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Synthesis of fluorinated analogues of the immunosuppressive drug FTY720

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ABSTRACT

Four fluorinated derivatives of the immunosuppressive drug FTY720 were synthesized by a convergent strategy, using the Sonogashira coupling as the key reaction to assemble the two major fragments.

1. Introduction

Myriocin (**1**) is an immunosuppressive natural product that has been isolated from three different fungal sources, *Myriococcum albomyces*, *Mycelia sterilia* and *Isaria sinclairii* (Fig. 1).[1] Based on structure activity relationship studies, FTY720 (**2**) was designed and synthesized in 1995 as a simplified analogue of **1**, and was found to have higher potency in vitro and in vivo and with less side effects compared with the parent compound (Fig. 1).[2] FTY720 has recently been approved by the FDA as the first oral and first-line drug for the treatment of relapsing-remitting multiple sclerosis (MS), an autoimmune disorder.[3] Its biological activity has been attributed to mimicking the MS-relevant metabolite, sphingosine (**3**) (Fig. 1).[4] Furthermore, **2** has been shown to induce apoptosis across a panel of human cancer cell lines.[5] In particular, studies at our institution have demonstrated its promising therapeutic potential in the treatment of liver[6] and prostate cancers.[7]

The occurrence of fluorine in pharmaceuticals by design has become increasingly prevalent over the last twenty years. It has been estimated that approximately 20% of pharmaceutical compounds currently in use are fluorinated.[8] Examples of fluorinated drugs include the anticancer 5-fluorouracil (**4**), the antidepressant fluoxetine (**5**) and the antiviral efavirenz (**6**) (Fig. 2).[9,10] The rationale for this design strategy is that at a minimal cost in steric demands, the replacement of hydrogen with electronegative fluorine can introduce different physicochemical properties to the molecule, including changes in lipophilicity, p*K*a, and the most stable conformations, leading to enhanced binding affinities at recognition sites, entry into alternative metabolic pathways or an increased stability and bioavailability in organisms.[11] Fluorination resulting in the improvement of the pharmacological profile made way for development of new drugs, such as the antibacterial flurithromycin (**7a**), developed base on its parent erythromycin (**7b**); the anti-hyperlipidemic ezetimib (**8a**) from its parent SCH 48461 (**8b**); and anticancer valrubicine (**9a**) based on doxorubicin (**9b**), all of which are currently on the market (Fig. 2).[9,12] The fluorinated derivatives showed an enhanced metabolic stability, bioavailability and/or reduced toxicity compared to their predecessors.

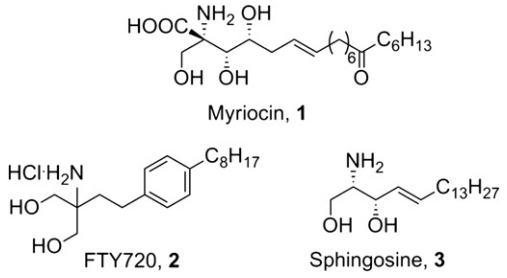

Fig. 1. Myriocin (**1**), FTY720 (**2**), and sphingosine (**3**).

Due to the therapeutic potential of FTY720, many studies have been carried out to explore the synthesis and bioactivities of its analogues.[2,13,14] In light of the biological significance of **2** and the potential to improve the pharmacological profile of drugs using

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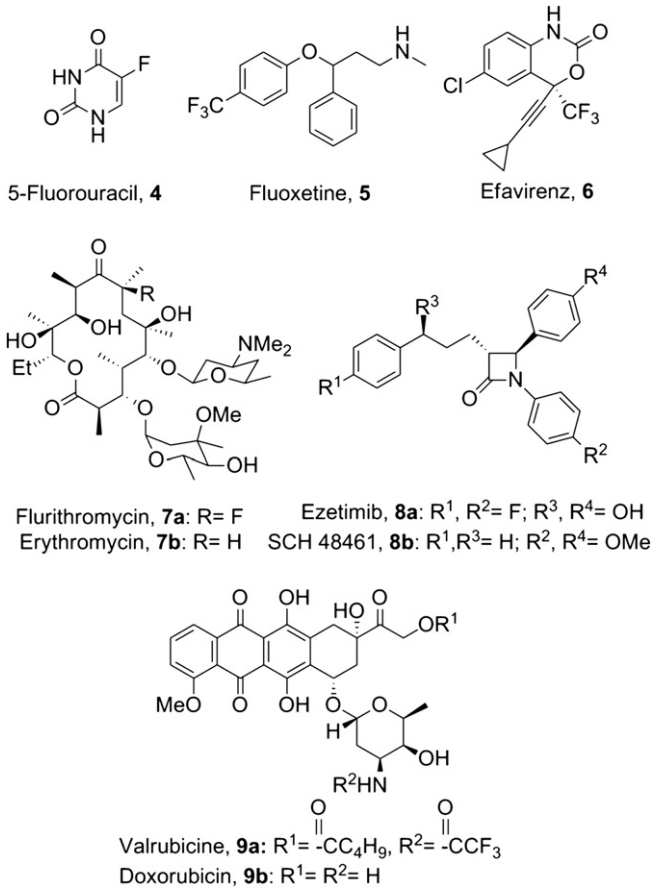


Fig. 2. Examples of fluorinated drugs.

fluorination as a strategy in medicinal chemistry, we initiated an effort directed at the design and synthesis of some fluorinated FTY720 analogues.

