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A Comprehensive Review on Synthetic Approach for Fingolimod

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ABSTRACT
Multiple sclerosis (MS) often consequences in chronic inflammatory and autoimmune disorders, and recent developments have lead to newer therapeutic options for the treatment of the disease. In this review, we have summarized the literature known synthetic strategies of fingolimod which is the key small molecule, and the first oral drug candidate for MS which have been launched in the market.

Key words: *Multiple sclerosis, T- and B-lymphocytes, Fingolimod, Synthesis.*

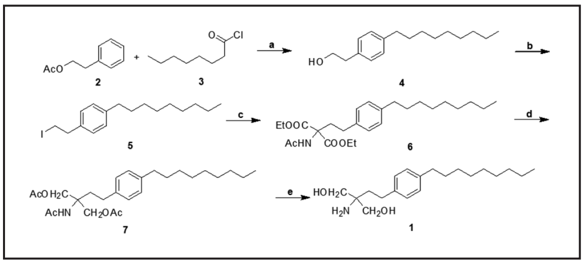
1. INTRODUCTION

FTY720 (fingolimod), a sphingosine 1-phosphate (S1P) receptor modulator, suppresses immune responses by inhibiting T-cell migration into target tissues; however, it does not alter T-cell functions. In this study, we investigated the biological effects of FTY720 on natural killer T (NKT cells). Unlike T cells, FTY720 suppressed the production of interleukin (IL-4), interferon-gamma (IFN-g), IL-10, and IL-13 by NKT cells through the S1P1 receptor. Moreover, FTY720 also inhibited the expression of T-bet and GATA-3 of NKT cells in the presence of TCR engagement. However, it did not inhibit NKT cell migration *in vitro* or *in vivo*. In a K/BxN serum transfer arthritis model, FTY720 suppressed arthritis in B6 but not in CD1d mice. Moreover, the adoptive transfer of control NKT cells restored arthritis in CD1d/mice, whereas FTY720-pretreated NKT cells did not. The number of NKT cells in the joints of B6 mice given FTY720 was similar to that in the joints of untreated B6 mice, whereas the production of IL-4 and IFN-g was reduced in the FTY720-treated B6 mice. Taken together, these data show that FTY720 suppresses cytokine production in NKT cells through S1P1 but not NKT cell migration. Thus, FTY720 may be useful in the treatment of NKT cell-promoted immune diseases.

Fingolimod (FTY720, Gilenya) 1 is a classic example of the drug which is inspired from a natural product myriocin (ISP-1) 1a a metabolite of the fungus *Isaria sinclairii* (Figure 1) [1]. USFDA has approved Gilenya (fingolimod) for the oral multiple sclerosis (MS) treatment recently. It is a structural analog of sphingosine that gets phosphorylated by sphingosine kinases in the cell [2-5]. Fingolimod 1 behaves as a nonselective agonist of the S1P receptor expressed by lymphocytes and prevents lymphocyte emersion from secondary lymphatic organs and subsequent movement into sites of inflammation. A significant reduction in the relapses was observed in patients treated with fingolimod.

2. REPORTED SYNTHESES OF FINGOLIMOD

Fingolimod (FTY720) can be synthesized starting from phenethyl acetate 2. Phenylethyl acetate 2 on Friedel-Crafts acylation using octanoyl chloride 3 followed by reduction of ketone with triethylsilane and reduction of ester to alcohol using sodium methoxide gave the 4-octylphenethyl alcohol 4. Alcohol 4 on mesylation followed by reaction with sodium iodide gave 4-octylphenethyl iodide 5. Iodo derivative 5 was converted to diethyl 2-acetamido-2-[2-(4-octylphenyl)ethyl]malonate 6 using diethyl acetamidomalonate, which on reduction with lithium aluminum hydride (LAH) followed by acetylation gave 2-acetamido-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol diacetate 7. Compound 7 on refluxing with LiOH gave 2-amino-2-[2-(4-octylphenyl)ethyl] propane-1,3-diol hydrochloride [6].



