Synthesis and Characterization of Novel Atazanavir Analogs

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Abstract:

In this work, we report the synthesis of diverse atazanavir analogues as possible potential novel drugs for human immunodeficiency virus (HIV-1). The synthesis was carried as follows: First, condensation of 4-oxiranylmethoxy-9H-carbazole **(1)** with N-1-(tert-butyloxycarbonyl)-N-2-(4-(pyridine-2-yl)-benzyl) hydrazine **(2)** in presence of isopropyl alcohol at 70-75 °C followed by deprotection with mineral acid yielded intermediate **4** which was subsequently coupled with carbamate amino acid **(5a-o)** in the presence of EDAC.HCl and HOBt at room temperature to produce atazanavir analogues containing the carbazole moiety (**6a-10c**). These compounds were characterized by the following analytical methods: IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopy.

Keywords: Carbamate amino acid; carbazole; hydrazine; human immunodeficiency virus; HIV-1 protease inhibitors; atazanavir

Introduction:

Human immunodeficiency virus, HIV a major worldwide disease, is of two types: HIV-1 and HIV-2. Out of these two, HIV-1 is the most prevalent[1,2]. Proteolytic processing of HIV-1 precursor protein is the most essential step of HIV-1 life cycle, where the processing is completed by a virally encoded enzyme (HIV-1 protease)[3, 4]. *In vivo* growth of HIV-1 can be suppressed by inhibiting HIV-1 protease[5-7] using chemotherapeutic process (administration of anti-HIV drugs to the patients)[8-13]. There were some reports on the estimation of Atazanavir in pure and its combination of drugs[14,15]. Atazanavir, one of the vital drugs administered orally to patients suffering with HIV,is constructed from three different moieties **A**, **B** and **C** as shown in Fig 1. Currently, researchersworldwide are looking out for new and better anti-HIV drugs with more activity than the existing ones. Compounds designated as analogs or derivatives of protease inhibitors have already been consecrated. Based on this, we hypothesize that structural modification of atazanavir with active moieties may result in better activity than the atazanavir itself. In this study, we focused on the synthesis of diverse analogues of atazanavir by changing the left (**A**) and right (**B**) part of atazanavir chemical structure (**Fig. 1**).

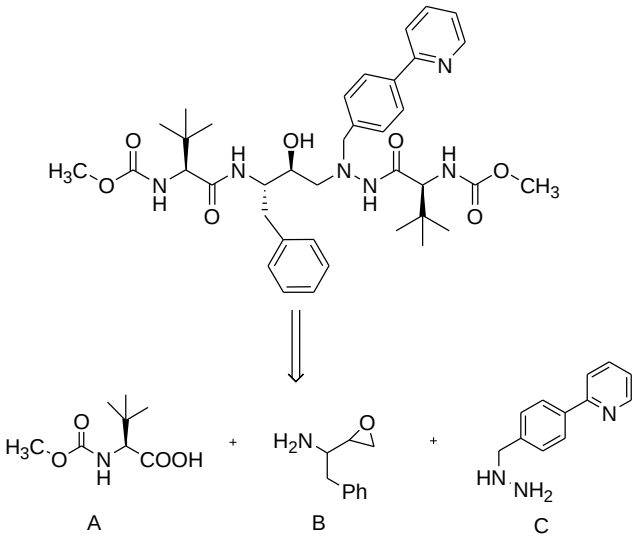


Fig. 1. Structure of Atazanavir

Materials and Methods

General: ^{1}H NMR spectra were recorded using a Bruker 300 spectrometer (300 MHz). ^{13}C NMR spectra were recorded using a Bruker 400 spectrometer (100 MHz), Infrared (IR) spectra were recorded on a Perkin-Elmer spectrophotometer (in KBr pellet form). API 2000 Perkin-Elmer PE-SCIEX mass spectrometer was employed to identify the molecular ions of the synthesized compounds.

