Design and Synthesisand Biological Activity of Piperidine Mediated Hetero Chalcones and8-Substituted-2, 5-dihydro-2-(2-furanyl)-4-(2-thienyl)-1,5-benzothiazepinesas Antibacterial Agents

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Abstract: The reactions of 5-substituted-2-Amino benzenethiols withhetero 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-benzothiazepines(**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}HNMR, 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;Prinylated Chalcones;Antibacterial activity

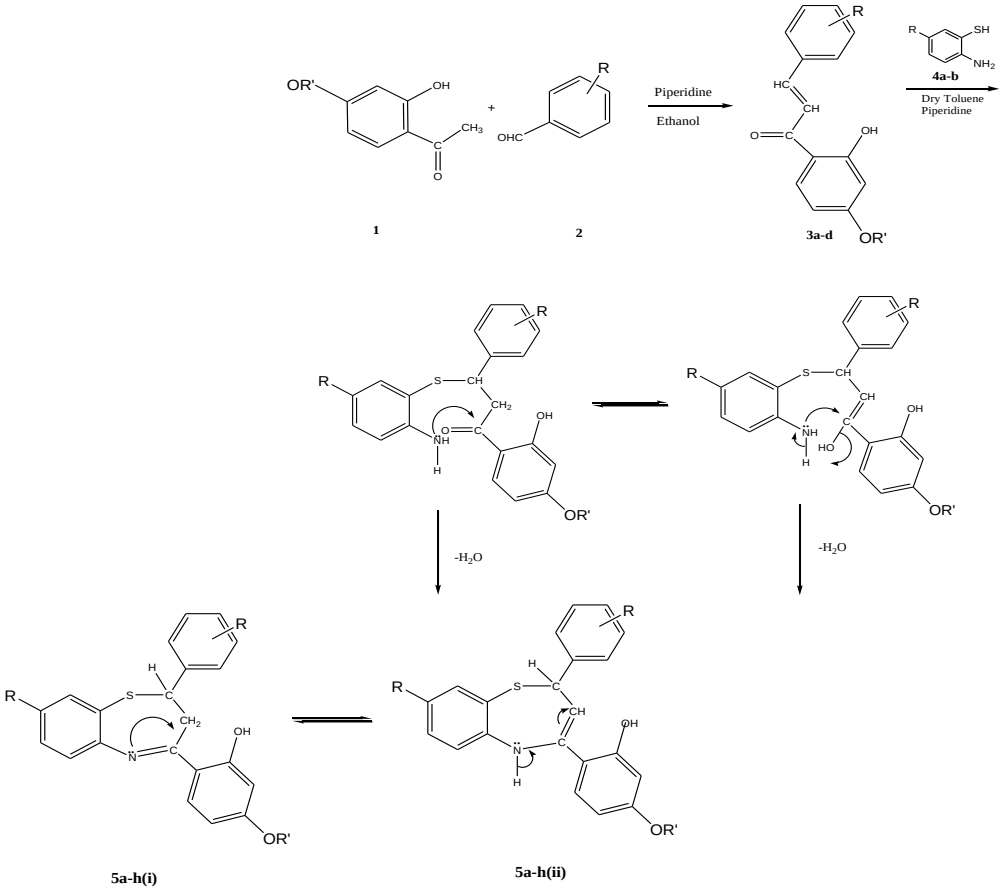
INTRODUCTION

1, 5-Benzothiazepines having different heterocyclic group at different positions having shown antiulcer[1, 2], analgesic,[3]vasodepressant, [4]antihypertensive,[5]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] andtetra cyclicbenzopyranobenzothiazepines[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.

RESULTS AND DISCUSSION

The hetero chalcone**3** was prepared by reacting furan-2-carbaldehyde **1** and1-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-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=Oand 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 3445-3200cm^{-1}, respectively. On the other hand, a broad band in the region 3150-3140cm^{-1} indicated the presence of a secondary amino 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}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-□ conjugation (scheme 1).



Scheme-1

RR^1 =-CH_2-CH=C (CH_3)$_2$
3a = p - OCH_3 R^{11} 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 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 400and 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. (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 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 2**).**

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 MHzspectrometer 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 chalcones3

To a mixture of furan-2-carbaldehyde**1** (0.01mol) and1-thiophen-2-yl-ethanol**2**(0.01 mol) were dissolved 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). 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 (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 ^{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* = 15.3Hz), 8.12 (d, 1H, C_β H, *J* = 15.3Hz), 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.

