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ORIGINAL RESEARCH ARTICLE

DESIGN, SYNTHESIS AND SPECTRAL CHARACTERIZATION OF DARUNAVIR ANALOGUE

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Abstract: The stereo selective novel synthesis of (3S,3aR,6aS)-Hexahydrofuro [2,3-b] furan-3-yl (1S,2R)-3-(4-amino-N-isobutylphenylsulfonamido)-1-(4-fluorophenyl)-2-hydroxypropylcarbamate (1), it involves the eight synthetic steps mainly which was accomplished from the intermediate 4-Amino-N-((2R,3S)-3-amino-3-(4-fluorophenyl)-2-hydroxypropyl)-N-isobutyl benzenes sulfonamide. This reaction gave 88% yield, with an optical purity of 99.5% and purity of 99% for chiral alcohol.

Kew words: Stereoselective, L-phenyl glycine, Carbamate, Biological properties

INTRODUCTION

AIDS (Acquired immunodeficiency syndrome) is a chronic, life-frightening ailment caused by the human immunodeficiency virus (HIV). HIV, which in turn interferes with the body's ability to fight effectively against viruses, bacteria and fungi that cause the disease by destroying the cells of the immune system. HAART (highly active antiretroviral therapy) introduced in 1996, combined with HIV-1 protease inhibitors and reverse transcriptase inhibitors has theatrically transformed the management of HIV/AIDS.[1] For current drug regimens to treat HIV infection, HIV protease inhibitors are essential components. By interfering with an enzyme known as HIV protease, HIV replication is interrupted by protease inhibitors at a later stage in its life cycle by interfering with an enzyme known as HIV protease.[2] The innovative therapeutic treatments and regimens frequently change the impact of disease. HIV-1 protease inhibitors are reported as the most potent anti-AIDS drugs to date and are necessary constituents of HAART.[3-5] Anti-AIDS chemotherapy based on HIV-1 protease and reverse-transcriptase inhibitors has been extremely effective in decreasing the mortality rates in HIV-infected patients. HIV protease inhibitors, for example indinavir, darunavir, amprenavir, atazanavir, nelfinavir, and saquinavir [6-11] all belong to the HEA class of inhibitors,[12] and synthesis of this class of inhibitors are reorted.[13] HIV-1 protease displays a critical role in the virus life cycle by processing the viral Gag and Gag-Pol poly proteins into structural and functional proteins necessary for viral maturation.

Antiretroviral therapy with HIV protease inhibitor drugs (PI) has been associated with abnormalities in carbohydrate metabolism including insulin resistance, hyperglycemia and development of diabetes mellitus in patients with HIV infection.[14, 15] Although the pathogenesis of glucose abnormalities during HIV infection is believed to be multifactorial, two independent short term studies of healthy HIV-seronegative volunteers showed that induction of insulin resistance is a direct effect of treatment with the PI indinavir (IDV).[16,17] The fixed-combination PI lopinavir/ritonavir (LPV/r) has also been shown to induce insulin resistance, as assessed by oral glucose tolerance testing in healthy volunteers.[18] Although induction of insulin resistance by IDV preceded any significant changes in plasma lipids, impairment in glucose tolerance with LPV/r was temporarily associated with increase in free fatty acids and triglycerides. It is not clear whether metabolic differences in insulin action by a PI primarily reflect direct effects on glucose uptake or represent consequences of an effect on adipose tissue. However, the earliest and most direct PI effect on carbohydrate metabolism appears to be on insulin-mediated glucose uptake, as insulin resistance is apparent even after a single dose of IDV.[19] Data from *in vitro* models of glucose uptake suggest that PI contribute to insulin resistance by inhibiting the insulin-regulated glucose transporter GLUT4.[20] Several investigators have independently confirmed inhibition of glucose uptake *in vitro* in various models of glucose uptake, including human adipocytes.[21,22] Previous studies from our laboratory and others have suggested that phosphorylated chemical entities having diversified biological properties including anti cancer[23, 24], antiviral [25], antimicrobial [26, 27] and anti-Alzheimer's.[28]

We herein report our efforts on this synthetic strategy and ultimately achieved a relatively short synthesis with high stereo selective darunavir analogue.

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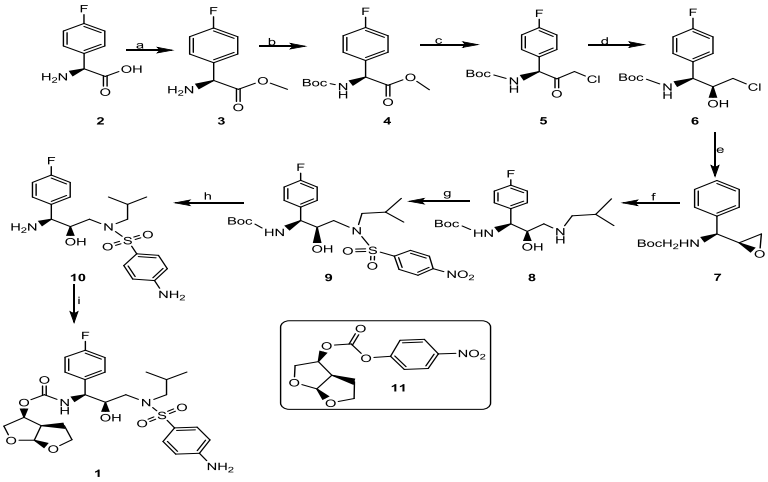
MATERIALS AND METHODS

All the raw materials were procured from Merck laboratories and reagents and solvents were used without further purification.

