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SPECTRAL, CONFORMATIONAL AND DOCKING STUDIES OF FURYL SUBSTITUTED HETEROCYCLIC COMPOUNDS

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ABSTRACT

A series of *N*-formyl-*t*(3),*t*(5)-dimethyl-r(2),*c*(6)-bis(2'-furyl)piperidin-4-one 1, *N*-acetyl-*t*(3),*t*(5)-dimethyl-r(2),*c*(6)-bis(2'-furyl)piperidin-4-one 2, *N*-propanoyl-*t*(3),*t*(5)-dimethyl-r(2),*c*(6)-bis(2'-furyl)piperidin-4-one 3, *N*-benzoyl-*t*(3),*t*(5)-dimethyl-r(2),*c*(6)-bis(2'-furyl)piperidin-4-one 4 have been synthesized and analyzed by ^{1}H and ^{13}C spectra at room temperature as well as low temperatures (30, 0, -15°C). For the symmetrical N-acyl-3,5-dimethyl derivatives, isochronous signals are observed at room temperature as well as low temperatures. Only at low temperatures, were the well-resolved signals observed. ^{1}H and ^{13}C spectra were obtained for the above series of compounds at -15ºC to confirm the signals. The structure of the compound was determined based on the coupling constant values, and the preferred conformation for compounds 1-4 was found to be boat form B_5, In docking studies, compounds 3 and 4 showed a strong hydrogen bond interaction with reference also compared with hydrophobic interactions, these two compounds have an ability to inhibit the protein.

Keywords: Conformational Studies, Furylpiperidin-4-Ones, Anisochronous Signals, Docking Studies, ^{1}H And ^{13}C NMR Spectrum.

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INTRODUCTION

It is known that nitrogen-containing heterocyclic compounds exhibit a wide variety of biological activities.[1] NMR spectroscopy is useful for studying most of the heterocyclic compounds.[2-6] Substituted alkyl piperidin-4-ones and their oxime derivatives, hydrozones, and azine derivatives reported by Manimekalai *et al.*[7] This paper also explained the conformational effect on chemical shift and coupling constant values. Reports state that N-benzoyl-t (3)-alkyl-piperidin-4-one possesses antifungal and antibacterial properties.[8] It is also reported that N-Nitroso-*t* (3)-alkyl-oxime derivatives.[9-10] *N*-acyl- oxime derivatives reported by Manimekalai *et al.*[11] Pharmaceutical applications of synthetic and natural piperidines are discussed.[12] Piperidines are used in the field of drug delivery applications.[13-14] At present studies acylation of precursor 5 to give compounds 1-4, analyzed and confirmed by ^{1}H, ^{13}C NMR spectrum. This paper also explains the conformational and docking studies of compounds 1-4.

EXPERIMENTAL

The precursor 5 was prepared by standard procedure.[15] Charged 0.05 mole of ammonium acetate, 0.01 mole of furfuraldehyde, and 0.05 mole of pentan-3-one in ethanol medium. The reaction mass continued to remain stirring until the completion of the reaction. After the reaction has concluded, concentrated sulfuric acid is added to the reaction mass. The piperidone hydrochloride salts were then filtered and aqueous ammonia was used to neutralize them. Diethyl ether was then used to filter and wash the compound. Yield:70%, m.p. 40ºC. The following procedure was used to prepare Compound 1.[16] At 0 - 5^{0}C, formic

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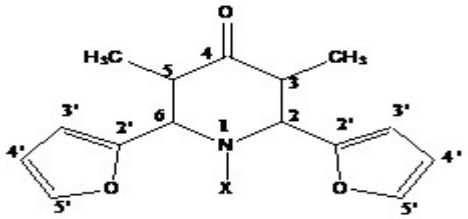
acid and acetic anhydride were added. Afterward, the temperature was raised to 60°C and kept there for 30 minutes at 55–65°C. Then the above solution was added to parent piperidone 5 in benzene solution. The reaction mass was kept constant while stirring. The compound 1 was obtained by distilling out the solvent. 1: Yield: 65%, m.p. 38ºC. The remaining compounds 2-4 were prepared by the following procedures.[17] Charged 0.01 mole of acylating reagents and 0.01 mole of parent piperidone followed by 0.01 mole of triethylamine in benzene. The reaction mass was kept constant while stirring. Once the reaction was complete, the product was obtained by concentrating the reaction mass. 2: Yield: 30-40%, melting point. 116ºC 3: Product %: 40-50%; m.p. 115ºC, 4: Output: 55-65%; m.p. 154ºC.

