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Piperidine Mediated Synthesis of Prenylated Chalcones and 8-Substituted -2, 5-dihydro-2-(4-tolybenzo)-5-(3-methylbut-2-enyloxy) phenol-1, 5-benzothiazepines as Anti bacterial Agents

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ABSTRACT

1,5-benzothiazepine is the main seven-membered heterocyclic ring system and having several cardiac, psychotherapeutic activities. Which has been synthesized by catalytic amount of piperidine mediated condensation of dry toluene with Prenyloxy chalcones (3) and 5-substituted-2-Amino benzenethiols (2). The corresponding prenyloxy chalcones (3) were synthesized by piperidine mediated claisen-schemidt condensation of an ethanolic solution of 4-prenyloxy 2-hydroxy acetophenone (1) with aromatic aldehydes. It was planned to use a weaker base like piperidine instead of using strong base to enhance the better yields. 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.

Introduction

1,5-Benzothiazepine and 1,5-benzodiazipine are the two main seven-membered heterocyclic ring systems reported for their cardiac and psychotherapeutic activities. Successful introduction of diltiazem and clentiazem for angina pectoris, hypertension, arrhythmias and other related cardiac disorders proved potential of 1,5-benzothiazepine moiety. Subsequently 1,5-benzodiazepines were highlighted as important biologically active scaffolds. Also, discovery of thiazesim and quetiapine fumarate as psychotropic agents attracted much attention worldwide.

1,5-benzothiazepines having different heterocyclic group at different positions having shown antiulcer[1, 2], analgesic,[3] vasodepressant,[4] antihypertensive,[5] antiamnesia and antidementia,[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] have 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-benzo-thiazepines,[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.

We mainly cover structural elucidation of newly synthesized compounds done along with the brief description of the targets and report piperidine mediated synthesis. 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 Prenyloxy chalcones **3** were prepared by reacting 4-prenyloxy 2-hydroxy acetophene and corresponding aldehydes 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 penyloxy chalcones **3**.

1,5-benzothiazepines **5** were prepared by reacting Prenyloxy chalcones **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

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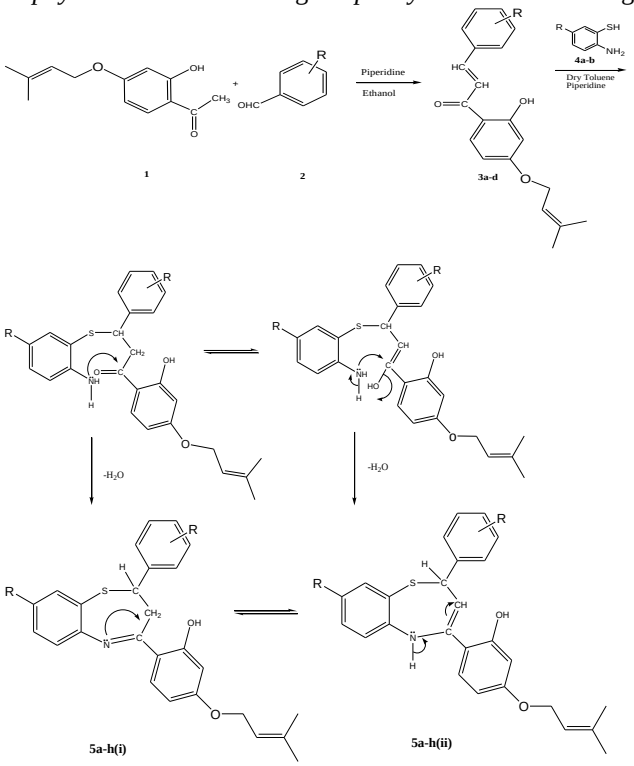
group. This indicated that the reactions between 5-substituted-2-aminobenzenethiols and α, β-unsaturated ketone had occurred in a concerted single step mechanism, without the isolation of any intermediate.

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).