RESULTS AND DISCUSSION

Herein, for the first time we report a new and an efficient method for the highly stereo selective synthesis of darunavir analogue from the readily available L-phenyl glycine. Our synthetic strategy involves esterification of L-phenyl glycine **2**, stereo selective reduction of α-haloketone**5** followed by SN_2 ring opening of chiral (S, S)-epoxide **7** with isobutyl amine. Finally the darunaviranalogue**1** was achieved from enantiomeric pure amino alcohol **10**and bis THF phenyl carbonate **11** (Scheme 1).

Synthesis of (3S, 3aR, 6aS)-Hexahydrofuro [2,3-b]furan-3-yl (1S,2R)-3-(4-amino-N-isobutylphenylsulfonamido)-1-(4-fluorophenyl)-2-hydroxypropylcarbamate **1** was achieved by the esterification of L-phenyl glycine **2** using thionyl chloride under reflux conditions. The amino group of methyl ester of L-phenyl glycine **2** was protected by $(Boc)_2O$. The ester **3** was treated with diisopropylamido magnesium chloride in THF and α-chloroacetic acid to obtain α-chloro ketone **4**. The diastereo selective reduction of α-chloro ketone **4** was achieved by using aluminum isopropoxide in isopropyl alcohol to get α-chlorohydrin **5** with 99% ee. The (S, S)-epoxide **7** was acquired by base-induced epoxide formation of α-chlorohydrin **6**. Then S_N2 ring opening of chiral (S, S)-epoxide **7** with isobutyl amine under solvent free conditions followed by *in situ* reaction of p-nitro benzene sulfonyl chloride yielded the intermediate compound **9**. The nitro group present in amido alcohol **9** is reduced to amine by Fe-HCl followed by deprotection of the Boc group afforded the required amino alcohol **10**. Finally, the stereo selective synthesis of darunaviranalogue**1**was achieved by reacting amino alcohol **10** with (3R,3aS,6aR)-hexahydrofuro [2,3-*b*]furan-3-yl 4-nitrophenyl carbonate **11**. Analogue of darunavir **1** with enantiomeric ratio of 99% was accomplished. The chemical structures of all the compounds were characterized by IR, ^1H, ^{13}C, and HRMS studies and their data are presented in the experimental section. Characteristic IR stretching absorptions were observed in the regions 3377-3345 and 3555-3452 cm-1 for N–H, O–H, respectively.[29-33] In the ^1H NMR spectra of the chemical shifts of aromatic hydrogens of the phenyl ring appeared as multiplets in the region m 7.11–7.36.[34-37] In ^{13}C NMR chemical shifts for compounds were observed in their expected regions.



Scheme 1

Reaction Conditions: (a). $SOCl_2$, MeOH, reflux 5 h, (b). $(Boc)_2O$, sat. $NaHCO_3$ solution, rt, 16 h, 88% (c). MeMgCl, $ClCH_2CO_2H$, Diisopropyl amine, THF, HCl, 80%; (d). $Al(OCHMe_2)_3$, IPA, reflux, 3 h, 90%; (e). 20% NaOH Solution, Methanol, 20 °C, 90 min, 85%; (f). Isobutyl amine, ethyl acetate; (g). p-nitro benzene sulfonyl chloride, TEA, Chloroform, 85%; (h). Fe/HCl, Conc.HCl, 96%; (i).Methylene dichloride, (3R,3aS,6aR)-hexahydrofuro [2,3-b]furan-3-yl 4-nitrophenyl carbonate (**10**), rt, 8 h, 93%.

EXPERIMENTAL SECTION

Material section

Chemicals were procured from Sigma-Aldrich, Merck and Lancaster, and were used as such without further purification. Melting points (m.p.) were determined using a calibrated thermometer by Guna Digital Melting Point apparatus. They expressed in degrees centigrade (°C) and are uncorrected. Infrared Spectra (IR) were obtained on a Perkin-Elmer Model 281-B spectrophotometer. Samples were analyzed as potassium bromide (KBr) disks. Absorptions were reported in wave numbers (cm^{-1}). ^1H and ^{13}C NMR spectra were recorded as solutions in DMSO-d_6 on a Bruker AMX 400 MHz spectrometer operating at 400 MHz for ^1H and 100 MHz for ^{13}C. The ^1H and ^{13}C chemical shifts were expressed in parts per million (ppm) with reference to tetramethylsilane (TMS). Optical rotations (in degrees, °) were recorded in methanol on a Perkin-Elmer Model 241 polarimeter at the sodium D line. APCI mass spectra were recorded on a Jeol SX 102 DA / 600 Mass spectrometer. Elemental analyses were performed by Central Drug Research Institute, Lucknow, INDIA.