Synthesis

General procedure forsynthesis of *tert*-butyl-2-(3-(9H-carbazol-4-yloxy)-2-hydroxypropyl)-2-(4-(pyridin-2-yl) benzyl) hydrazinecarboxylate (3):

N-1-(*tert*-butyloxycarbonyl)-*N*-2-(4-(pyridine-2-yl)-benzyl) hydrazine (**2**) (41.28 g, 0.1378 mol) was dissolved in isoproanol (100 mL) at20-30°C followed by heating the solution to 70-75°C. To this solution, 4-oxiranylmethoxy-9H-carbazole **(1)** (30 g, 0.1253 mol) was added slowly at 70-75 °C. The reaction was left stirring at similar temperature for next 16 h. After 16 h, the temperature of the reaction mixture was brought back to 20-30 °C followed by concentration under reduced pressure. The crude mixture was then dissolved in a 300 mL ethyl acetate solution and treated with 100 mL water. The separated ethyl acetate layer was dried over anhydrous Na_2SO_4, filtered, concentrated and dried under vacuum for several hours to yield compound **3** (76.5 %).

Anal. Calcd for $C_{32}H_{34}N_4O_4$: C, 71.35; H, 6.36; N, 10.40; O, 11.88 found: C, 71.38; H, 6.36; N, 10.40; O, 11.88**. IR** (KBr cm^{-1}): 3412 (NH); 3313 (OH); 1691 (C=O); 1263 and 1102 (C-O-C). **^{1}H NMR** (DMSO-d_6, 300 MHz) δ1.33 (s, 9H), 3.03-3.05 (m, 2H), 4.04-4.09 (m, 2H), 4.19-4.22 (m, 2H), 4.95 (m, 1H), 6.68-8.66 (m, 16H), 11.21(s, 1H); **^{13}C NMR** (DMSO-d_6, 100 MHz): δ 155.9(C-8'), 155.5 (C-1''), 149.4 (C-6''), 141.1 (C-5''), 139.0 (C-5'), 138.9 (C-12'), 137.4, (C-9'), 137.1 (C-11'),129.2 (C-10'), 126.4 (C-2'), 126.3 (C-4',6'), 124.3 (C-3',7'), 122.4 (C-10''), 122.3 (C-8''), 121.7 (C-9''), 119.9 (C-3''), 118.5 (C-7''), 111.6 (C-11''), 110.2 (C-4''), 103.7 (C-2''), 100.4 (C-12''), 78.4 (O-$\underline{C}(CH_3)_3$), 70.6 (C-3), 67.1 (C-2), 65.9 (C-1'), 61.3 (C-1), 28.1 (C($\underline{C}H_3)_3$) ; **MS**: *m/z* 539.2 [M+H]$^+$.

General protocol forsynthesis of 1-(9H-carbazol-4-yl-oxy)-3-(1-(4-(pyridin-2-yl) benzyl) hydrazinyl) propan-2-ol (4):

To Compound **3** (47 g, 0.0872 mol) in 150 mL of methylene chloride, 39.83 g (0.03926 mol) of Conc. HCl was added slowly at 20-30 °C. The resulting mixture was stirred at same temperature for next 10 h. After 10 h, the aqueous layer was separated and treated with methylene chloride followed by adjusting the pH of aqueous layer to 9.0 using 10% w/w aqueous sodium carbonate solution. The aqueous layer was then treated with methylene chloride solution. The collected methylene chloride layers were concentrated and dried under vacuum for six hours to yield compound **4** in 81.9 % yield.

Anal. Calcd for $C_{27}H_{26}N_4O_2$: C, 73.95; H, 5.98; N, 12.78; O, 7.30; Found: C, 74.05; H, 5.88; N, 12.85; O, 7.35**. IR** (KBr cm^{-1}**)**:3403 (NH); 3236 (OH); 1097 (C-O-C). **^{1}H NMR** (DMSO-d_6, 300 MHz) δ2.72 -2.85 (m, 2H), 3.64 (br, 2H) 3.80 (s, 2H), 4.14-4.23 (m, 2H), 4.35 (m, 1H), 5.55 (br, 1H), 6.67-8.65 (m, 15H), 11.20(s, 1H); **^{13}C NMR** (DMSO-d_6, 100 MHz): δ155.9 (C-8'), 155.1 (C-1"), 149.4 (C-6"), 141.1 (C-5"), 139.0 (C-5'), 138.9 (C-12'), 137.4, (C-9'), 137.0 (C-11'), 129.2 (C-10'), 126.4 (C-2'), 126.3 (C-4',6'), 124.3 (C-3',7'), 122.4 (C-10"), 122.3 (C-8"), 121.7 (C-9"), 119.9 (C-3"), 118.5 (C-7"), 111.6 (C-11"), 110.2 (C-4"), 103.7 (C-2"), 100.4 (C-12"), 70.6 (C-3) , 68.4 (C-2), 65.9 (C-1'), 61.3 (C-1); **MS**: *m/z* 439.2 $[M+H]^+$.

