4. SUMMARY

Synthesis, Spectral, Antimicrobial and X-ray Crystallographic studies of 1-(cyclopropanecarbonyl)-3-methyl-2,6-diphenyl piperidin-4-ones 73-78

1. 1-(cyclopropanecarbonyl)-3-methyl-2,6-diphenylpiperidin-4-ones 73-78 have been synthesized and characterized by IR, \(^1\)H and \(^{13}\)C NMR spectra. HSQC spectrum has also been recorded for compound 76 to confirm the 1D NMR spectral assignments.

2. The absence of NH stretching band and the appearance of new amide carbonyl stretching band (1600-1641 cm\(^{-1}\)) supports the conversion of NH into N-acylated derivatives (73-78).

3. Broad singlets observed for H-2a (5.34-5.41 ppm) and H-6a (5.88-5.94 ppm) confirmed the involvement of lone pair of electrons on the ring nitrogen in conjugation with the –COR group. This conjugation creates a partial double bond character about N-C=O bonds.

4. In \(^{13}\)C NMR spectra, all carbon signals of the target compounds (73-78) are observed in the expected regions. The benzylic carbon, C-2 is observed around 61.0 ppm and C-6 carbon is observed around 54.0 ppm. The deshielding magnitude of C-2 carbon signal is due to the β-effect of the methyl group present at C-3 position of the piperidine ring.

5. X-ray crystallographic analysis revealed that compound 76 crystallizes in triclinic form with P1 space group. The asymmetric unit contains two independent molecules (A and B). The central piperidine ring adopts boat
confirmation. In this crystal, the A and B molecules are linked by C-H···O hydrogen bonds enclosing R\textsubscript{12} (6) ring motifs and forming ribbons running along the \(a\)-axis direction.

6. The observed bond lengths of C(5)-N(1) 1.476\(\AA\), C(1)-N(1) 1.478\(\AA\), C(21)-N(2) 1.361 and C21-O1 (1.233\(\AA\)) obtained from X-ray crystallographic analysis of compound 76 are compared with the true C-N (1.47 \(\AA\)) and C=O (1.21 \(\AA\)) bond lengths. The variation in the bond length values indicated the existence of partial double character in N-C=O [C(21)-N(2) and C(21)-O(1)] bonds.

**Synthesis, Spectral, Antimicrobial and X-ray Crystallographic studies of (\(E\))-cyclopropyl(4-(hydroxyimino)-3-methyl-2,6-diphenylpiperidin-1-yl)methanones (79-83)**

7. (\(E\))-cyclopropyl(4-(hydroxyimino)-3-methyl-2,6-diphenyl piperidin-1-yl)methanones (79-83) have been synthesized and characterized by IR, \(^1\)H NMR and \(^{13}\)C NMR spectral techniques.

8. The disappearance of carbonyl stretching around 1700 \(\text{cm}^{-1}\) and the appearance of C=N stretching band around 1500 \(\text{cm}^{-1}\) confirmed the formation of oxime derivatives.

9. In \(^1\)H NMR spectra, a signal observed around 10 ppm and in \(^{13}\)C NMR spectra, C=N carbon observed around 155 ppm confirmed the formation of oxime derivatives.

10. HSQC spectrum of 81 and its obtained correlations confirmed their \(^1\)H and \(^{13}\)C NMR spectral assignments.

11. Compounds 79-83, the chemical shifts of H-5e are greater than that of H-5a proton. Also C-5 has lower chemical
shift than C-3. These observations suggested the
E configuration about the C(4)=N.

12. In HRMS analysis, the M+ peak observed at 348.1913 (79), 417.1136 (80), 385.1727 (81), 377.2260 (82) and
409.2126 (83) further confirmed the formation of the target
compounds (79-83).