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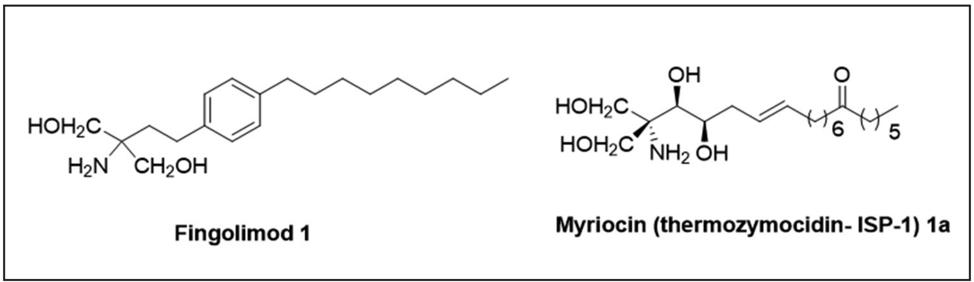
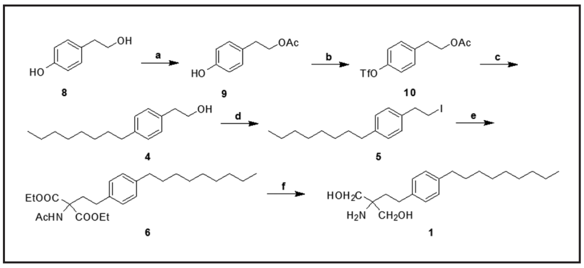


Figure 1: Structures of fingolimod 1 and myriocin 1a.

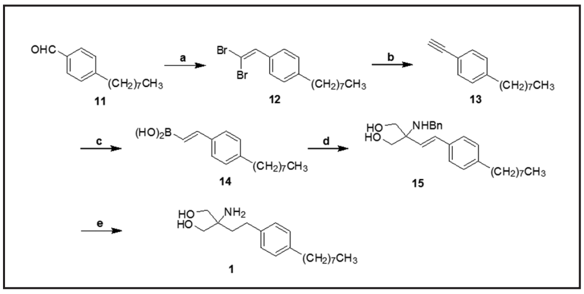
Reagents and conditions: a: (i) $AlCl_3$, 1,2-dichloroethane; (ii) Et_3SiH, trifluoroacetic acid (TFA); (iii) NaOMe, MeOH; b: (i) MsCl, Et_3N, CH_2Cl_2; (ii) NaI, 2-butanone; c: Diethyl acetamidomalonate, NaOEt, EtOH; d: (i) $LiAlH_4$, tetrahydrofuran (THF); (ii) Ac_2O, pyridine; e: 2 N aq LiOH, MeOH.

Fingolimod (FTY720) also be synthesized starting from 2-(4-hydroxyphenyl) ethanol 8. Diol 8 was selectively protected as acetic acid 2-(4-hydroxyphenyl)ethyl ester 9 using $NaHSO_4$/SiO_2 as a solid promoter [7]. Compound 9 was directly converted to its triflate derivative 10 using triflic anhydride. Compound 10 on Grignard reaction with octylmagnesium bromide in the presence of $Fe(acac)_3$ gave acetic acid 2-(4-octylphenyl) ethyl ester, which on reaction with NaOMe gave 4-octylphenethyl alcohol 4. Alcohol 4 on mesylation followed by reaction with lithium iodide gave 4-octylphenethyl iodide 5. Iodo derivative 5 was on reaction with diethyl acetamidomalonate gave diethyl 2-acetamido-2-[2-(4-octylphenyl) ethyl]malonate 6, which on reduction with LAH, acetylation [6,8-10] followed by refluxing with LiOH gave 2-amino-2-[2-(4-octylphenyl)ethyl] propane-1,3-diol hydrochloride [11].



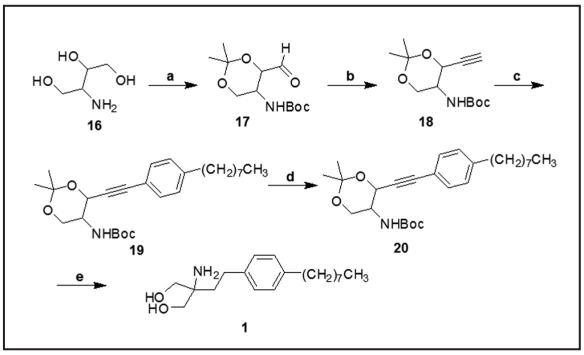
Reagents and conditions: (a) $NaHSO_4$/SiO_2, EtOAc, hexane; (b) Tf_2O, pyridine; (c) $C_8H_{17}MgBr$, Cat $Fe(acac)_3$; (d) MsCl, Et_3N, CH_2Cl_2; (d) i) $MeSO_2Cl$, Et_3N, ii) LiI, THF; (e) diethyl acetamidomalonate, NaH, dimethylformamide (DMF); (f) i) $LiAlH_4$, THF; ii) Ac_2O,pyridine; iii) 2 N aq LiOH, MeOH.