General procedure for the synthesis of L-*tert*-leucine analogs (6a-6c); L-valine analogous (7a-7c); L-leucine analogs (8a-8c) and L-norvaline analogous (9a-9c) and D-phenyl alanine) analogs (10a-10c):

To a solution of compound **5a-o** (0.32 g, 0.0016 mol) in methylene chloride (15 mL), EDAC.HCl (0.33 g, 0.0017 mol) and HOBt (0.3 g, 0.0022 mol), were added at a temperature of 20-30°C. This reaction mixture was stirred for next 3 h at similar temperature. After 3h, compound **4** (0.7 g, 0.0015 mol) was added and the reaction mixture was further stirred for another 8-10 h at room temperature. Afterwards distilled water (20 mL) was added to the reaction mixture. The organic layer was separated, washed with 10% w/w aqueous sodium bicarbonate solution and brine (10 mL) solution. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under pressure to yield **6a-7c.**

Methyl 1-(2-(3-(9H-carbazol-4-yl-oxy)-2-hydroxypropyl)-2-(4-(pyridin-2-yl) benzyl) hydrazinyl)-3,3-dimethyl-1-oxobutan-2-yl-carbamate (6a):

Anal. Calcd for **$C_{35}H_{39}N_5O_5$:** C, 68.95; H, 6.45; N, 11.49; O, 13.12 found: C, 68.99; H, 6.50; N, 11.42; O, 13.09. **IR**(KBr cm^{-1}**)**: 3408 (NH); 3346 (OH); 1722 (C=O), 1260 (C-O-C). **^{1}H NMR** (DMSO-d_6, 300 MHz) δ 0.77 (s, 9H), 3.08-3.10 (m, 2H), 3.50 (s, 3H), 3.76-3.89 (m, 1H), 4.07-4.16 (m, 2H), 4.21-4.49 (m, 2H), 4.99-5.12 (m, 1H), 6.70-8.16 (m, 15H), 8.64 (s, 1H), 9.28 (s, 1H), 11.21 (s, 1H); **^{13}C NMR** (DMSO-d_6, 100 MHz): δ169.4 (C-1'"), 155.9 (O-C= O), 155.1 (C-8'), 155.0 (C-1"), 149.4 (C-6"), 141.1 (C-5"), 138.9 (C-5'), 138.7 (C-12'), 138.6 (C-9'), 137.5 (C-11'), 137.4 (C-10'), 137.0 (C-2'), 128.9 (C-4',6'), 126.4 (3',7'), 126.1 (C-10"), 126.0 (C-8"), 124.4 (C-9") 122.5 (C-3"), 122.3 (C-7"), 121.8 (C-11"), 110.2 (C-4"), 103.7 (C-2"), 100.5 (C-12"), 70.3 (C-3), 67.0 (C-2), 66.8 (C-1'), 61.3 (C-1), 60.2 (OCH_3), 51.4 (C-2'"), 33.6 (C-3'"), 26.4 (C-4'",5'", 6'"). **MS:***m/z* 610.0 $[M+H]^+$.

Ethyl-1-(2-(3-(9H-carbazol-4-yl-oxy)-2-hydroxypropyl)-2-(4-(pyridine-2-yl)benzyl) hydrazinyl)-3,3-dimethyl-1-oxobutan-2-yl-carbamate (6b):

