The thesis entitled, “Synthetic Studies towards Tamiflu and Biotin” is divided into three chapters. Chapter one deals with the introduction and synthetic studies towards Tamiflu. The second chapter deals with introduction of aziridine and aziridine based synthetic strategies. The third chapter deals with introduction of Biotin and synthetic studies towards Biotin.

Chapter 1: Synthetic studies towards Tamiflu.

Section 1: Introduction to Tamiflu

The present section describes introduction and literature review on synthetic approaches for the tamiflu (Oseltamivir phosphate).

![Fig 1: Tamiflu 1](image)

Section 2: Attempted synthesis towards Tamiflu.

![Scheme 1: Retrosynthesis for Tamiflu employing stereospecific amidoalkylation protocol](image)
This section describes the attempted synthesis of Tamiflu 1 using stereospecific amidoalkylation of imidazothiazolone and Ramberg-Backlund reaction as the key reactions. The retrosynthetic analysis was planned which is described in Scheme 1.

Scheme 2: Synthesis of sulfide 8

The compound 5 was subjected for stereospecific amidoalkylation protocol followed by C-S cleavage leading to thiol 4. Thiol 4 under DBU condition afforded cyclic sulfide 8 in 54% low yield (Scheme 2).

Scheme 3: Stereospecific amidoalkylation protocol based attempt for Tamiflu 1 synthesis

The yield of reaction was improved by stirring thiol 4 in water to afford sulfide 8 in 81% yield. Sulfide 8 was oxidized to sulfone 9 by oxone, which when subjected to Ramberg-
Backlund conditions furnished cyclohexene 3 in 62% yield. Cyclohexene 3 on dihydroxylation afforded diol 10, which was converted to pentaniod acetal 11 using 3-pentanone, trimethyl orthoformate in HCl/MeOH afforded pentaniod acetal 11 in 69% yield. Pentaniod acetal 11 was treated with BH₃,DMS/TMSOTf to afford regioisomeric ethers 2:2a in 1:1 ratio. Desired hydroxy compound 2 was oxidized to ketone 12 using IBX. Attempts were failed to obtain compound 13 from ketone 12 (Scheme 3).

An alternate strategy was planned starting from alcohol 2. Accordingly, alcohol 2 was converted into its mesylate 14 using mesyl chloride, cat DMAP and pyridine to furnish mesylate 14 in 76% yield. Next task was to obtain olefin 15. Accordingly, mesylate 14 was subjected to DBU treatment but it failed to afford the desired olefin 15 (Scheme 4).

After failure to convert the mesylate 14 into olefin 15, an alternative strategy was planned for Tamiflu 1 synthesis from cyclohexene 3. Accordingly cyclohexene 3 was subjected under different allylic oxidation conditions like SeO₂, Pd-C/TBHP, PCC, PDC, SeO₂/H₂O₂ and PhI(OAc)₂/Pd(OAc)₂ which lead to aromatized urea 17 (Scheme 5).

Scheme 4: Mesylate 14 based strategy for Tamiflu 1

Scheme 5: Allylic oxidation attempt for Tamiflu
Section 3: Formal synthesis of Tamiflu employing stereospecific amidoalkylation and Ramberg-Backlund reaction.

This section describes the formal synthetic approach towards Tamiflu 1 based on Ramberg-Backlund reaction. The retrosynthesis for Tamiflu 1 is shown in Scheme 6.

According to retrosynthetic analysis thiol 4 was converted to cyclohexene 3 which is discussed in Chapter 1 Section 2. Generally cyclic ureas are chemically inert to basic as well as acidic conditions. But fruitfully it was possible to successfully hydrolyze urea 3 via LAH reduction followed by hydrolysis in 1% HCl/NH₂OH.HCl and resultant crude diamine was protected as carbamate derivative using neat Boc anhydride to furnish compound 20 in 67% yield over 3 steps.

Scheme 6: Retrosynthesis for Tamiflu 1 based on Ramberg-Backlund reaction

Scheme 7: Synthesis of Enone 18
Having succeeded to hydrolyze urea 3 to vicinal trans diamine 20, next task was to synthesise unsaturated ketone 18. Accordingly diboc derivative 20 on Birch reduction followed by epoxidation using \textit{m}-CPBA gave stereospecific epoxide 21 which was fully characterized by NOSEY mult and single crystal X-ray analysis. Epoxide 21 under Sharpless-Reich protocol was rearranged to afford allylic alcohol 22 followed by DMP oxidation afforded enone 18 well known intermediate for tamiflu 1 synthesis by Shibasaki \textit{et al} (Scheme 7).

