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Research Article

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Synthesis, Spectral, Stereochemical and Antimicrobial Evaluation of Some 3*t*-pentyl-2*r*,6*c*-diarylpiperidin-4-one Thiosemicarbazone Derivatives

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Abstract: Seven 3t-pentyl-2r,6c-diphenylpiperidin-4-one thiosemicarbazones **1-7** (aryl =C_6H_5, *p*-ClC_6H_4, *p*-FC_6H_4, *p*-$CH_3OC_6H_4$, 3,4-$(CH_3O)_2C_6H_3$, *p*-$NO_2C_6H_4$ and *p*-$CH_3C_6H_4$) have been synthesised and their IR, ^1H and ^{13}C and mass spectra recorded. For compound **2** HOMOCOSY, NOESY, HSQC, HMBC spectra also have been recorded. The spectral data showed that compounds **1-7** exist in chair conformation with equatorial orientation for all the substituents. All signals could be assigned unambiguously by using 2D NMR in the case of compound **2**. The compounds were screened for their antibacterial activity against *E.coli, B.subtilis, S.aureus, V.cholerae* and antifungal activity against *A.niger, C.albicans, A.flavues, T.mentagrophytes*. They exhibited significant activities against all the tested bacterial and fungal strains.

Keywords: Piperidin-4-one thiosemicarbazone; NMR spectra; Mass Spectra; Antibacterial Activity; Antifungal Activity

1. INTRODUCTION

NMR spectroscopy is a powerful tool in determining the structure and stereochemistry of organic compounds [1-5]. From the vicinal proton-proton coupling constants, the torsional angles between the protons could be determined using DAERM equation [6]. Many natural compounds, vitamins, haemoglobin and synthetic drugs contain the piperidine ring system as a structural element. As this class of compounds exhibits pharmacological properties the elaboration of versatile, flexible, regio and stereo selective synthesis of chiral piperidine is of major interest to organic chemists [7-15]**.** Among the family of heterocyclic compounds, nitrogen containing heterocycles, especially piperidine-4-ones are of considerable importance owing to their biological properties [16-22] such as antiviral, antitumor, analgesic, local anaesthic, antimicrobial, bactericidal, fungicidal, herbicidal, insecticidal, antihistaminic, antiinflammatory, anticancer, CNS stimulant and depressant activities. Thiosemicarbazone were reported to be associated with antimicrobial activity [23, 24]. Several semicarbazones as well as their sulphur analogues and it derivatives have proved their efficiency and efficacy in combating various diseases. In

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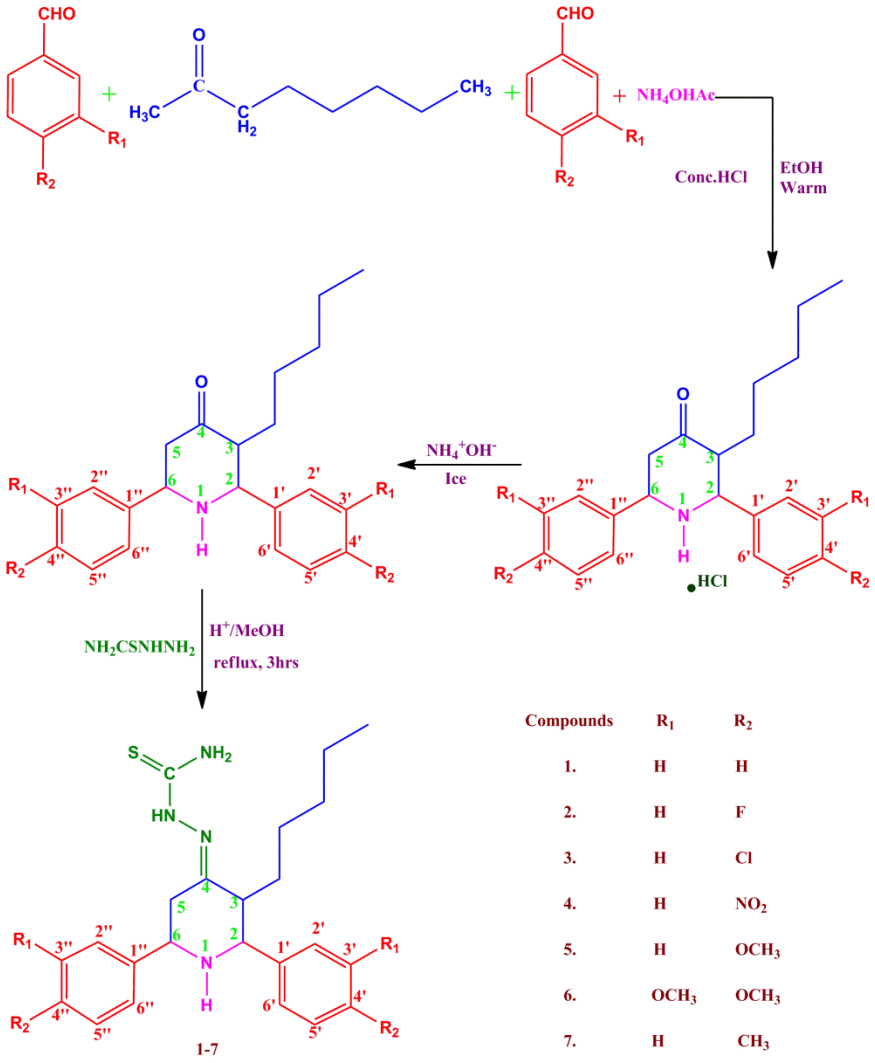
this article, we report the synthesis, detailed ^{1}H, ^{13}C, 2D NMR, mass and antimicrobial studies of 3t-pentyl-2r, 6c-diarylpiperdin-4-one thiosemicarbazones (**1-7**)



Compounds	R_1	R_2
1.	H	H
2.	H	F
3.	H	Cl
4.	H	NO_2
5.	H	OCH_3
6.	OCH_3	OCH_3
7.	H	CH_3

Scheme1. Synthetic route for 3t-pentyl-2r,6c-diarylpiperidin-4-one thiosemicarbazone derivatives

2. EXPERIMENTAL SECTION

2.1 Materials and Methods

All the solvents used were of spectral grade. The melting points of the compounds were measured in open capillaries and are uncorrected. IR spectra were recorded on an AVATAR-330 FT-IR spectrometer (Thermo Nicolet) using KBr (pellet form). ^{1}H NMR spectra were recorded at 400 MHz and ^{13}C NMR spectra at 100MHz on a BRUKER model using $CDCl_3$ / DMSO-d_6 as solvent for all the compounds. Tetramethylsilane (TMS) was used as internal reference for all NMR spectra, with chemical shifts reported in δ units (parts per million) relative to the standard. ^{1}H NMR splitting patterns are designated as singlet (s), doublet (d), doublet of doublet (dd), triplet (t), quartet (q) and multiplet (m). Coupling constants are expressed in Hertz (Hz). Mass spectra were recorded on a JEOL GCMATE II GC-

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MS. Microanalyses were performed on VarioMicro V2.2.0 CHN analyser. Microbial screening studies were made at Centre for biological sciences in Pondicherry.

