Chapter. 3

Synthesis of Analogues of Epibatidine

"Where nature finishes producing its own species man begins, using natural things and in harmony with this very nature, to create an infinity of species."

J. -M. Lehn.

1. Introduction

(±)-Epibatidine (1), isolated from the skin extracts of poison frog, Epipedobates Tricolor, is found to be a potent analgesic about 200-500 times more potent than that of morphine, whose mode of action is suggested to involve non-opiod mechanism due to its indifference towards naloxone. Further studies have found 1 to have potent antinociceptive activity due to activation of central nicotinic receptors. Both the antipodes [(+) as well as (-)] of 1 showed selectivity for central neuronal α2β2 and ganglionic α3β4 nicotinic receptors, unlike other nicotinic receptors viz. Anatoxin-a. These pharmacological properties have led to recognise Epibatidine as a therapeutically important drug target.

However, Epibatidine is found to be highly toxic causing death in mice (six out of six) when injected at 10 μl/kg scale. This high toxicity of 1 has become major concern towards the therapeutic development of 1. Thus, the high affinity of 1 towards central nicotinic receptors and its non-compliance with current nicotine receptor pharmacophore model suggests that a new nicotine receptor pharmacophore needs to be developed. As a result there is a renewed interest towards searching a pharmacophore related to the structure of 1, that would exhibit
pharmacological properties similar to 1 but with better ratios of pharmacological to toxicological activity. In this direction, chemist and pharmacologist have begun perceiving compounds analogous to 1 by

- altering, extending or cleaving the 7-azabicyclo(2.21)heptane framework of 1, keeping the pyridyl moiety intact;
- adding extra functionalities in the original framework of 1 along with the features described above or
- keeping in view the earlier known alkaloids having high affinity towards nicotinic receptors and then designing a molecule having a combination of structural features of both the earlier known alkaloid and 1, and study their activity.

Utilizing the above mentioned parameters few groups have synthesized a variety of new pharmacophore (Fig.1) analogous to 1 and have studied their pharmacological properties in comparison to 1, also evaluating their toxicity at the same time.

Fig. 1

Homoepibatidine (2)

Activity: Weaker Analgesic than 1.
Toxicity: Not reported.

3-Oxo-Homoepibatidine (3)

Activity: Inactive.
Toxicity: Not reported.
Desethyl Epibatidine (4)

Activity: Inactive.

Toxicity: Not reported.

Bis-Homoepibatidine (5)

Activity: Inactive.

Toxicity: Not reported.

UB-165 (6)

Activity: Potent nicotinic receptor ligand.

Toxicity: Not reported

(1R, 2S, 5S)-2-(2-chloro-5-pyridinyl)-8-azabicyclo(3.2.1)octane (7)

Activity: Nicotinic receptor and stimulant.

Toxicity: Not reported.

Epiboxidine (8)

Activity: Potent nicotinic receptor agonist and ten fold less potent than 1 as antinociceptive agent.

Toxicity: Twenty fold less toxic than 1.
2. Synthetic Approaches towards Epibatidine Analogues.

Synthetic approaches reported so far towards analogues of Epibatidine have utilized the reductive coupling of 6-chloro-3-iodo-pyridine (9) or its metalated derivatives with the corresponding X-azabicyclo(m.2.1)alkene ring system.

Bai et al\textsuperscript{21} have synthesized Homoepibatidine (2) and its 3-oxo derivative 3 along with its nicotine related analogue (Scheme 1), Desethyl epibatidine (4), in their pursuit for a better pharmacophore and evaluated its activity.

Scheme 1

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {\includegraphics[width=0.8\textwidth]{scheme1.png}};
\node (b) at (a) {\textbf{Scheme 1}};
\end{tikzpicture}
\end{center}

\textit{Reagents and conditions:} i) NH\textsubscript{2}NH\textsubscript{2}, H\textsubscript{2}O, Ethanol, KOH, 100 °C, 3h.; ii) DHP, p-TsOH, DCM (90%); iii) CICO\textsubscript{2}Et, CHCl\textsubscript{3}, Δ, 2h; iv) PPTs, ethanol, Δ, 5h (97%); v) MsCl, pyridine, 24h, (93%); vi) DBU, Collidine, Δ, 8h (79%); vii) (PPh\textsubscript{3})\textsubscript{2}Pd(OAc)	extsubscript{2}, 9, piperidine, DMF, 70 °C, 5h (75%); viii) TMSI, DCM, 0 °C (95%).
Homoepibatidine (2) was synthesized starting from commercially available 6β-hydroxy tropionone (10). Wolff-Kisner reduction of 10 followed by the protection of the hydroxyl group and demethylation with ethyl chloroformate afforded carbamate 12. Deprotection of the hydroxyl group and its elimination via mesylate 13, in refluxing collidine gave the crucial precursor 14 in 79 % yield (Scheme 1). Usual stereoselective reductive palladium catalysed coupling of 14 with 9 followed by cleavage of the carbamate moiety with TMSI yielded 2, which has also been converted to its N-Methyl and N-iPropyl derivatives 2a and 2b, respectively, by reductive amination of formaldehyde and acetone, respectively.

Scheme 2

Reagents and conditions: i) Ac₂O, Et₃N, THF; ii) ClCO₂Et, CHCl₃, Δ, 2 h (90%); iii) (CH₂OH)₂, p-TsOH, benzene, Δ, 12 h (92%); iv) 3N NaOH, MeOH, 6 h (96%); v) MsCl, Et₃N, DCM, 0 °C, 1 h (97%); vi) DBU, toluene, Δ, 56 h (67%); vii) (Ph₃P)₂Pd(OAc)₂, 9, DMF, piperidine, 70 °C, 5 h (70%); viii) HBr, AcOH, 60 h (70%).
3-Oxohomoepibatidine (3) is also prepared\textsuperscript{21} from 10 by protecting the keto group as 1,3-dioxalan after acetylation and demethylation. Further synthetic transformation as described for 2, by the same authors, afforded 3 as shown in Scheme 2.

Desethyl epibatidine (4), nicotine related analogue, is prepared\textsuperscript{21} from N-carboethoxy-3-pyrroline (20) by reductive coupling with 9 followed by the hydrogenation over Pd/C and the cleavage of carbamate moiety (Scheme 3).

**Scheme 3**

\[ \text{Reagents and conditions: } i) \text{ 9, } \text{Pd(OAc)}_2, n-\text{Bu}_4\text{Br, KOAc, DMF, 40 }^\circ\text{C, 4 d (62%); } ii) \text{ Pd/C, H}_2; iii) TMSI, CH}_2\text{Cl}_2 \]

Pharmacological studies\textsuperscript{21} with 2, 3 and 5, showed marked analgesic effect with 2 at a dose of 40 \( \mu \text{g/kg} \) comparable to that exhibited by 1 at 10 \( \mu \text{g/kg} \). N-Methyl derivative 2a showed similar analgesic activity to that of 2, whereas N-Pr derivative 2b was less active and imparted analgesia at a higher dose of 190 \( \mu \text{g/kg} \). However the 3-oxo derivative 3 and nicotinic analogue exhibited no activity even at a dose of 4 mg/kg. Toxicity data of these molecules, however, are not reported.

Malpass et al\textsuperscript{22} have also synthesized Homoepibatidine (2) and Bis-homoepibatine (5) by a protocol earlier developed in their laboratory for the
construction of azabicyclic ring system. Crucial precursors 30 and 35 are prepared from cyclohepta-1,3-diene (23) and cycloocta-1,3-diene (31) by [4+2]-cycloaddition with nitroso derivatives followed by further synthetic manipulations as shown in Scheme 4 and Scheme 5.

The overall yields during the synthesis of 2 were improved by transforming the olefin functionality in 25 to epoxide before carrying out intramolecular trans-annular nucleophilic ring closure reaction. Regeneration of the olefin was achieved by deoxygenating the epoxide in 29 using Zn-Cu couple (Scheme 4).

Scheme 4

Reagents and conditions: i) CBZN=O, Δ; ii) Na/Hg, MeOH (95%); iii) CrO3, pyridine iv) m-CPBA, DCM, O°C; v) NaBH₄, MeOH; vi) n-BuLi, p-TsCl, THF; vii) NaH, THF (93%); viii) Zn/Cu, EtOH, 150 °C, 48 h (77%); ix) Pd(PPh₃)₄, DMF, piperidine, HCO₂H, 75 °C, 24 h (63%); x) TMSI, CH₂Cl₂, rt.

However, the synthesis of 5 did not require epoxidation of the olefinic moiety in 33 and instead, involved the bromination of hydroxyl group in 33 with thionyl
bromide followed by intramolecular trans-annular nucleophilic ring closure in refluxing collidine (Scheme 5).