2. Results and discussion

2.1. Design of fluorinated analogues of FTY720

The design and rapid synthesis of novel fluorinated analogues of FTY720 was contingent on the availability of fluorinated aromatic bromides or iodides. Most commercially available fluorinated aromatics were in the form of aryl fluorides or trifluoromethylarenes. Access to other fluorinated analogues would require additional synthetic efforts. With these considerations in mind, analogues **10a**–**c** were designed based on the commercial availability of the corresponding fluorinated aromatic iodides (Fig. 3).

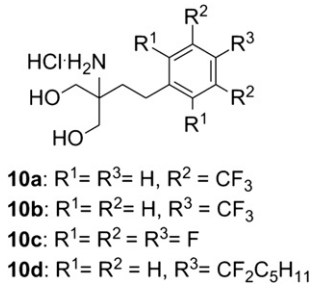
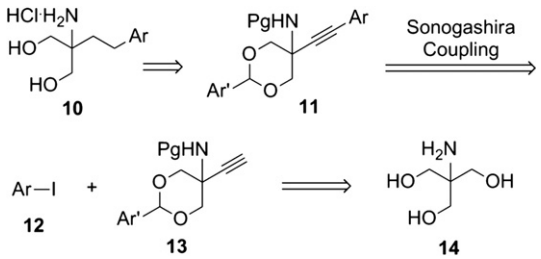


Fig. 3. Novel fluorinated analogues of FTY720 **10a**–**d**.

We have also considered that the aryl ring or the benzylic positions of **2** might be susceptible to oxidation by liver enzymes and thus resulting in an attenuated metabolic stability. Fluorine was introduced in **10a**–**d** to block these potentially metabolically labile sites to undermine the putative oxidative processes.[15] None of the analogues **10a**–**d** are known in the literature (Fig. 3).

2.2. Retrosynthetic analysis

To maximize the efficiency of the synthesis, we sought to develop a convergent and unified strategy towards all four of the fluorinated analogues **10** (Scheme 1). We envisioned that all of them could be obtained from a Sonogashira coupling reaction between a common intermediate alkyne **13** bearing the highly polar terminus, and the corresponding fluorinated aryl iodides **12**. The desired analogues **10** could be obtained from **11** by an exhaustive reduction which could in one step yield not only the ethylene linker from the alkyne, but also a deprotection of the diol if it were protected as a benzylidene derivative. The common intermediate **13** could be accessed readily from commercially available tris (hydroxymethyl)aminomethane **14**.

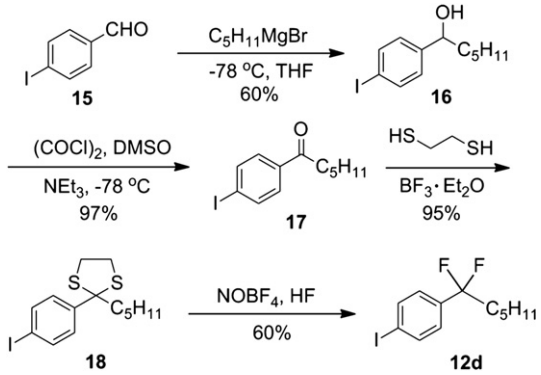


Scheme 1. Retrosynthetic analysis.

Coincidentally, about the time we had began our work on the design and synthesis of analogues **10a**–**d**, Kim et al. published a similar Sonogashira coupling strategy for the synthesis of the parent compound FTY720.[16] Other approaches to FTY720 and its analogues have also been reported.[2,13,14]

2.3. Synthesis of 12d

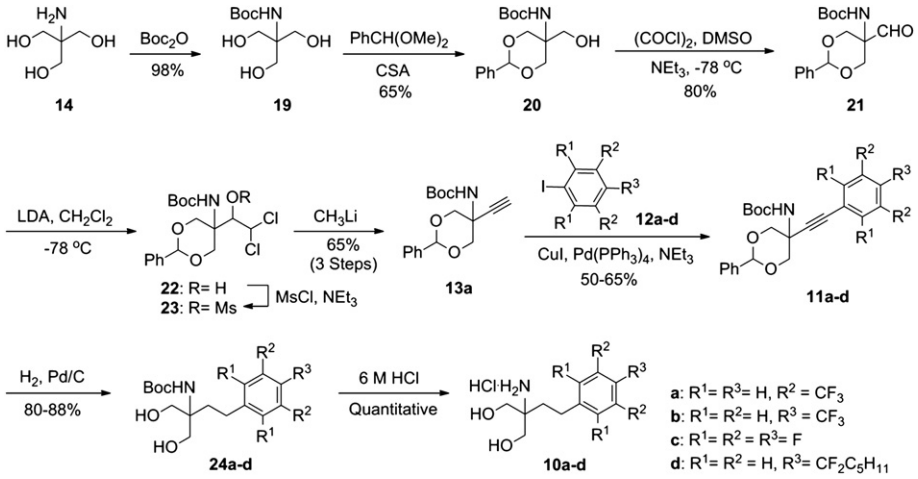
All of the aryl iodides **12** required for the synthesis of **10a**–**d** were commercially available except for **12d**, which was a novel compound and had to be prepared (Scheme 2). A Grignard addition by *n*-pentylmagnesium bromide to 4-iodobenzaldehyde **15**, followed by a Swern oxidation, afforded ketone **17**. It was converted to dithiane **18** in high yield. Fluorine was introduced by a desulfurative fluorination of **18** using HF in the presence of $NOBF_4$.[17]



Scheme 2. Synthesis of aryl iodide **12d**.

