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# THE DEVELOPMENT, SYNTHESIS, AND BIOLOGICAL ACTIVITY OF 8-SUBSTITUTED PIPERIDINE AND HETEROCHALCONES MEDIATE THE 2-FURANYL-2, 5-DIHYDRO (2-THIENYL) AGENTS -1,5-BENZOTHIAZEPINES AS ANTIBACTERIAL AGENTS.

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#### Abstract

The reactions of 5-substituted-2-Amino benzenethiols with hetero chalcones (3) were conducted in dry toluene containing catalytic amounts of piperidine. The products, 8-substituted-2,5-dihydro-2-(2-furanyl)-4-(2-thienyl)-1,5-benzothiazepines (5), and hetero chalcones (3), were produced by the pipe (1). The structures were constructed using data from mass spectrometers, IR, 1HNMR, and elemental (C, H, and N) analyses. The antibacterial properties of compounds (3) and (5) were examined against various bacterial agents.

#### **Keywords:**

8-substituted-2, 5-dihydro-2-(2-furanyl)-4-(2-thienyl)-1, 5-benzothiaze pines;Prinylated Chalcones; Antibacterial activity

#### **INTRODUCTION**

5, 5-Benzothiazepines have demonstrated anti-ulcer, analgesic, vasodepressant, anti-hypertensive, anti-amnesia and anti-dementia, antibacterial and antifungal, and insecticidal activities. It has been discovered that 1, 5-Benzothiazepines with heterocyclic groups at various positions of the ring are used psychopharmacologically. a number of other beneficial traits 5-Benzothiazepines and other compounds with heterocyclic function have been created, as demonstrated by 9–20. The present synthesis of 1, 5-benzothiazepines, which have different substituents at positions 2, 4, and 8, may show to be medicinally effective because to the biodynamic nature of 1, 5-benzothiazepine derivatives. in this endeavour. The conjugation of molecules with, -unsaturation with the carbonyl system in acidic, basic, and neutral conditions using 5-substituted-2-aminobenzenethiols results in There are several new types of benzodiazepines, including 2, 4-diaryl-2, 5-dihydro-1, 5-benzo-thiazepines, 212-carboxy-2, 3-dihydro-4-aryl-1, 5-benzothiazepines, 222, 5-dihydro-2-(4-pyridyl)-4-(2-thienyl)-1, 5-benzothiazepines, and tetracyclic. Here in is reported the synthesis of having various substituent's 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.

#### **RESULTS AND DISCUSSION**

The hetero chalcone 3 was prepared by reacting furan-2-carbaldehyde 1 and 1-thiophen-2-yl-ethanone 2 in EtOH (50mL) 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 (100mL). 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 reactingheterochalcones**3**and freshly prepared 5-substituted-2acetylthiophene**4** in dry toluene containing piperidine. The reaction are known<sup>25-29</sup>to be initiated by nucleophilic attack of the sulpydryl electrons, whose nucleophilicity is increased in the basic medium, <sup>30</sup> on the  $\beta$ -carbon atom of the 2-propenone to give the cyclized product. Through the formation of Michaeladduct intermediate, in a single step. The structures of the final products were ascertained by microanalysis for C, H, N and spectral

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studies comprising IR, <sup>1</sup>H NMR and MS all compounds were screened antibacterial activities. In the IR spectrum of **3** Strong absorptions for C=Oand vinylic C=C were observed at 1646 and 1625 cm<sup>-1</sup>, 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 NH2 in the regions 1690-1650 cm<sup>-1</sup> and 3445-3200cm<sup>-1</sup>, respectively. On the other hand, a broad band in the region 3150-3140cm<sup>-1</sup> indicated the presence of a secondary amino group. This indicated that the reactions between 5-substituted-2-aminobenzenethiols and  $\alpha$ ,  $\beta$ -unsaturated ketone had occurred in a concerted single step mechanism, without the isolation of any intermediate. The <sup>1</sup>HNMR 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- (scheme 1).



Scheme-1

 $R^{11}$  4a = p - CH3

Scheme-1

RR<sup>1</sup> =-CH2-CH=C (CH3)2 3a = p - OCH3 3b = p - CH34b = p - OCH3 3c = p - C13d = p - NO2 3e = p - N (CH3)23f = o - Cl

**ANTIBACTERIAL ACTIVITY** 

All the hetero chalcones3 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  $\mu$ g / mL concentration were prepared in acetone and used for testing growth inhibition by filter paper disc technique of Vincent and Vincent<sup>31</sup>. 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. The3a,5a,5e,5f,5h showed excellentactivity 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. (30mg) of different hetero chalcones and 1, 5-benzothiazepines compounds **3**, **5** were dissolved in (15mL) 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 wascalculated (600 and 900  $\mu$ g/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 2).