**Scheme 5**

![Scheme 5](image)

**Reagents and conditions:** i) MeN=O, Δ; ii) Na/Hg, MeOH; iii) SOBr₂; iv) TMP, Δ; v) α-Chloroethyl chloroformate, EDC, Δ; vi) MeOH, Δ (99%); vii) CBZCl, NEt₃ (57%); viii) Pd(PPh₃)₄, DMF, piperidine, HCOOH, 75 °C, 24 h (53%); ix) TMSI.

Activity and toxicity of 5 is hitherto not reported.

UB-165 (6) a hybrid analogue of Anatoxin-a and 1, has been synthesized by Gallgher et al.²³ by combining the bulky 8-azabicyclo(4.2.1)nonane moiety of anatoxin-a with the pyridyl unit, a known hydrogen bond acceptor component in the general pharmacophore model, of epibatidine and possessing absolute configuration of natural Anatoxin-a. Synthesis of UB-165 utilized a protocol reported by Wiseman and Lee²⁴ for the preparation of precursor azabicyclic ketone 39 from cis-1,5-cyclooctanediol (37) (Scheme 6). Racemic 39 was resolved using (-)-dibenzoyl
tartarate to obtain pure enantiomers. Both (+) and (-) - 39 were independently transformed to UB-165 by employing a sequence of synthetic transformation.

Scheme 6

\[ \text{Reagents and conditions: } i) \text{ CrO}_3 (1 \text{ eq}), \text{ H}_2\text{SO}_4, \text{ acetone}; \text{ ii) 40\% aq. CH}_3\text{NH}_2, \text{ TsOH, 100 °C, 2 d}; \text{ iii) Pyr.HBr.Br}_2, \text{ AcOH, 115 °C, 15 h}; \text{ iv) (−)-Dibenzoyl tartarate, EtOH, Δ; v) Vinyl chloroformate, K}_2\text{CO}_3, \text{ CH}_2\text{Cl}_2; \text{ vi) KHMDS, 2-NTf}_2-5\text{-chloro-pyridine, THF, -78°C; vii) 9, n-BuLi, THF, ZnCl}_2, \text{ Pd(PPh}_3)_4; \text{ viii) HCl, aq. dioxan, Δ.} \]

Trudell and co-workers\textsuperscript{25} have synthesized both 2α- and 2β-isomers of 7 in enantiomerically pure forms using (1R)-2-tropionone 44 as a starting precursor (Scheme 7). 44 is transformed to 45 by reductive palladium catalyzed coupling of its enol triflate to 2-methoxy-pyridinyl zinc chloride. Demethylation followed by hydrogenation yielded 46 as a 10:1 mixture of α- and β-isomers. Methoxy group in 46 is converted to chloro substituent using Vilsmeier conditions and later the carbamate moiety cleaved with trimethylsilyl iodide to give 7.
Reagents and conditions: i) HCl, Δ; ii) (PhO)₂PON₃, DMAP, 10% HCl (78%); iii) NaHMDS, THF, -78 °C, PhNTf₂ (96%); iv) 2-methoxy-5-pyridinyl zinc chloride, Pd(OAc)₉, dppb, THF, Δ (93%); v) CICO₂Et, KMnO₄, benzene, Δ (76%); vi) 10% Pd/C, H₂, 1%OH:10% HCl (10:1) (96%); vii) POCl₃, DMF, 100 °C (48%); viii) TMSI, CH₂Cl₂ (90%).

Stimulant activity (arterial pressure response) in vivo for both α and β-7 is found to be 30-100 fold less potent than (±)-1. The nicotinic receptor binding ability of 7 to displace [³H]-1 is significantly lower than that of (±)-1.

Epiboxidine (8), a methyl isoxazole analogue (where the pyridyl unit is replaced by methyl isoxazole ring), was devised and synthesized by Daly et al²⁰ by taking a clue from ABT 418, well known nicotinic receptor agonist. The key 7-aza bicyclic precursor 49 was prepared by employing a protocol developed by Bai et al²¹ via Favorskii rearrangement of tropinone. Isoxazole ring was constructed from the ester moiety via the acetone oxime, by a reported procedure²⁶ (Scheme 8).
Reagents and conditions: i) \((\text{CH}_3)_2\text{C}=\text{N-OH}\) (1 eq), n-BuLi (2 eq), THF, -78 °C; ii) Conc. Hcl; iii) 100 °C (47%).

Epiboxidine (8) is found to be five fold less potent than 1 and 30 fold more potent than ABT 418 in TE671 cells with \(\alpha_1\beta_1\gamma_6\) nicotinic receptors. In a hot plate antinociceptive assay with mice, 8 was about 10 fold less potent than 1. However, 8 was much less toxic than 1 in mice.
3. Results and Discussion

Keeping in pace with the above mentioned recent upsurge in designing a novel pharmacophore, related to 1, having a better ratio of pharmacological to toxicological activity, we have also extended the scope of our methodology for the synthesis of X-azabicyclo(m.2.1)alkane framework towards this purpose.

Earlier results, described in Chapter 2, have demonstrated the retention of olefin geometry of the dipolarophile and the exo-selectivity for the electron withdrawing substituent in the [3+2] cycloaddition processes. These salient feature of the cycloaddition processes are utilized towards the synthesis of various endo/exo analogues of 1. Thus, in this direction, we chose to introduce various functionality in the 7-azabicyclic framework in addition to 6-chloro-3-pyridyl moiety by tethering vinyl pyridine 55 to various electron withdrawing moieties (Scheme 9) and

Scheme 9
performing their cycloaddition with pyrrolidine or piperidine based azomethine ylide 54 towards the synthesis of analogues of Epibatidine.

Thus, the synthesis of substituted epibatidines and Homoepibatidine was undertaken.

3.1. Synthesis of Cyano Substituted Epibatidine: 7-Benzyl-2-(6-choro-3-pyridyl)-3-cyano-7-azabicyclo(2.2.1)heptane

For the synthesis of 63, 64, 65 and 66, 3-(6-chloro-3-pyridyl)-propionitrile (60 and 61) was required. Wittig olefination of 56 with cyanomethylene triphenyl phosphorane in acetonitrile at reflux for 11 h (Scheme 10) afforded a 1:1 mixture of trans-60 and cis-61. The synthesis of azomethine ylide precursor 62 is already described in detail in Chapter 2.

Towards the synthesis of nitrile substituted epibatidines the cycloadditions of trans-60 and cis-61 with 62 were carried out as follows:

3.1.1. Cycloaddition of 60 and 62:

The cycloaddition was carried out by the addition of 62 to the stirring solution of Ag(I)F and 60 in dichloromethane, in the identical manner as described in Chapter II, Section 4.3. After the completion of the reaction, mixture was filtered through a plug of celite and the residue obtained was purified by silica gel column
chromatography, eluting with hexane:EtOAc (8:2) to afford minor diastereomer 64 (18%) as a yellow oil. Further elution with the same eluent gave major diastereomer 63 (45%) as a yellow oil (Scheme 11). Both diastereomers are characterised by IR, $^1$H NMR, $^{13}$C NMR and mass spectral analyses and their respective stereochemistries are assigned on the similar basis as mentioned in Chapter 2 for the corresponding ester analogues.

**Scheme 11**

3.1.1.1. Spectral Analysis of Major Cycloadduct 63:

IR spectrum indicated the presence of nitrile moiety as a weak absorption band at 2221 cm$^{-1}$ along with other bands at 1462 and 1107 cm$^{-1}$ (Fig 3).

$^1$H NMR spectrum displayed a multiplet between $\delta$ 1.40-1.52, integrating for two protons, corresponds to $H_{\text{endo}}$ and $H_{\text{endo}}$. Two multiplets appearing between $\delta$ 1.70-1.90 and 1.95-2.15, integrating for one proton each, could be attributed to either of $H_{\text{exo}}$ and/or $H_{\text{exo}}$. Two diagnostic signals at $\delta$ 2.65 and $\delta$ 3.65, equivalent to one proton each, as a doublet ($J = 5.94$ Hz) and a triplet ($J = 4.15$ Hz) corresponds to $H_{\text{endo}}$ and $H_{\text{exo}}$, respectively. A multiplet overlapping with singlet at $\delta$ 3.75, integrating for four protons, is attributed to the two benzylic protons and bridgehead...
H$_1$ and H$_4$ protons together. A broad multiplet appearing between $\delta$ 7.25-7.5, integrating for seven protons, is characterized to five aromatic protons of phenyl moiety and H$_4'$ and H$_5$ of pyridyl moiety. A doublet at $\delta$ 8.25 ($J = 2.46$ Hz) corresponds to H$_2'$ of pyridyl moiety (Fig 2).