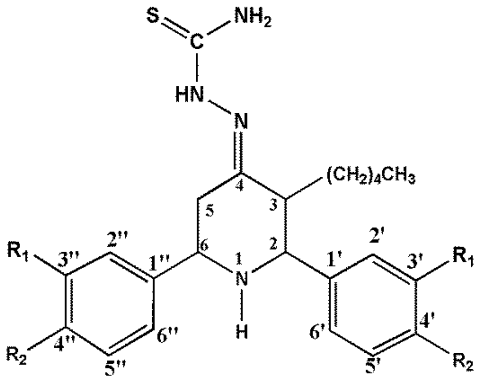

Figure 1. Numbering of carbon atoms in 3t-pentyl-2r,6c-diarylpiperidin-4-one thiosemicarbazones (**1-7**)

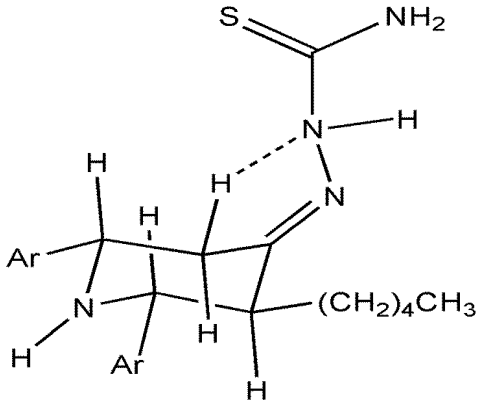

Figure 2. Chair conformation of 3t-pentyl-2r,6c-diarylpiperidin-4-one thiosemicarbazones

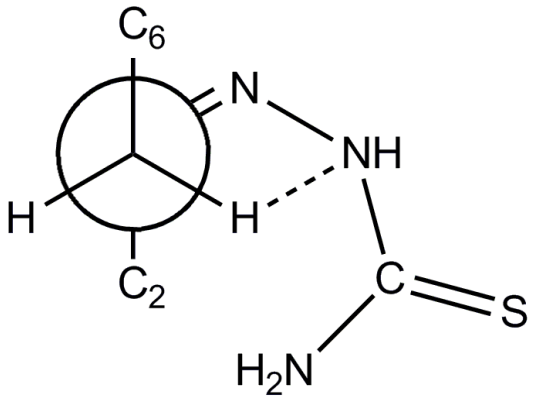

Figure 3. *Gauche* interaction of 3t-pentyl-2r,6c-diarylpiperidin-4-one thiosemicarbazones

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2.2 General procedure

2.2.1 Synthesis of 3t-pentyl-2r,6c-diarylpiperidin-4-one (1a-7a)

The compounds (**1a-7a)** were prepared according to the procedure given in literature for the preparation of 2,6-diarylpiperidin-4-ones [25, 26]. A mixture of ammonium acetate (0.05mol), substituted benzaldehyde (0.1mol) and 2-octanone (0.05 mol) in distilled ethanol was heated to boiling. After cooling, the viscous liquid obtained was dissolved in ether (200 ml) and shaken with 10 mL concentrated hydrochloric acid, the precipitated hydrochloride of 3*t*-pentyl-2r,6*c*-diarylpiperidin-4-one was removed by filtration and washed first with a mixture of ethanol and ether (1:1) and then with ether to remove most of the coloured impurities. The base was liberated from an alcoholic solution by adding aqueous ammonia and then diluted with water. The product was recrystallized from alcohol.

2.2.2 Synthesis of 3t-pentyl-2r,6c-diarylpiperidin-4-one thiosemicarbazone (1-7)

To a boiling solution of respective compound (0.01 mol) in 45 ml methanol, a few drops of conc. HCl were added. There-after, thiosemicarbazide (previously dissolved in 20 ml methanol) solution (0.01 mol) was added drop wise with stirring. The reaction mixture was refluxed for 3 hour on a heating mantle. After cooling, the solid product was filtered off and recrystalised from 20 ml methanol. The dried compound was purified by column chromatography using neutral alumina; benzene: ethyl acetate mixture as eluting solvent. The chemical reactions are shown in Scheme 1.

2.2.2.1 3t-pentyl-2r, 6c–diphenylpiperidin-4-one thiosemicarbazone (1)

Yield 65%; m.p.: 95 (ºC); MF: $C_{23}H_{30}N_4S$; Elemental analysis: Calcd (%): C, 70.01; H, 7.66; N, 14.20; S, 8.13; Found (%): C, 69.89; H, 7.71; N, 13.89; S, 8.05; IR (KBr) (cm^{-1}): 3424 (N-H stretching), 3367(NH_2), 3247(NH), 3143 (aromatic CH stretching), 2925 (aliphatic CH stretching), 1587 (C=N stretching), 1493 (C=C stretching), 1287(C=S), 1076 (C-N stretching), 754-699 (aromatic C-H out of plane bending vibration);^{1}H NMR (400 MHz, $CDCl_3$, δ,ppm): 8.94 (s,1H, NH), 7.30-7.49 (m, Ar-H), 6.58-7.23 (d, 2H, NH_2), 3.90 (dd,1H, H_6) , 3.67 (d, 1H, H_2,), 2.58 (t, 1H, H_{3a}), 2.28 (q, 1H, $H_{5ax,}$), 2.95 (dd, 1H, H_{5eq}), 1.01-1.66 (m, 8H, CH_2), 0.81 (t, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 179.19 (C=S),154.43 C(4), 126.76, 128.04, 128.34, 128.55, 128.71, 141.87 (Ar-C), 67.75 C(2), 60.93 C(6), 50.02 C(3), 36.32 C(5), 22.44-32.13 (CH_2), 14.03 (CH_3); Mass (m/e): 394 (M^+), 368, 344, 319, 273, 259, 215, 194, 158, 130, 104, 91, 77.