RESULTS AND DISCUSSION

Analysis of Chemical Shifts

Proton NMR spectra of 1-4 have been recorded in $CDCl_3$ at -15ºC. The anisochronous signals were obtained in compounds 1-4 (Fig.-1). The ^1H NMR chemical shift values and coupling constant values are shown in Table-1. The ^{13}C chemical shifts are displayed in Table-2.



X
1; CHO
2; COCH3
3; COCH2CH3
4; COC6H5

Fig.-1

α –Protons

Table-1 reveals the acylation effect of 1-4. The α protons of 1-4 with the parent compound of 5 reveal that N-acylation causes the resonances of 2, and 6 positions to move downfield (to higher frequency) considerably. Furyl substituted heterocyclic compounds 1-4, the deshielding magnitude observed for *anti* α proton (+0.94 ppm). However, for *syn* α proton considerable difference in the deshielding magnitude is observed (+1.52 ppm).

β-Protons

Table-1 also reveals the acylation effect observed on the β protons. The deshielding magnitude showed on syn β and anti β for 1-4.

Conformational Studies

The coupling constant and dihedral angle values are different from normal chair conformation (Table-3), we concluded the favoured conformation for compounds 1-4 is found to be in boat form B_5. The various possible conformations of compound 4 are shown in Scheme-1.

Table-1: Proton NMR Spectra of 1-4 and their Precursor 5

Organic Molecule	H(2) syn α	H(3) syn β	H(5) anti β	H(6) anti α	Alkyl protons	Formyl protons	Aromatic protons
1	5.27 (d, 6.47)	3.17 – 3.28	3.17 – 3.28	4.69 (d, 5.20)	1.09 (d, 6.96) (*syn*) 1.05 (d, 6.83) (*anti*)	8.27	6.12 (1H) 6.27 (1H) 6.19 (2H) 7.14 (1H) 7.28 (1H)
2	5.61 (d, 6.36)	3.25 – 3.28	3.25 – 3.28	4.89 (d, 4.68)	1.19 (d, 6.64) (*syn*) 1.06 (d, 6.55) (*anti*)	2.21	6.01 (1H) 6.15 (1H) 6.27 (1H) 6.31 (1H) 7.21 (1H) 7.29 (1H)

3	5.60 (d, 6.27)	3.21 – 3.24	3.21 – 3.24	4.91 (d, 4.79)	1.14 (d, 6.39) (*syn*) 1.00 (d, 6.40) (*anti*)	1.06 (t, 6.92) ($COCH_2\mathbf{CH_3}$) 2.35 – 2.44 ($CO\mathbf{CH_2}CH_3$)	5.96 (2H) 6.12 (1H) 6.21-6.24 (1H) 7.16 (1H) 7.23 (1H)
4	5.46 (d, 11.02)	3.34	3.11	5.08 (s)	1.12 (d, 6.40) (*syn*) 0.97 (d, 5.31) (*anti*)	_	6.31 (1H) 6.36 (2H) 6.43 (1H) 7.27 (1H) 7.35-7.41, 7.56-7.58 (COC_6H_5)
5	3.75 (d, 10.74)	2.94	2.94	3.75 (d, 10.74)	0.91 (d, 6.83)	_	6.27 H(3′) and H(3″) 6.32 H(4′) and H(4″) 7.38 H(5′) and H(5″)