Anal. Calcd for **$C_{36}H_{41}N_5O_5$:** C, 69.32; H, 6.63; N, 11.23; O, 12.83 Found: C, 69.24; H, 6.58; N, 11.25; O, 12.76. **IR**(KBr cm^{-1}**)**: 3416 (NH); 3321 (OH); 1721 (C=O), 1257 (C-O-C). **^{1}H NMR** (DMSO-d_6, 300 MHz) δ0.77 (s, 9H), 1.03-1.10 (m, 3H), 2.98-3.15 (m, 2H), 3.76-3.89 (m, 1H), 3.93-4.07 (m, 2H), 4.09-4.16 (m, 4H), 4.99-5.14 (m, 1H), 6.70-7.99 (m, 15H), 8.65 (s, 1H), 9.26 (s, 1H), 11.21 (s, 1H); **^{13}C NMR** (DMSO-d_6, 100 MHz): δ169.3 (C-1'"), 155.7 (O-C= O), 155.1 (C-8'), 155.0 (C-1"), 149.4 (C-6"), 141.1 (C-5"), 138.9 (C-5'), 138.7 (C-12'), 138.6 (C-9'), 137.5 (C-11'), 137.4 (C-10'), 137.0 (C-2'), 128.9 (C-4',6'), 126.4 (3',7'), 126.1 (C-10"), 126.0 (C-8"), 124.4 (C-9") 122.5 (C-3"), 122.3 (C-7"), 121.8 (C-11"), 110.2 (C-4"), 103.7 (C-2"), 100.5 (C-12"), 70.3 (C-3), 67.1 (C-2), 66.8 (C-1'), 64.3 ($O\underline{CH_2}CH_3$), 61.3 (C-1), 51.4 (C-2'"), 33.6 (C-3'"), 26.4 (C-4'", 5'", 6'"), 14.7 ($OCH_2\underline{CH_3}$); **MS:***m/z* 624.0 $[M+H]^+$.

***Tert*-butyl-1-(2-(3-(9H-carbazol-4-yl-oxy)-2-hydroxypropyl)-2-(4-(pyridin-2-yl)benzyl) hydrazinyl)-3,3-dimethyl-1-oxobutan-2-yl-carbamate (6c):**

Anal. Calcd for **$C_{38}H_{45}N_5O_5$:** C, 70.02; H, 6.96; N, 10.74; O, 12.27; Found: C, 69.97; H, 7.02; N, 10.55; O, 12.35. **IR**(KBr cm^{-1}**)**: 3405 (NH); 3233 (OH); 1715 (C=O), 1667 (C=O), 1259 and 1167 (C-O-C).**^{1}H NMR** (DMSO-d_6, 300 MHz) δ0.77 (s, 9H), 1.33 (s, 9H), 3.08-3.10 (m, 2H), 3.78-3.86 (m, 1H), 4.10-4.16 (m, 4H), 5.01-5.12 (m, 1H), 6.71-8.00 (m, 15H), 8.65 (s, 1H), 9.23 (s, 1H), 11.31 (s, 1H); **^{13}C NMR** (DMSO-d_6, 100 MHz): δ170.1 (C-1'"), 156.2(O-C= O), 155.1 (C-8'), 155.0 (C-1"), 149.4 (C-6"), 141.1 (C-5"), 138.9 (C-5'), 138.7 (C-12'), 138.6 (C-9'), 137.5 (C-11'), 137.4 (C-10'), 137.0 (C-2'), 128.9 (C-4',6'), 126.4 (3',7'), 126.1 (C-10"), 126.0 (C-8"), 124.4 (C-9") 122.5 (C-3"), 122.3 (C-7"), 121.8 (C-11"), 110.2 (C-4"), 103.7 (C-2"), 100.5 (C-12"),75.8 (O-C[CH_3]$_3$), 70.3 (C-3), 67.0 (C-2), 66.8 (C-1'), 61.3 (C-1), 51.4 (C-2'"), 33.6 (C-3'"), 26.4 (C-4'", 5'", 6'"), 24.7 (O-C[CH_3]$_3$); **MS:***m/z* 652.0 $[M+H]^+$.

Methyl-1-(2-(3-(9H-carbazol-4-yl-oxy)-2-hydroxypropyl)-2-(4-(pyridin-2-yl)benzyl) hydrazinyl)-3-methyl-1-oxobutan-2-yl-carbamate (7a):