2.2.2.2 3t-pentyl-2r, 6c–di (4-fluorophenyl) piperidin-4-one thiosemicarbazone (2)

Yield 70%; m.p.: 110 (ºC); MF: $C_{23}H_{28}F_2N_4S$; Elemental analysis: Calcd (%): C, 64.16; H, 6.55; N, 13.01; S, 7.45; Found (%): C, 64.38; H, 6.64; N, 12.80; S, 7.36; IR (KBr) (cm^{-1}): 3425 (N-H stretching), 3372 (NH_2), 3242 (NH), 3144 (aromatic CH stretching), 2927 (aliphatic CH stretching), 1594 (C=N stretching), 1506 (C=C stretching), 1291 (C=S), 1083 (C-N stretching), 764-721 (aromatic C-H out of plane bending vibration); ^{1}H NMR (400 MHz, $CDCl_3$, δ,ppm): 8.87 (s,1H, NH), 7.01-7.07, 7.39-7.45 (m, Ar-H), 6.47-7.19 (d, 2H, NH_2), 3.85 (dd,1H, H_6) , 3.61 (d, 1H, H_2,), 2.45 (m, 1H, H_{3a}), 1.95 (d, 1H, $H_{5ax,}$), 2.89 (dd, 1H, H_{5eq}), 1.03-1.65 (m, 8H, CH_2), 0.79 (t, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 179.29 (C=S),154.15 C(4), 115.33, 115.47, 115.54, 115.69, 128.31, 128.39, 129.44, 129.52, 137.85, 137.88, 138.33, 138.36, 161.19, 163.64 (Ar-C), 66.92 C(2), 60.14 C(6), 50.42 C(3), 36.72 C(5), 22.43-32.13 (CH_2), 14.02 (CH_3); Mass (m/e): 430 (M^+), 413, 380, 355, 295, 247, 230, 194, 176, 148, 122, 95, 77.

2.2.2.3 3t-pentyl-2r, 6c–di (4-chlorophenyl) piperidin-4-one thiosemicarbazone (3)

Yield 68%; m.p.: 112 (ºC); MF: $C_{23}H_{28}Cl_2N_4S$; Elemental analysis: Calcd (%): C, 59.60; H, 6.09; N, 12.09; S, 6.92; Found (%): C, 59.66; H, 6.13; N, 11.77; S, 7.03; IR (KBr) (cm^{-1}): 3424 (N-H stretching), 3368 (NH_2), 3240 (NH), 3143 (aromatic CH stretching), 2953 (aliphatic CH stretching), 1588

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(C=N stretching), 1494 (C=C stretching), 1289 (C=S), 1087 (C-N stretching), 719-629 (aromatic C-H out of plane bending vibration); ^{1}H NMR (400 MHz, $CDCl_3$, δ,ppm): 8.96 (s,1H, NH), 7.31-7.40 (m, Ar-H), 6.50-7.19 (d, 2H, NH_2), 3.85 (d,1H, H_6) , 3.60 (d, 1H, H_2,), 2.46 (q, 1H, H_{3a}), 2.18 (q, 1H, $H_{5ax,}$), 2.91 (d, 1H, H_{5eq}), 1.09-1.62 (m, 8H, CH_2), 0.80 (t, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 179.33 (C=S), 153.69 C(4), 127.98,128.07, 128.36, 128.80, 128.95, 129.10, 129.30, 133.77, 133.80, 140.48, 140.96 (Ar-C), 66.96 C(2), 60.17 C(6), 50.26 C(3), 36.54 C(5), 22.47-32.15 (CH_2), 14.04 (CH_3); Mass (m/e): 463 (M^+), 446, 388, 318, 263, 193, 165, 139, 126, 78.

2.2.2.4 3t-pentyl-2r, 6c–di (4-nitrophenyl) piperidin-4-one thiosemicarbazone (4)

Yield 59%; m.p.: 120 (ºC); MF: $C_{23}H_{28}N_6O_4S$; Elemental analysis: Calcd (%): C, 57.01; H, 5.82; N, 17.34; S, 6.62; Found (%): C, 56.96; H, 5.82; N, 17.33; S, 6.61; IR (KBr) (cm^{-1}): 3424 (N-H stretching), 3355 (NH_2), 3255 (NH), 3152 (aromatic CH stretching), 2947 (aliphatic CH stretching), 1598 (C=N stretching), 1516 (C=C stretching), 1281 (C=S), 1067 (C-N stretching), 747-698 (aromatic C-H out of plane bending vibration); ^{1}H NMR (400 MHz, DMSO, δ,ppm): 10.72 (s,1H, NH), 7.78-8.27 (m, Ar-H), 7.23-7.37 (d, 2H, NH_2), 4.00 (d,1H, H_6) , 3.76 (d, 1H, H_2,), 2.48 (d, 1H, H_{3a}), 2.06 (q, 1H, $H_{5ax,}$), 3.27 (s, 1H, H_{5eq}), 0.90-1.70 (m, 8H, CH_2), 0.73 (t, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO, δ, ppm): 179.06 (C=S), 153.55 C(4), 123.21, 123.33, 128.08, 128.28, 129.42, 146.55, 146.81, 150.57, 151.39 (Ar-C), 66.18 C(2), 59.06 C(6), 49.27 C(3), 36.34 C(5), 21.81-31.38 (CH_2), 13.75 (CH_3); Mass (m/e): 484 (M^+), 467, 450, 431, 338, 283, 254, 203, 115, 106, 77.

2.2.2.5 3t-pentyl-2r, 6c–di (4-methoxyphenyl) piperidin-4-one thiosemicarbazone (5)

Yield 65%; m.p.: 102 (ºC); MF: $C_{25}H_{34}N_4O_2S$; Elemental analysis: Calcd (%): C, 66.05; H, 7.54; N, 12.32; S, 7.05; Found (%): C, 66.24; H, 7.54; N, 12.06; S, 6.91; IR (KBr) (cm^{-1}): 3423 (N-H stretching), 3358 (NH_2), 3240 (NH), 3142 (aromatic CH stretching), 2958 (aliphatic CH stretching), 1584 (C=N stretching), 1509 (C=C stretching), 1298 (C=S), 1077 (C-N stretching), 755-681 (aromatic C-H out of plane bending vibration); ^{1}H NMR (400 MHz, $CDCl_3$, δ,ppm): 8.86(s,1H, NH), 6.86-6.89, 7.33-7.36 (m, Ar-H), 6.47-7.20(d, 2H, NH_2), 3.80 (d,1H, H_6), 3.80 (t, 6H, OCH_3), 3.56 (d, 1H, H_2), 2.47 (t, 1H, H_{3a}), 2.20 (t, 1H, H_{5ax}), 2.86 (d, 1H, H_{5eq}), 1.06-1.61 (m, 8H, CH_2), 0.79 (t, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 179.25 (C=S), 154.92 C(4), 113.84, 114.03, 127.77, 128.36, 128.46, 128.62, 128.96, 134.90, 134.88, 159.26, 159.29, 134.88 (Ar-C), 67.18 C(2), 60.34 C(6), 50.43 C(3), 36.65 C(5), 22.50-32.22 (CH_2), 14.07 (CH_3); Mass (m/e): 454 (M^+), 437, 377, 319, 302, 254, 244, 160, 121, 77.