## EXPERIMENTAL

Melting points were determined in open capillary tubes and were not corrected. IR spectra (KBr,  $\lambda$  max in cm<sup>-1</sup>) were recorded on a Bruker IFS 66V spectrometer, <sup>1</sup>H NMR spectra (chemical shifts in  $\delta$ , Ppm)on a Gemini-400 MHzspectrometer in CDCl3 using tetramethylsilane as the internal standard and MS spectra on a VG 7070H spectrometer. The purity of the compounds was verified by TLC (benzene/ethylacetate, 9:1), using Merck brand Silica Gel-G plates and spotting was done using iodine.

#### Preparation of hetero chalcones3

To a mixture of furan-2-carbaldehyde1 (0.01mol) and1-thiophen-2-yl-ethanol2(0.01 mol) weredissolved in EtOH (50mL). 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 (100mL). Itwas 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-benzenethiol4(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 (1mL) for 7 h. The crude solid obtained on removal of solvent gave a solid, which on purification by recrystallization from dry methanol gave8-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 6h heating with reflux. The total spectral data, physical data and analytical data ofnewly synthesizedcompounds have been given

#### Data Compound 3a

Dirty Yellow solid, mp 87-88 °C. IR (KBr, cm<sup>-1</sup>): 1646(vC=O), 1625(vCH=CH):<sup>1</sup>H NMR (CDCl3, 400MHz): 7.92 (d, 1H, C $\alpha$  H, *J* = 15.3Hz), 8.12 (d, 1H, C $\beta$  H, *J* = 15.3Hz), 7.23-7.56(m, 6H).MS (m/z, %): 204 (M<sup>+</sup>, 100), 188 (34), 176 (27), 172 (52), 112 (13), 93 (12). Anal.Calcd. for C11 H8 O2 S: C, 64.52; H, 3.86; O, 15.50. Found: C, 64.71; H, 3.95; O, 15.68.

#### Compound3b

Yellow solid,mp 91-92°C. IR (KBr, cm<sup>-1</sup>): 1650(vC=O), 1630(vCH=CH); <sup>1</sup>H NMR (CDC13, 400 MHz): 6.92 (d, 1H, C $\alpha$  H, *J* = 15.3Hz), 7.82 (d, 1H, C $\beta$  H, *J* = 15.3Hz), 7.13-7.26 (m, 6H):. MS (m/z, %): 220 (M<sup>+</sup>); 220 (M<sup>+</sup>, 100) 203 (37), 188 (72), 110 (28), 109 (42), 93 (12), 84 (14), 30 (18), 28 (15). Anal. Calcd. for C 11H8 OS2: C, 59.82; H, 3.54; O, 7.21.Found: C, 59.97; H, 3.66; O, 7.26.

#### Compound3c

Light yellow solid, mp 185-186°C. IR (KBr, cm<sup>-1</sup>): 1646(vC=O), 1625(vCH=CH):<sup>1</sup>H NMR (CDCl3, 400 MHz); 6.82 (d, 1H, C $\alpha$  H, *J* = 15.3Hz), 7.64 (d, 1H, C $\beta$  H, *J* = 15.3 Hz), 7.03-7.29(m, 6H,).MS (m/z, %): 204 (M<sup>+</sup>, 88), 188 (100), 176 (36), 175 (27), 173 (13), 112 (11), 94 (22), 72 (8), 67 (48), 17 (10), 14 (12).Anal. Calcd for C11 H8 O2S; C, 64.81; H, 3.82; O, 15.64. Found: C, 64.89; H, 3.95; O, 15.68.

#### Compound3d

Dork Yellow solid, mp 95-96 °C. IR (KBr, cm<sup>-1</sup>): 1648(vC=O), 1627(vCH=CH); <sup>1</sup>H NMR (CDCl3, 400 MHz); 6.92 (d, 1H, C $_{\alpha}$  H, *J* = 15.3Hz), 7.82 (d, 1H, C $_{\beta}$  H, *J* = 15.3Hz), 7.13-7.26(m, 6H). MS (m/z, %) 188 (M<sup>+</sup>, 100), 172 (36), 112 (52), 88 (23), 64 (56), 30 (12),18 (10). Anal. Calcd. for C11 H8 O3: C,

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70.20; H, 4.25; O, 25.46. Found: C, 70.21; H, 4.29; O, 25.51;

## Compound5a

Yellow solid,mp 92-94 °C. IR (KBr, cm<sup>-1</sup>): 1608(VN=C);<sup>1</sup>H NMR (CDCl3,400 MHz): 3.83(s, 3H,-OCH3), 4.12(br, 1H, -NH), 6.84(d, 1H, *J*=8Hz, C-2-H), 6.92(d, 1H, *J*=8Hz, C-3-H), 6.44(s, 1H, C9-H), 6.82-7.85(m, 9H). MS (m/z, %): 341 (M<sup>+</sup>, 67), 343 (M+2<sup>+</sup>, 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 C18H15O2S2N (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.