The above $^1$H NMR spectral analyses clearly indicates that the coupling of H$_3$ proton at $\delta$ 2.65 (d, $J = 5.94$ Hz) is observed only with the adjacent H$_2$ proton at $\delta$ 3.65 (t, $J = 4.15, 5.58$ Hz) and not with the bridgehead H$_4$. H$_2$ is found to couple with bridgehead H$_1$ proton at $\delta$ 3.75. This pattern of coupling suggested exo-orientation for the nitrile moiety and endo-orientation for the chloro pyridyl moiety. Hence, the structure and stereochemistry of 63 is assigned as 7-benzyl-2-endo-(6-chloro-3-pyridyl)-3-exo-cyano-7-azabicyclo(2.2.1)heptane.

$^{13}$C NMR spectrum revealed the presence of a total seven signals upfield at $\delta$ 20.5, 27.2, 36.6, 49.9, 51.2, 63.5 and 64.4 for the azabicyclic part and ten signals downfield at $\delta$ 121.4, 124.0, 127.1, 128.1, 128.3, 132.2, 137.9, 138.5, 148.7 and 150.1 for the aromatic and nitrile moieties (Fig. 2). INEPT experiment revealed the existence of C$_3$ and C$_6$ methylene carbons at $\delta$ 20.5 and 27.2 and methylene carbon of benzylic moiety (NCH$_2$Ph) at $\delta$ 51.2. C$_3$, C$_2$, C$_1$ and C$_4$ methine carbons are observed at $\delta$ 36.6, 49.9, 63.5 and 64.4, respectively. Quarternary carbon of nitrile moiety was observed at $\delta$ 150.1 and rest of the downfield signals are accountable to the aromatic carbons of phenyl and pyridyl moieties.
Mass spectrum revealed the molecular ion peak at 323 (1) and a base peak at 91 alongwith other prominent fragments at 159 (34), 140 (55), 126 (54), 105 (39) and 83 (55) (Fig 3).

**3.1.1.2. Spectral Analysis of Minor Cycloadduct 64:**

IR spectrum of 64 revealed the presence of nitrile group at 2400 cm⁻¹.

¹H NMR spectrum displayed two multiplets between δ 1.55-1.70 and δ 2.00-2.15, integrating for one and three protons, respectively, attributable to H₅exo, H₅endo, H₆exo and H₆endo protons, respectively. A doublet of doublet appearing at δ 2.85 (J = 4.76, 9.73 Hz), equivalent to two protons, is characterised to H₂endo and H₂exo. Two singlets observed at δ 3.30 and δ 3.65, corresponding to one proton each, is assigned to bridgehead H₁ and H₄ protons, respectively. Another singlet at δ 3.55, integrating for two protons, corresponds to the two benzylic protons. A broad multiplet between δ 7.25-7.45, integrating for six protons, corresponds to the five aromatic protons of the phenyl moiety and H₅' proton of pyridyl moiety. A doublet of doublet at δ 7.58 (J = 2.45, 8.24 Hz, 1H) and a doublet at δ 8.45 (J = 2.45 Hz, 1H) corresponds to H₄' and H₂ protons, respectively.

Based on the above spectral analysis the structure and stereochemistry for compound 64 can be assigned as 7-benzyl-2-exo-(6-chloro-3-pyridyl)-3-endocyan-7-azabicyclo(2.2.1)heptane.

¹³C NMR revealed seven carbon signals upfield at δ 22.0, 26.8, 41.4, 51.2, 51.7, 61.59 and 65.7 and nine signals downfield at δ 119.9, 124.0, 127.3, 128.4, 128.5, 137.5, 138.4, 148.5 and 150.2. INEPT experiment revealed the presence of C₅ and C₆.
methylenic carbons at δ 22.0 and δ 26.8 while C₂ and C₃ methine carbons appeared at δ 41.4 and δ 51.2, respectively. The benzylic carbon was observed at δ 51.7 and the two bridgehead carbons C₁ and C₄ at δ 61.59 and δ 65.7. Rest of the downfield carbon signals corresponds to pyridyl and phenyl ring carbons along with a quaternary nitrile carbon signal at δ 150.2.

3.1.2. Cycloaddition of 61 with 62:

Cycloaddition of 61 with 62 was carried out by following the same experimental protocol as described previously with 60 (Scheme 11). Silica gel column chromatographic purification afforded the major diastereomer 65 (55%) and the minor diastereomer 66 (13%) as a pale yellow oil (Scheme 12).

Scheme 12

\[ 61 + 62 \xrightarrow{\text{Ag(I)F}} 65 \text{ (55\%)} + 66 \text{ (13\%)} \]

Both the diastereomeric cycloadducts 65 and 66 were characterized by IR, \(^1\)H NMR, \(^13\)C NMR and mass spectral analysis and their stereochemistries ascertained by \(^1\)H NMR COSY experiment.

3.1.2.1. Spectral Analysis of Major Cycloadduct 65:

IR spectrum displayed the nitrile moiety at 2400 cm\(^{-1}\) as medium absorption band along with other absorption bands at 1398, 1461, 1271 and 1105 cm\(^{-1}\) (Fig. 5).
$^1$H NMR spectrum of 65 displayed sets of two multiplet at $\delta$ 1.55-1.75 and $\delta$ 2.05-2.15, each integrating to two protons, assignable to $\text{H}_2^\text{endo}$, $\text{H}_3^\text{endo}$ and $\text{H}_2^\text{exo}$, $\text{H}_3^\text{exo}$, respectively. A singlet observed at $\delta$ 3.0, integrating for two protons, could be attributed to endo protons of $\text{H}_2$ and $\text{H}_3$. Two sharp doublets at $\delta$ 3.38 and 3.8 with coupling constant, $J = 4.17$ Hz, equivalent to one proton each, is attributed to bridgehead $\text{H}_1$ and $\text{H}_4$ protons. A singlet, equivalent to two protons, at $\delta$ 3.67 is attributed to the two benzylic protons. Downfield multiplet between $\delta$ 7.25-7.50, integrating for six protons, corresponds to the five aromatic protons of phenyl ring and $\text{H}_5^\prime$ of the pyridyl moiety, while $\text{H}_4^\prime$ and $\text{H}_5^\prime$ of pyridyl moiety appeared at $\delta$ 8.05 (dd, $J = 2.45, 8.30$ Hz, 1H) and $\delta$ 8.26 (d, $J = 2.45$ Hz), respectively (Fig 4).

From the above $^1$H NMR spectral analysis, the stereochemistry and the structure for 65 is assigned as 7-benzyl-2-exo-(6-chloro-3-pyridyl)-3-exo-cyano-7-azabicyclo(2.2.1)heptane, however, ambiguity arising due to the appearance of $\text{H}_2^\text{endo}$ and $\text{H}_3^\text{endo}$ together as a singlet at $\delta$ 3.0 is clarified by carrying out the $^1$H NMR COSY experiment and recording the spectrum in deuterated benzene ($\text{C}_6\text{D}_6$). $^1$H COSY spectrum revealed the absence of coupling for the assigned $\text{H}_2^\text{endo}$ and $\text{H}_3^\text{endo}$ with any of the other protons, including bridgehead $\text{H}_1$ and $\text{H}_4$.

$^1$H NMR spectrum of 65 in $\text{C}_6\text{D}_6$ resolved and separated signals for the two $\text{H}_2$ and $\text{H}_3$ protons. $\text{H}_2^\text{endo}$ appeared as doublet at $\delta$ 2.60 ($J = 5.6$ Hz) and $\text{H}_3^\text{endo}$ merged with the two benzylic and bridgehead ($\text{H}_1$ and $\text{H}_4$) protons at $\delta$ 3.0-3.2 and appeared as a part of multiplet. Though the spectrum in $\text{C}_6\text{D}_6$ could not define the stereochemistry of $\text{H}_3$ as endo due to overlapping of signals, it is possible to suggest
that H₃ must be *endo* oriented considering the retention of dipolarophile geometry in the cycloadducts.

¹³C NMR displayed total seven signals upfield at δ 21.3, 24.0, 34.9, 44.7, 51.5, 63.0 and 63.9, and ten signals downfield at δ 119.3, 123.7, 127.4, 128.3, 128.5, 130.9, 138.4, 139.4, 150.4 and 150.5 (Fig. 4). INEPT experiment revealed the presence of C₅ and C₆ methylene carbon at δ 21.3 and 24.0, while C₂ and C₃ methine carbons at δ 34.9 and 44.7, respectively. The benzylic methylene carbon was observed at δ 51.5. The two bridgehead C₁ and C₄ methine carbons appeared at δ 63.0 and 63.9, respectively. The quarternary nitrile carbon is assigned to the signal appearing at δ 150.4. The rest of the downfield signals are accountable for the aromatic carbons from the phenyl and pyridyl moieties.