2.2.2.6 3t-pentyl-2r, 6c–di (3, 4-dimethoxyphenyl) piperidin-4-one thiosemicarbazone (6)

Yield 55%; m.p.: 106 (ºC); MF: $C_{27}H_{38}N_4O_4S$; Elemental analysis: Calcd (%): C, 63.01; H, 7.44; N, 10.89; S, 6.23; Found (%): C, 63.13; H, 7.57; N, 10.62; S, 6.41; IR (KBr) (cm^{-1}): 3420 (N-H stretching), 3326 (NH_2), 3252 (NH), 3147 (aromatic CH stretching), 2932 (aliphatic CH stretching), 1591 (C=N stretching), 1513 (C=C stretching), 1262 (C=S), 1076 (C-N stretching), 760-683 (aromatic C-H out of plane bending vibration); ^{1}H NMR (400 MHz, $CDCl_3$, δ,(ppm)): 8.88 (s,1H, NH), 6.83-7.36 (m, Ar-H), 6.46 (d, 2H, NH_2), 3.81 (d,1H, H_6), 3.79-3.95 (m, 12H, OCH_3), 3.56 (d, 1H, H_2,), 2.51 (q, 1H, H_{3a}), 2.21 (q, 1H, $H_{5ax,}$), 2.90 (d, 1H, H_{5eq}), 0.90-1.61 (m, 8H, CH_2), 0.80 (t, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 179.27 (C=S), 154.66 C(4), 109.74, 109.74, 110.60, 110.88, 111.18, 118.76, 120.39, 134.72, 135.30, 148.69, 148.71, 149.03, 149.08 (Ar-C), 67.61 C(2), 60.73 C(6), 50.35 C(3), 36.66 C(5), 22.51-32.20 (CH_2), 14.07 (CH_3); Mass (m/e): 514 (M^+), 497, 437, 332, 314, 274, 218, 190, 164, 151, 95, 77.

2.2.2.7 3t-pentyl-2r, 6c–di (4-methylphenyl) piperidin-4-one thiosemicarbazone (7)

Yield 70%; m.p.: 94 (ºC); MF: $C_{25}H_{34}N_4S$; Elemental analysis: Calcd (%): C, 71.05; H, 8.11; N, 13.26; S, 7.59; Found (%): C, 70.99; H, 8.10; N, 13.25; S, 7.58; IR (KBr) (cm^{-1}): 3425 (N-H stretching),

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3366 (NH_2), 3245 (NH), 3143 (aromatic CH stretching), 2947 (aliphatic CH stretching), 1588 (C=N stretching), 1495 (C=C stretching), 1287 (C=S), 1078 (C-N stretching), 721-639 (aromatic C-H out of plane bending vibration); ^{1}H NMR (400 MHz, $CDCl_3$, δ,ppm):8.85(s,1H, NH), 7.15-7.39 (m, Ar-H), 6.52-7.26(d, 2H, NH_2), 3.82 (d,1H, H_6), 2.35 (t, 6H, CH_3), 3.58 (d, 1H, H_2), 2.52 (q, 1H, H_{3a}), 2.08 (t, 1H, H_{5ax}), 2.88 (d, 1H, H_{5eq}), 0.90-1.34 (m, 8H, CH_2), 0.79 (t, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 179.22 (C=S),154.90 C(4), 126.54, 127.02, 127.85, 129.36, 129.64, 137.62, 137.71, 139.13, 139.20, 139.69, 152.83, 139.69, 152.83 (Ar-C), 67.49 C(2), 60.65 C(6), 50.24 C(3), 36.60 C(5), 21.17-26.87 (CH_2), 14.08 (CH_3); Mass (m/e): 422 (M^+), 405, 377, 347, 303, 222, 118, 105, 77.

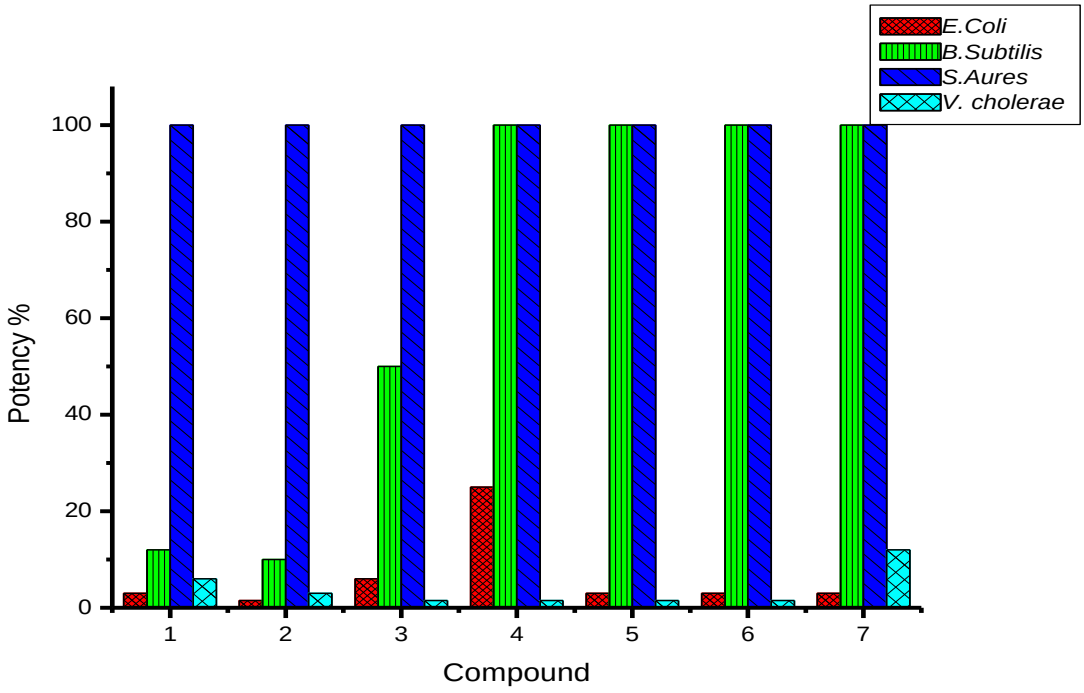

Figure 4. Potency diagram of antibacterial activity of compounds (**1-7**)

2.3 Antibacterial activity by disc diffusion method

Nutrient agar plates were prepared under steriled conditions and incubated overnight to detect contamination. About 0.2ml of working stock culture was transferred into separate nutrient agar plates and spread thoroughly using a glass spreader. Whatmann No.1 discs (6 mm in diameter) were impregnated in the test compounds dissolved in DMSO (200 mg/ml) for about half an hour. Commercially available drug disc *(Ciprofloxacin* 10 µg/disc) was used as positive reference standard. Negative controls were also prepared by impregnating the disc of same size in DMSO solvent. The discs were placed on the inoculated agar plates and incubated at 37 ± 1°C for about 18-24 h. Antibacterial activity was evaluated by measuring the zone of inhibition against the test organism.