Table-2: Carbon NMR of N-Acylpiperidin-4-ones 1-4 and Starting Material 5

Organic Molecule	C(2) syn α	C(3) syn β	C(4)	C(5) anti β	C(6) anti α	Alkyl carbons	Acyl carbons
1	52.04	43.87	209.88	44.44	56.97	14.21 (*syn*) 14.37 (*anti*)	163.09
2	53.18	44.42	210.70	45.03	58.03	14.10 (*syn* CH_3) 14.47 (*anti* CH_3)	22.45 ($COCH_3$) 171.32 ($COCH_3$)
3	53.32	44.38	210.16	44.98	56.87	13.98 (*syn* CH_3) 14.39 (*anti* CH_3)	9.40 ($COCH_2CH_3$) 26.73 ($COCH_2CH_3$) 174.28 ($COCH_2CH_3$)
4	54.11	43.30	210.73	45.70	58.50	12.52 (*syn* CH_3) 15.47 (*anti* CH_3)	172.80
5	61.11	49.60	209.68	49.60	61.11	10.47	_

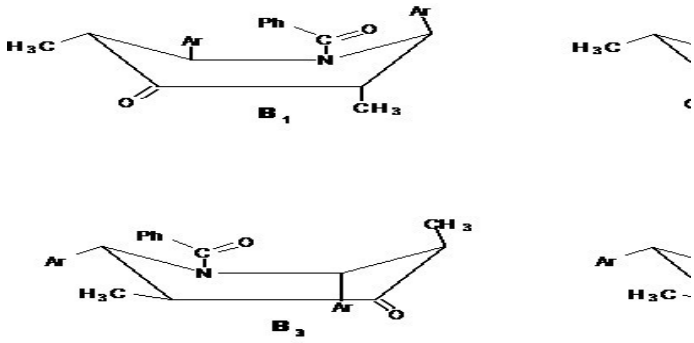
Table-3: Observed Coupling Constant (Hz) of 1-4

Compound	$J_{\alpha\text{-}\beta}$ (*syn*)	$J_{\alpha\text{-}\beta}$ (*anti*)	$J_{H,\ CH_3}$ (*syn*)	$J_{H,\ CH_3}$ (*anti*)
1	6.47	5.20	6.96	6.83
2	6.36	4.68	6.64	6.55
3	6.27	4.79	6.39	6.40
4	11.02	-	6.40	5.31

Docking Studies

The synthesized compounds 1, 2, 3, and 4 underwent the molecular docking study. The structure-based drug design approach gives an idea about above-said molecules have drug ability or not. We synthesized piperidone derivatives, which have antibacterial, anticancer, and antioxidant activities.[18-20] Herein we concentrate on cancer, hence, the related target protein (PDB 3EQM) was directly downloaded from RCSB with 4-Androstene-3-17-dione (ASD) for our docking study.[21] Molecular docking study performed through the Glide (Schrodinger 2018 Platform). *Protein preparation* wizard and *LigPrep* tool were used

to prepare both protein and compounds, respectively. Before performing a docking study, we validate the docking method by the redocking procedure. Hence, retrieve the ASD from the protein active site and restock the in-active site. The docked pose and protein pose were superimposed; it showed the RMSD value of 0.90 Fig.-2.



Possible conformations of 1
Scheme-1

Hence, we confirm the docking tool is good for further study. After docking the compounds 1 to 4, which are utilized for redocking. Of the 4 compounds, 3 docked within the active region of the protein, and compound 2 did not indicate any docking poses at the protein's active site. The redocked structure ASD (reference) showed a Glide score of -7.901 and it is stabilized in the active by forming the hydrogen bond interaction with Met 437(Fig.-3a) and hydrophobic interaction Fig.-3b. Compound 1 scored -3.871 and it doesn't show any bond with the protein active site but it stabilized in the active site through the hydrophobic interaction (Fig.-4a) with phe430, lys440,gly439,ala438,cys437,gly436, etc., Fig.-4b. Carbonyl oxygen and furfurylidene oxygen of compound 3 (Glide score -4.431) make a strong two hydrogen bond with Ala438 in the active site Fig.-4c, this interaction confirmed the very strong position in the active site. Further, the hydrophobic interactions are shown in the Fig.-4d. Furfurylidene oxygen of compound 4 (Glide score -3.593) showed the hydrogen bond interaction with Ala438 Fig.-4e as well as hydrophobic interactions Fig.-4f were confirmed strong position in the active site. While comparing compounds with reference, compounds 3 and 4 showed a strong hydrogen bond interaction as like as reference one also compares with hydrophobic interactions, these 2 compounds can inhibit the protein. Hence, we recommended these two compounds be further studied in *vitro.*