3.1.2.2. Spectral Analysis of the Minor Cycloadduct 66:

IR spectrum of 66 displayed nitrile functionality at 2400 cm⁻¹ along with other absorption bands at 1522, 1463, 1217 and 1046 cm⁻¹ (Fig. 7).

¹H NMR spectrum displayed sets of two multiplets, integrating for two protons each, between δ 1.80-1.95 and 2.05-2.15, assignable to H₅*endo*, H₆*endo* and H₅*exo*, H₆*exo*, respectively. Another set of two multiplets appearing at δ 3.55 and δ 3.75, integrating for two and four protons each, is attributed to H₂*exo*, H₃*exo* and the two benzylic and bridgehead H₁ and H₄*, respectively. Downfield multiplet observed between δ 7.30-7.45, equivalent to six protons, corresponds to the five aromatic protons of phenyl ring and H₇ of the pyridyl moiety. H₄* and H₂* of pyridyl moiety
are observed at δ 7.70 (J = 2.45, 8.23 Hz) and δ 8.26 (d, J = 2.44 Hz), respectively (Fig. 6).

Based on the above spectral analyses the stereochemistry of 66 is tentatively assigned as 7-benzyl-2-endo-(6-chloro-3-pyridyl)-3-endo-cyano-7-azabicyclo (2.2.1) heptane which is further confirmed by studying the ¹H NMR spectrum in deuterated benzene (C₆D₆) and recording its ¹H NMR COSY spectrum.

The ¹H NMR was well resolved in C₆D₆ and the individual protons could be characterized properly. Characteristic H₂exo proton appeared as a multiplet at δ 2.6 and H₁ as a multiplet at δ 2.75. H₃exo appeared as a doublet of doublet at δ 2.85 (J = 4.2, 8.5 Hz). The bridgehead H₄ appeared as a triplet at δ 2.96 (J = 4.35 Hz) and the two benzylic protons at δ 3.15 as singlet (Fig 6).

Above stereochemical assignment finds further support from the observed coupling between the two bridgehead H₁ and H₄ with the adjacent H₂ and H₃ exo protons, respectively, in the ¹H NMR COSY spectrum.

¹³C NMR spectrum displayed a total of seven carbon signals upfield at δ 21.3, 24.0, 34.9, 44.7, 51.4, 63.0 and 63.9, and ten carbon signals downfield at δ 119.3, 123.7, 127.4, 128.3, 128.5, 128.8, 130.9, 138.4, 139.4, 150.4 and 150.5 (Fig. 7). INEPT experiment revealed the presence of C₅ and C₆ methylene carbons at δ 21.3 and δ 24.0. Methine carbons C₂ and C₃ appeared at δ 34.9 and δ 44.7, respectively, while the benzylic carbon appeared at δ 51.4. The bridgehead methine carbons C₁ and C₄ are observed at δ 63.0 and δ 63.9, respectively. Rest of the downfield signals were
assignable to the aromatic carbons of pyridyl and phenyl moieties. The quarternary carbon signal for the nitrile moiety appeared at δ 150.4.

3.2. Synthesis of Nitro-substituted Epibatidine derivative: 7-benzyl-2-exo-(6-chloro-3-pyridyl)-3-endo-nitro-7-azabicyclo(2.2.1)heptane (70).

In order to synthesize 70, the required dipolarophile 69 was prepared in three steps starting from 6-chloro-3-pyridyl carboxaldehyde (56) as shown in Scheme 13.

Scheme 13

Nitroaldol condensation of 56 (1 eq) with nitromethane (67, 1.2 eq) in tPrOH using catalytic amount of potassium fluoride (0.5 eq) afforded 2-(6-chloro-3-pyridyl)-1-nitro-ethan-2-ol (68, 90%). Tosylation of 68 (1 eq) by using p-TsCl (1.1 eq) followed by elimination in the presence of triethyl amine (2.2 eq) gave 69 (75 %). Compound 69 is fully characterised by IR, H NMR and mass spectral analyses.

IR spectrum displayed strong absorption bands at 1637, 1583 and 1506 cm\(^{-1}\) indicating the presence of nitro moiety conjugated to vinyl pyridine along with other absorption bands at 1340 and 1099 cm\(^{-1}\).

H NMR spectrum exhibited a doublet at δ 7.45 (J = 8.30 Hz) corresponding to pyridyl H5' proton. The two vinylic H1 and H2 protons appeared as doublets, each integrating for one proton, at δ 7.65 (J = 12.25 Hz) and δ 8.0 (J =12.25 Hz),
respectively. Remaining pyridyl H4' and H5' protons appeared at δ 7.85 (dd, J = 2.38, 8.30 Hz) and δ 8.55 (d, J = 2.38 Hz).

Mass spectrum indicated molecular ion peak at 184 (41) and a base peak at 102 alongwith other prominent fragments at 137 (91), 126 (19) and 75 (79).


The cycloaddition of dipolarophile 69 with 62 by following the identical protocol as mentioned in previous section gave cycloadduct 70 (65%) as the only product as a pale yellow thick oil (Scheme 14).

IR spectrum of 70 indicated the presence of nitro moiety by displaying a strong absorption band at 1550 cm⁻¹ alongwith other absorption bands at 1470, 1230 and 1120 cm⁻¹ (Fig. 9).

¹H NMR spectrum of 70 revealed H₅endo and H₆endo protons as a multiplet between δ 1.60-1.75, and H₅exo and H₆exo as multiplet between δ 2.0-2.2. A doublet at δ 3.35 (J = 4.5 Hz), equivalent to one proton, is attributed to H1 and another doublet at δ 3.45 (J = 5.36 Hz) corresponding to one proton is assigned to H2endo. A singlet, equivalent to two protons, appearing at δ 3.63 corresponds to the two benzylic protons. A set of two multiplets observed at δ 4.02 and δ 4.75, integrating for one
proton each, is attributed to bridgehead H_4 and H_3exo protons, respectively. A doublet observed at δ 7.28 (J = 8.45 Hz, 1H) is attributed to H_5 of pyridyl moiety while the multiplet between δ 7.35-7.45(5H) corresponds to the five aromatic protons of the phenyl ring. H_4' and H_2 of pyridyl moiety were observed at δ 7.78 (dd, J = 2.45, 8.3 Hz) and δ 8.5 (d, J = 2.46 Hz), respectively (Fig 8).

Based on the coupling pattern and chemical shifts observed for the diagnostic H_1, H_2, H_3 and H_4, the structure and stereochemistry for 70 is assigned as 7-benzyl-2-exo-(6-chloro-3-pyridyl)-3-endo-nitro-7-azabicyclo(2.2.1)heptane.

^{13}C NMR spectrum revealed a total of seven signals upfield at δ 20.3, 26.5, 48.4, 51.8, 62.8, 66.9 and 93.0, and nine signals downfield at δ 124.0, 127.5, 128.5, 128.6, 137.2, 137.9, 138.1, 148.9 and 150.1 (Fig. 8). INEPT experiment revealed the presence of C_5 and C_6 methylene carbons at δ 20.3 and 26.5, respectively. C_2 methine carbon, bearing the pyridyl moiety, was observed at δ 48.5 while the benzylic carbon at δ 51.8. The two bridgehead methine carbons C_1 and C_4 were observed at δ 62.8 and δ 66.9, respectively. A characteristic signal for C_3 methine carbon, bearing nitro moiety, was observed at δ 93.0. Rest of the signals were characterised as aromatic carbons.

The exo-selectivity for 6-chloro-3-pyridyl moiety observed in the cycloaddition reaction using 69 as dipolarophile appears to be in contrast to the cycladdition stereochemistries observed with dipolarophiles 60 as well as 61. Although, at present we do not have explanations for the reversal of stereochemistry in 70, difference in the orbital coefficients of nitro olefin than ester or cyano may be considered for this observation.
3.3. Formal Synthesis of Homoepibatidine (2):

The two synthetic strategies reported so far towards the synthesis of Homoepibatidine have employed Heck-coupling of iodo-pyridyl derivative with 8-azabicyclo(3.2.1)oct-6-ene with overall poor yields due to the involvement of multiple steps. In this context, it was envisaged that the cycloaddition of piperidine based azomethine ylide 72 with pyridyl acrylates 73 would provide an easy access to a shorter and stereoselective synthetic route towards the synthesis of Homoepibatidine (Scheme 15).