Anal. Calcd for **$C_{34}H_{37}N_5O_5$:** C, 68.55; H, 6.26; N, 11.76; O, 13.43 Found: C, 68.38; H, 6.32; N, 11.65; O, 13.38. **IR**(KBr cm^{-1}**)**: 3405 (NH); 3294 (OH); 1704 (C=O), 1671(C=O), 1262 and 1099 (C-O-C). **^{1}H NMR** (DMSO-d_6, 300 MHz) δ 0.68-0.70 (m, 6H), 1.62-1.87 (m, 1H),2.97-3.10 (m, 2H), 3.49 (s, 3H), 3.76-3.89 (m, 1H), 4.06-4.12 (m, 2H), 4.21-4.49 (m, 2H), 4.92-5.12 (m, 1H), 6.68-8.16 (m, 15H), 8.65 (s, 1H), 9.22 (s, 1H), 11.20 (s, 1H); **^{13}C NMR** (DMSO-d_6, 100 MHz): δ170.4 (C-1'"),155.9 (O-C= O), 155.1 (C-8'), 155.0 (C-1"), 149.4 (C-6"), 141.1 (C-5"), 138.9 (C-5'), 138.7 (C-12'), 138.6 (C-9'), 137.4 (C-11'), 137.1 (C-10'), 136.8 (C-2'), 129.0 (C-4', 6'), 126.4 (3', 7'), 126.1 (C-10"), 125.7 (C-8"), 124.4 (C-9"), 122.5 (C-3"), 122.3 (C-7"), 121.8 (C-11"), 110.2 (C-4"), 103.7 (C-2"), 100.5 (C-12"), 70.3 (C-3), 66.9 (C-2), 60.9 (C-1), 59.9 (C-1'), 59.2 (OCH_3), 51.3 (C-2'"), 30.0 (C-3'"), 18.9 (C-4'"), 18.0 (C-5'"); **MS:***m/z* 596.0 $[M+H]^+$.

Ethyl-1-(2-(3-(9H-carbazol-4-yl-oxy)-2-hydroxypropyl)-2-(4-(pyridin-2-yl)benzyl) hydrazinyl)-3-methyl-1-oxobutan-2-yl-carbamate (7b):

Anal. Calcd for **$C_{35}H_{39}N_5O_5$:** C, 68.95; H, 6.45; N, 11.49; O, 13.12 Found: C, 69.02; H, 6.52; N, 11.35; O, 13.22. **IR**(KBr cm^{-1}**)**: 3403 (NH); 3325 (OH); 1718 (C=O), 1646 (C=O), 1261 and 1102 (C-O-C). **^{1}H NMR** (DMSO-d_6, 300 MHz) δ 0.61-0.68 (m, 6H), 1.06-1.11 (m, 3H),1.61-1.79 (m, 1H), 2.96-3.12 (m, 2H), 3.38-3.54 (m, 1H), 3.75-3.86 (m, 2H), 3.95-4.10 (m, 4H), 4.98-5.16 (m, 1H), 6.68-7.99 (m, 15H), 8.66 (s, 1H), 9.20 (s, 1H), 11.21 (s, 1H); **^{13}C NMR** (DMSO-d_6, 100 MHz): δ170.4 (C-1'"),155.9 (O-C= O), 155.1 (C-8'), 155.0 (C-1"), 149.4 (C-6"), 141.1 (C-5"), 138.9 (C-5'), 138.7 (C-12'), 138.6 (C-9'), 137.4 (C-11'), 137.1 (C-10'), 136.8 (C-2'), 129.0 (C-4', 6'), 126.4 (3', 7'), 126.1 (C-10"), 125.7 (C-8"), 124.4 (C-9"), 122.5 (C-3"), 122.3 (C-7"), 121.8 (C-11"), 110.2 (C-4"), 103.7 (C-2"), 100.5 (C-12"), 70.3 (C-3), 66.9 (C-2), 64.3 (O$\underline{CH_2}CH_3$), 60.9 (C-1), 59.9 (C-1'), 51.3 (C-2'"), 30.0 (C-3'"), 18.9 (C-4'"), 18.0 (C-5'"), 14.7 ($OCH_2\underline{CH_3}$);**MS**: *m/z* 610.0 $[M+H]^+$.