Compound3b

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* = 15.3Hz), 7.82 (d, 1H, C_β H, *J* = 15.3Hz), 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$_8$ OS$_2$: 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^{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* = 15.3Hz), 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_8 O_2S; 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 ^{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* = 15.3Hz), 7.82 (d, 1H, C_β H, *J* = 15.3Hz), 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_8 O_3: C, 70.20; H, 4.25; O, 25.46. Found: C, 70.21; H, 4.29; O, 25.51;

Compound5a

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*=8Hz, C-2-H), 6.92(d, 1H, *J*=8Hz, 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.

Compound5b

Yellow solid, mp 97-98ºC. 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*=8Hz), 6.91(d, 1H, *J*=8Hz), 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 ºC. 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*=8Hz), 6.92(d, 1H, *J*=8Hz), 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 95-96ºC. 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=8Hz), 6.92(d, 1H, J=8Hz), 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;

Compound5e

Yellow solid,mp 85-86ºC. 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*=8Hz), 6.92(d, 1H, *J*=8Hz), 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;

Compound5f

Dark yellow solid,mp 89-90ºC. 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*=8Hz), 6.92(d, 1H, *J*=8Hz), 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 $C_{18}H_{15}O_2S$ 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 83-84ºC. 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*=8Hz), 6.92(d, 1H, *J*=8Hz), 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-f, and 4a-d.**

R	Compound	Antibacterial activity Inhibition (mm)	
		E.Coli (-)	*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(CH_3)$_2$	**3f**	3.8	4.0
e: O-Cl	**4a**	8.2	8.0
f: M-NO_2	**4b**	7.8	8.3
	4c	7.7	6.2
	4d	6.7	6.5
	Streptomycin	9.3	8.5

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REFERENCES

1. Yamamoto H, Nakamura Y,Kumoh Y, Ichihara K,Nagasaka M,&Asai H,1986 *Jpn.J.Pharmacol*.**41** 283-287; 1986*Chem. Abstr*. **105** 72405v.
2. Ohno S, Izumi K,Mizukoshi S, Yamamoto H,Nagasaka M,&Nakumara Y,Jpn. Kokai.Tokkyo. Koho. JP. 6, 72,772(86, 72,772)[Cl.C07 D281/10] 1986; **1986***Chem Abstr*. **105** 208946q.
3. Sandhya Jonnala, Bhaskar Nameta, Murthy Chavali,Sunil Misra, B.V. Subba Reddy Letters in organic chemistry 16(10),837-845,2019