**Section 4: Formal synthesis of Tamiflu employing stereospecific amidoalkylation protocol and ring closing metathesis (RCM)**

This section describes the formal synthetic approach towards Tamiflu using stereospecific amidoalkylation protocol and ring closing metathesis (RCM). The retroanalysis for Tamiflu synthesis is outlined in Scheme 8.

![Scheme 8: Retrosynthesis for Tamiflu based on RCM](image)

Accordingly, thiol 4 was treated with phenyl boronic acid, Cu(OAc)$_2$ and pyridine to afford phenyl sulfide 25. The next task was to obtain RCM precursor 24. Accordingly sulfide 25 was treated with NCS followed by treatment of CuCl$_2$.H$_2$O/CuO led to aldehyde 27, which on vinyl magnesium bromide addition afforded 24 in 76 \% yield over 3 steps. The diastereomeric mixture 24 on RCM using Grubbs’ 1$^{st}$ gen. catalyst afforded alcohol 28a:28b in 4:1 ratio in 97\% yield (Scheme 9).

Having cyclohexene skeleton of the Tamiflu with desired diamine in trans fashion, next task was to obtain enone 18. Accordingly compound 28a was subjected to LAH reduction, led to the diamine 29 which was hydrolyzed in 1\% HCl to afford diamine.
Resultant diamine without purification was masked as carbamate derivative using neat (Boc)$_2$O to furnish diboc derivative 23a in good yield. Further diboc 23a was subjected for chemoselective debenzylation under Birch reduction conditions to afford allylic alcohol 22. Conversion of 22 to enone 18 is discussed in Chapter 1 Section 3 (Scheme 10).

Similarly other diastereomer 28b was subjected for LAH reduction gave amine 30, which was hydrolyzed using 1% HCl/NH$_2$OH.HCl to diamine and resultant diamine on treatment with (Boc)$_2$O/DMAP provided triboc derivative 31. Triboc 31 on Birch reduction conditions provided 32 and 19 in ratio 1:2 respectively. The 32 is reported for tamiflu 1 by Shibasaki et al where as transformation of diboc 19 to enone 18 is discussed in Chapter 1 Section 2 (Scheme 11).
Chapter 2: Aziridine based synthetic strategies

Section 1: Introduction to aziridine

The present section describes the introduction, synthetic methods of aziridines and its chemical application in natural product synthesis.

Section 2: Lactone based strategy towards Tamiflu and shortest synthesis of major building block of mitomycins.

This section describes the attempted synthesis of Tamiflu 1 starting from D-mannitol. The retrosynthetic analysis for Tamiflu 1 is described in Scheme 12.

According to retrosynthetic analysis cis-aziridine 35 which was prepared from D-mannitol using reported procedure. The cis-aziridine 35 subjected for acetonide deprotection using TMSOTf in dry DCM at 0 °C to afford dihydroxy compound 38, which on treatment with K₂CO₃ in DCM gave exclusively five membered lactone 34 in
Scheme 12: Retrosynthetic analysis for Tamiflu starting from D-mannitol

85% yield.

Scheme 13: Synthesis of lactone 34 and attempts to explore it for Tamiflu 1

After successfully synthesizing crucial intermediate lactone 34, next task was to obtain the compound 41. Accordingly lactone 34 was subjected under Appel conditions, but failed to furnish the desired halides. So lactone 34 was subjected for tosylation to furnish tosylate 39, which on NaI treatment failed to afford 40 (Scheme 13).
With the *cis*-aziridine 35 compound in hand, to synthesis of 43 was planned as a major building of the mitomycinoids family. Accordingly dihydroxy 38 on oxidative cleavage with NaIO₄ afforded aldehyde followed by NaBH₄ reduction provided alcohol 42. The hydroxy 42 on mesylation gave mesylate 43 in 82% yield (Scheme 14).

Scheme 14: Synthesis of mesylate 43 major building block of mitomycinoids

**Section 3: Formal synthesis of Tamiflu using cis-aziridine as the key precursor and RCM.**

Scheme 15: Retrosynthetic analysis for Tamiflu based on cis –aziridine 35

The present section describes formal synthesis of Tamiflu starting from *cis* -aziridine 35
as the key precursor and ring closing metathesis (RCM). The retroanalysis is outlined in Scheme 15.