Synthesis

(S)-Methyl 2-(tert-butoxycarbonylamino)-2-(4-fluorophenyl) acetate (**4**) was prepared from L-phenyl glycine **2** according to reported method.[38]

Synthesis of (S)-tert-butyl 3-chloro-1-(4-fluorophenyl)-2-oxopropylcarbamate (5):[38-41]

Part-A: Diisopropylamine (22.4 g, 0.2 mol) was added to a refluxed solution of methyl magnesium chloride (74.5 mL) in THF (3N solution) under nitrogen atmosphere. The reaction mixture was stirred for 1h at ambient temperature and it was cooled to room temperature.

Part-B: Meanwhile, monochloro aceticacid (7.08 g, 0.0749 mol) in tetrahydrofuran (7 mL) was taken into a 250 mL 4-neck round bottomed flask. Methyl magnesium chloride (28 mL) in THF (3N solution) was added at 10 °C under N_2 atmosphere. (S)-Methyl2-(tert-butoxycarbonylamino)-2-(4-fluorophenyl) acetate (14 g, 0.049mol) in THF was added to the reaction mixture during 30 min at 10°C, later diisopropylamido magnesium chloride (Part-A) complex was added below 10°C during 45 min, then the reaction mixture was refluxed for 2 h. Progress of the reaction was monitored by thin layer chromatography (hexane: ethyl acetate, 7:3), after completion of the reaction, it was cooled to room temperature, quenched into water, pH was adjusted to 2.5 with conc. HCl and separated the two layers, aqueous layer was extracted with ethyl acetate (2x50 mL). The total extract was washed with saturated aqueous $NaHCO_3$ solution and 10% aqueous NaCl solution, organic layer was dried over Na_2SO_4 and concentrated in a rotary evaporator to obtain the crude product, it was recrystallised from n-hexane to get the light pink colored solid (**3**) (12.22 g, 82 %); mp 130-133 °C. R_f0.42; (hexane: ethyl acetate, 7:3 v/v): IR (KBr). 3345, 2965, 2341, 1748, 1686, 1566, 1300, 1264, 1166, 711 cm^{-1}.^{1}H NMR (400 MHz, DMSO-d_6) δ 7.28-7.36 (m, 2H), 7.14 (d, J = 6.8 Hz, 2H), 5.08 (d, J = 5.6 Hz, 1H), 4.61 (q, 1H), 4.17 (d, J = 16.4 Hz, 1H), 3.88 (d, J = 16.0 Hz, 1H), 1.36 (s, 9H) ppm. ^{13}C NMR: 176.2, 151.5, 131.4, 127.2, 125.1, 121.3, 81.2, 69.5 41.5, 36.5, 25.6. $[\alpha]_D^{25}$= +35.8° (c = 1 in MeOH).LCMS (m/z): 303 $[M+H]^+$.

Synthesis of tert-butyl (1S,2S)-3-chloro-1-(4-fluorophenyl)-2-hydroxypropylcarbamate (6):[38,42]To a stirred solution of (S)-*Tert*-butyl 3-chloro-1-(4-fluorophenyl)-2-oxopropylcarbamate (**5**) (9.5 g, 0.03 mol) in 20 mL of isopropanol, aluminum isopropoxide (3.32 g, 0.02 mol) in isopropyl alcohol (95 mL) was added at room temperature. The resulting mixture was refluxed for 3 h, after completion of the reaction half of the isopropyl alcohol was concentrated in a rotary evaporator, and then water was added, pH was adjusted to 3.5 with glacial acetic acid at 30 °C. Further the reaction mixture was stirred for 2 h at room temperature, pink colored solid was separated and it was filtered, washed with water, dried under vacuum at 45 °C to get the light pink colored solid **(4)** (8.17 g,86%); mp 155-157 °C. R_f0.52; (hexane: ethyl acetate, 7:3 v/v): IR (KBr). 3356, 2970, 1682, 1535, 1438, 1156, 1001, 695 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.18-7.28 (m, 2H), 7.11 (d, J = 6.8 Hz, 2H), 6.56 (d, J = 8.4 Hz, 1H), 5.44 (d, J = 6.0 Hz, 1H), 3.55-3.66 (m, 3H), 3.59 (q, 1H), 2.89 (d, J = 2.4 Hz, 1H), 2.79 (d, J = 9.6 Hz, 1H),1.37 (s, 9H) ppm. ^{13}C NMR: 160.5, 136.8, 129.1, 126.3, 124.5, 82.1, 79.2, 53.5 46.8, 38.5, 26.6. $[\alpha]_D^{25}$= +16.5° (c = 1 in MeOH). LCMS (m/z): 305$[M+H]^+$.

Synthesis of tert-butyl formate (S, S)-oxiran-2-yl)(phenyl)methanamine (7): To a stirred solution of *tert*-butyl (1S,2S)-3-chloro-1-(4-fluorophenyl)-2-hydroxypropylcarbamate (**6**) (7 g, 0.02 mol) in Methanol (56 mL), 20% NaOH solution (14 mL) was added at 20°C and continued stirring for 90 min. Progress of the reaction was monitored by TLC (hexane: ethyl acetate 7:3), then the organic layer was taken into a reaction flask and heated to 45 °C, water was added slowly at ambient temperature, the resulting mixture was cooled to room temperature, stirred for 2 h, the solid that separated was filtered and washed with water, product was dried under vacuum at 45°C to get white colored solid (**5**) (5.95 g, 85 %); mp 123-126 °C. R_f0.45; (hexanes: ethyl acetate, 7:3 v/v): IR (KBr). 3377, 2981, 1680, 1524, 1170, 928, 605 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.21-7.33 (m, 5H), 4.43 (s, 1H), 3.69 (s, 1H), 2.76-2.99 (m, 5H), 1.38 (s, 9H) ppm. ^{13}C NMR: 156.3, 138.2, 128.5, 127.6, 125.2, 80.3, 61.4, 56.6, 40.1, 38.4, 26.5. $[\alpha]_D^{25}$ = +17.6° (c =1 in acetonitrile) LCMS (m/z): 250$[M+H]^+$.