In an alternate method, fingolimod (FTY720) can be synthesized using 4-octylbenzaldehyde 11. 4-octylbenzaldehyde 11 was treated with triphenylphosphine and carbon tetrabromide to give 1,1-dibromostyrene 12. The reaction of *n*-butyllithium with 12 in THF gave 1-ethenyl-4-octylbenzene (13) [7]. The hydroboration [12-14] of 13 using catecholborane in THF following hydrolysis gave 2-(4-octylphenyl)-vinylboronic acid 14. The Petasis reaction using dihydroxyacetone, benzylamine, and boronic acid 14 gave the desired 2-amino-1,3-propanediol 15, and the subsequent catalytic hydrogenolysis of 15 gave FTY720 1 [15].



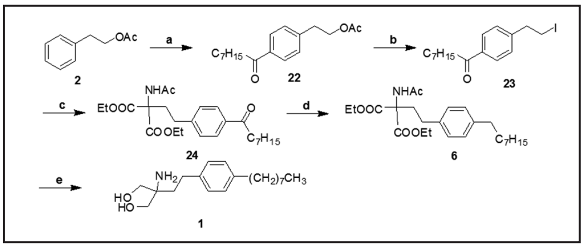
Reagents and conditions: (a) Triphenylphosphine, CBr_4, TEA, DCM, 1 h at 0°C, 83%; (b) n-BuLi, THF, −78°C – RT, 84%; (c) cathecolborane, THF, 4 h, 80°C; (d) dihydroxyacetone, benzylamine, ethanol, 1.5d, RT, 44%; (e) 10% Pd/C, ethanol, 10% HCl, 90%.

Fingolimod (FTY720) was synthesized starting from 2-amino-2-(hydroxymethyl)propane-1,3-diol 16. Compound 16 on protecting the diols and amine followed by swern oxidation gave the aldehyde 17 [16]. Aldehyde [17] 17 was converted to alkyne 18 using one pot protocol by Roth [18]. Tert-butyl 4-ethynyl-2,2-dimethyl-1,3-dioxan-5-ylcarbamate 18 on reaction with 4-octyl iodobenzene [19] under Sonogashira conditions [20] using $Pd(PPh_3)_4$ to give compound 19. Hydrogenation of the internal alkyne of 19 was achieved using Pd/C in benzene to give 20 in quantitative yield. Removal of the acetonide and Boc protecting groups in 20 was accomplished in a single step using TFA–CH_2Cl_2– H_2O (2:2:1) at room temperature to give the free base of 1 in 96% yield after purification.



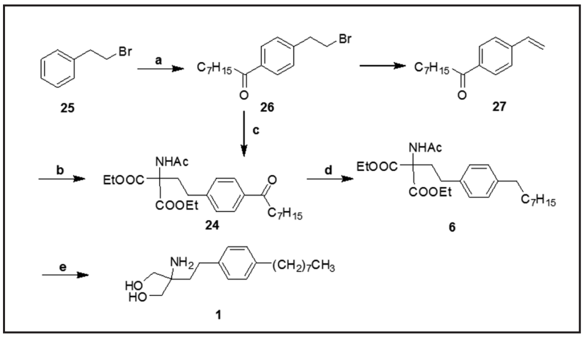
Reagents and conditions: (a) Boc_2O, $(MeO)_2CMe_2$, cat.TsOH, DMF, RT, 3 h; (b) $(COCl)_2$, dimethyl sulfoxide (DMSO), Et_3N, CH_2Cl_2, −78°C to r.t., 5 h; (c) $MeCOCH_2P(O)(OMe)_2$, TsN_3, K_2CO_3, MeCN–MeOH (1:1), RT, 5 h; (d) **3**, $Pd(PPh_3)_4$, CuI, DMF–Et_3N (4:1), RT, 3 h; (e) H_2, 10% Pd/C, benzene, RT, 5 h; (f) TFA–CH_2Cl_2–H_2O (2:2:1), RT, 12 h; (g) anhyd HCl, THF, RT, 3 h.

