 10.32; S,10.36. Found: C, 69.95; H, 4.93; N, 4.62; O, 10.45; S, 10.48.

Compound ***5g***

Yellow solid, mp 83-84 ^{o}C. IR (KBr, cm^{-1}): 1607 (($V_{N=C}$). ^{1}H NMR ($CDCl_3$, 400 MHz): 3.83 (s, 3H), 4.12 (br, 1H), 6.84 (d, 1H, *J* = 8Hz), 6.92 (d, 1H, *J* = 8Hz), 6.31 (s, 1H, C_9-H), 6.82-8.85 (m, 9H). MS (*m/z*, %): 341 (M^+, 55), 343 ($M+2^+$, 48), 310 (100), 254 (22), 237 (89), 170 (9), 164 (16), 109 (36), 73 (10), 67 (32), 47 (28), 27 (23). Anal. Calcd for $C_{18}H_{15}O_2S_2N$: C 63.32; H, 4.45; N, 4.10; O, 9.37; S, 18.71. Found: C, 63.45; H, 4.53; N, 4.42; O, 9.47; S, 18.93.

Compound ***5h***

Light yellow solid, mp 93-94 ^{o}C. IR (KBr, cm^{-1}): 1650 ($V_{N=C}$). ^{1}H NMR ($CDCl_3$, 400 MHz): 2.42 (s, 3H), 4.12 (br, 1H), 6.84 (d, 1H, *J* = 8 Hz), 6.92 (d, 1H, *J* = 8 Hz), 6.34 (s, 1H, C_9-H), 6.82-8.85 (m, 9H). MS (*m/z*, %): 325 (M^+,48) 327 ($M+2^+$,34) 310 (100), 258 (60), 253 (22), 201 (10), 156 (12), 154 (15), 109 (29), 89 (18), 73 (20), 67 (52), 27(16). Anal. Calcd. for $C_{18}H_{15}OS_2N$: C, 66.43; H, 4.65; N, 4.30; O, 4.92; S, 19.71. Found: C, 66.75; H, 4.83; N, 4.72; O, 4.98; S, 19.87.

Results and Discussion

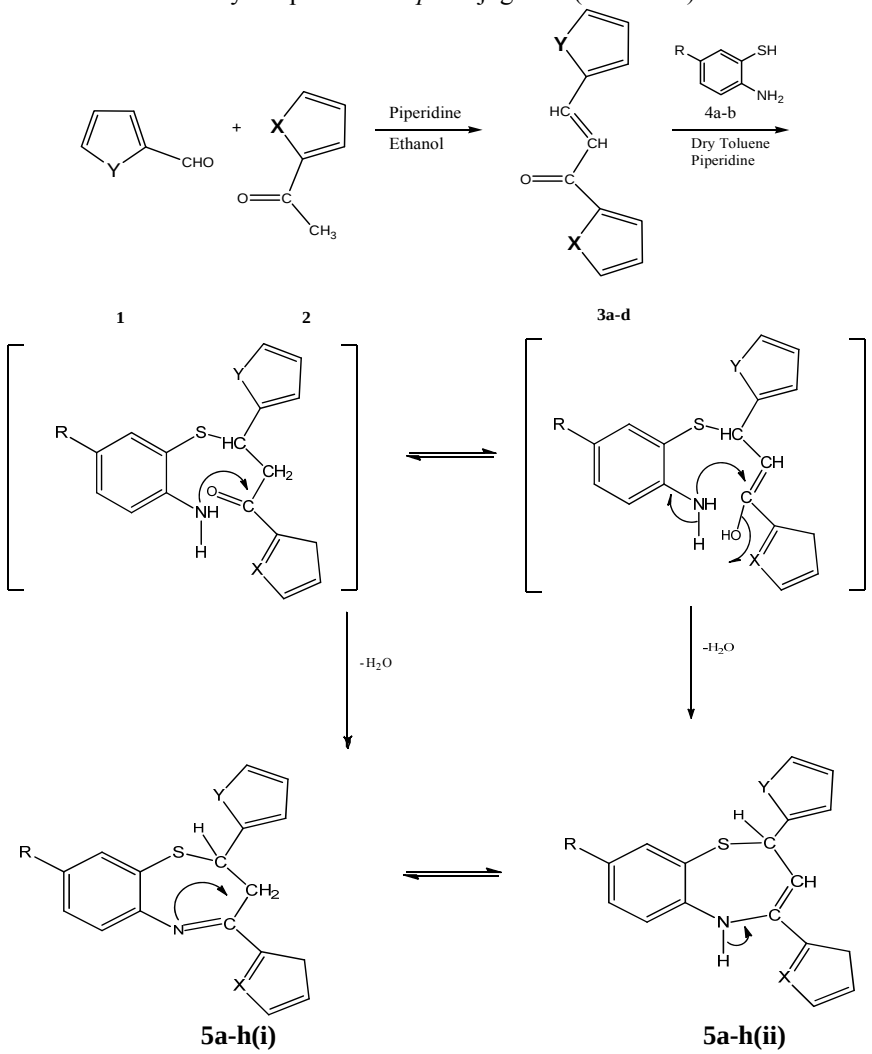
The hetero chalcone **3** was prepared by reacting furan-2-carbaldehyde **1** and 1-thiophen-2-yl-ethanone **2** in EtOH (50 mL) and piperidine (1 mL) was added refluxed. After the completion of reaction, which was monitored by TLC, ethanol was distilled off and residue was poured on ice water (100 mL). It was kept overnight in the refrigerator. The resulting solid was collected by filtration, washed with distilled water and crystallized from methanol to give corresponding chalcone **3**.