## Compound5b

Yellow solid, mp 97-98°C. IR (KBr, cm<sup>-1</sup>): 1605(V N =C).<sup>1</sup>H NMR (CDCl3,400 MHz,); 2.41(s, 3H), 4.00(br, 1H), 6.86(d, 1H, *J*=8Hz), 6.91(d, 1H, *J*=8Hz), 6.36(s, 1H, C9-H), 6.82-7.91(m, 9H). MS (m/z, %): 325 (M<sup>+</sup>, 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 C18H15OS2N: 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<sup>-1</sup>): 1605(VC=N).<sup>1</sup>H NMR (CDCl3,400 MHz,); 3.83(s, 3H), 4.12(br, 1H), 6.84(d, 1H, *J*=8Hz), 6.92(d, 1H, *J*=8Hz), 6.42(s, 1H, C9–H), 6.82-8.85(m, 9H). MS (m/z, %): 357 (M<sup>+</sup>, 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 C18H15OS3N: 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<sup>-1</sup>): 1608(VN=C).<sup>1</sup>H NMR (CDCl3,400 MHz): 2.43(s, 3H), 4.12(br, 1H), 6.84(d, 1H, J=8Hz), 6.92(d, 1H, J=8Hz), 6.48(s, 1H, C9-H), 6.82-8.85(m, 9H). MS (m/z, %): 341 (M<sup>+</sup>, 65), 343 (M+2<sup>+</sup>, 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 C18H15S3N: 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;

#### Compound5e

Yellow solid,mp 85-86°C. IR (KBr, cm<sup>-1</sup>): 1610(V<sub>N=C</sub>).<sup>1</sup>H NMR (CDCl3,400 MHz): 3.83(s, 3H),4.12(br, 1H), 6.84(d, 1H, *J*=8Hz), 6.92(d, 1H, *J*=8Hz), 6.52(s, 1H, C9-H), 6.82-8.85(m, 9H). MS (m/z, %): 325 (M<sup>+</sup>, 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 C18H15O3S 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;

## Compound5f

Dark yellow solid,mp 89-90°C. IR (KBr, cm<sup>-1</sup>): 1606((VN=C). <sup>1</sup>H NMR (CDCl3,400 MHz,): 2.40(s, 3H), 4.12(br, 1H), 6.84(d, 1H, *J*=8Hz), 6.92(d, 1H, *J*=8Hz), 6.32(s, 1H, C9-H), 6.82-8.85(m, 9H).MS (m/z, %): 309 (M <sup>+</sup>, 56), 294 (58), 242 (100), 227 (67), 206 (40), 160 (45), 134 (16), 122 (23), 67 (46), 48 (10).Anal. Calcd. for C18H15O2S N: 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.

## Compound5g

Yellow solid,mp 83-84°C. IR (KBr, cm<sup>-1</sup>): 1607((VN=C). <sup>1</sup>H NMR (CDCl3,400 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, C9-H), 6.82-8.85(m, 9H). MS (m/z, %): 341 (M<sup>+</sup>, 55), 343 (M+2<sup>+</sup>, 48), 310 (100), 254 (22), 237 (89), 170 (9), 164 (16), 109 (36), 73 (10), 67 (32), 47 (28), 27 (23).Anal. Calcd for C18H15O2S2N: 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 °C. IR (KBr, cm<sup>-1</sup>): 1650(V<sub>N=C</sub>).<sup>1</sup>H NMR (CDCl3,400 MHz): 2.42(s, 3H),

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4.12(br, 1H), 6.84(d, 1H, *J*=8Hz), 6.92(d, 1H, *J*=8Hz), 6.34(s, 1H, C9-H), 6.82-8.85(m, 9H).MS(m/z, %): 325 (M<sup>+</sup>,48) 327 (M+2<sup>+</sup>,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 C18H15OS2N: 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.

R	Compound	Antibacterial activity Inhibition (mm)		
		E.C oli (-)	S.aures (+)	
	3a	7.8	8.5	
	3b	6.9	7.8	
a: P-OMe	3c	5.4	6.5	
b: P-Me	3d	4.8	4.3	
c: P-Cl	3e	3.6	5.0	
d:P-N(CH3)2	3f	3.8	4.0	
e: O-Cl	4a	8.2	8.0	
f: M-NO2	4b	7.8	8.3	
	4c	7.7	6.2	
	<b>4d</b>	6.7	6.5	
Streptomycin		9.3	8.5	

<b>Table-1:</b> Antibacterial activity of compound <b>5a-1, and 4a-0</b>	Table-1:	Antibacterial	activity of com	pound <b>3a-f, and</b>	4 <b>a-d</b> .
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