***Tert*-butyl-1-(2-(3-(9H-carbazol-4-yl-oxy)-2-hydroxypropyl)-2-(4-(pyridin-2-yl)benzyl) hydrazinyl)-3-methyl-1-oxobutan-2-yl-carbamate (7c):**

Anal. Calcd for **$C_{37}H_{43}N_5O_5$:** C, 69.68; H, 6.80; N, 10.98; O, 12.54Found: C, 69.82; H, 6.90; N, 11.02; O, 12.44. **IR** (KBr cm^{-1}**)**: 3407 (NH); 3321 (OH); 1675(C=O), 1165 and 1100 (C-O-C). **^{1}H NMR** (DMSO-d_6, 300 MHz) δ 0.67-0.71(m, 6H), 1.33 (s, 9H), 1.62-1.87 (m, 1H),2.97-3.10 (m, 2H), 3.46-3.72 (m, 1H), 4.06-4.36 (m, 4H), 4.92-5.12 (m, 1H), 6.68-8.00 (m, 15H), 8.65 (s, 1H), 9.20 (s, 1H), 11.21 (s, 1H); **^{13}C NMR** (DMSO-d_6, 100 MHz): δ170.4 (C-1'"),155.9 (O-C= O), 155.1 (C-8'), 155.0 (C-1"), 149.4 (C-6"), 141.1 (C-5"), 138.9 (C-5'), 138.7 (C-12'), 138.6 (C-9'), 137.4 (C-11'), 137.1 (C-10'), 136.8 (C-2'), 129.0 (C-4', 6'), 126.4 (3', 7'), 126.1 (C-10"), 125.7 (C-8"), 124.4 (C-9"), 122.5 (C-3"), 122.3 (C-7"), 121.8 (C-11"), 110.2 (C-4"), 103.7 (C-2"), 100.5 (C-12"), 75.8 (O-C[CH_3]$_3$), 70.3

(C-3), 66.9 (C-2), 60.9 (C-1), 59.9 (C-1'), 51.3 (C-2'"), 30.0 (C-3'"), 24.7 (O-C[$\underline{CH_3}$]$_3$), 18.9 (C-4'"), 18.0 (C-5'"); **MS:***m/z* 638.0 $[M+H]^+$.

Methyl-1-(2-(3-(9H-carbazol-4-yl-oxy)-2-hydroxypropyl)-2-(4-(pyridin-2-yl)benzyl) hydrazinyl)-4-methyl-1-oxopentan-2-yl-carbamate (8a):

Anal. Calcd for **$C_{35}H_{39}N_5O_5$:** C, 68.95; H, 6.45; N, 11.49; O, 13.12 Found: C, 68.99; H, 6.35; N, 11.19; O, 13.35. **IR**(KBr cm^{-1}**)**: 3390 (NH); 3256 (OH); 1722 (C=O), 1649 (C=O), 1257 and 1104 (C-O-C). **^{1}H NMR** (DMSO-d_6, 300 MHz): δ 0.67-0.69 (m, 6H), 1.04-1.36 (m, 3H),3.04-3.13 (m, 2H), 3.49 (s, 3H), 3.67-3.89 (m, 1H), 4.04-4.29 (m, 4H), 4.98-5.11 (m, 1H), 6.69-8.17 (m, 15H), 8.64 (s, 1H), 9.20 (s, 1H), 11.21 (s, 1H); **^{13}C NMR** (DMSO-d_6, 100 MHz): δ171.4 (C-1'"), 155.9 (O-C= O), 155.1 (C-8'), 149.4 (C-1"), 141.1 (C-6"), 138.9 (C-5"), 138.6 (C-5'), 137.4 (C-12'), 137.1 (C-9'), 129.0 (C-11'), 126.4 (C-10'), 126.1 (C-2'), 124.4 (C-4', 6'), 122.5 (3', 7'), 122.3 (C-10"), 121.8 (C-8"), 119.9 (C-9"), 118.5 (C-3"), 117.2 (C-7"), 111.7 (C-11"), 110.2 (C-4"), 103.7 (C-2"), 100.5 (C-12"), 70.3 (C-3), 66.9 (C-2), 60.8 (OCH_3), 59.9 (C-1), 51.9 (C-1'), 51.3 (C-2'"), 40.7 (C-3'"), 23.9 (C-4'"), 22.6 (C-5'"), 21.6 (C-6'"); **MS:***m/z* 610.0 $[M+H]^+$.