Synthesis of *tert*-butyl (1S,2R)-1-(4-fluorophenyl)-2-hydroxy-3-(N-isobutyl-4-nitrophenylsulfonamido) propylcarbamate (9):[38,43-50]*tert*-butyl formate (S, S)-oxiran-2-yl)(phenyl) methanamine (7) (4.6 g, 0.02 mol) in isobutyl amine (13.8 g, 0.12 mol) was refluxed for 3 h, reaction progress was monitored by TLC (hexane: ethyl acetate, 7:3), excess isobutyl amine was completely removed under reduced pressure. A white colored solid was obtained and it was cooled to room temperature, chloroform (60 mL) and triethylamine (2.3 g, 0.02 mol) were added, the resulting mixture was raised to reflux, *p*-nitro benzenesulphonyl chloride (4.0 g, 0.02 mol) in chloroform(25 mL) was added to the above reaction mixture at ambient temperature during 2 h, the resulting reaction mixture was stirred for 2 h. Reaction progress was monitored by TLC (hexane: ethyl acetate, 7:3), then the reaction mixture was cooled to room temperature, further it was washed with water, organic layer was concentrated in vacuum, finally the solid mass was recrystalised from Ethanol to obtain the white colored solid (**6**) (6.9 g, 75 %); mp 151-153 °C. IR (KBr). 3555, 3378, 2950, 1683, 1547, 1311, 1172, 986, 781 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.31 (d, J = 8.4 Hz, 2H), 8.15 (d, J = 8.8 Hz, 2H), 7.11-7.34 (m, 2H), 7.19

(d, J = 6.8 Hz, 2H), 6.57 (d, *J* = 8.8 Hz, 1H), 4.86 (d, *J* = 6.4 Hz, 1H), 3.39-3.51 (m, 3H), 3.04-3.18 (m, 2H), 1.95-2.01 (m, 1H), 1.25 (s, 9H), 0.85 (d, *J* = 7.2 Hz, 6H) ppm. ^{13}C NMR: 156.2, 150.4, 146.5, 138.0, 129.1, 128.2, 126.4, 126.1, 124.7, 80.2, 73.5, 58.5, 57.3, 50.1, 36.4, 26.1 19.5, 24.2. R_f0.45; (hexane: ethyl acetate, 7:3 v/v). $[\alpha]_D^{25}$ = -27.7° (*c* =1 in $CHCl_3$). LCMS (m/z): 526[M+H]$^+$.

Synthesis of 4-Amino-N-((2R,3S)-3-amino-3-(4-fluorophenyl)-2-hydroxypropyl)-N-isobutylbenzenesulfonamide (10): *Tert*-butyl (1S,2R)-1-(4-fluorophenyl)-2-hydroxy-3-(N-isobutyl-4-nitrophenylsulfonamido)propylcarbamate (**9**) (5.9 g, 0.01 mol), Fe-HCl (0.59 g) were suspended in methanol and the reaction mixture was taken into round bottom flask (RBF), rendered inert and evacuated. At an inside temperature of 45 °C, during 12 h, then catalyst was removed by filtration, progress of this reaction was monitored by TLC (methylenedichloride: methanol, 9:1). Concentrated HCl (3.7 mL) was added to the filtrate at room temperature, heated to reflux and stirred for 2 h. After complete conversion, pH of the reaction mixture was adjusted to 9.5 with 20% NaOH solution, most of the methanol was removed by distillation to get the crude product, it was recrystallised from a mixture of ethanol and water (40%). It was yielded 4.2 g, 96% of an off-white powder (**7**); mp 171-173 °C. R_f0.62; (methylenedichloride: methanol, 9:1 v/v): IR (KBr). 3452, 3352, 3240, 2957, 1651, 1600, 1321, 1149, 969, 959, 761 cm^{-1}.^{1}H NMR (400 MHz, DMSO-d_6)δ 7.40 (d, *J* = 8.4 Hz, 2H), 7.24-7.34 (m, 2H), 7.16 (d, J = 6.8 Hz, 2H), 6.61 (d, *J* = 8.4 Hz, 2H), 5.95 (s, 2H), 4.62 (d, *J* = 5.2 Hz, 1H), 3.49 (brs, 1H), 3.31-3.38 (m, 1H), 2.69-2.91 (m, 3H), 2.91 (s, 1H), 2.33-2.36 (t,1H), 1.91-1.95 (t, 1H), 1.22 (brs, 2H), 0.79- 0.83 (m, 6H) ppm.^{13}C NMR: 150.2, 138.5, 130.0, 129.2, 128.2, 127.5, 125.6, 115.2, 78.2, 60.5, 58.2, 50.4, 38.9, 25.5, 18.3. $[\alpha]_D^{25}$ = -23.6°(*c* =1 in DMF). LCMS (m/z): 396[M+H]$^+$.