2.4 Antifungal activity by disc diffusion method

Sabouraud's dextrose agar (SDA) medium was used for the growth of fungi and testing was done

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Table 1. Karplus constants, coupling constant (Hz) and torsional angles (Φ) t- about C(2)-C(3) and C(2)-C(3) bonds in compounds (**1-7**)

Compound	J_{6a5a}	J_{6a5e}	k_1	k_2	Φ_{6a5a}	Φ_{6a5e}	J_{2a3a}	Φ_{2a3a}
1	11.2	1.6	10.3	11.5	184.6	64.6	10.0	158.5
2	11.6	2.4	10.7	11.9	179.8	59.8	10.0	158.5
3	10.8	-	10.0	11.1	-	-	10.4	169.1
4	11.6	1.2	10.7	11.9	188.0	68.0	10.0	158.5
5	10.0	-	9.3	10.3	-	-	9.2	163.8
6	10.0	1.2	9.3	10.3	186.3	66.3	9.2	163.8
7	11.2	-	10.3	11.5	-	-	10.0	158.5

Table 2. Chemical shift difference between the α-carbons ($\Delta\delta_\alpha$) in thiosemicarbazones (**1-7**) and piperidones[a] (**1a-7a**)

Thiosemicarbazone	piperidone	$\delta_{anti} - \delta_{syn}$ (ppm)		
		Thiosemicarbazone	Piperidone	Thiosemicarbazone - piperidone
1	1a	13.7	5.51	8.19
2	2a	13.77	13.7	0.07
3	3a	13.72	5.84	7.88
4	4a	12.93	5.74	7.19
5	5a	13.78	5.53	8.25
6	6a	13.69	5.45	8.24
7	7a	13.74	-	-

[a] – data taken from ref [27]

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in Sabouraud's dextrose broth (SDB) medium. The subculture and the viable count were carried out by the same procedure used for in antibacterial studies except the temperature, which should be maintained at 28 ± 1°C for about 72 h. Similarly for disc diffusion method, the petridishes were incubated at 28 ± 1°C for about 72 h. The same concentration of the test compound, solvent (DMSO) and *Cetramazole* (standard) prepared previously were used for the antifungal studies.

2.5 Minimum Inhibitory Concentration (MIC)

The lowest concentration of the test compounds which caused apparently the inhibition of growth of organism, was taken as the minimum inhibitory concentration (MIC). The minimum inhibitory concentration was recorded by visual observation after 24 h (bacteria) and 72-96 h (fungi) of incubation. The sterile distilled water and DMSO did not show any inhibition.

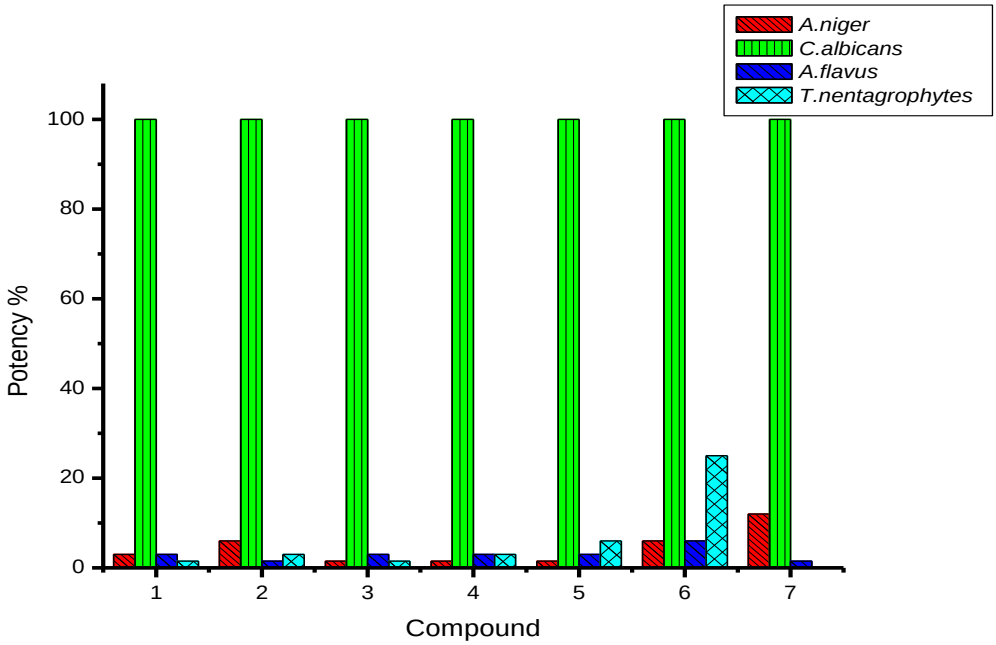

Figure 5. Potency diagram of Antifungal activity of compounds (**1-7**)

3. RESULTS AND DISCUSSION

3.1 Synthesis of compounds

The synthetic pathway that leads to the formation of compounds **(1-7)** is presented in Scheme1. By adopting the procedure already reported by Noller and Balliah [23], 2, 6-diarylpiperidin-4-ones were prepared in one pot multi component Mannich reaction by condensing suitably substituted aromatic aldehydes, 2-octanone and ammonium acetate in 2:1:1 ratio using ethanol as solvent and then converted into their respective thiosemicarbazones **(1-7)** by treatment with thiosemicarbazide hydrochloride in methanol. They are soluble in chloroform, methanol, ethanol, actonitrile, etc. and insoluble in pet-ether and water, etc.

The numbering of carbon atoms is shown in Fig.1. The protons of piperidine ring are given the numbers of the carbons to which they are attached. The methylene protons at C(5) and methine proton at C(3) are denoted as H_{5e}, H_{5a} and H_{3a}, respectively. The synthesised compounds **1-7** were characterised by

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various spectral techniques. The mass spectral data are in agreement with the proposed molecular formula of the respective compounds.

In general, IR spectra of thiosemcarbazones showed C=N peaks at 1610-1580 cm^{-1} and the NH stretching vibrations at 3450 cm^{-1}. Normally, the C=S stretching vibration of thiosemicarbones are found around 1235 cm^{-1}.