Scheme 15

Synthesis of 2 commenced with the preparation of both 80 and 83 as described for their preparation in Chapter 2. Azomethine ylide precursor 74 was prepared in five steps starting from commercially available piperidine (75) as shown in Scheme 16.
N-Boc piperidine 76 was disilylated to 78 and later the Boc moiety was deprotected to obtain the free base 79 by following the experimental protocol as described in Chapter 2 for the corresponding pyrrolidine analogue. Reductive amination of formaldehyde with 79 using sodium cyanoborohydride in acetonitrile after usual workup and purification by silica gel column chromatography, eluting with hexane:EtOAc (4:96), afforded 74 (80%) as a thick yellow oil.

Azomethine ylide precursor 74 is characterised by IR, $^1$H NMR, $^{13}$C NMR and mass spectral analyses as N-methyl-2,6-bis(trimethyl silyl)piperidine.

$^1$H NMR spectrum displayed the two trimethylsilyl moieties at δ 0.06 as a singlet integrating for eighteen protons. A multiplet corresponding to the six axial and equatorial H$_3$, H$_4$ and H$_5$ protons is observed between δ 1.52-1.67. H$_2$ and H$_6$ protons adjacent to two silyl moieties appeared as a multiplet between δ 2.20-2.30. Singlet at δ 2.55, equivalent to three protons, corresponds to the methyl group on nitrogen (Fig 10).
\(^{13}\)C NMR spectrum displayed a total of five signals upfield at \(\delta -1.2, 20.7, 24.3, 42.4\) and 54.1 (Fig. 10). INEPT experiment showed the presence of methyl carbons of two TMS moieties at \(\delta -1.2\). \(C_3, C_4\) and \(C_5\) methylene carbons appeared at \(\delta 20.7\) and 24.3. Methyl on nitrogen was observed at \(\delta 42.4\) and the two \(C_2\) and \(C_6\) methine carbons appeared at \(\delta 54.1\).

Mass spectrum displayed the presence of a molecular ion peak at 243 (<1) and a base peak at 170 along with other prominent fragments at 228 (4.3) and 96 (4.5).

3.3.1. Cycloaddition Reaction of 74 with 80:

Cycloaddition of 74 with 80, carried out by following the protocol analogous to that employed for the pyrrolidine based azomethine ylide, afforded cycloadduct 81 (64%) as the only isolable product as a yellow thick oil (Scheme 17).

Scheme 17

Compound 81 is characterised by IR, \(^1\)H NMR, \(^{13}\)C NMR and mass spectral analyses as described below.
IR spectrum showed a strong absorption band corresponding to carboethoxy moiety at 1724 cm\(^{-1}\) along with other absorption bands at 1582, 1241 and 1103 cm\(^{-1}\) (Fig 12).

\(^1H\) NMR spectrum displayed six \(H_2\), \(H_3\) and \(H_4\), axial and equatorial hydrogens as a set of two multiplets, each integrating for three protons, between \(\delta 1.5-1.75\) and \(\delta 1.85-2.05\). The methyl group on nitrogen was observed as a singlet at \(\delta 2.5\). \(H_{7exo}\) and \(H_{endo}\) appeared together as a multiplet at \(\delta 3.17\). Another multiplet observed between \(\delta 3.50-3.55\), equivalent to one proton, is attributed to bridgehead \(H_1\) proton. Bridgehead \(H_5\) proton was observed as doublet at \(\delta 3.65\) \((J = 6.65\) Hz\). Methyl and methylene groups of carboethoxy moiety appeared as a triplet and quartet at \(\delta 1.25\) \((J = 7.21\) Hz\) and \(\delta 4.20\) \((J = 7.20\) Hz, 2H), respectively. Pyridyl ring protons \(H_5\), \(H_4'\) and \(H_2'\) were observed at \(\delta 7.27\) \((d, J = 8.24\) Hz, 1H\), 7.88 \((dd, J = 2.73, 8.25\) Hz, 1H\) and 8.42 \((d, J = 2.75\) Hz, 1H\), respectively (Fig 11).

Based on the above \(^1H\) NMR spectral analyses, the structure and stereochemistry for the cycloadduct 81 is assigned as 8-methyl-6-exo-carboethoxy-7-endo-(6-chloro-3-pyridyl)-8-azabicyclo(3.2.1)octane.

\(^{13}C\) NMR displayed a total of ten carbon signals upfield at \(\delta 14.1, 16.7, 19.5, 23.21, 34.6, 45.9, 57.1, 60.5, 62.0\) and 66.1 and six signals downfield at \(\delta 123.9, 137.2, 142.2, 148.4, 149.1\) and 171.9 (Fig. 11). INEPT experiment revealed the presence \(C_2\), \(C_3\) and \(C_4\) methylene carbons of azabicyclic ring systems at \(\delta 16.7, 19.5\) and 23.2, respectively. N-Methyl carbon signal appeared at \(\delta 34.6\). \(C_7\) and \(C_8\) methine carbon signals were observed at \(\delta 45.99\) and \(\delta 57.11\), respectively. Methyl and methylene
The carbons of carboethoxy moiety were observed at δ 14.1 and δ 60.59, respectively. The two bridgehead C₁ and C₅ methine carbons appeared at δ 62.04 and δ 66.19, respectively. Quarternary carbonyl carbon of carboethoxy moiety was observed at δ 171.9. The rest of the downfield signal were assignable to the aromatic carbons of pyridyl moiety.

Mass spectrum indicated the molecular ion peak at 308 (3) and a base peak at 97 alongwith other prominent fragments at 235 (6), 166 (10) and 83 (73) (Fig 12).

3.3.2. Cycloaddition of 74 with Cis-pyridyl acrylate 83:

Cycloaddition of 74 with 83, carried out as described for the preparation of 81, afforded cycloadduct 84 (61%) as the only isolable diastereomer (Scheme 18).

Scheme 18

The cycloadduct 84 is characterised by IR, ¹H NMR, ¹³C NMR and mass spectral analyses as follows.

IR spectrum displayed the presence of carboethoxy moiety as a strong absorption band at 1728 cm⁻¹ (Fig 14)

¹H NMR spectrum displayed the six H₂, H₃ and H₄ axial and equatorial protons as a set of three multiplets, each integrating for two protons, at δ 1.10-1.22, 1.62-1.75 and 1.92-2.05, respectively. A singlet at δ 2.58 equivalent to three protons
corresponds to N-methyl group. H1 was observed as a broad singlet at δ 3.08, whereas H7endo was identified as a doublet at δ 3.25 (J = 10.2 Hz). A multiplet, appearing as a broad singlet and a doublet signals, between δ 3.60-3.65, corresponding to two protons, is attributed to the H6endo and bridgehead H5. Methyl and methylene protons of carboethoxy moiety are observed as a triplet and mixed quartet at δ 0.8 (J = 7.21 Hz, 3H) and δ 3.42 (J = 7.21 Hz, 2H), respectively. Pyridyl ring protons were observed at δ 7.12 (d, J = 3.37 Hz, 1H), 7.92 (dd, J = 2.76, 8.34 Hz, 1H) and 8.24 (d, J = 2.78 Hz, 1H) (Fig 13).

Thus, the appearance of H6 and H7 protons as doublets and the retention of olefin geometry observed confirms the structure and stereochemistry of 84 as 8-methyl-6-exo-carboethoxy-7-exo-(6-chloro-3-pyridyl)-8-azabicyclo(3.2.1)octane.

13C NMR spectrum revealed total sixteen carbon signals (Fig. 13). INEPT experiment revealed the presence of the three methylene carbons C3, C4 and C2 of azabicyclic ring at δ 17.4, 20.5 and 21.2, respectively. Methyl on nitrogen was observed at δ 32.6. The two methine carbons C6 and C7, bearing carboethoxy and pyridyl moiety, were observed at δ 47.7 and δ 53.5, respectively. Methylene and methyl group (OCH2CH3) of carboethoxy moiety was observed at δ 13.4 and δ 59.5, respectively. The two bridgehead C1 and C3 methine carbons appeared at δ 60.0 and 66.2, respectively. Pyridyl moiety was observed as a set of three methine carbon signals downfield at δ 123.5, 138.1 and 149.7, and two quartenary carbon at δ 138.5 and 149.2. Quartenary carbonyl carbon of carboethoxy moiety appeared at δ 171.8.
Cycloadducts 81 and 84 would obviously lead to both the *endo* and *exo* isomers of Homoepibatidine on further synthetic transformations as already described for Epibatidine in Chapter 2.