Ethyl-1-(2-(3-(9H-carbazol-4-yl-oxy)-2-hydroxypropyl)-2-(4-(pyridin-2-yl)benzyl) hydrazinyl)-4-methyl-1-oxopentan-2-yl-carbamate (8b):

Anal. Calcd for **$C_{36}H_{41}N_5O_5$:** C, 69.32; H, 6.63; N, 11.23; O, 12.83 Found: C, 68.99; H, 6.45; N, 11.19; O, 13.59. **IR** (KBr cm^{-1}**)**: 3228 (NH, OH); 1719 (C=O), 1667 (C=O), 1263 and 1103 (C-O-C). **^{1}H NMR** (DMSO-d_6, 300 MHz): δ 0.68-0.70 (m, 6H), 1.04-1.46 (m, 6H), 2.97-3.22 (m, 2H), 3.89-3.91 (m, 3H), 4.06-4.30 (m, 4H),5.03-5.06 (m, 1H), 6.68-8.18 (m, 15H), 8.63 (s, 1H), 9.16 (s, 1H), 11.20 (s, 1H); **^{13}C NMR** (DMSO-d_6, 100 MHz): δ171.4 (C-1'"),155.9 (O-C= O), 155.1 (C-8'), 149.4 (C-1"), 141.1 (C-6"), 138.9 (C-5"), 138.6 (C-5'), 137.4 (C-12'), 137.1 (C-9'), 129.0 (C-11'), 126.4 (C-10'), 126.1 (C-2'), 124.4 (C-4', 6'), 122.5 (3', 7'), 122.3 (C-10"), 121.8 (C-8"), 119.9 (C-9"), 118.5 (C-3"), 117.2 (C-7"), 111.7 (C-11"), 110.2 (C-4"), 103.7 (C-2"), 100.5 (C-12"), 70.3 (C-3), 66.9 (C-2), 64.3 (O$\underline{CH_2}CH_3$), 59.9 (C-1), 51.9 (C-1'), 51.3 (C-2'"), 40.7 (C-3'"), 23.9 (C-4'"), 22.6 (C-5'"), 21.6 (C-6'"), 14.7 ($OCH_2\underline{CH_3}$); **MS:***m/z* 624.0 $[M+H]^+$.

***Tert*-butyl-1-(2-(3-(9H-carbazol-4-yl-oxy)-2-hydroxypropyl)-2-(4-(pyridin-2-yl)benzyl) hydrazinyl)-4-methyl-1-oxopentan-2-yl-carbamate (8c):**

Anal. Calcd for **$C_{38}H_{45}N_5O_5$:** C, 70.02; H, 6.96; N, 10.74; O, 12.27 Found: C, 69.99; H, 6.55; N, 11.02; O, 12.55. **IR** (KBr cm^{-1}**)**: 3388 (NH); 3225 (OH); 1708 (C=O), 1666 (C=O), 1256 and 1169 (C-O-C). **^{1}H NMR** (DMSO-d_6, 300 MHz): δ 0.67-0.71 (m, 6H), 1.01-1.28 (m, 3H),1.32 (s, 9H), 2.98-3.15 (m, 2H), 3.67-3.89 (m, 1H), 4.07-4.28 (m, 4H), 4.97-5.10 (m, 1H), 6.69-8.18 (m, 15H), 8.66 (s, 1H), 9.11 (s, 1H), 11.20 (s, 1H); **^{13}C NMR** (DMSO-d_6, 100 MHz): δ171.4 (C-1'"),155.9 (O-C= O), 155.1 (C-8'), 149.4 (C-1"), 141.1 (C-6"), 138.9 (C-5"), 138.6 (C-5'), 137.4 (C-12'), 137.1 (C-9'), 129.0 (C-11'), 126.4 (C-10'), 126.1 (C-2'), 124.4 (C-4', 6'), 122.5 (3', 7'), 122.3 (C-10"), 121.8 (C-8"), 119.9 (C-9"), 118.5 (C-3"), 117.2 (C-7"), 111.7 (C-11"), 110.2 (C-4"), 103.7 (C-2"), 100.5 (C-12"), 75.8 (O-$\underline{C}$[CH_3]$_3$), 70.3 (C-3), 66.9 (C-2), 60.8 (OCH_3), 59.9 (C-1), 51.9 (C-1'), 51.3 (C-2'"), 40.7 (C-3'"), 24.7 (O-C[$\underline{CH_3}$]$_3$), 23.9 (C-4'"), 22.6 (C-5'"), 21.6 (C-6'"); **MS:***m/z* 652.0 $[M+H]^+$.