2.4. Synthesis of 10a–d

The synthesis of alkyne **13a** commenced with tris(hydroxylmethyl)aminomethane (Scheme 3). Protection of the amine with Boc_2O and the diol with benzaldehyde dimethyl acetal yielded alcohol **20**, which was subject to a Swern oxidation to give aldehyde **21**. Nucleophilic attack by deprotonated CH_2Cl_2 to give alcohol **22** and subsequent activation with mesyl chloride provide the requisite leaving groups in **23**. Elimination was effected with MeLi to provide alkyne **13a**.[18]



Scheme 3. Synthesis of fluorinated analogues **10a**–**d**.

We then executed the key Sonogashira coupling reactions. As shown in Scheme 3, alkyne **13a** was successfully coupled with all aryl iodides **12a**–**d** in moderate yields to give disubstituted alkynes **11a**–**d**. Treatment of **11a**–**d** with hydrogen and palladium on carbon resulted in the concomitant reduction of the alkyne and hydrogenolysis to deprotect the diol to yield **24a**–**d**. Finally, deprotection of the Boc group afforded FTY720 analogues **10a**–**d** as hydrochloric acid salts in quantitative yields.

3. Conclusion

We have successfully employed a convergent and unified strategy to synthesize four fluorinated analogues of FTY720. The common intermediate **13a** was synthesized in six steps, which was then parlayed into the four analogues **10a**–**d** in three additional steps. We believe this approach can be readily extended to access other analogues of FTY720 with aromatic ring variations and will thus be useful in further studies on structure-activity relationships of FTY720 analogues. The biological studies of these analogues will be reported due course.

4. Experimental

4.1. General experimental

All reactions were performed in oven-dried flasks under an inert atmosphere of argon. Solvents were dried over calcium hydride prior to use. Flash column chromatography was performed with E. Merck silica gel 60 (230–400 mesh ASTM). TLC was performed with E. Merck 0.2 mm pre-coated silica gel plates (Kieselgel 60 F_{254+}). ^1H and ^{13}C NMR spectra were recorded on Bruker DPX 300, 400 Fourier Transform spectrometers. IR spectroscopy was performed with a Bio-Rad Fourier Transform 165 Spectrophotometer. Mass spectra were recorded on a Finnigan MAT 95 Mass Spectrometer or API QSTAR PULSAR *i*LC/MS/TOF System.

4.2. Synthesis of aryl iodide 12d

*4.2.1. Synthesis of **16**.* To a cooled (−78 °C) and stirred solution of **15** (2.01 g, 8.65 mmol) in THF (80 mL) was added *n*-pentylmagnesium bromide in THF (30 mL, 13.0 mmol). The reaction was stirred at −78 °C for 1.5 h. It was then poured into saturated NH_4Cl and the organic layer was separated. The aqueous layer was extracted with EtOAc (3×100 mL) and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography (8% EtOAc in hexane) to afford **16** (1.58 g, 60% yield) as a colourless oil. R_f (10% EtOAc in hexane) 0.36; ^1H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, J=8.4 Hz, 2H), 7.09 (d, J=8.4 Hz, 2H), 4.65–4.59 (m, 1H), 1.82–1.64 (m, 3H), 1.43–1.28 (m, 6H), 0.87 (t, J=4.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.6, 137.5, 128.0, 92.8, 74.1, 39.1, 31.7, 25.4, 22.6, 14.1; IR (CH_2Cl_2): 3683, 2837, 2801, 2740, 1705, 1655, 1583, 1568, 1481, 1372, 1205, 1170, 1054; LRMS (EI): *m*/*z* 304 (10), 233 (100); HRMS (EI): *m*/*z* calcd for $C_{12}H_{17}OI$ 304.0321, found: 304.0324.

*4.2.2. Synthesis of **17**.* To a round bottom flask containing $(COCl)_2$ (0.53 mL, 6.07 mmol) in anhydrous CH_2Cl_2 (60 mL) at −78 °C was added DMSO (0.86 mL, 12.1 mmol) dropwise. After stirring for 15 min at −78 °C, **16** (923.2 mg, 3.04 mmol) in CH_2Cl_2 (5 mL) was added via cannula. At this temperature, the mixture was stirred for 1 h, followed by the addition of Et_3N (3.4 mL, 24.3 mmol). The mixture was stirred for 30 min at −78 °C, then the cooling bath was removed and the reaction was allowed to warm to room temperature. Water was added and the aqueous layer was extracted with CH_2Cl_2 (3×60 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to give **17** (859.3 mg, 97% yield) as a colourless oil. R_f (10% EtOAc in hexane) 0.79; ^1H NMR (500 MHz, $CDCl_3$) δ 7.82 (dd, J=6.7, 1.9 Hz, 2H), 7.67 (dd, J=6.7, 1.8 Hz, 2H), 2.91 (t, J=7.5 Hz, 2H), 1.75–1.69 (m, 2H), 1.37–1.34 (m, 4H), 0.91 (t, J=2.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.9, 137.9, 136.3, 129.5, 100.8, 38.5, 31.5, 24.0, 22.5, 14.0; IR (CH_2Cl_2):3689, 2963, 2929, 2855, 1685, 1582, 1393, 1006; LRMS (EI): *m*/*z* 302 (4), 259 (3), 231 (96), 203 (20); HRMS (EI): *m*/*z* calcd for $C_{12}H_{15}OI$ 302.0153, found: 302.0161. The ^1H NMR spectroscopic data corresponded to those of **17** in literature.[19]