4. Summary

In summary, we have successfully demonstrated the synthesis of various substituted epibatidine derivatives and a formal synthetic approach for both the stereoisomers of Homoepibatidine by utilizing $[3+2]$-cycloaddition of non stabilized azomethine ylide derived from cyclic amines.
5. Experimental

General experimental techniques which have been described in the experimental section of Chapter 2 were followed.

5.1. Preparation of 3-(6-Chloro-3-pyridyl)propionitriles (60 and 61):

To a stirring solution of 56 (1.69 g, 12 mmol) in 20 mL of acetonitrile was added cyanomethyl triphenyl phosphoranylidine (3.62 g, 12 mmol) dissolved in 40 mL of acetonitrile. The reaction mixture was refluxed for 10 h. After the completion of the reaction, solvent was removed under vacuum. The crude solid obtained was repeatedly tritratued with 20 % ethyl acetate in hexane (5×50 mL) to remove triphenyl phosphine oxide formed in the reaction. The combined hexane fractions were evaporated to afford a solid residue which was purified by silica gel column chromatography eluting with hexane:EtOAc (9:1) to give 0.78 g of 60 (40%) and 0.59 g of 61 (30%) as a 1:1 mixture.

*Trans*-3-(6-chloro-3-pyridyl)-propionitrile (60): mp. 167-168 °C.

\[
\begin{align*}
\text{IR (Nujol)} & : 2120, 1580, 1460 \text{ cm}^{-1}. \\
\text{\textsuperscript{1}H NMR (200MHz)} & : \delta 6.00 (d, J = 16.67 \text{ Hz}, 1\text{H}), 7.40 (d, J = 16.67 \text{ Hz}, 1\text{H}), 7.45 (d, J = 8.36 \text{ Hz}, 1\text{H}), 7.45 (d, J = 8.36 \text{ Hz}, 1\text{H}), 7.80 (dd, J = 2.55, 8.34 \text{ Hz}, 1\text{H}), 8.50 (d, J = 2.49 \text{ Hz}, 1\text{H}). \\
\text{\textsuperscript{13}C NMR (50.32 MHz)} & : \delta 98.6, 116.3, 123.5, 127.6, 135.4, 144.5, 148.0, 151.9. \\
\text{Mass} & : 164 (M^+, 100), 137 (29), 129 (82), 102 (59).
\end{align*}
\]
Ci’s-3-(6-chloro-pyridyl)-propionitrile (61): mp. 97-98 °C.

IR (Nujol) : 2120, 1580, 1460 cm⁻¹.

\(^1\)H NMR (200MHz) : \(\delta\) 5.65 (d, \(J = 12.00\) Hz, 1H), 7.10 (d, \(J = 12.00\) Hz, 1H), 7.45 (d, \(J = 8.50\) Hz, 1H), 8.40 (dd, \(J = 2.40, 8.49\) Hz, 1H), 8.60 (d, \(J = 2.40\) Hz, 1H).

\(^13\)C NMR (50.32 MHz) : \(\delta\) 98.3, 116.2, 124.4, 128.2, 137.0, 143.5, 150.5, 153.1.

Mass : 164 (M\(^+\), 100), 129 (82), 102 (59).

5.2. Cycloaddition reaction of 60 and 62:

A two neck flask, equipped with a magnetic stirring bar and argon gas balloon, was charged with Ag(I)F (0.77 g, 4.72 mmol) (dried previously under vaccum at 40 °C) and with a solution of dipolarophile 60 (0.95 g, 6.26 mmol) in 30 mL of dry dichloromethane. Compound 62 (1.20 g, 3.93 mmol), dissolved in 25 mL of dry DCM, was introduced into the reaction flask dropwise over a period of 10 min. The color of the reaction mixture gradually turned dark brown with concomitant deposition of silver on the surface of the flask in the form of mirror and the progress of the reaction was periodically monitored by TLC. After stirring for 8-10 h, the reaction mixture was filtered through a small plug of celite and the solvent was evaporated to give a crude brown residue. Purification of the crude residue by silica gel column chromatography, eluting with hexane:EtOAc (9:1), afforded 0.22 g (18 %) of 64 yield. Further elution with hexane:EtOAc (9:2) afforded 0.56 g (45 %) of 63 as a thick yellow oil.
7-Benzyl-2-endo-(6-chloro-3-pyridyl)-3-exo-cyano-7-azabicyclo[2.2.1]heptane (63):

IR (CHCl₃) : 2221, 1462, 1107 cm⁻¹;

¹H NMR (200MHz) : δ 1.40-1.52 (m, 2H), 1.70-1.90 (m, 1H), 1.95-2.12 (m, 1H), 2.65 (d, J = 5.94 Hz, 1H), 3.65 (t, J = 4.15 Hz, 1H), 3.75 (m, 4H), 7.25-7.50 (m, 7H), 8.25 (d, J = 2.46 Hz, 1H).

¹³C NMR (75.3 MHz) : δ 20.5, 27.2, 36.6, 49.9, 51.2, 63.5, 64.4, 121.4, 124.0, 127.1, 128.1, 128.3, 132.3, 137.5, 138.5, 148.7, 150.1.

Mass : 323 (M⁺, 1), 159 (34), 140 (55), 126 (54), 105 (39), 91 (100), 83 (55).

7-Benzyl-2-exo-(6-chloro-3-pyridyl)-3-endo-cyano-7-azabicyclo[2.2.1]heptane (64):  

IR (CHCl₃) : 2400, 1461, 1217, 1046 cm⁻¹;

¹H NMR (200MHz) : δ 1.55-1.70 (m, 1H), 2.00-2.15 (m, 3H), 2.85 (dd, J = 4.76, 9.73 Hz, 2H), 3.30 (s, 1H), 3.55 (s, 2H), 3.65 (s, 1H), 7.25-7.45 (m, 6H), 7.58 (dd, J = 2.45, 8.24 Hz, 1H), 8.45 (d, J = 2.45 Hz, 1H).

¹³C NMR (75.3 MHz) : δ 22.0, 26.8, 41.4, 51.2, 51.7, 61.59, 65.7, 119.9, 124.0, 127.3, 128.4, 128.5, 137.5, 138.4, 148.5, 150.2.

5.3. Cycloaddition of 61 and 62:

A two neck flask, equipped with a magnetic stirring bar and argon gas balloon, was charged with Ag(I)F (0.54 g, 4.29 mmol) (dried previously under vaccum at 40 °C) and solution of dipolarophile 61 (0.47 g, 2.92 mmol) in 20 mL of dry dichloromethane. Compound 62 (0.59 g, 1.96 mmol), dissolved in 15 mL of dry DCM, was introduced into the reaction flask dropwise over a period of 10 min. After stirring for 8-10 h, the reaction mixture was worked up as mentioned in the previous
experiment, to afford a crude brown residue which on purification by silica gel column chromatography, eluting with hexane:EtOAc (9:1) afforded 0.34 g (55%) of 65. Further elution with hexane:EtOAc (9:2) afforded 0.08 g (13 %) of 66 as a thick yellow oil.

7-Benzyl-2-exo-(6-chloro-3-pyridyl)-3-exo-cyano-7-azabicyclo[2.2.1]heptane (65):
IR (Nujol) : 2400, 1461, 1271, 1105 cm\(^{-1}\).

\(^1\)H NMR (200 MHz) : \(\delta \) 1.55-1.75 (m, 2H), 2.05-2.15 (m, 2H), 3.0 (s, 2H), 3.38 (d, \(J = 4.17\) Hz, 1H), 7.25-7.50 (m, 6H), 8.05 (dd, \(J = 2.45, 8.30\) Hz, 1H), 8.26 (d, \(J = 2.45\) Hz, 1H).

\(^1\)H NMR (C\(\text{D}_{6}\), 300 MHz) : \(\delta \) 1.35-1.40 (m, 2H), 1.95 (d, \(J = 8.5\) Hz, 2H), 2.60 (d, \(J = 5.6\) Hz, 1H), 3.0-3.15 (m, 5H), 6.92 (d, \(J = 8.03\) Hz, 1H), 7.15-7.22 (m, 5H), 7.55 (d, \(J = 2.03\) Hz, 1H), 8.12 (d, \(J = 2.03\) Hz, 1H).

\(^13\)C NMR (75.3 MHz) : \(\delta \) 21.3, 24.0, 34.9, 44.7, 51.5, 63.0, 63.9, 119.3, 123.7, 127.4, 128.3, 128.5, 130.9, 138.4, 139.4, 150.4, 150.5.

Mass : 323 (M\(^+\), <1 ), 159 (61 ), 131 (25), 91 (100 ).

7-Benzyl-2-endo-(6-chloro-3-pyridyl)-3-endo-cyano-7-azabicyclo[2.2.1]heptane (66):
IR (CHCl\(_3\)) : 2400, 1522, 1463, 1217, 1046 cm\(^{-1}\).