In present communication, mainly covers structural elucidations of newly synthesized compounds done along with the brief description of the targets and we report piperidine mediated synthesis. The structures of the compounds 3a-b and 5a-h have been established on the basis of elemental (C, H, and O) analysis, IR, ^{1}H NMR, MS spectral data and they were screened for antibacterial activity against *Escherichia coli* and *staphylococcus aureus* using *streptomycin* as standard drug.



Scheme-1

R	R^{11}
3a = p - OCH_3	4a = p - CH_3
3b = p - CH_3	4b = p - OCH_3
3c = p - Cl	
3d = p - NO_2	
3e = p - N $(CH_3)_2$	
3f = o - Cl	

Antibacterial activity

All the Prenyloxy 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, 5g,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.

Preparation Method

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 (400 and 600 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**).**

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, $_1$H 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.

4-prenyloxy 2-hydroxy acetophenone 1

A solution of β-resacetophenone (0.5g) in acetone (10ml) was refluxed with prenyl bromide (0.4ml) and anhydrous potassium carbonate (2gms) for 3hrs. The product crystallized from light petroleum ether at low temperature as colorless thick needles (0.5gms), m.p. 45 - 47^{o}c, red ferric reaction; R_F 0.30, solvent (benzene - light petroleum 1:1); V_{max} 1640cm^{-1}**.**

General procedure for synthesis of 4-prenyloxy 2-hydroxy chalcones 3

To a mixture of 4-prenyloxy 2-hydroxyAceto phenone (0.01mole) and aromatic aldehyde (0.01 moles) were dissolved in EtOH (50mL) and 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). 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 **3a-f**.

Compound 3a

Dirty Yellow solid, mp 87-88 ^{o}C. IR (KBr, cm^{-1}): 1646 ($\nu_{C=O}$), 1625 ($\nu_{CH=CH}$): ^{1}H 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_8 O_2 S: 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 ^{o}C. IR (KBr, cm^{-1}): 1650 ($\nu_{C=O}$), 1630 ($\nu_{CH=CH}$); ^{1}H 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 ^{o}C. IR (KBr, cm^{-1}): 1646 ($\nu_{C=O}$), 1625 ($\nu_{CH=CH}$): ^{1}H 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 ^{o}C. IR (KBr, cm^{-1}): 1648 ($\nu_{C=O}$), 1627 ($\nu_{CH=CH}$); ^{1}H 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;

General procedure for synthesis of 5-substituted-1, 5-benzothiazepines 5

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

Compound 5a

Yellow solid, mp 92-94 ^{o}C. IR (KBr, cm^{-1}): 1608 ($V_{N=C}$); ^{1}H 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 ^{o}C. IR (KBr, cm^{-1}): 1605 ($V_{N=C}$). ^{1}H 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 ^{o}C. IR (KBr, cm^{-1}): 1605 ($V_{C=N}$). ^{1}H 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 ^{o}C. IR (KBr, cm^{-1}): 1608 ($V_{N=C}$). ^{1}H 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 ^{o}C. IR (KBr, cm^{-1}): 1610 ($V_{N=C}$).^{1}H 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 $C_{18}H_{15}O_3SN$: 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.

Table 1: Antibacterial activity of compound 3a-d, and 5a-h

R	Compound	Antibacterial activity Inhibition (mm)	
		E.Coli (-)	*S.aures (+)*
	3a	7.8	8.5
	3b	6.3	7.8
a: P-OMe	**3c**	5.4	6.5
b: P-Me	**3d**	4.8	4.3
c: P-Cl	**5a**	7.6	7.0
d:P-$N(CH_3)_2$	**5b**	3.8	4.0
	5c	6.2	5.4
e: O-Cl	**5d**	6.8	4.3
f: M-NO_2	**5e**	7.7	7.2
	5f	7.7	7.5
	5g	7.3	7.2
	5h	7.6	6.8
	Streptomycin	9.8	8.3

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