13. XRD-analysis of compound 79 revealed that the
compound 79 crystallizes monoclinic system with space
group Pa. In compound 79, the methyl group present at C-3
is in the equatorial orientation and the corresponding torsion
angle is (N1–C5–C4–C10) 180.0°(8). The phenyl rings at C-1
is in axial and C-5 is in the equatorial positions with their
torsion angles C3–C2–C1–C11 and C3–C4–C5–C17 being
equal to -75(1)° and 178.4(8)°, respectively. The six membered
heterocyclic piperidine ring of compound 79 adopts boat
conformation.

14. The XRD analysis of 76 further informed that the bond
lengths of C(1)-N(1), C(5)-N(1), C(6)-N(1) and C(6)-O(2) are
1.466 Å, 1.446 Å, 1.401 Å and 1.244 Å, respectively. But the
true C-N bond distance is 1.47 Å and the C=O bond distance
is 1.21 Å. The variation in the bond length value in C(6)-N(1)
(1.401 Å) and C(6)-O(2) (1.244 Å) clearly indicated the
existence of partial double bond character.

15. In vitro antibacterial activities have been studied for
compounds 73-83 against a panel bacterial strains viz.,
Staphylococcus aureus, Bacillus subtilis, Salmonella typhi,
Escherichia coli and Pseudomonas aeruginosa and fungal
strains viz., Candida albicans, Aspergillus niger, Rhizopus sp.,
Candida 6 and Aspergillus flavus.
16. Antibacterial activity of compounds 73-83 revealed that compound 77 against *Staphylococcus aureus*, compounds 77 and 78 against *Bacillus subtilis*, compounds 78 and 82 against *Salmonella typhi*, compound 74 against *Escherichia coli*, compounds 76 and 77 against *Pseudomonas aeruginosa* shows equal antibacterial activity as compared with standard drug streptomycin.

17. The compound 80 against *Staphylococcus aureus*, compound 74 against *Salmonella typhi*, compounds 77 and 81 against *Escherichia coli* showed one fold higher antibacterial activity than the standard drug. In particular compounds 75, 77 and 81 exhibited two fold enhanced excellent antibacterial activity against *Salmonella typhi*.

18. *In vitro* antifungal activity of the synthesized compounds 73-83 revealed that compounds 74, 77 and 81 against *Candida albicans*, 77, 78, 80 82 and 83 against *Aspergillus niger*, 77 against *Rhizopus sp*, 77 against *Candida* 6, 75, 77 and 81 against *Aspergillus flavus* showed excellent antifungal activity than the standard drug amphotericin B.

**Synthesis, Spectral and Antimicrobial studies of 2,6-bis(9-ethyl-9H-carbazol-3-yl)-3-methylpiperidin-4-one and its derivatives 84-88**

19. 2,6-bis(9-ethyl-9H-carbazol-3-yl)-3-methyl piperidin-4-ones (84) is prepared using one pot multicomponent Mannich reaction by the condensation of ketone, 9-ethyl-9H-carbazole-3-carbaldehyde and ammonium acetate in 1:2:1 ratio using ethanol as a solvent. Compound 84 on reaction with various hydrazides afforded the target compounds 85-87. The compound 84 reacted with hydroxylamine hydrochloride in the presence of acetic acid
afforded the oxime derivative (88). The synthesized compounds (84-88) were confirmed by their IR, $^1$H and $^{13}$C NMR spectral studies.

20. In $^1$H NMR spectrum of 84, the H-2a, H-6a, H-5a, H-5e and NH protons are observed at 3.86, 4.33, 2.92, 2.76 and 1.40 ppm. In $^{13}$C NMR spectrum of 84, the carbon signals observed at 69.1, 62.1, 52.3, 51.7 and 210.5 respectively for C-2, C-6, C-3, C-5 and C=O carbons confirmed the formation of compound 84. HSQC and DEPT spectrum analysis also confirmed the formation of compound 84.