1,5-Benzothiazepines **5** were prepared by reacting heterochalcones **3** and freshly prepared 5-substituted-2-acetylthiophene **4** in dry toluene containing piperidine. The reaction are known[25-29] to be initiated by nucleophilic attack of the sulpydryl electrons, whose nucleophilicity is increased in the basic medium[30], on the *β*-carbon atom of the 2-propenone to give the cyclized product. Through the formation of Michael adduct intermediate, in a single step. The structures of the final products were ascertained by microanalysis for C, H, N and spectral studies comprising IR, ^{1}H NMR and MS all compounds were screened antibacterial activities.

In the IR spectrum of **3** strong absorptions for C=O and vinylic C=C were observed at 1646 and 1625 cm^{-1}, respectively. The position of the vinylic C=C appearing at a frequency lower than for an isolated double bond may be due to C=C conjugation with the lone pair electrons of nitrogen in the molecule.

The IR spectra of the final products **5** did not show the characteristic absorptions for C=O and NH_2 in the regions 1690-1650 cm^{-1} and 3445-3200 cm^{-1}, respectively. On the other hand, a broad band in the region 3150-3140 cm^{-1} indicated the presence of a secondary amino group. This indicated that the reactions between 5-substituted-2-aminobenzenethiols and the *α,β*-unsaturated ketone had occurred in a concerted single step mechanism, without the isolation of any intermediate. The ^{1}H NMR showed a broad one proton absorption in the

region 4.00-4.38 due to NH. In addition, the presence of two doublets, integrating for one proton each, at 6.60-6.95 and 7.25-7.46 support the formation of 2.5-dihydroderivatives, in preference to the 2, 3-dihydro tautomer. The occurrence of the final products in the enamino–form is favored by the presence of *p*-conjugation (Scheme 1).



Scheme 1

R *= P-CH_3, P-OCH_3, X= O, S Y= O, S,* ***3a****, X=O, Y=S,* ***5a****, X= S, Y=O, R=P-OCH3,* ***3b****, X=O, Y=S,* ***5b****, X=S, Y=O, R=P-CH_3,* ***3c****, X=S, Y=O,* ***5c****, X=S, Y=O, R=P-OCH_3,* ***3d****, X=S, Y=S,* ***5d****, X=S, Y=S, R=P-CH_3,* ***5e****, X=O, Y=S, R=P-OCH_3,* ***5f,*** *X=O, Y=O, R=P-CH_3,* ***5g,*** *X=O, Y=S, R=P-OCH_3,* ***5h****, X=O, Y =S, R=P-CH_3*

Antibacterial activity

All the hetero chalcones **3** and 1, 5-benzothiazepines **5** were screened for their antibacterial activity against *Escherichia coli* and *staphylococcus aureus* using *streptomycin* as standard drug. Nutrient agar was used as culture medium. Test solution and standard drug having

400 and 600 µg/mL concentration were prepared in acetone and used for testing growth inhibition by filter paper disc technique of Vincent and Vincent[31]. The results revealed that majority of the synthesized compounds showed varying degrees of inhibition against the tested microorganisms. In general, the inhibitory activity against the Gram-negative bacteria was higher than that of the Gram-positive bacteria. The **3a, 5a, 5e, 5f, 5h** showed excellent activity against gram-negative bacteria, *E. coli* and **3a, 3b, 5a, 5b, 5f, 5h** showing good activity against gram-positive bacteria *S. aureus*. And **3c, 3d, 5d** showed weak activities against *E. coli* and *S. aureus* respectively. The preliminary result confirms the importance of prenyloxy nucleus and hetero nucleus with respect to antibacterial activity.

The antibacterial activity of the compounds thus prepared has been evaluated following the filter paper disc technique of Vincent and Vincent. (Gram-negative) bacteria namely *Escherichia coil* (Gram-positive) bacteria, namely *S. aureus* have been used as test organisms. (30 mg) of different hetero chalcones and 1, 5-benzothiazepines compounds **3, 5** were dissolved in (15 mL) of acetone. They were apportioned into 6ml to 9ml into china dishes. The walkman filter paper disc (mm diameter) was added and shaken thoroughly. They were allowed to dry. The amount of substance per paper disc was calculated (600 and 900 µg/mL). Paper discs treated without chemical agent served as control. The filter paper discs with chemical substances were implanted onto a log phase bacterial seeded nutrient, agar plates, Petri plates thus prepared were incubated at 37 °C for 72 h and the zone of inhibition of bacterial growth was measured. Then, the antimicrobial activity of the test agents was determined by measuring the diameter of zone of inhibition expressed in mm. the experiment was carried out in triplicate. The results of the compounds of preliminary antibacterial testing are shown in Table 1.

Table1. Antibacterial activity Compounds (**3a-d, 5a-h)**

Compd. No	Antibacterial activity Inhibition(mm)		Compd. No	Antibacterialactivity Inhibition(mm)	
	E.coli (-)	*S.aures(+)*		*E.coli (-)*	*S.aures(+)*
3a	7.8	8.5	5a	8.9	7.1
3b	7.6	7.8	5b	8.8	5.6
3c	6.4	6.5	5c	7.8	6.7
3d	6.8	5.3	5d	7.9	6.6
			5e	7.2	6.4
			5f	7.5	7.2
			5g	7.0	6.0
			5h	8.6	7.1
			Streptomycin	9.0	6.5

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