(3R, 3aS, 6aR)-Hexahydrofuro [2,3-b]furan-3-yl 4-nitrophenyl carbonate (**7a**) was prepared from (3R, 3aS, 6aR)-hexahydrofuro [2,3-b]furan-3-ol according to reported method.[38, 51]

Synthesis of (3S,3aR,6aS)-Hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-(4-amino-N-isobutylphenylsulfonamido)-1-(4-fluorophenyl)-2-hydroxypropylcarbamate (1): (3S, 3aR, 6aS)-Hexahydrofuro[2,3-b]furan-3-yl 4-nitrophenyl carbonate(1.96 g, 0.01 mol) (**11**)[51] in methylene dichloride (15 mL) was added to a solution of 4-Amino-N-((2R,3S)-3-amino-3-(4-fluorophenyl)-2-hydroxypropyl) -N-isobutylbenzenesulfonamide (**10**) (2.6 g, 0.01 mol) and methylene dichloride (10 mL) at 0 °C during 2 h. The resulting mixture was raised to room temperature and stirred for 8 h. After completion of the reaction, monitored by HPLC, the reaction mixture was quenched into mixture of water (26 mL) and ethyl acetate (30 mL), the aqueous layer was further extracted with ethyl acetate (2x15 mL), both organic layers were mixed and washed with 10% Na_2CO_3 solution (2x15 mL) followed by 10% NaCl solution (15 mL). The organic layer was dried over Na_2SO_4, and concentrated in vacuum to get the off-white colored residue with 96% HPLC purity. It was purified by column chromatography by eluting with 5-10% methanol in methylene dichloride and concentrated in a rotary evaporator to get off-white crystals of **8** (3.26 g, 90%) with 99% HPLC purity; mp116-118°C. IR (KBr): 3461, 3368, 3062, 2961, 1709, 1631, 1455, 1316, 1258, 1149, 1091, 833, 703 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.39 (d, *J* = 17.4 Hz, 2H), 7.24-7.34 (m, 2H), 7.16 (d, J = 6.8 Hz, 2H), 7.13-7.29 (m, 1H),6.60 (d, *J* = 17.4 Hz, 2H), 5.96 (br s,2H), 5.54 (d, *J* = 10.2 Hz 1H),), 4.94 (d, *J* = 12.6 Hz, 1H), 4.77-4.84 (m, 1H 3.49 (br s, 1H), 3.54-3.84 (m, 1H), 3.54-3.84 (m, 1H), 3.54-3.84 (m, 1H), 3.34-3.41 (m, 1H), 3.34-3.41 (m, 1H), 3.25-3.26 (m, 1H), 2.87-3.03 (m, 1H), 2.87-3.03 (m, 1H), 2.57-2.78 (m, 1H), 2.57-2.78 (m, 1H), 1.86-1.96 (m, 1H), 1.86-1.96 (m, 1H), 1.69-1.72 (m, 1H), 0.84 (d, *J* = 13.2 Hz 6H) ppm. ^{13}C NMR:155.18, 152.67, 139.43, 129.12, 128.96, 127.86, 125.71, 123.70, 112.62, 108.62, 72.16, 72.16, 70.29, 68.71, 57.03, 55.77, 52.52, 44.64, 35.14, 26.36, 25.51, 20.01. $[\alpha]_D^{25}$ = -22.8° (*c* =1 in $CHCl_3$). LC-MSD: 574 [M+Na]$^+$, 552 [M+H]$^+$. The enantiomeric ratio (% *ee*) was determined to be 99% by HPLC using Intersil ODS 3V 250*4.65 µm column (30% ethanol/ hexane + 1mL diethyl amine, 1 mL/min, 265 nm), t_R (minor, 8.33 min), t_R (major, 13.72 min).

CONCLUSION

In conclusion, we have developed first time a straightforward and novel synthetic methodology for (3S,3aR,6aS)-Hexahydrofuro [2,3-b]furan-3-yl (1S,2R)-3-(4-amino-N-isobutylphenylsulfonamido)-1-(4-fluorophenyl)-2-hydroxypropylcarbamate **1** from a readily available starting material, optically active L-phenylglycine **2**, through the key intermediate *tert*-butyl formate (S, S)-oxiran-2-yl)(phenyl)methanamine **7** which was obtained as an exclusive product without its stereoisomer. Darunavir analogue **1** was prepared on a gram scale in an overall yield of 43% with only one column chromatography separation in the eight-step synthesis.

REFERENCES

1. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents, November 3, 2008, Developed by the DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents – A Working Group of the Office of AIDS Research Advisory Council (OARAC).

2. Condra JH, Schleif WA, Blahy OM, Gabryelski LJ, Graham DJ, Quintero JC, Rhodes A, Robbins HL, Roth E and Shivaprakash M, Genetic correlates of in vivo viral resistance to indinavir, a human

immunodeficiency virus type 1 protease inhibitor, Nature, 1995, 374, 569.