Accordingly aziridine 35 was reduced to aldehyde 46 using DIBAL-H to afford aldehyde 46. The crude aldehyde 46 on Wittig olefination gave olefin 47. Olefin 47 was treated with TMSOTf to afford diol 48, which on NaIO₄ cleavage provided aldehyde 49. The crude aldehyde 49 on Barbier addition of bromo-methacrylate/Zn afforded 45:45a in 2:3 ratio respectively. The undesired diastereomer 45a was readily converted into desired isomer 45 using Mitsunobu conditions followed by basic hydrolysis (Scheme 16).

Scheme 16 Synthesis of RCM precursor 45

Having the RCM precursor 45 in hand it was subjected to RCM reaction by refluxing in DCM with Grubbs’ II<sup>nd</sup> gen. catalyst/Ti (i-PrO)₄, gave alcohol 50. Alcohol 50 was converted to its mesylate 44 using MsCl/TEA in 79% yield. The spectral data of mesylate 44 was in well agreement with the reported data by Ishiwata et al. Finally mesylate 44 was treated with BF₃.Et₂O/3-pentanol to furnish aziridine 51 in 80% yield. The spectral data of 51 was fully in agreement with the data reported in the literature (Scheme 17).
Chapter 3: Synthetic studies towards Biotin

Section 1: Introduction to Biotin

This section described the introduction and review on reported synthetic strategies for Biotin.

Section 2: C-alkylation strategy towards Biotin.

This section describes the C-alkylation strategy towards Biotin, the retrosynthetic analysis shown as per Scheme 18.

Accordingly synthesis began with C-alkylation of bromide 56 and imine 57 (which was prepared from cyclohexanone 58 and glycinate ester hydrochloride salt 60 as described in Scheme 19) in 10% NaOH and TBAHSO₄ as PTC gave compound 62, which was directly subjected for hydrolysis in conc. HCl afforded amine 55. The crude amine 55 on treating with benzyl isocyanate afforded urea 63 in 70% over three steps.
The next task was to obtain cyclic urea 54. Accordingly acyclic urea 63 was subjected under different reaction conditions like Rh$_2$(OAc)$_4$/Phl(OAc)$_2$, NBS/AIBN and SeO$_2$. All these attempts led to complex reaction mass (Scheme 20).
Section 3: Formal synthesis of Biotin: MgCl₂/Et₃N mediated coupling and Mitsunobu reaction.

The present section describes the formal synthesis of Biotin employing the MgCl₂/Et₃N mediated coupling and Mitsunobu reaction as the key steps. The retrosynthetic analysis is highlighted in Scheme 21.

According to retrosynthetic analysis, the synthesis of Biotin began with coupling of the acid 70 and acyl chloride 72 (which was prepared from diethyl malonate 68 and cyclohexanone 58 respectively as shown in Scheme 22) by using MgCl₂/Et₃N to furnish β-keto ester 67. β-Keto ester 67 on chemoselective reduction with NaBH₄ to afford β-hydroxy ester 73, which on the Mitsunobu inversion using N₃H gave azide 74 in 82% yield. The azide 74 on Staudinger reduction followed by ethylchloroformate/TEA treatment provided urea 66 in 93% yield.

After having urea 66 in hand, the ester functionality was reduced to alcohol 75 followed
by TBS protection with TBSCl furnished compound 65 in 88% yield. The compound 65 on ozonolysis provided ketone ester 76. The TBS deprotection of 76 was carried out by using CSA/MeOH followed by treatment with CBr₄ afforded bromide 77. Bromide 77 was subjected for thiol 78 substitution under different reaction conditions but unfortunately it ended up in uncharacterized reaction mass (Scheme 23).

Scheme 23: Attempt towards synthesis of thiol 78

The retrosynthetic plan was revised for Biotin 53 synthesis which is summarized in Scheme 24.

Scheme 24: Revised retrosynthetic analysis for Biotin 53
According to retroanalysis urea 65 was treated with benzyl bromide/NaH to afford dibenzyl urea which on ozonolysis furnished into keto ester 81. Next task was to access thioacetate 79. Accordingly 81 was subjected to TBS deprotection using CSA followed by tosylation gave tosylate 82 in 90% yield. The tosylate 82 was treated with KSAc in DMF:THF to afford thioacetate 79 in 90% yield. The hydrolysis of thioacetate 79 was carried out using lipase strain to furnish the thiol 83 in 80% yield. The thiol 83 was cyclized to known intermediate 84 via base mediated cyclisation using DBU as the base followed by hydroxy elimination was carried out with $p$-TSA to furnish olefin 84 in 82% over two steps. Using usual reported procedure reported elsewhere and from this lab olefin 84 can be converted into Biotin 53 (Scheme 25). This constitutes a formal synthesis of biotin.

Scheme 25: Synthesis of intermediate 84