Table 3. Correlation in HOMOCOSY, NOESY, HSQC and HMBC spectra of compound **2 (**δ, ppm)

^{1}H NMR signal	Correlation in HOMOCOSY	Correlation in NOESY	Correlation in HSQC	Correlation in HMBC
3.85 (H_6)	2.17 (H_{5a}), 2.92 (H_{5e})	2.17 (H_{5a}), 2.92 (H_{5e}), 7.01-7.45 Aromatic protons	60.17 (C_6)	-
3.61 (H_2)	2.45 (H_{3a})	2.45 (H_{3a}), 7.01-7.45 Aromatic protons	66.94 (C_2)	60.17 (C_6, β), 50.42(C_3, α), 154.52 (C_4, β)
2.17 (H_{5a})	2.92 (H_{5e}), 3.85 (H_6)	2.92 (H_{5e}) 3.85 (H_6), Aromatic protons	36.65 (C_5)	60.17 (C_6, α), 154.52 (C_4, β)
2.45 (H_{3a})	3.61 (H_2), 1.03-1.65 (CH_2)	1.03-1.65 (CH_2), 7.01-7.45 Aromatic protons	50.42 (C_3)	66.94 (C_2, α), 154.52 (C_4, β)
2.92 (H_{5e})	2.17 (H_{5a}), 3.85 (H_6)	2.17 (H_{5a})	36.65 (C_5)	60.17 (C_6, α), 50.42(C_3, β), 154.52 (C_4, β)
0.79 (CH_3)	1.03-1.65 (CH_2)	1.03-1.65 (CH_2)	14.02 (CH_3)	22.26-32.14 (CH_2,α)
1.03-1.65 (CH_2)	1.03-1.65 (CH_2)	1.03-1.65 (CH_2)	22.26-32.14 (CH_2)	14.02 (CH_3, α), 22.26-32.14 (CH_2,α)
6.59 (NH_2)	7.19 (NH_2)	7.19 (NH_2)	-	-
7.19 (NH_2)	6.59 (NH_2)	6.59 (NH_2)	-	-
7.01-7.45 (Aromatic Proton)	7.01-7.45 (Aromatic Proton)	7.01-7.45 (Aromatic Proton)	115.34-138.33 (Aromatic Carbon)	66.94 (C_2, α), 60.17 (C_6, α)

3.2 NMR spectral analysis

The ^{1}H NMR spectral signals are assigned based on their position, multiplicity and integral values.

3.2.1 Coupling constants

The coupling constant values are extracted from ^{1}H NMR spectra and the relevant coupling constants and torsinal angles are given in Table 1. In all the compounds **(1-7),** the benzylic proton at C(6) couples with adjacent methylene protons, the two vicinal coupling constants have a value of 10.0-11.6 and 1.2-2.4 Hz, respectively. One value is characteristic of a diaxial coupling and the other an axial-equatorial coupling about C(6)-C(5). When the benzylic proptons couple with only one adjacent proton, the observed vicinal coupling constant is around 10.5 Hz about C(2)-C(3). This value is peculiar of diaxial coupling. These values indicate that compounds adopt chair conformation with all the substituents

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in equatorial positions. The coupling constant about C(2)-C(3) bond is considerably lower than the diaxial coupling about C(5)-C(6) bond. The pentyl group at C(3) experiences severe *gauche* interaction with the phenyl group at C(2) and in order to avoid this interaction the ring is flattened about C(2)-C(3) bond. Due to this flattening, J_{2a3a} is of lower magnitude compared with J_{6a5a}. Increasing bulkiness of substituent at C(3) decreases J_{2a3a} to a greater extent. The geminal axial-equatorial coupling constant J_{5a5e} is around 13Hz. Based on the above discussion, normal chair conformation is proposed for compounds **1-7** as depicted in Fig. 2. These values also supported the fact that all the synthesised compounds exist in normal chair conformation.

3.2.2 Analysis of chemical shifts

In the ^{1}H NMR spectrum of compound **1**, besides the aryl protons, signal around 7.28-7.49 ppm, is a multiplet due to aromatic protons in phenyl ring carbons at C(2) and C(6). The two downfield signals (3.90 ppm doublet of doublet and 3.67 ppm doublet) are assigned to H_{6a} and H_{2a}, benzylic protons, respectively. The signal at 2.95 ppm, doublet of doublet, is assigned to H_{5e} *syn* α proton. Consequently, the signal at 2.28 ppm is assigned to methylene proton of H_{5a}. Obviously, the signal at 2.58 ppm is due to H_{3a}. The most downfield singlet at 8.94 ppm is assigned to NH proton of thiosemicarbazone group and the two downfield signals at 6.58 ppm and 7.23 ppm are due to NH_2 protons of thiosemicarbazone group. Unlike compound **1**, in compounds **2** (*p*-fluorophenyl), **5** (*p*-methoxyphenyl) and **7** (*p*-methylphenyl) two sets of aryl signals are observed at C(2) and C(6) (with eight protons integral value of the two sets of aryl signals). The upfield multiplet is due to protons *ortho* to the substituent in **2** and **7**, while in **5** the multiplet in the upfield region is due to the protons *meta* to methoxy substituents i.e $H_{2'}$, $H_{2''}$ and $H_{6'}$, $H_{6''}$. Contrary to **2** and **7**, in **5**, the *ortho* protons are observed in the downfield region due to the *ortho* effect of the methoxy group. But compound **3** gave a single multiplet with an integral vaule for eight protons (p-chlorophenyl) at C(2) and C(6). Comparison of the chemical shifts of 3*t*-pentyl-2*r*,6*c*-diarylpiperidin-4-one thiosemicarbazone (**1-7**) with those of 3*t*-pentyl-2*r*,6*c*-diarylpiperidin-4-one reveals that formation of thiosemicarbazone shields all heterocyclic ring protons except H_{5e} in **1-7**. The shielding magnitudes observed on H_{5a} in **1-7** are considerably greater than those observed on the protons. The equatorial protons at C(5)[H_{5e}] resonate considerably at downfield in **1** (0.30 ppm), **2** (0.38 ppm), **3** (0.22 ppm), **4** (0.41ppm), **5** (0.29 ppm), **6** (0.20 ppm) and **7** (0.3 ppm). The observed downfield and upfield resonances of H_{5e} and H_{5a} in **1-7** can be explained as follows.

In thiosemicarbazones severe interaction exists between N-N bond and equatorial *syn* α C-H bond. Due to this interaction, the equatorial *syn* α C-H bond is said to be polarised. As a result of this polarisation, the equatorial hydrogen acquires a slight positive charge. Therefore, axial hydrogen at C(5) is shielded whereas equatorial hydrogen at C(5) is deshielded in thiosemicarbazones.