3. Clavel F and Hance AJ, HIV Drug Resistance, The New England Journal of Medicine, 2004, 350, 1023.

4. Ghosh AK, Dawson ZL and Mitsuya H, Darunavir, a conceptually new HIV-1 protease inhibitor for the treatment of drug-resistant HIV, Journal of Medicinal Chemistry, 2007, 15, 7576.

5. Jose VM, Daniel B, Marilyn M, Fredy S, Denes B, Kiat R, Dorece N, Eric L, Marie PB, Frank T, Martine DP, Tony V and Sabrina SG, Efficacy and safety of darunavir-ritonavir compared with that of lopinavir-ritonavir at 48 weeks in treatment-experienced, HIV-infected patients in TITAN: a randomised controlled phase III trial, The Lancet, 2007, 370, 49.

6. Kempf DJ, Marsh KC, Denissen JF, McDonald E, Vasavanonda S, Flentge CA, Green BE, Fino L, Park CH, Kong XP, Wideburg NE, Saldivar A, Ruiz L, Kati WM, Sham HL, Robins T, Stewart KD, Hsu A, Plattner JJ, Leonard JM and Norbeck DW, ABT-538 is a potent inhibitor of human immunodeficiency virus protease and has high oral bioavailability in humans, Proceedings of the National Acadamy of Sciences of the United States of America, 1995, 92, 2484.

7. Robinson BS, Riccardi KA, Gong YF, Guo Q, Stock DA, Blair WS, Terry BJ, Deminie CA, Djang F, Colonno RJ and Lin PF, BMS-232632, a highly potent human immunodeficiency virus protease inhibitor that can be used in combination with other available antiretroviral agents, Antimicrobial Agents and Chemotherapy, 2000, 44, 2093.

8. Sham HL, Kempf DJ, Molla A, Marsh KC, Kumar GN, Chen CM, Kati W, Stewart K, Lal R, Hsu A, Betebenner D, Korneyeva M, Vasavanonda S, McDonald E, Saldivar A, Wideburg N,. Chen X, Niu P, Park C, Jayanti V, Grabowski B, Granneman GR, Sun E, Japour AJ, Leonard JM, Plattner JJ and Norbeck DW, ABT-378, a highly potent inhibitor of the human immunodeficiency virus protease, Antimicrobial Agents and Chemotherapy, 1998, 42, 3218.

9. Kaldor SW, Kalish VJ, Davies JF 2nd, Shetty BV, Fritz JE, Appelt K, Burgess JA, Campanale KM, Chirgadze NY, Clawson DK, Dressman BA, Hatch SD, Khalil DA, Kosa MB, Lubbehusen PP, Muesing MA, Patick AK, Reich SH, Su KS, Tatlock JH Viracept (nelfinavir mesylate, AG1343): a potent, orally bioavailable inhibitor of HIV-1 protease Journal of Medicinal Chemistry, 1997, 40, 3979.

10. Koh Y, Nakata H, Maeda K, Ogata H, Bilcer G, Devasamudram T, Kincaid JF, Boross P, Wang YF, Tie Y, Volarath P, Gaddis L, Harrison RW, Weber IT, Ghosh AK, Mitsuya H, Novel bis-tetrahydrofuranylurethane-containing nonpeptidic protease inhibitor (PI) UIC-94017 (TMC114) with potent activity against multi-PI-resistant human immunodeficiency virus in vitro, Antimicrobial Agents and Chemotherapy, 2003, 47, 3123.

11. Tomasselli G and Heinrikson RL, Targeting the HIV-protease in AIDS therapy: a current clinical perspective, Biochimica et Biophysica *Acta,* 2000, 189.

12. Arun KG, Wayne JT, Holloway MK, McKee SP, Duong TT, Lee HY, Munson PM, Anthony M. Smith, Jenny M. Wai, Potent HIV protease inhibitors: the development of tetrahydrofuranylglycines as novel P2-ligands and pyrazine amides as P3-ligands, Journal of Medicinal Chemistry, 1993, 36, 2300.

13. Parkes KEB, Bushnell DJ, Cracjeff PH, Dunsdon SJ, Freeman AC, Gunn MP, Popkins RA, Lambert RW and Thomas GJ, Studies toward the Large-Scale Synthesis of the HIV Proteinase Inhibitor Ro 31-8959, Journal of Organic Chemistry, 1994, 59, 3656.

14. Gurjar MK and Devi NR, An expedient approach to (2R,3S)-3-azido-1,2-epoxy-4-phenyl butane: A key intermediate for HIV protease inhibitors, Tetrahedron Asymmetry, 1994, 5, 755.

15. Beaulieu PL and Wernic D, Preparation of Aminoalkyl Chlorohydrin Hydrochlorides: Key Building Blocks for Hydroxyethylamine-Based HIV Protease Inhibitors, Journal of Organic Chemistry, 1996, 61, 3635.

16. Shibata N, Katohand T and Terashima S, An expeditious synthesis of (2R,3S)-3-tert-butoxycarbonylamino-1-isobutylamino-4-phenyl-2-butanol, a key building block of HIV protease inhibitors, Tetrahedron Letters, 1997, 38, 619

17. Beaulieu PL, Lavallee P, Abraham A, Anderson PC, Boucher C, Bousquet Y, Duceppe JS, Gillard J, Gorys V, Grand MC, Grenier L, Guindon Y, Guse I, Plamondon L, Soucy F, Valois S, Wernic D and Yoakim C, Practical, Stereoselective Synthesis of Palinavir, a Potent HIV Protease Inhibitor, Journal of Organic Chemistry, 1997, 62, 3440.