*4.2.3. Synthesis of **18**.* To a cooled (0 °C) stirred solution of **17** (850 mg, 2.81 mmol) in anhydrous CH_2Cl_2 (25 mL) was added dithioethane (5.9 mL, 7.03 mmol). $BF3{\cdot}Et_2O$ (1.86 mL, 7.03 mmol) was then added at 0 °C and the reaction mixture was stirred at

room temperature for 2 h. The reaction mixture was diluted with hexane (20 mL) and washed with saturated $NaHCO_3$ (20 mL) and 15% NaOH (20 mL), respectively. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by chromatography (5% EtOAc in hexane) to afford **18** (1.01 g, 95% yield) as a pale yellow oil. R_f (pure hexane) 0.53; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, J=8.3 Hz, 2H), 7.44 (d, J=8.3 Hz, 2H), 3.42–3.31 (m, 2H), 3.24–3.14 (m, 2H), 2.32–2.27 (m, 2H), 1.23–1.20 (m, 6H), 0.82 (t, J=6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.4, 137.0, 129.4, 92.5, 73.9, 45.6, 39.2, 31.8, 27.6, 22.4, 14.0; IR (CH_2Cl_2): 3683, 2960, 2932, 2848, 1482, 1387, 1004; LRMS (EI): m/z 378 (2), 307 (100), 247 (8), 203 (2); HRMS (EI): m/z calcd for $C_{14}H_{19}IS_2$ 377.9958, found: 377.9961.

*4.2.4. Synthesis of **12d**.* To a plastic bottle containing $NOBF_4$ (782 mg, 6.68 mmol), HF (3 mL) in anhydrous CH_2Cl_2 (15 mL) was added via cannula at 0 °C. Dithiane **18** (1.26 g, 3.34 mmol) in anhydrous CH_2Cl_2 (6 mL) was then added dropwise via cannula. The reaction mixture was stirred at 0 °C for 5 min and then warmed to room temperature and stirred for another 10 min. The reaction mixture was then poured into petroleum ether (80 mL) and extracted with petroleum and CH_2Cl_2 (1:1, 3×50 mL). The organic layer was then filtered through silica gel and concentrated in vacuo. The residue was purified by chromatography (3% EtOAc in hexane) to afford **12d** (649.6 mg, 60% yield) as a pale yellow oil. R_f (10% EtOAc in hexane) 0.72; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J=8.2 Hz, 2H), 7.20 (d, J=8.3 Hz, 2H), 2.14–2.02 (m, 2H), 1.56–1.38 (m, 2H), 1.37–1.25 (m, 4H), 0.88 (t, J=6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.6, 126.9, 126.9, 126.8, 95.8, 39.2, 38.9, 38.7, 31.4, 22.4, 22.2, 22.1, 22.1, 13.9; IR (CH_2Cl_2): 3684, 2958, 2937, 2845, 1433, 1392, 1387, 1007.

4.3. Synthesis of alkyne 13a

*4.3.1. Synthesis of **20**.* To a stirred solution of **19**[20] (7.21 g, 32.6 mmol) and camphorsulfonic acid (757 mg, 3.26 mmol) in DMF (40 mL) was added benzaldehyde dimethyl acetal (7.4 mL, 48.9 mmol). The mixture was stirred at room temperature overnight and quenched with excess Et_3N. The mixture was stirred for 20 min and poured into H_2O, and extracted with EtOAc (3×150 mL). The combined organic layers were washed with H_2O, brine and dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography using 20% EtOAc in hexane to afford **20** (6.53 g, 65% yield) as a white solid. R_f (20% EtOAc in hexane) 0.48; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53–7.50 (m, 2H), 7.44–7.35 (m, 3H), 5.63 (br s, 1H), 5.44 (s, 1H), 4.69 (br s, 1H), 4.21 (d, J=11.7 Hz, 2H), 3.82 (d, J=11.7 Hz, 2H), 3.70 (d, J=6.6 Hz, 2H), 1.47 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.5, 137.5, 129.0, 128.2, 125.9, 101.7, 80.4, 71.4, 64.4, 53.4, 28.2; IR ($CHCl_3$): 3534, 3423, 2983, 2874, 1741, 1508, 1443, 1375, 1162, 1047; LRMS (EI): m/z 252 (6), 236 (5), 204 (35), 173 (15); HRMS (EI): m/z calcd for $C_{12}H_{14}NO_5$ ($M^+-C_4H_9$) 252.0872, found: 252.0872. The ^{1}H NMR spectroscopic data corresponded to those of **20** in literature.[21]