In another method, phenethyl acetate 2 was used as a starting material for the synthesis of fingolimod. phenethyl acetate 2 on Friedel-Crafts reaction with octanoyl chloride gave the compound 22. Compound 22 was converted to its iodo derivative 23 via deacylation as well as reaction with sodium iodide. Iodo derivative 23 on reaction with diethyl acetamidomalonate to give diethyl 2-acetamido-2-(4-octanoylphenethyl)malonate 24. Compound 24 on reduction with 10% Pd/C to yield diethyl 2-acetamido-2-[2-(4-octylphenyl)ethyl]malonate 6 which on reduction with LAH, acetylation followed by refluxing with LiOH gave FTY720 1 [21,22].



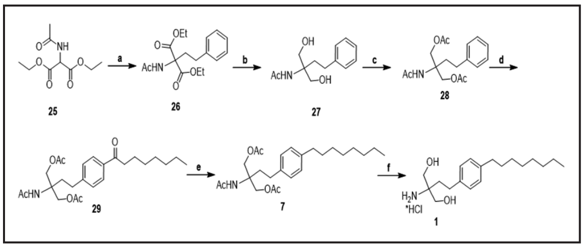
Reagents and conditions: (a) $C_7H_{15}COCl$, $AlCl_3$, 1,2-dichloroethane, RT, 2.5 h; (b) 28% NaOMe in MeOH, MeOH, RT, 1 h; (c) diethyl acetamidomalonate, 60% NaH, DMF, 60°C, 2-6 h; (d) H_2, 10% Pd/C, EtOH, overnight; (e) 2 N aq LiOH, MeOH.

Fingolimod was synthesized starting from phenethyl bromide 25. phenethyl bromide 25 on Friedel-Craft's reaction with octanoyl chloride gave compound 26, which on hydrogen bromide elimination to give the styrene 27. Stryrene 27 on reaction with diethyl acetamidomalonate to give diethyl 2-acetamido-2-(4-octanoylphenethyl)malonate 24. Compound 24 on reduction with 10% Pd/C to yield diethyl 2-acetamido-2-[2-(4-octylphenyl)ethyl]malonate 6 which on reduction with LAH, acetylation followed by refluxing with LiOH gave FTY720 1 [21,22].



Reagents and conditions: (a) $C_7H_{15}COCl$, $AlCl_3$, 1,2-dichloroethane, RT, 2.5 h; (b) i) NaOEt, EtOH, RT, 1 h; ii) diethyl acetamidomalonate, DMF, 60°C, 2-6 h; (c) diethyl acetamidomalonate, 60% NaH, DMF, 60°C, 2-6 h; (d) H_2, 10% Pd/C, EtOH, overnight; (e) 2 N aq LiOH, MeOH.

Fingolimod was synthesized starting from diethyl acetamidomalonate 25. Diethyl acetamidomalonate 25 on reaction with phenethyl bromide gave compound 26, which on reduction with sodium borohydride to give compound 27. Compound 27 on protection gave compound 28 which on reaction with octnoyl chloride afforded compound 28. Compound 28 on reduction with 10% Pd/C to yield compound 6 which on reaction with aq HCl gave FTY720 1 [23].



Reagents and conditions: (a) Phenylethyl bromide, Cs_2CO_3, DMSO, 65°C, 5 h, (b) $NaBH_4$, MeOH, 0°C – RT, 16 h, (c) Ac_2O, pyridine, RT, 16 h, (d) octanoyl chloride, $AlCl_3$, EDC, 0°C – RT, 16 h, (e) 10% Pd-C, EtOH, H_2, RT, 2 h, (f) aq.HCl, 100°C, 1 h.

3. CONCLUSIONS

In this review, we have presented a summary of the various synthetic strategies known in the literature for fingolimod which is using to cure MS. The role of organic chemists in devising efficient and viable routes to the small molecule drugs for the treatment of MS has complemented the design efforts of medicinal chemists, in the discovery of drugs with improved efficacy, better tolerability, and suitable for oral administration.

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***Bibliographical Sketch**

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