18. Rieger DL, A Concise Formal Synthesis of the Potent HIV Protease Inhibitor Nelfinavir Mesylate, Journal of Organic Chemistry, 1997, 62, 8546.

19. Ghosh AK and Fidanze S, Transition-State Mimetics for HIV Protease Inhibitors: Stereocontrolled Synthesis of Hydroxyethylene and Hydroxyethylamine Isosteres by Ester-Derived Titanium Enolate Syn and Anti-Aldol Reactions, Journal of Organic Chemistry, 1998, 63, 6146.

20. Corey EJ and Zhang FY, re- and si-face-selective nitroaldol reactions catalyzed by a rigid chiral quaternary ammonium salt: A highly stereoselective synthesis of the HIV protease inhibitor amprenavir (Vertex 478), Angewandte Chemie International Edition, 1999, 38, 1931.

21. Inaba T, Yamada Y, Abe H, Sagawa S and Cho H, (1S)-1-[(4R)-2,2-Dimethyl-1,3-dioxolan-4-yl]-2-hydroxyethylammonium Benzoate, A Versatile Building Block for Chiral 2-Aminoalkanols: Concise Synthesis and Application to Nelfinavir, a Potent HIV-Protease Inhibitor, Journal of Organic Chemistry, 2000, 65, 1623.

22. Zook SE, Busse JK and Borer BC, A concise synthesis of the HIV-protease inhibitor nelfinavir via an unusual tetrahydrofuran rearrangement, Tetrahedron Letters, 2000, 41, 7017.

23. Koteswara RV, Sanapalli SR, Balam SK, Cirandur SR, Nimmanapalli PR, Tamatam CMR, Chamarthi NR, and Ghosh SK, Design, synthesis and anti-colon cancer activity evaluation of phosphorylated derivatives of lamivudine (3TC), Letters in Drug Design & Discovery 2011, 8(1), 59.

24. Babu KR, Koteswara RV, Nanda KY, Hari PO, Chandra SK, Bhaskar M, and Naga RC, Design, synthesis, in silico and in vitro studies of novel 4-methylthiazole-5-carboxylic acid derivatives as potent anti-cancer agents, Bioorganic & medicinal chemistry letters, 2014, 24(18), 4580.

25. Babu KR, Rao VK, Kumar YN, Polireddy K, Subbaiah KV, Identification of substituted [3, 2-a] pyrimidines as selective antiviral agents: Molecular modeling studies, Antiviral Research, 2012, 95, 118.

26. Reddy SS, Koteswara VR, Satheesh BK, Suresh CR, Visweswara PR, and Naga CR. Synthesis, antimicrobial, and antioxidant activity of new α-aminophosphonates, Phosphorus, Sulfur, and Silicon and the Related Elements, 2011, 186(7), 1411.

27. Sanapalli SR, Ravi AUS, Naga CR, Koteswara VR, Synthesis and antimicrobial activity of new α-aminophosphonic acid esters. South African Journal of Chemistry, 2008, 61, 97.

28. Rao VK, Rao AJ, Reddy SS, Raju CN, Rao PV, Synthesis, spectral characterization and biological evaluation of phosphorylated derivatives of galanthamine. European journal of medicinal chemistry, 2010, 45(1), 203.

29. Kovalevsky AY, Ghosh AK, Weber IT, Solution kinetics measurements suggest HIV-1 protease has two binding sites for darunavir and amprenavir, Journal of Medicinal Chemistry, 2008,51(20), 6599.

30. Dierynck I, De Wit M, Gustin E, Keuleers I, Vandersmissen J, Hallenberger S, Hertogs K, Binding kinetics of darunavir to human immunodeficiency virus type 1 protease explain the potent antiviral activity and high genetic barrier. Journal of Virology, 2007, 81(24), 13845.

31. Valasani KR, Vangavaragu JR, Day VW, Yan SS, Structure Based Design, Synthesis, Pharmacophore Modeling, Virtual Screening, and Molecular Docking Studies for Identification of Novel Cyclophilin D Inhibitors. Journal of chemical information and modeling, 2014, 54(3), 902.

32. Valasani KR, Hu G, Chaney MO, Yan SS, Structure-based design and synthesis of benzothiazole phosphonate analogues with inhibitors of human ABAD-Aβ for treatment of Alzheimer's disease, Chemical Biology & Drug Design, 2013, 81(2):238.

33. Rao VK, Reddy SS, Krishna BS, Naidu KRM, Raju CN,. Synthesis of Schiff's bases in aqueous medium: a green alternative approach with effective mass yield and high reaction rates. Green Chemistry Letters and Reviews, 2010, 3(3), 217.

34. Vangavaragu, JR, Koteswara RV, Xueqi G, and Shirley SY, Identification of human presequence protease (hPreP) agonists for the treatment of Alzheimer's disease, European journal of medicinal chemistry, 2014, 76, 506.

35. Valasani KR, Chaney MO, Day VW, Shidu Yan S, Acetylcholinesterase inhibitors: structure based design, synthesis, pharmacophore modeling, and virtual screening. Journal of Chemical Information and Modeling, 2013, 53(8), 2033.