*4.3.2. Synthesis of **21**.* To a solution of oxalyl chloride (2.85 mL, 32.4 mmol) in CH_2Cl_2 (140 mL) at −78 °C was added DMSO (4.6 mL, 64.9 mmol). The mixture was stirred for 15 min. Alcohol **20** (5.03 g, 16.3 mmol) in CH_2Cl_2 (15 mL) was added at −78 °C. The mixture was stirred for 30 min Et_3N (18 mL, 130 mmol) was added at −78 °C. The resulting mixture was stirred for 30 min at −78 °C. The reaction was quenched with H_2O (200 mL) and extracted with CH_2Cl_2 (3×150 mL). The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography using 20% EtOAc in hexane to afford **10** (4.01 g, 80% yield) as a white solid. R_f (10% EtOAc in hexane) 0.43; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.59 (s, 1H), 7.51–7.48 (m, 2H), 7.41–7.39 (m, 3H), 5.69 (br s, 1H), 5.50 (s, 1H), 4.28 (d, J=11.3 Hz, 2H), 1.48 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.4, 155.8, 137.1, 129.4, 128.4, 125.9, 101.7, 81.3, 69.6, 60.5, 28.3; IR ($CHCl_3$): 3432, 2877, 1728, 1705, 1490, 1370, 1161; LRMS (EI): m/z 278 ([M−CHO]$^+$, 10), 221 (7), 163 (5); HRMS (EI): m/z calcd for $C_{15}H_{20}NO_4$ [M^+−CHO]: 278.1392, found: 278.1392. The ^{1}H NMR spectroscopic data corresponded to those of **21** in literature.[21]

*4.3.3. Synthesis of **13a**.* To CH_2Cl_2 (6 mL, 93.3 mmol) was added pre-cooled lithium diisopropylamide (160 mL, 0.22 M) in THF dropwise at −78 °C. The mixture was stirred at −78 °C for 15 min and **21** (3.59 g, 11.7 mmol) in anhydrous THF (35 mL) was added via cannula. The mixture was stirred at −78 °C for 1.5 h and then quenched with H_2O (150 mL). The reaction mixture was stirred at room temperature and saturated NH_4Cl was added. The mixture was extracted with EtOAc (3×200 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was then diluted with anhydrous CH_2Cl_2 (85 mL). To this solution were added, Et_3N (2.5 mL, 17.5 mmol) and MsCl (1.35 mL, 17.5 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 18 h and then quenched with H_2O (100 mL) and extracted with CH_2Cl_2 (3×100 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was then diluted with anhydrous THF (120 mL) and cooled to −60 °C. MeLi (40 mL, 1.6 M) was added dropwise. The reaction was stirred at 0 °C for 2 h and then quenched with H_2O (100 mL) and saturated NH_4Cl. The mixture was extracted with EtOAc (3×120 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography using 20% EtOAc in hexane to afford **13a** (2.30 g, 65% yield) as a white solid. R_f (10% EtOAc in hexane) 0.34; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.46 (m, 2H), 7.21–7.37 (m, 3H), 5.51 (s, 1H), 5.25 (br s, 1H), 4.45 (d, J=11.6 Hz, 2H), 3.99 (d, J=10.4 Hz, 2H), 2.48 (s, 1H), 1.48 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4, 137.2, 129.3, 128.4, 126.0, 101.9, 80.4, 79.4, 74.0, 73.0, 47.2, 28.4; IR ($CHCl_3$): 3448, 3320, 2909, 2849, 1719, 1490, 1160, 1080; LRMS (EI): m/z 230 ([M−C_4H_9]$^+$, 6), 217 (3), 199 (3), 185(6), 172 (2); HRMS (EI): m/z calcd for $C_{13}H_{12}NO_3$ [M^+−OC_4H_9]: 230.0817, found: 230.0817.

4.4. Synthesis of fluorinated analogues FTY720 10a–d

*4.4.1. Synthesis of **10a**.*

*4.4.1.1. Synthesis of **11a**.* To a solution of compound **13a** (125 mg, 0.412 mmol), and Et_3N (1 mL) in DMF (4 mL), 1-iodo-3,5-bis(trifluoromethyl)benzene (146 μL, 0.824 mmol), CuI (15.7 mg, 0.082 mmol) and $Pd(PPh_3)_4$ (47.7 mg, 0.041 mmol) were added. The reaction mixture was stirred at room temperature overnight and filtered through a SiO_2 pad. The residue was washed with 50% EtOAc/hexane (4×15 mL) and concentrated in vacuo. The residue was purified by flash chromatography using 10% EtOAc in hexane to afford **11a** (138 mg, 65% yield) as white solid. R_f (20% EtOAc in hexane) 0.71; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (s, 2H), 7.82 (s, 1H), 7.54–7.51 (m, 2H), 7.45–7.40 (m, 2H), 5.57 (s, 1H), 5.39 (br s, 1H), 4.55 (d, J=11.3 Hz, 2H), 4.11 (d, J=11.5 Hz, 2H), 1.50 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.3, 137.1, 131.9, 129.4, 128.4, 128.4, 126.0, 124.6, 122.1, 102.0, 88.3, 82.9, 80.5, 72.8, 47.9, 28.4; IR (CH_2Cl_2): 3702, 3669, 3602, 3426, 2983, 2923, 2869, 1720, 1606, 1491, 1457, 1385, 1372, 1181, 1142; LRMS (EI): m/z 496 ([M^+−F], 2), 459 (3), 430 (2), 399 (1); HRMS (EI): m/z calcd for $C_{25}H_{23}NO_4F_5$ [M^+−F]: 496.1544, found: 496.1547.