4. Murako pharmaceutical, Co. Ltd.;Jpn.Kokai.Tokkyo. Koho. JP. 81,127,367(86, 72,772)[Cl.C07 D281/10] 1981; *Chem Abstr*. **1986,***96,* 85601b.
5. Itoh, K.; Mori, M.; Inada, Y.; Nishikawa, K.;Kawamatsu, V.;& Sugihara, H.;*Chem.Pharm. Bull.***1986,** *34(4),* 3747; *Chem. Abstr.***1987,***106,* 122593r.
6. Floyd, D. M.;&Krapcho, J.U.S. Patent 4,584,131(Cl.260-239,3B.C07 D281/10)1986; *Chem Abstr*.**1986,** *105,* 78963x.
6. M.V. Sathya Narayana, J. Sandhya, A.G. Gopi, M.V.B. Rao Russian journal of general chemistry 91(7),1393-1396,2021
7. Murase, O.;Ikebe, T.;Nakamata, I.;&Anami, K.;Jpn.Kokai.Tokkyo. Koho. JP. 03,220,184 (91,220,184) [Cl.C07. D281/10] 1991; *Chem Abstr*.**1992,***116*,59416g.
8. Mane R A & Ingle D B, *Indian. J. Chem*.**1982,** *21B (10),* 973; *Chem Abstr*.**1983**, *99*, 22439w.
9. Yanamori, T.;Harda, H.;Oosugi, E.;& Sakai, K.; Eur. Pat. Appl. E.P 609,031 (Cl.C07 C323/56), 1994; JP Appl. 93 / 11, 492; *Chem Abstr*.**1995,***122*, 10074d.
10. Yun, Li.; Na, Sun.;& Sheng. *Jin..Chin.Chem..Lett.*,**1999,** *10(6),*447; *Chem Abstr,***1999,***131,* 322450c.
11. Somogy, L, I.;*Synth. Commun*.**1999,** *29(1),* 1857; *Chem Abstr*. **1999,** *131*, 58670h.
12. Li, Yuan.; Shi, Jian.; Dong, Zhang.; Yuan Jing Jin Sheng & Xing Qi, Yi.; ChinChem Lett, 10(1), 1999, 23; *Chem Abstr*, **1999,** *131*, 281800g.
13. Mais, Franz-Josef.; Bloodworth, Robert. Horst.;&Karsten, Bruch.; Von, Dem.; Ger,Offen, D. E. 19,810,392 (Cl.C07 C27/13) 1999, Appl. 19,810,392,1998. 10;*Chem Abstr,* **1999**, *131*, 199498v.
14. Waisser, K.;Kubikova, L.;Kaustova, J.; Bartsch, H.;Erker, T.;&Hanus, V.*Sci.Pharm*.**1999,** *67(2),* 123; *Chem Abstr*, **1999,***131*, 226009v.
15. Christensen, Hege.; Carlson, Erlend.;Asberg, Anders.; Schram.; Lita &Berg Knut. *J. Chin.Chim. Acta*.**1999**, *63*, 283(1-2); *Chem Abstr*, **1999,** *131*, 1779208x.
16. Amblard, Muriel.;Daffix, Isabelle.;Bedos, Philippe.; Berge, Gilbert.;Pruneau, Didier.; Paquet, Jean-Luc.;Luccarini, Jean- Michel.;Belichard, Pierre.;Doddy, Pierre & Martinez.*J. Med. Chem*.**1999,** *42(20),* 4185; *Chem.Abstr*.**1999,** *131*,351646b.
17. Lapointe-Nathalie.; Chen, H.; Xu, S.Qi.D.;Daloge, P.;&Dumount Louis.*Eur. Surg.Res*.1999, 31(3),259;*Chem. Abstr*.**1999**, *131*, 39484j.
18. Eckmiller Marion, P.C.T. Int. Appl. W.O.1998, 98, 50, 056 (Cl A 61 K38/55), D.E.Appl.1997, 19, 718, 826,70pp.*Chem.Abstr*. **1999**, *130*, 20593b.
19. Yadav, K.P.;& Ingle, D.B. *Indian. J. Chem*.**1983**, *22B*,180.*Chem.Abstr*.**1983**, *99*, 105221v.

20. Muller, J.C.; Lassalle, G.;& Denys, C.; Fr-Demande, F.R.1992, 2, 670,785 (Cl.C07 D417/12). Appl. 90/15, 1990, 988, 22pp.*Chem.Abstr*. **1993,***118*, 124574.
21. Yanamori, T.;Harda, H.; Sakai, K.;&Matasunaga, K.;*Eur. Pat. Appl*. EP 541,263 (Cl.C07 C281/10), **1993**.*J.P. Appl*. 91/302, 1991, 348.*Chem. Abstr*.**1993,***119*, 180837k.
22. Pant Umesh, C.; & Bhatia-Anshu.;*Indian. J. Het. Chem*. **1996**, *6*, 131.
23. Pant Umesh, C.;Upreti Mani.; Pant Seema.; DandiaAnshu.; Patnaik, G. K.;& Goyal, A.K. *Phosphorus. Sulphur and Silicon*.**1997**, *126*, 193.
24. Seema-Pant.; Hem-Chandra.; Priyanka-Sharma.;& Umesh, C.Pant.*Indian.J.Chem. 2006, Vol. 45B*, June. pp, 1525-1530.
25. Pant Umesh, C.; Sharma Anita.; Pant-Seema.; & Sharma, C.K. *Phosphorus.Sulphur and Silicon*.**1996**, *117*, 121.
26. Levai, A.;&Duddeck, H.*Acta.Chim. Acad. Sci. Hung*.**1976**, *88*, 293-298.
27. Duddeck, H.; Kaiser, M.;&Levai, A.;Leibig's.*Ann. Chem*. **1985**, 869-872.
28. Levai, A.;&Duddeck, H.*Pharmazie*.**1983**, *38*, 827-829.
29. Levai, A.*Pharmazie*. **1980**,*35*, 680-686.
30. Hankovszky, C.H.;&Hideg, K. *Acta.Chim. Acad. Sci. Hung*.**1971**, *68*, 403-406.
31. Pant Umesh, C.; Chandra Hem.; Goyal-Shweta.;Dandia, A.;& Pant Seema.*Phosphorus.Sulphar. Silicon and Releted Elements*.**2005**, 180-186.
32. Vincent, J.C.;& Vincent, H.W.*Proc. Exptl. Biol Med*.**1944**, *55*, 162-165.