36. Koteswara Rao V, Hari Babu B, Raveendra Babu K, Srinivasulu D, Naga Raju, C. Ecofriendly synthesis of tetrahydropyrimidine derivatives in aqueous medium under ultrasonic irradiation. Synthetic Communications, 2012, 42(22), 3368.

37. Koteswara Rao V, Subba Reddy S, Dada Peer E, Janardhan Rao A, Naga Raju C, Synthesis and Antimicrobial Activity of Novel Iminophosphocin Derivatives, Chinese Journal of Chemistry, 2009, 27, 2379.

38. Konrad H, Cyrille T, Jörg Kurt W, Bart K, Bruno L, Disubstituted Bis-THF Moieties as New P2 Ligands in Nonpeptidal HIV-1 Protease Inhibitors, ACS Medicinal Chemistry Letters, 2011, 2(6), 461.

39. De Clercq E, Strategies in the design of antiviral drugs, Nature Reviews Drug Discovery, 2002, 1(1), 13.

40. Yarasheski KE, Tebas P, Sigmund C, Dagogo-Jack S, Bohrer A, Turk J, Halban PA, Cryer PE, Powderly WG. Insulin resistance in HIV protease inhibitor-associated diabetes, Journal of Acquired Immune Deficiency Syndrome, 1999, 21(3), 209.

41. Noor MA, Lo JC, Mulligan K, Schwarz JM, Halvorsen RA, Schambelan M, Grunfeld C. Metabolic effects of indinavir in healthy HIV-seronegative men, AIDS, 2001 May 4; 15(7), F11.

42. Lee GA, Seneviratne T, Noor MA, Lo JC, Schwarz JM, Aweeka FT, Mulligan K, Schambelan M, Grunfeld C. The metabolic effects of lopinavir/ritonavir in HIV-negative men, AIDS, 2004, 18(4), 641.

43. Noor MA, Seneviratne T, Aweeka FT, Lo JC, Schwarz JM, Mulligan K, Schambelan M, Grunfeld C, Indinavir acutely inhibits insulin-stimulated glucose disposal in humans: a randomized, placebo-controlled study, AIDS, 2002 Mar 29, 16(5), F1.

44. John GC, Nduati RW, Mbori-Ngacha DA, Richardson BA, Panteleeff D, Mwatha A, Overbaugh J, Bwayo J, Ndinya-Achola JO, Kreiss JK, Correlates of mother-to-child human immunodeficiency virus type 1 (HIV-1) transmission: association with maternal plasma HIV-1 RNA load, genital HIV-1 DNA shedding, and breast infections, Journal of Infectious Diseases, 2001, J183(2), 206.

45. Kind C, Rudin C, Siegrist CA, Wyler CA, Biedermann K, Lauper U, Irion O, Schüpbach J, Nadal D, Prevention of vertical HIV transmission: additive protective effect of elective Cesarean section and zidovudine prophylaxis. Swiss Neonatal HIV Study Group, AIDS, 1998, 12(2), 205.

46. Coutsoudis A, Dabis F, Fawzi W, Gaillard P, Haverkamp G, Harris DR, Jackson JB, Leroy V, Meda N, Msellati P, Newell ML, Nsuati R, Read JS, Wiktor S, Late postnatal transmission of HIV-1 in breast-fed children: an individual patient data meta-analysis, Journal of Infectious Diseases, 2004,189(12), 2154.

47. McDonald H, Brocklehurst P, Parsons J, Vigneswaran R, Antibiotics for treating bacterial vaginosis in pregnancy, Cochrane Database Syst Rev., 2003, (2), CD000262.

48. Connor EM, Sperling RS, Gelber R, Kiselev P, Scott G, O'Sullivan MJ, VanDyke R, Bey M, Shearer W, Jacobson RL, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group, The New England Journal of Medicine, 1994, 331(18), 1173.

49. Shaffer N, Chuachoowong R, Mock PA, Bhadrakom C, Siriwasin W, Young NL, Chotpitayasunondh T, Chearskul S, Roongpisuthipong A, Chinayon P, Karon J, Mastro TD, Simonds RJ, Short-course zidovudine for perinatal HIV-1 transmission in Bangkok, Thailand: a randomised controlled trial. Bangkok Collaborative Perinatal HIV Transmission Study Group, Lancet, 1999, 353(9155), 773.

50. Lallemant M, Jourdain G, Le Coeur S, Kim S, Koetsawang S, Comeau AM, Phoolcharoen W, Essex M, McIntosh K, Vithayasai V, A trial of shortened zidovudine regimens to prevent mother-to-child transmission of human immunodeficiency virus type 1. Perinatal HIV Prevention Trial (Thailand) Investigators, The New England Journal of Medicine, 2000, 343(14), 982.

51. Surleraux DL, Tahri A, Verschueren WG, Pille GM, de Kock HA, Jonckers TH, Peeters A, De Meyer S, Azijn H, Pauwels R, de Bethune MP, King NM, Prabu-Jeyabalan M, Schiffer CA, Wigerinck PB, Discovery and selection of TMC114, a next generation HIV-1 protease inhibitor, Journal of Medicinal Chemistry, 2005, 48(6), 1813.

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