*4.4.1.2. Synthesis of **24a**.* To a solution of compound **11a** (100 mg, 0.194 mmol) in EtOAc (2 mL), Pd/C (30 mg, 0.0194 mmol) was added and the reaction mixture was stirred at room temperature overnight under a H_2 atmosphere. The mixture was then

filtered using a Celite pad and washed with EtOAc (5×10 mL). The combined organic layers were concentrated in vacuo. The residue was purified by flash chromatography using 10% EtOAc in hexane to afford **24a** (71.1 mg, 85% yield) as a white solid. R_f (20% EtOAc in hexane) 0.07; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.64 (s, 2H), 5.14 (br s, 1H), 3.86 (d, J=11.3 Hz, 2H), 3.67 (d, J=11.3 Hz, 2H), 2.79–2.75 (m, 2H), 2.63 (br s, 2H), 1.97–1.93 (m, 2H), 1.46 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.3, 132.2, 131.9, 131.6, 131.4, 128.6, 124.5, 122.3, 120.2, 80.5, 66.3, 59.1, 34.4, 29.6, 28.3; IR (CH_2Cl_2): 2683, 2426, 2976, 2942, 2861, 1714, 1616, 1519, 1500, 1465, 1381, 1175, 1136; LRMS (FAB): m/z 400 ([M^+−CH_2OH], 8), 345 (2), 300 (100), 227 (16); HRMS (EI): m/z calcd for $C_{17}H_{20}NO_3F_6$ [M^+−CH_2OH]: 400.1352, found: 400.1347.

*4.4.1.3. Synthesis of **10a**.* To a solution of compound **24a** (20 mg, 0.0464 mmol) in dioxane (five drops), 6 M HCl (five drops) was added and the mixture was stirred at room temperature overnight. The mixture was dried by azeotropic evaporation with benzene and pumped to dryness. Compound **10a** (17 mg, quantitative) was obtained as a white solid. ^{1}H NMR (500 MHz, MeOD) δ 7.88 (s, 2H), 7.82 (s, 1H), 4.89 (s, 1H), 3.70 (s, 4H), 2.88–2.84 (m, 2H), 2.04–1.97 (m,2H); ^{13}C NMR (125 MHz, MeOD) δ146.0, 133.2, 130.2, 126.1, 121.3, 62.6, 62.4, 34.3, 30.9; IR (CH_2Cl_2): 3166, 1738, 1603, 1376, 1271, 1048; LRMS (FAB): m/z 332; HRMS (FAB): m/z calcd for $C_{13}H_{16}NO_2F_6$ [M^+−Cl]: 332.1085, found: 332.1085.

*4.4.2. Synthesis of **10b**.*

*4.4.2.1. Synthesis of **11b**.* To a solution of compound **13′** (100 mg, 0.329 mmol) in Et_3N (1 mL) and DMF (4 mL), iodobenzotrifluoride (97 μL, 0.659 mmol), CuI (12.6 mg, 0.066 mmol) and $Pd(PPh_3)_4$ (38 mg, 0.033 mmol) were added. The reaction mixture was stirred at room temperature overnight and filtered through a SiO_2 pad. The residue was washed with 50% EtOAc/hexane (4×15 mL) and concentrated in vacuo. The residue was purified by flash chromatography using 10% EtOAc in hexane to afford **11b** (95.4 mg, 65% yield) as a white solid. R_f (10% EtOAc in hexane) 0.72; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58–7.49 (m, 6H), 7.44–7.38 (m, 3H), 5.56 (s, 1H), 5.33 (br s, 1H), 4.53 (d, J=11.3 Hz, 2H), 4.08 (d, J=11.5 Hz, 2H), 1.59 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4, 137.2, 132.2, 129.4, 128.4, 126.1, 125.2, 102.0, 87.2, 84.4, 80.4, 73.0, 47.9, 28.4; IR ($CHCl_3$): 3738, 2983, 2877, 1718, 1492, 1324, 1170, 1128, 1064; LRMS (EI): m/z 391 ([M−C_4H_9]$^+$, 4), 361 (5); HRMS (EI): m/z calcd for $C_{20}H_{16}$ NF_3O_4 [M^+−C_4H_9]: 391.1030, found: 391.1031.

*4.4.2.2. Synthesis of **24b**.* To a solution of compound **11b** (95.4 mg, 0.214 mmol) in EtOAc (2.5 mL), Pd/C (33 mg, 0.0214 mmol) was added and the reaction mixture was stirred at room temperature overnight under a H_2 atmosphere. The mixture was then filtered using a Celite pad and washed with EtOAc (5×10 mL). The combined organic layers were concentrated in vacuo. The residue was purified by flash chromatography using 10% EtOAc in hexane to afford **24b** (68 mg, 88% yield) as a white solid. R_f (20% EtOAc in hexane) 0.29; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, J=8.2 Hz, 2H), 7.30 (d, J=7.1 Hz, 2H), 5.05 (br s, 1H), 3.88 (dd, J=5.8, 11.4 Hz, 2H), 3.66 (dd, J=6.1, 11.4 Hz, 2H), 3.28 (br s, 2H), 2.71–2.66 (m, 2H), 1.94–1.88 (m, 2H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.4, 146.0, 128.7, 128.6, 128.3, 125.4, 80.3, 66.3, 59.2, 34.6, 29.6, 28.4; IR (CH_2Cl_2): 3615, 3421, 2977, 2929, 1684, 1624, 1503, 1449, 1368, 1322, 1260, 1160, 1119, 1059; LRMS (EI): m/z 332 ([M−C_2H_6]$^+$, 18), 276 (35), 258 (14); HRMS (EI): m/z calcd for $C_{16}H_{21}NO_3F_3$ [M^+−C_2H_6]: 332.1479, found: 332.1474.