The ^{13}C NMR spectra data of compounds **1-7** are analysed. In compound **1**, the aromatic carbons could be easily distinguished by their characteristic absorption around 126.76-141.87 ppm. The *ipso* carbons should absorb at higher frequency compared to other aromatic carbons. For all the 3*t*-pentyl-2*r*,6*c*-diarylpiperidin-4-one thiosemicarbazones the upfield signals around 14.03 ppm is assigned to methyl carbon of pentyl group at C(3) and other upfield signals in the region 22.44-32.13 ppm are assigned to methylene carbons of pentyl group at C(3). In all the compounds, C(4) could readily be distinguished from other heterocyclic ring carbons by their characteristic downfield signals observed around 154.43 ppm and also by their low intensities. The signal around 67.75 and 60.93 ppm are due to benzylic carbons at C(2) and C(6) and remaining signals at 50.02 and 36.32 ppm are due to C(3) and C(5) carbons. Among the benzylic carbon signals based on the known deshielding β-effect of the pentyl group the one at higher frequency i.e 67.75 ppm is assigned to C(2). Therefore, the remaining signal around 60.93 ppm is due to C(6). The signals around 50.02 and 36.32 ppm are due to C(3) and C(5). The higher

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Table 4. Minimum inhibitory concentration (μg/mL) of 3t-pentyl-2r, 6c-diarylpiperidin-4-one thiosemicarbazones (**1-7**)

Compound	Minimum inhibitory concentration in μg/mL							
	Anti bacterial				Anti fungal			
	E.coli	*B.subtilis*	*S.aureus*	*V.cholerae*	*A.niger*	*C.albicans*	*A.flavus*	*T.mentagrophytes*
1	100	25	6.25	50	100	6.25	100	200
2	200	6.25	6.25	100	50	6.25	200	100
3	50	12.5	6.25	200	200	6.25	100	200
4	12.5	6.25	6.25	200	200	6.25	100	100
5	100	6.25	6.25	25	25	6.25	200	200
6	100	6.25	6.25	200	50	6.25	50	12.5
7	100	6.25	6.25	200	200	6.25	100	50
Ciprofloxacin	6.25	6.25	6.25	6.25	-	-	-	-
Cetramazole	-	-	-	-	6.25	6.25	6.25	6.25

frequency signal is assigned to C(3) based on the known deshielding α- effect of the pentyl group at C(3). Obviously the remaining signal around 36.32 ppm is due to C(5). The most downfield signal around 179.19 ppm is assigned to C=S carbon of thiosemicarbazone group. Rest of the compounds **2**-7 also showed similar partten of splitting as that of **1**.

Generally, in six-membered heterocycles, decrease in electronegativity of a particular group in the ring skeleton shields the α-carbon and deshields the β- and γ-carbons. Inspite of the less polar nature of the C=N than C=O bond, the electronegativity of the C=N-NH-CS-NH_2 group must be less than that of C=O group. All the Δδ ($\delta_{piperidone}$-$\delta_{thiosemicarbazone}$) values for the piperidone ring carbons of the synthesised compounds (**1-7**) are furnished in Table 2.

Table 2 reveals that thiosemicarbazone moiety shields all the heterocyclic ring carbons except C(2). The α-effect can be studied by comparing the chemical shifts of the α- carbons C(3) and C(5) of the thiosemicarbazones with the corresponding piperidones. In thiosemicarbazones, the C=N group shields the α- carbon due to its lower electronegativity than C=O, and this is due to the interaction of the N-O bond with the *syn* α C-H bond (Fig.3). This interaction induces a polarity in the *syn* α C-H bond so that the *syn* α- equatorial proton H_{5e} gets slight positive charge and the C(5) carbon gets slight negative charge and consequently the proton is deshielded and the carbon is shielded significantly i.e. In total, the shielding magnitude on *syn* α- carbon is around 15-16 ppm for **1-7** whereas that on *anti* α- carbon is only about 6-7 ppm. Owing to inductive effect all the carbons are deshielded except C(4) for **2** and **3**.

Generally in thiosemicarbazones, the *syn* α- carbon is more shielded than the *anti* α-carbon, probably the chemical shift difference between the α-carbons ($\Delta\delta_\alpha$) varying by 13-12 ppm depending on the structure of the thiosemicarbazone (Table 2). The difference in the chemical shift increases with a decrease in the dihedral angle between C=N and α(C-H) bonds.

The β-effect can be studied by comparing the chemical shifts of the β- carbons C(2) and C(6) of the thiosemicarbazone derivatives with the corresponding piperidones. In six membered heterocycles, decrease in electronegativity of a group in the ring deshields β-carbons and shields β-protons. The γ-effect is studied by comparing the chemical shifts of the *ipso* carbons C(2') and C(6') in piperidones with

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thiosemicarbazone in accordance with the electronegativity effect.

The deshielding of *anti* β-carbon is in accordance with the expected electronegativity effect. But the *syn* β-carbons are shielded. Moreover, the shielding magnitude is increased from compounds **1-7**. The reason for the shielding is due to the negative charge on the *syn* α-carbon, which is transmitted to a small extent on the *syn* β-carbon. Thus, the shielding produced on the β-carbon by the transmittance of the negative charge overcomes the deshielding produced by the electronegativity effect.

3.3 2D NMR

For compound **2**, HOMOCOSY, HSQC, HMBC and NOESY specra were recorded and the possible correlations are given in Table 3. In HOMOCOSY spectrum, the doublet at 3.85 ppm correlated with the multiplet centered at 2.71 and 2.92 ppm. This clearly shows that doublet at 3.85 ppm and two multiplets centered at 2.17 and 2.92 ppm are due to H_6 and methylene protons at C(5) [H_{5a} and H_{5e}]. The other doublet at 3.61 ppm reveals cross peak with multiplet centered at 2.45 ppm thus confirming the assignments of the signals at 3.61 and 2.45 ppm for H_2 proton and axial methine proton H_{3a} at C(3), respectively.

The above assignments are further confirmed by NOESY spectrum of compound **2**. The observed significant NOEs are reproduced in Table 3. The strong NOEs between H_{6a} and H_{5e} clearly confirm that the benzylic protons occupy axial and equatorial dispositions respectively. All the signals corresponding to the piperidone thiosemicarbazone moiety are further confirmed from the HSQC (Hetero Nuclear Single Quantum Coherence) spectrum recorded for compound **2** and the observed correlations are listed in Table 3. As the proton NMR chemical shift values of the piperidone ring system in **2** are assigned perfectly, the respective carbon signals are also established on the basis of the observed HSQC correlations.