21. $^1$H NMR signals of the NH proton of the piperidine ring appeared at 1.72 ppm and NH protons of thiosemicarbazide moiety observed at 8.57 and 7.62 ppm confirmed the formation of compound 85. The hydrazone NH proton observed at 2.29 ppm (86), 2.15 ppm confirmed the formation of compounds 86 and 87. The oxime N-OH proton observed at 10.91 ppm confirmed the formation of compound 88.

22. In all the hydrazones (85-87), the C-5 carbon is more shielded than the C-3 carbon. This observation revealed that the cyclohexyl ring adopts syn to the C-5 carbon.

23. The $^1$H NMR and $^{13}$C NMR spectral studies indicated that the piperidine ring adopts chair conformation with equatorial orientation of carbazole rings.

24. The observed m/z values 500.2703 for 84, 655.3581 for 85 and 572.3025 for 86 are consistent with the proposed molecular formula of the respective compounds.

25. The in vitro antimicrobial activities revealed that compounds 85, 86 and 88 exhibited good antibacterial activity against *Staphylococcus aureus* and compound 86 showed good antibacterial activity against *Bacillus subtilis*. The antifungal activity revealed that compound 85 against
mucor and 88 against A. Flavus showed good antifungal activity.

Synthesis, Spectral, Antimicrobial and X-ray Crystallographic studies of N-cyclohexyl-2-(2,4-diphenyl-3-azabicyclo[3.3.1]nonan-9-ylidene)hydrazinecarbothioamides 94-98

26. 2,4-diphenyl-3-azabicyclo[3.3.1]nonan-9-ones was treated with N-cyclohexylhydrazinecarbothioamide in the presence of acetic acid, which afforded N-cyclohexyl-2-(2,4-diphenyl-3-azabicyclo[3.3.1]nonan-9-ylidene)hydrazinecarbothioamides 94-98.

27. Appearance of C=N and C=S stretching frequency around at 1550 and 1221 cm⁻¹, respectively confirmed the formation of thiosemicarbazone derivatives.

28. For all the synthesized compounds (94-98), IR and one dimensional NMR (¹H and ¹³C) spectra were recorded and their signals were assigned suitably. In addition HOMOCOSY and NOESY spectrum were recorded for compound 94 to confirm their 1D NMR spectral assignments.

29. The bridgehead proton H-5e is more deshielded than the H-1e proton. The observed deshielding of H-5e proton is due to the interaction with the nitrogen atom of the thiosemicarbazone ring. This revealed that the thiosemicarbazone ring is syn to C-5 carbon.

30. In NOSEY spectrum 94, the nOe between the NH proton of thiosemicarbazone analogue and H-5e proton suggest that the thiosemicarbazone analogue is syn to C-5 carbon.

31. Based on the observed chemical shifts and coupling constant values, twin chair conformation is proposed for the compounds 94-98.
32. In HRMS analysis M⁺ peak observed at 447.2581 (94), 483.2396 (95), 507.2794 (96), 515.1805 (97) and 507.2795 (98) are consistent with the proposed molecular formula of the respective compounds.

33. X-ray crystallographic analysis of 94 revealed that the compound 94 crystallizes in a triclinic system with a space group P1. The ketone condenses with thiosemicabazide resulted a new C=N bond whose bond length is 1.265(7)Å [C3–N2]. The observed dihedral angle between the S1 and N2 is 175.4(5)° [S1–C21–N3–N2]. The torsion angles of phenyl rings C3–C4–C5–C15 and C3–C2–C1–C9 are −177.0(6)° and −178.7(7)°, respectively. Thus, all parameters clearly indicated the twin–chair conformation of the bicyclic system with an equatorial orientation of the phenyl rings. The cyclohexyl ring in the thiosemicarbazone fragment also adopts chair conformation.

34. Antibacterial and antifungal studies against panel of pathogenic strains revealed that compound 95 against *Staphylococcus aureus*, *Klebsiella pneumoniae* and *Salmonella typhi* demonstrated remarkable antibacterial inhibition at a minimum concentration of 12.5µg/mL.