*4.4.2.3. Synthesis of **10b**.* To a solution of compound **24b** (30 mg, 0.0829 mmol) in dioxane (six drops), 6 M HCl (six drops) was added. The mixture was stirred at room temperature overnight. The mixture was dried by azeotropic evaporation with benzene and pumped to dryness. Compound **10b** (25 mg, quantitative) was obtained as a white solid. ^{1}H NMR (500 MHz, CD_3OD) δ 7.58 (d, J=8.1 Hz, 2H), 7.44 (d, J=8.0 Hz, 2H), 3.70 (s, 4H), 2.78–2.75 (m, 2H), 1.99–1.96 (m, 2H); ^{13}C NMR (125 MHz, CD_3OD) δ 147.3, 130.2, 129.9, 127.0, 126.6, 124.9, 62.6, 62.2, 34.4, 30.1; IR ($CHCl_3$): 3688, 3588, 3340, 2896, 1606, 1509, 1457, 1408; LRMS (FAB): m/z 264 [M^+−Cl]; HRMS (FAB): m/z calcd for $C_{12}H_{16}NO_2F_3$ [M^+−Cl]: 264.1217, found: 264.1211.

*4.4.3. Synthesis of **10c**. 4.4.3.1. Synthesis of **11c**.* To a solution of compound **13a** (125 mg, 0.412 mmol), Et_3N (1 mL) in DMF (4 mL), pentafluoroiodobenzene (110 μL, 0.824 mmol), CuI (15.7 mg, 0.066 mmol) and $Pd(PPh_3)_4$ (48 mg, 0.041 mmol) were added. The reaction mixture was stirred at room temperature overnight and filtered through a SiO_2 pad. The residue was washed with 50% EtOAc/hexane (4×15 mL) and concentrated in vacuo. The residue was purified by flash chromatography using 10% EtOAc in hexane to afford **11c** (97.3 mg, 50% yield) as a white solid. R_f (10% EtOAc in hexane) 0.46; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52–7.49 (m, 2H), 7.43–7.38 (m, 3H), 5.57 (s, 1H), 5.57 (br s, 1H), 4.54 (d, J=11.5 Hz, 2H), 4.10 (d, J=11.6 Hz, 2H), 1.49 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 137.1, 129.5, 128.5, 126.1, 102.1, 77.3, 72.7, 48.2, 29.8, 28.9; IR (CH_2Cl_2): 2429, 2982, 2936, 2872, 1723, 1456, 1393, 1369, 1170, 1083; LRMS (EI): m/z 413 ([M^+−C_4H_8], 2), 277 (100), 259 (21), 233 (96); HRMS (EI): m/z calcd for $C_{19}H_{12}NO_4F_5$ [M^+−C_4H_8]: 413.0694, found: 413.0686.

*4.4.3.2. Synthesis of **24c**.* To a solution of compound **11c** (80 mg, 0.169 mmol) in EtOAc (2 mL), Pd/C (26 mg, 0.0169 mmol) was added and the reaction mixture was stirred at room temperature overnight under a H_2 atmosphere. The mixture was then filtered using a Celite pad and washed with EtOAc (5×10 mL). The combined organic layers were concentrated in vacuo. The residue was purified by flash chromatography using 10% EtOAc in hexane to afford **24c** (54 mg, 83% yield) as a white solid. R_f (20% EtOAc in hexane) 0.14; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.07 (br s, 1H), 3.88 (d, J=11.4 Hz, 2H), 3.66 (d, J=11.3 Hz, 2H), 2.73 (t, J=8.5 Hz, 2H), 1.89–1.83 (m, 2H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.2, 136.6, 80.4, 66.5, 59.0, 32.4, 31.6, 28.3; IR (CH_2Cl_2): 3154, 1738, 1453, 1386, 1171, 1058; LRMS (EI): m/z 354 ([M^+−CH_2OH], 8), 297 (34), 266 (23); HRMS (EI): m/z calcd for $C_{15}H_{17}NO_3F_5$ [−CH_2OH] 354.1054, found: 354.1058.

*4.4.3.3. Synthesis of **10c**.* To a solution of compound **24c** (30 mg, 0.0778 mmol) in dioxane (six drops), 6 M HCl (six drops) was added and the mixture was stirred at room temperature overnight. The mixture was dried by azeotropic evaporation with benzene and pumped to dryness. Compound **10c** (25 mg, quantitative) was obtained as a white solid. ^{1}H NMR (500 MHz, MeOD) δ 3.70 (s, 4H), 2.80–2.76 (m, 2H), 2.01–1.95 (m, 2H); ^{13}C NMR (125 MHz, MeOD) δ 136.9, 62.6, 62.4, 34.3, 30.1; IR (CH_2Cl_2): 3164, 2693, 2296, 1590, 1408; LRMS (FAB): m/z 286; HRMS (FAB): m/z calcd for $C_{11}H_{13}NO_2F_5$ [M^+−Cl]: 286.0860, found: 286.0866.