The assignment of ^{1}H and ^{13}C NMR data are also confirmed by HMBC spectrum of **2**. The chemical shift values are given in Table 3.

Generally, in HMBC spectrum cross peaks are obtained between carbon and hydrogen separated by two or three bonds. The one bond coupling between carbon and hydrogen may be absent or appear as straddled peak.

The peak at 60.17 ppm cross peaks with signals at 3.61, 2.17 and 2.92 ppm. The signals at 3.61, 2.17 and 2.92 ppm are assigned to H_2, H_{5a} and H_{5e} at C(2) and C(5) carbons, respectively. Hence, the signals at 60.17 ppm should be due to C(6) carbon. The peak at 66.94 ppm shows cross peaks with the signal at 2.45 ppm and is assigned to H_{3a} proton at C(3) carbon. Hence, the peak at 66.94 ppm should be due to C(2) carbon. The peak at 50.42 ppm shows cross peaks with the signals at 3.61 and 2.92 ppm, the signals at 3.61 and 2.92 ppm are already assigned to H_2 and H_{5e} protons of C(2) and C(5) carbons, respectively. Hence, the signal at 50.42 ppm should be due to C(3) carbon. The peak at 154.52 ppm observed cross peaks with the signals at 3.61, 2.45, 2.17, 2.92 and 8.98 ppm. The signals at 3.61, 2.45, 2.17, 2.92 and 8.98 ppm are assigned to H_2, H_{3a}, H_{5a}, H_{5e} and NH protons of thiosemicarbazone group. Hence, the signal at 154.52 is due to C(4)carbon.

3.4 Antimicrobial studies

The preliminary antimicrobial activity of compounds **1-7** is examined using disc diffusion method.

3.4.1 Antibacterial studies

The bacterial strains *viz, S.aureus, B. subtilis, E. coli* and *V.cholerae* were used for this study. DMSO is used as control while *ciprofloxacin* is used as a standard for bacterial strains. The minimum inhibitory concentration values of **1-7** are given in Table 4.

The percentage of antimicrobial potency of the tested compounds compared with reference

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standard was calculated by adopting the following equation.

Antimicrobial potency (%)

$$= \frac{\text{MIC}(\mu g/mL) \text{ of reference compound}}{\text{MIC}(\mu g/mL) \text{ of test compound}} \text{ X } 100$$

The obtained MIC values of the tested compounds and standard are depicted in Table 4 which indicates that all the tested compounds exhibit a varied range 6.25-200 µg/mL. The unsubstituted phenyl groups in compound **1** show moderate activity in the range 100-50 µg/mL against *E.coli* and *V.cholerae* whereas *S.aureus* and *B.subtilis* exhibit excellent and good activity, respectively.

However, introduction of fluoro substituent in to compound **2** shows significant activity against the tested bacterial strains at concentration 200-6.25 µg/mL. The compound showed excellent and good activity against *S.aureus* and *B.subtilis* while exhibited moderate and poor activity against *E.coli* and *V.cholerae*. But the replacement of fluoro with chloro Substituents (compound 3), enhanced the activity against *E.coli* whereas decreased the activity against *V.cholerae* (moderate to poor) no significant change in the activity was observed against *B.subtilis* and *S.aureus.* Substitution of *p*-nitrophenyl group in the place phenyl groups at C(2) and C(6) positions in **1** (compound **4**) gave excellent activity against all the bacterial strains except against *V.cholerae*. Compound **5**, which has *p*-methylphenyl susbtituent instead of phenyl group registered excellent activity against *V.choreae*, *B.subtilis* and *S.aureus* while showed moderate activity against *E.coli*.

However, introduction of *p*-methoxyphenyl groups at C(2) and C(6) positions in **1** (compound **6**) showed excellent activity against *B.subtilis* and *S.aureus* while exhibited moderate and poor activity against *E.coli* and *V.cholerae*, respectively. Introduction of 3,4-dimethoxy phenyl group instead of *p*-methoxy phenyl group at C(2) and C(6) positions of piperidone ring **6** (compound **7**) showed no change in activity against all the tested bacterial strains.

3.4.2 Antifungal activity

The *invitro* antifungal activities of compounds **1-7;** here *cetramazole* was chosen as standard drug on a list of fungal strains such as *C.albicans*, *A. niger*, *A. flavus* and *T.mentagraphytes* whose potencies were measured as minimum inhibitory concentrations (MIC, µg/mL).

Among these compounds, which bear phenyl groups at C(2) and C(6) positions i.e compounds (**1-7**), compound **1** has excellent activity against *C.albicans* while exhibited moderate and poor activities against *A.niger*, *A.flavus* and *T.mentagraphytes*.

However, substitution of fluoro at the *para* position of phenyl group in **1**(compound **2**) has excellent activity against *C.albicans* whereas showed better activity against *A.niger*, *T.mentagraphytes* and *A.flavus*.

Introduction of chloro and nitro groups at the *para* positions of phenyl group C(2) and C(6) position in **1** (compound **3**) had poor activity against all the fungal strains except *C.albicans*. However, substitution of nitro group at the *para* position of phenyl groups in **1**(compound **4**) had poor activity against all the fungal strains except *C.albicans*. Among the compounds in which the heterocyclic nitrogen is flanked by *p*-methyl groups, compound **5** has excellent activity against *A.niger* and *C.albicans* while poor activity against *A.flavus*.

However, substitution of methoxyphenyl group at C(2) and C(6) positions in **1** (compound **6**) has excellent activity against *C.albicans* and *T.mentagraphytes* whereas poor activity against *A.niger* and *A.flavus*.

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Likewise, substitution of dimethoxy phenyl groups at C(2) and C(6) positions has excellent activity against *C.albicans* while show poor, moderate and better activity against *A.niger*, *A.flavus* and *T.mentagraphytes*, respectively.

4. CONCLUSION

All the synthesized 3t-pentyl-2r, 6c–diphenyl piperidin-4-one thiosemicarbazones were characterized by IR, NMR and Mass spectra. The spectral data supported and confirmed the formation of thiosemicarbazone derivatives. From the observed chemical shifts and coupling constants, the conformation of the compounds was proposed and equatorial preference of the alkyl substituent at C(3) also established. The compounds **1-7** adopt normal chair conformation with equatorial disposition of substituents at C(2), C(6) and C(3) carbons. All the compounds (**1-7**) were screened for their antimicrobial activity and they exhibited excellent activity against *B.substilis*, *S.aureus* and *C.albicans*.

SUPPORTING INFORMATION

^{1}H NMR, ^{13}C NMR and Mass spectra all of compounds are included

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