\(^1\)H NMR (C\(\text{D}_{6}\), 200 MHz) : \(\delta \) 1.80-1.95 (m, 2H), 2.05-2.15 (m, 2H), 3.55 (m, 4H), 7.30-7.45 (m, 6H), 7.70 (dd, \(J = 2.45\)Hz, 8.23 Hz, 1H), 8.26 (d, \(J = 2.44\) Hz, 1H).

\(^1\)H NMR (C\(\text{D}_{6}\), 300 MHz) : \(\delta \) 1.08-1.25 (m, 2H), 1.30-1.42 (m, 1H), 1.65 -1.85 (m, 1H), 2.6 (m, 1H), 2.75 (m, 1H), 2.85 (dd, \(J = 4.2\) Hz, 8.5, 1H), 2.96 (t, \(J = 4.35\) Hz, 1H), 3.15 (s, 2H), 6.82 (d, \(J = 8.35\) Hz, 1H), 7.1-7.25 (m, 6H), 7.95 (d, \(J = 2.5\)Hz, 1H).

\(^13\)C NMR (75.3 MHz) : \(\delta \) 21.3, 24.0, 34.9, 44.7, 51.4, 63.0, 63.9, 119.3, 123.7, 127.4, 128.3, 128.5, 128.8, 130.9, 138.4, 139.4, 150.4, 150.5.

Mass : 323 (M\(^+\), 1 ), 189 (26 ), 159 (73 ), 91 (100 ).
5.4. Preparation of 2-(6-Chloro-3-pyridyl)-1-nitro ethan-2-ol (68):

A 10 mL i-PrOH solution of 56 (1.41g, 10 mmol) was treated with KF (0.03 g, 0.5 mmol) and nitromethane (0.65 mL, 12 mmol). After stirring for 6 h at rt, solvent was evaporated to dryness and the residue was purified by silica gel column chromatography eluting with hexane:EtOAc (8:2) to obtain 2-hydroxy-2-(6-chloro-3-pyridyl)nitroethane (68) (1.81 g, 90 %) as thick dark yellow oil.

$^1$H NMR (200MHz) : $\delta$ 4.6 (d, $J = 4.36$ Hz, 2H), 5.6 (dd, $J = 9.72$, 4.32 Hz, 1H), 7.3 (d, $J = 8.40$ Hz, 1H), 7.80 (dd, $J = 2.6$, 8.41 Hz, 1H), 8.40 (d, $J = 8.35$ Hz, 1H).

$^{13}$C NMR (50.32 MHz) : $\delta$ 67.9, 80.7, 124.7, 134.0, 137.3, 147.2, 151.2;

Mass : 202 (M$,^+$, 4), 155 (82), 140 (100), 128 (20).

5.5. Preparation of 2-(6-Chloro-3-pyridyl)-1-nitroethylene (69):

Compound 68 (1 g, 4.94 mmol) dissolved in 50 mL of dry DCM was cooled to 0 °C and was treated with TEA (1.0 g, 9.89 mmol) followed by p-toluene sulfonyl chloride (0.59 g, 5.43 mmol). After the completion of the reaction, the reaction mixture was stirred at rt overnight. The mixture was successively washed with aqueous 1 M NaHCO$_3$ solution (2×25 mL), water, brine and finally dried over Na$_2$SO$_4$. Evaporation of the solvent gave crude solid which was purified by silica gel column chromatography eluting with hexane:EtOAc (9:1) to get 69 (0.68 g, 75 % ) as a white solid, mp. 138-140 °C.

IR (Nujol) : 1637, 1583, 1506, 1340, 1099 cm$^{-1}$.

$^1$H NMR (200MHz) : $\delta$ 7.45 (d, $J = 8.30$ Hz, 1H), 7.65 (d, $J = 12.25$ Hz, 1H), 7.85 (dd, $J = 2.38$, 8.30 Hz, 1H), 8.0 (d, $J = 12.25$ Hz, 1H), 8.55 (d, $J = 2.38$ Hz, 1H).

$^{13}$C NMR (50.32 MHz) : 124.4, 125.6, 134.2, 138.6, 139.4, 150.8, 152.9.
5.6. Cycloaddition of 69 and 62: Synthesis of 7-Benzyl-2-exo-(6-chloro-3-pyridyl)-3-endo-nitro-7-azabicyclo[2.2.1]heptane (70):

A two neck flask, equipped with a magnetic stirring bar and argon gas balloon, was charged with Ag(I)F (0.36 g, 2.82 mmol) (dried previously under vaccum at 40 °C) and solution of dipolarophile 69 (0.28 g, 1.57 mmol) in 30 mL of dry dichloromethane. Compound 62 (0.40 g, 1.31 mmol), dissolved in 20 mL of dry DCM, was introduced into the reaction flask dropwise over a period of 10 min. After stirring for 8-10 h, the reaction mixture was worked up as mentioned in the previous experiment, to afford a crude brown residue which on purification by silica gel column chromatography, eluting with hexane:EtOAc (9:1) afforded 0.19 g (65%) of 70 as yellow oil.

IR (CHCl₃) : 1550, 1470, 1230, 1120, 770 cm⁻¹.

¹H NMR (200MHz) : δ 1.60-1.75 (m, 2H), 2.0-2.2 (m, 2H), 3.35 (d, J = 4.5 Hz, 1H), 3.45 (d, J = 5.36 Hz, 1H), 3.63 (s, 2H), 4.02 (m, 1H), 4.75 (m, 1H), 7.28 (d, J = 8.45 Hz, 1H), 7.35-7.45 (m, 5H), 7.78 (dd, J = 2.45, 8.3 Hz, 1H), 8.5 (d, J = 2.46 Hz, 1H).

¹³C NMR (75.3 MHz) : δ 20.3, 26.5, 48.4, 51.8, 62.8, 66.9, 93.0, 124.0, 127.5, 128.5, 128.6, 137.2, 137.9, 138.1, 148.9, 150.1.

Mass : 221 (6), 191 (14), 140 (9), 83 (100).

5.7. Preparation of N-(tert-butoxycarbonyl) piperidine (76):

To a solution of piperidine (8.76 g, 92.3 mmol) and triethylamine (11.6 g, 115.3 mmol) in dioxane (50 mL), tert-butyl azidoformate (11 g, 76.9 mmol) was added dropwise over 15 min. The pH of the reaction mixture was maintained at 12 by the
addition of excess triethylamine if required. The reaction mixture was stirred until a clear solution resulted. After the evaporation of dioxan, the residue was taken up in ether, washed twice with water (75 mL) followed by brine (75 mL). Ether was evaporated and the resultant brown oil obtained was purified by vacuum distillation (bp. 55-57°C/1mm) to obtain 15.3 g (90%) of 76 as a clear colorless oil.

IR : 2940, 1695, 1420, 1385, 1260, 1170 cm⁻¹.

$^1$H NMR (200MHz) : δ 1.45 (s, 9H), 1.58 (m, 6H), 3.31-3.45 (m, 4H).

Mass : 185 (M+, 66), 129 (53), 84 (63), 57 (100).

5.8. Preparation of N-(tert-butoxy carbonyl)-2-trimethylsilyl piperidine(77):

A solution of N-Boc piperidine (76) (5.55 g, 30.0 mmol) in 40 mL of dry ether charged into a 250 mL flask, equipped with a magnetic stirring bar and argon gas balloon, was cooled to -78°C. TMEDA (4.18 g, 36.0 mmol) followed by s-BuLi (1.5 M solution in cyclohexane, 23.93 mL, 36.0 mmol) were introduced to the stirring mixture dropwise over 15 min. The mixture was further allowed to stir for 2 h at -78°C. Chlorotrimethylsilane (3.91 g, 36.0 mmol) was added dropwise into the flask. The reaction mixture was allowed to warm to rt and diluted with 15 mL of saturated aqueous NH₄Cl solution. The organic layer was separated and the aqueous layer was extracted with ether (2x30 mL). The combined extracts were washed with water (80 mL), brine (80 mL) and dried over Na₂SO₄. The organic extract was concentrated and the crude oily residue obtained was purified by fractional distillation (bp 55-57°C/0.5 mm) to give 6.96 g (90%) of 77 as a colorless oil.

IR (neat) : 1688, 1415, 1159, 1098, 838 cm⁻¹.