35. The antifungal studies concluded that compounds 95 and 98 registered excellent antifungal activities against all the fungal strains with minimum concentration of 6.5-12.5 µg/mL.
Synthesis and Spectral Characterization of 2,4-bis(4-((trimethylsilyl)ethynyl)phenyl)-3-azabicyclo[3.3.1]nonan-9-ones and their derivatives (99-103)

36. 2,4-bis(4-((trimethylsilyl)ethynyl)phenyl)-3-azabicyclo[3.3.1]nonan-9-one (99) on reaction with various hydrazides afforded the target compounds 101-103. Further the compounds 99 on reaction with hydroxylamine hydrochloride in the presence of sodium acetate trihydrate afforded the oxime derivatives 100.

37. For all the synthesized compounds (100-104), IR and one dimensional NMR spectra were recorded and their signals were assigned suitably. The HSQC spectrum was recorded for compound 99 to confirm the 1D NMR spectral assignments.

38. In $^1$H NMR spectrum of compound 99, the signals observed at 4.38, 2.44 and 1.68 ppm are respectively assigned for H-2 & H-4, H-1e & H-5e and NH protons of ABN system. Further in $^{13}$C NMR spectrum of 99, the signals observed at 64.4, 53.7, 104.7 and 210.5 are assigned for C-2 & C-4, C-1 & C-5, C≡C, C=O carbons, respectively. $^1$H and $^{13}$C NMR spectral studies confirmed the formation of 99.

39. The observed chemical shift values of H-5e & H-1e and C-3 & C-5 carbons revealed that hydrazone analogue of compounds 100-104 adopts syn to C-5 carbon atoms. The observed $^1$H and $^{13}$C NMR chemical shift values concluded that the bicyclic system adopted twin chair confirmation.

40. The observed $m/z$ values 484.2494 ($M^+$) for 99, 556.2814 ($M^+$) for 101 and 639.3374 ($M^+$) for 103 are consistence with the proposed molecular formula of the respective compounds.
Synthesis, Spectral and X-ray Crystallographic studies of Alkyl 2-(2,4-diaryl-3-azabicyclo[3.3.1]nonan-9-ylidene) hydrazinecarboxylates (111-117).

41. Reaction of 2,4-diaryl-3-azabicyclo[3.3.1]nonan-9-ones reacting with alkyl carbazate in the presence of acetic acid afforded the target compounds 111-117.

42. IR spectrum of the synthesized compounds (111-117) showed the C=O stretching frequencies in the region of 1692-1736 cm\(^{-1}\) and the NH stretching frequencies in the region of 3025-3314 cm\(^{-1}\) confirmed the formation of target compounds 111-117.

43. The synthesized compounds 111-117 were confirmed by their IR, \(^1\)H NMR and \(^{13}\)C spectral studies.

44. The observed m/z values 364.2025 (M\(^+\)) for 111, 400.1835 (M\(^+\)) for 112, 424.2234 (M\(^+\)) for 114, 378.2180 (M\(^+\)) for 115 and 414.1995 (M\(^+\)) for 116 and 438.2397 (M\(^+\)) for 117 are consistent with the proposed molecular formula of the respective compounds.

45. The single crystal XRD analysis of compound 113 revealed that the compound 113 crystallized in monoclinic system with C2/C space group with unit cell parameters \(a = 19.751\ (6)\) Å, \(b = 7.087\ (2)\) Å, \(c = 28.492\ (9)\) Å, \(\alpha = 90^\circ\), \(\beta = 102.997^\circ\) and \(\gamma = 90^\circ\). The observed dihedral angle between O2 and N3 is -179.1 [O2-C12-N5-N3]. The torsion angles of phenyl rings C3-C2-C1-C9 and C3-C4-C5-C15 are 178.9 and 179.7, respectively.

46. The signal position and splitting patterns of the synthesized compounds 111-117 and XRD analysis of 113 clearly indicated the twin-chair conformation of the bicyclic system with an equatorial orientation of the phenyl rings.