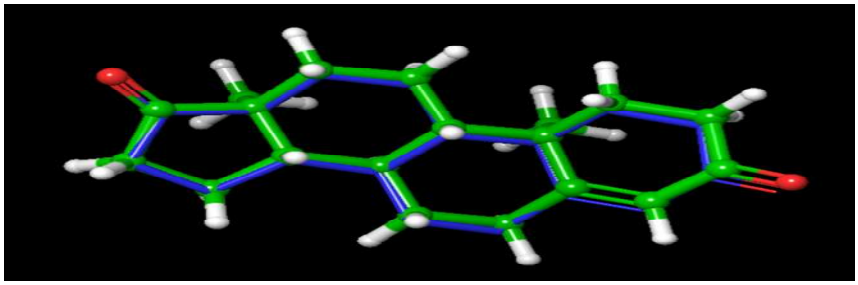


Fig.-2: Superimposed of Docked Pose and Protein Pose

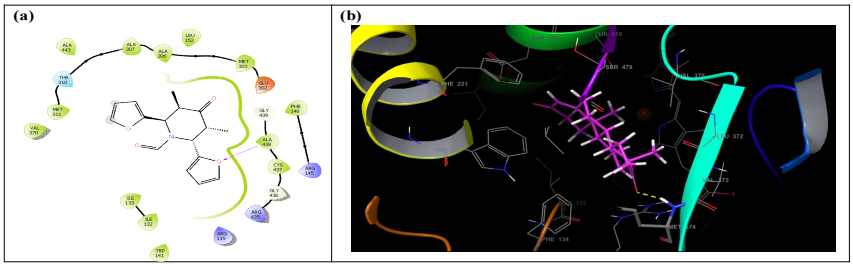


Fig.-3: (a) and (b) Molecular Interaction of ASD with Catalytically Important Residues

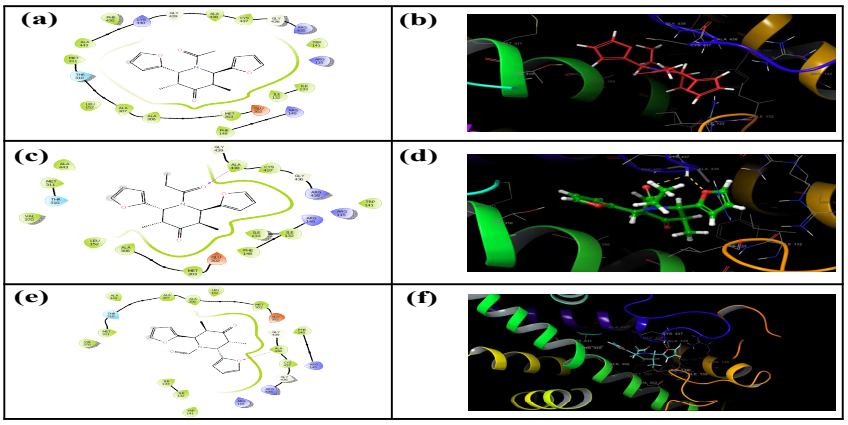


Fig.-4: Various Active and Binding Modes of **1-4**

CONCLUSION

The N-acyl-3,5-dimethyl derivatives 1-4 are analyzed at room temperature as well as at low temperatures. The well-resolved signals were obtained at low temperatures only (-15ºC). ^{1}H and ^{13}C spectrum was recorded at -15ºC for 1-4 and also calculated coupling constant values. The possible conformation for N-acyl derivatives 1-4 is found to be B_5 where distortion occurs to some extent. The observed coupling constants suggest boat form B_5 for compounds 1-4. Based on the molecular docking studies, compounds 3 and 4 showed strong hydrogen bond interaction as like as reference one also compares with hydrophobic interactions, these two compounds can inhibit the protein.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

All the authors contributed significantly to this manuscript, participated in reviewing/editing, and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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