*4.4.4. Synthesis of **10d**. 4.4.4.1. Synthesis of **11d**.* To a solution of compound **13a** (68.3 mg, 0.225 mmol), Et_3N (0.5 mL) in DMF (2 mL), **12d** (182 mg, 0.563 mmol), CuI (8.6 mg, 0.045 mmol) and $Pd(PPh_3)_4$ (26 mg, 0.023 mmol) were added. The reaction mixture was stirred at room temperature overnight and filtered through a SiO_2 pad. The residue was washed with 50% EtOAc/hexane (4×15 mL) and concentrated in vacuo. The residue was purified by flash chromatography using 10% EtOAc in hexane to afford **11d** (63.3 mg, 57% yield) as a white solid. R_f (10% EtOAc in hexane) 0.49; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52–7.48 (m, 4H), 7.40 (d, J=7.0 Hz, 5H), 5.55 (s, 1H), 5.32 (br s, 1H), 4.52 (d, J=11.3 Hz, 2H), 4.07 (d, J=11.2 Hz, 2H), 2.14–2.02 (m, 2H), 1.49 (s, 9H), 1.39–1.36 (m, 2H), 1.29–1.27 (m, 4H), 0.86 (t, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.3, 137.3, 131.9, 129.4, 128.4, 126.0, 125.0, 125.0, 124.9, 123.6, 122.9, 101.9, 85.8,

84.9, 80.3, 73.1, 47.9, 39.2, 38.9, 38.7, 31.4, 28.4, 22.4, 22.2, 22.1, 22.1, 13.9; IR (CH_2Cl_2): 3683, 3428, 2960, 2934, 2868, 1715, 1673, 1618, 1501, 1456, 1393, 1368, 1328, 1168, 1136, 1078; LRMS (EI): *m*/*z* 442 (1), 413 (2), 308 (20), 289(30), 263 (56); HRMS (EI): *m*/*z* calcd for $C_{25}H_{27}NF_2O_4$ 442.1805, found: 442.1808.

*4.4.4.2. Synthesis of **24d**.* To a solution of compound **11d** (50 mg, 0.101 mmol) in EtOAc (1.5 mL), Pd/C (16 mg, 0.0101 mmol) was added and the reaction mixture was stirred at room temperature overnight under a H_2 atmosphere. The mixture was then filtered using a Celite pad and washed with EtOAc (5×10 mL). The combined organic layers were concentrated in vacuo. The residue was purified by flash chromatography using 10% EtOAc in hexane to afford **24d** (34 mg, 80% yield) as a white solid. R_f (20% EtOAc in hexane) 0.27; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, *J*=8.2 Hz, 2H), 7.22 (d, *J*=8.1 Hz, 2H), 5.07 (br s, 1H), 3.87 (dd, *J*=11.4, 5.9 Hz, 2H), 3.64 (dd, *J*=11.4, 6.4 Hz, 2H), 3.48 (br s, 2H), 3.67–2.61 (m, 2H), 2.16–2.00 (m, 2H), 1.92–1.87 (m, 2H), 1.45 (s, 9H), 1.43–1.37 (m, 4H), 0.86 (t, *J*=6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.4, 143.3, 135.4, 128.3, 125.3, 125.2, 125.1, 123.2, 80.3, 66.5, 59.3, 39.4, 39.1, 38.7, 34.9; IR (CH_2Cl_2): 3697, 3602, 3421, 2964, 2929, 2855, 1696, 1507, 1167; LRMS (EI): *m*/*z* 384 (8), 328 (10), 310 (12), 267 (12), 211 (21); HRMS (EI): *m*/*z* calcd for $C_{21}H_{32}O_3NF_2$ 384.4887, found: 384.4883.

*4.4.4.3. Synthesis of **10d**.* To a solution of compound **24d** (34 mg, 0.0819 mmol) in dioxane (six drops), 6 M HCl (six drops) was added and the mixture was stirred at room temperature overnight. The mixture was dried by azeotropic evaporation with benzene and pumped to dryness. Compound **10d** (29 mg, quantitative) was obtained as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, *J*=8.0 Hz, 2H), 7.55 (d, *J*=8.1 Hz, 2H), 3.93 (s, 4H), 2.97–2.93 (m, 2H), 2.37–2.33 (m, 2H), 2.22–2.18 (m, 2H), 1.60–1.52 (m, 6H), 1.10 (t, *J*=6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.9, 128.1, 125.0, 108.6, 61.1, 60.7, 38.5, 33.1, 31.1, 28.5, 22.1, 12.8; IR (CH_2Cl_2): 3239, 3047, 2872, 2761, 1682, 1611, 1522, 1168, 1057; LRMS (FAB): *m*/*z* 316 [M^+–HCl]; HRMS (FAB): *m*/*z* calcd for $C_{17}H_{28}NO_2F_2$ 316.2084, found: 316.2088.

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Supplementary data

The ^{1}H and ^{13}C NMR spectra of **10a**,**b**,**d**, **11a**–**d**, **12d**, **13a**, **16**, **18** and **24a**–**d** are available. Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2011.02.028. These data include MOL files and InChiKeys of the most important compounds described in this article.

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