$^1$H NMR (200MHz) : δ 0.06 (s, 9H), 1.43 (s, 9H), 1.55-1.75 (m, 6H), 2.15-2.30 (m, 2H), 3.60-3.75 (bs, 1H).
5.9. Preparation of N-Boc-2,6-bis(trimethylsilyl)piperidine (78):

A 250 mL two neck flask, equipped with a magnetic stirring bar and argon gas balloon, was charged with a solution of 77 (5.14 g, 20 mmol) in 30 mL of ether and was cooled to -45°C. TMEDA (2.79 g, 24 mmol) followed by s-BuLi (1.5 M in cyclohexane, 16.0 mL, 24 mmol) were added to the flask dropwise while stirring. After 15 min of stirring at -45°C, temperature was raised to -30°C. After 30 min, it was recooled to -45°C and chlorotrimethylsilane (2.60 g, 24 mmol) was added dropwise. The reaction mixture was allowed to warm to rt, diluted with 10 mL of saturated aqueous NH₄Cl solution and worked up as mentioned in previous experiment, to get an oily residue which was purified by silica gel column chromatography eluting with hexane:EtOAc (99:1) to give 4.93 g (75 %) of 78 as a pale yellow oil.

IR : 1684, 1421, 1175, cm⁻¹.

¹H NMR (200MHz) : δ 0.08 (s, 18H), 1.45 (s, 9H), 1.55-1.75 (m, 6H), 2.15 (m, 1H), 3.60-3.75 (bs, 1H).

¹³C NMR (50.32 MHz) : δ -0.7, 0.1, 24.7, 26.2, 26.9, 28.7, 47.7, 48.5, 78.8, 155.8.

Mass : 272 (100), 258 (46), 242 (66), 228 (51), 200 (80), 156 (44), 73 (98).

5.10. Preparation of N-Methyl-2,6-bis(trimethylsilyl)piperidine (74):

To a stirring solution of 78 (5.0 g, 15.2 mmol) in 40 mL of dry CH₂Cl₂ at 0 °C contained in a 100 mL round bottom flask equipped with argon gas balloon, was added trifluoroacetic acid (8.66 g, 76 mmol) dropwise over 15 mins. The mixture was
allowed to warm to rt and allowed to stir further for 4 h. The reaction mixture was recooled to 0°C and basified with 20% aqueous NaOH solution (pH =10). The organic layer was separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (2×30 mL). The combined extracts were washed with brine, dried over Na$_2$SO$_4$ and concentrated to give 3.12 g of crude 79 which was utilised as such without further purification.

To a stirring solution of crude amine 79 (3.1 g, 13.67 mmol) in CH$_3$CN (120 ml), 37 % aqueous solution of HCHO (1.5 mL) and NaBH$_3$CN (1.71 g, 27.35 mmol) were added. The reaction mixture was stirred for an additional 15 min. Neutralisation of the reaction mixture by adding glacial acetic acid followed by basification by the slow addition of conc. NH$_4$OH and extraction with hexane (3×50 mL) followed by concentration and purification of the residue by silica gel column chromatography, eluting with EtOAc:hexane (3:97), gave 74 (2.65 g, 80 % yield) as a colorless viscous liquid.

$^1$H NMR (200MHz) : $\delta$ 0.06 (s, 18H), 1.52-1.67 (m, 6H), 2.2-2.3 (m, 2H), 2.55 (s, 3H)

$^{13}$C NMR (50.32 MHz) : $\delta$ -1.2, 20.7, 24.3, 42.4, 54.1.

Mass : 243 (M$^+$, <1 ), 228 (4.3), 170 (100 ), 96 (4.5), 73 (5.2).

5.11. Synthesis of 8-Methyl-6-exo-carbethoxy-7-endo-(6-chloro-3-pyridyl)-8-azabicyclo [3.2.1]octane (81): Cycloaddition of 74 with 80

A two neck flask, equipped with a magnetic stirring bar and argon gas balloon, was charged with Ag(I)F (0.57 g, 4.51 mmol) (dried previously under vaccum at 40 °C) and solution of dipolarophile 80 (0.52 g, 2.47 mmol) in 40 mL of dry dichloromethane. Compound 74 (0.50 g, 2.05 mmol), dissolved in 20 mL of dry DCM,
was introduced into the reaction flask dropwise over a period of 10 min. After stirring for 8-10 h, the reaction mixture was worked up as mentioned in the previous experiment, to afford a crude brown residue which on purification by silica gel column chromatography, eluting with hexane:EtOAc (9:1) afforded 0.40 g (65%) of 81 as yellow oil.

**IR (Neat)**

\[ \text{IR (Neat)} : 1724, 1582, 1241, 1103 \text{ cm}^{-1}. \]

**\(^1\text{H NMR (200MHz)}**

\[ \text{\(^1\text{H NMR (200MHz)} : \delta 1.25 (t, J = 7.21 \text{ Hz, 3H}), 1.50-1.75 (m, 3\text{H}), 1.85-2.05 (m, 3\text{H}), 2.52 (s, 3\text{H}), 3.17 (m, 2\text{H}), 3.50-3.55 (m, 1\text{H}), 3.65 (d, J = 6.65 \text{ Hz, 1H}), 4.2 (q, J = 7.2 \text{ Hz, 2H}), 7.27 (d, J = 8.24 \text{ Hz, 1H}), 7.88 (dd, J = 2.73, 8.25 \text{ Hz, 1H}), 8.42 (d, J = 2.75 \text{ Hz, 1H}).} \]

**\(^1\text{C NMR (75.3 MHz)}**

\[ \text{\(^1\text{C NMR (75.3 MHz)} : \delta 14.1, 16.7, 19.5, 23.2, 34.6, 45.9, 57.1, 60.5, 62.0, 66.1, 123.9, 137.2, 142.2, 148.4, 149.1, 171.9.} \]

**Mass**

\[ \text{Mass : 308 (M\text{+}, 3), 166 (10), 97(100), 83 (72).} \]

5.12. **Synthesis of 8-Methyl-6-exo-carbethoxy-7-exo-(6-chloro-3-pyridyl)-8-azabicyclo[3.2.1]octane (84):** Cycloaddition of 74 with 83

A two neck flask, equipped with a magnetic stirring bar and argon gas balloon, was charged with Ag(I)F (0.57 g, 4.51 mmol) (dried previously under vaccum at 40°C) and solution of dipolarophile 83 (0.52 g, 2.47 mmol) in 40 mL of dry dichloromethane. Compound 74 (0.50 g, 2.05 mmol), dissolved in 20 mL of dry DCM, was introduced into the reaction flask dropwise over a period of 10 min. After stirring for 8-10 h, the reaction mixture was worked up as mentioned in the previous experiment, to afford a crude brown residue which on purification by silica gel column chromatography, eluting with hexane:EtOAc (9:1) afforded 0.40 g (65%) of 84 as yellow oil.
IR (CHCl₃) : 1728, 1106 cm⁻¹.

¹H NMR (200 MHz) : δ 0.80 (t, J = 7.21 Hz, 3H), 1.10-1.22 (m, 2H), 1.62-1.75 (m, 2H), 1.92-2.05 (m, 2H), 2.58 (s, 3H), 3.08 (bs, 1H), 3.25 (d, J = 10.2 Hz, 1H), 3.42 (m, 2H), 3.60-3.65 (q, 2H), 7.12 (d, J = 3.37 Hz, 1H), 7.92 (dd, J = 2.76, 8.34 Hz, 1H), 8.24 (d, J = 2.78 Hz, 1H).

¹³C NMR (75.3 MHz) : δ 13.4, 17.4, 20.5, 21.2, 32.6, 47.7, 53.5, 59.5, 60.0, 66.2, 123.5, 138.1, 138.5, 149.2, 149.7, 171.8.

Mass : 308 (M⁺, 16), 235 (37), 194 (18), 97 (100), 82 (14).
6. References


Spectra
Fig. 2

SAMPLE NO. TO-EXD-CN-EP1 / EDCL3
Fig. 3
Fig. 4

![Chemical Structure](image_url)
**Fig. 5**

**Infrared Spectroscopy**

- **Wave number:** 3000 - 2000 cm⁻¹
- **Resolution:** 4 cm⁻¹
- **Scans:** 33

**Sample:** Epoxide-BS

**Comments:** In liquid.
Fig. 7

WinFIRST Report
Name: Mr. T. D. Bagul
Date: 17/04/96
Sample: Ep. on TPS
Comments: in Choroform

Filename: c:\WinData\Impikameh\49 res
Title: NCL Operator: R. B. Malvankar code:
Starting wavenumber: 399.19
Ending wavenumber: 3999 66
Resolution: 4.0
Scans: 32
Gain Detector Iris 1 Standard 0

N=Organic Tech
Fig. 8
Fig. 9

[Chemical structure image]

[Graph with various axes and labels]

[Table with headings and data]

[Additional text and numbers]
Fig. 12
Fig. 13