Methyl-1-(2-(3-(9H-carbazol-4-yl-oxy)-2-hydroxypropyl)-2-(4-(pyridin-2-yl)benzyl) hydrazinyl)-1-oxopentan-2-yl-carbamate (9a):

Anal. Calcd for **$C_{34}H_{37}N_5O_5$:** C, 68.55; H, 6.26; N, 11.76; O, 13.43 Found: C, 67.99; H, 6.35; N, 10.99; O, 13.09. **IR**(KBr cm^{-1}**)**: 3403 (NH); 3291 (OH); 1706 (C=O), 1669 (C=O), 1262 and 1100 (C-O-C). **^{1}H NMR** (DMSO-d_6, 300 MHz): δ 0.63-0.68 (m, 3H), 0.89-1.16 (m, 2H),1.30-1.32 (m, 2H),3.04-3.08 (m, 2H), 3.48 (s, 3H), 3.63-3.84 (m, 1H), 4.06-4.50 (m, 4H), 4.97-5.09 (m, 1H), 6.68-8.16 (m, 15H), 8.65 (s, 1H), 9.18 (s, 1H), 11.21 (s, 1H); **^{13}C NMR** (DMSO-d_6, 100 MHz): δ171.0 (C-1'"),155.9 (O-C= O), 155.1 (C-8'), 149.4 (C-1"), 141.1 (C-6"), 138.9 (C-5"), 138.6 (C-5'), 137.4 (C-12'), 137.1 (C-9') , 129.0 (C-11'), 126.4 (C-10'), 126.1 (C-2'), 124.4 (C-4', 6'), 122.5 (3', 7'), 122.3

(C-10"), 121.8 (C-8"), 119.9 (C-9"), 118.5 (C-3"), 117.2 (C-7"), 111.7 (C-11"), 110.2 (C-4"), 103.7 (C-2"), 100.5 (C-12"), 70.3 (C-3), 66.9 (C-2), 60.8 (C-1'), 59.9 (C-1), 53.3 (OCH_3), 51.3 (C-2'''), 33.9 (C-3'''), 18.3 (C-4'''), 13.5 (C-5'''); **MS**: *m/z* 596.0 $[M+H]^+$.

Ethyl-1-(2-(3-(9H-carbazol-4-yl-oxy)-2-hydroxypropyl)-2-(4-(pyridin-2-yl)benzyl) hydrazinyl)-1-oxopentan-2-yl-carbamate (9b):

Anal. Calcd for **$C_{35}H_{39}N_5O_5$:** C, 68.95; H, 6.45; N, 11.49; O, 13.12 Found: C, 68.52; H, 6.18; N, 11.39; O, 13.07. **IR**(KBr cm^{-1}**)**: 3402 (NH); 3288 (OH); 1670 (C=O), 1262 and 1099 (C-O-C).**^{1}H NMR** (DMSO-d_6, 300 MHz): δ 0.60-0.66 (m, 3H), 0.84-1.46 (m, 6H),2.97-3.17 (m, 2H),3.55-3.86 (m, 1H), 3.89-4.09 (m, 2H), 4.12-4.45 (m, 4H), 4.98-5.07 (m, 1H), 6.69-8.01 (m, 15H), 8.64 (s, 1H), 9.18 (s, 1H), 11.22 (s, 1H); **^{13}C NMR** (DMSO-d_6, 100 MHz): δ171.0 (C-1'''),155.9 (O-C= O), 155.1 (C-8'), 149.4 (C-1''), 141.1 (C-6''), 138.9 (C-5''), 138.6 (C-5'), 137.4 (C-12'), 137.1 (C-9') , 129.0 (C-11'), 126.4 (C-10'), 126.1 (C-2'), 124.4 (C-4', 6'), 122.5 (3', 7'), 122.3 (C-10''), 121.8 (C-8''), 119.9 (C-9''), 118.5 (C-3''), 117.2 (C-7''), 111.7 (C-11''), 110.2 (C-4''), 103.7 (C-2''), 100.5 (C-12''), 70.3 (C-3), 66.9 (C-2), 64.3 ($O\underline{CH_2}CH_3$), 60.8 (C-1'), 59.9 (C-1),51.3 (C-2'''), 33.9 (C-3'''), 18.3 (C-4'''), 14.7 ($OCH_2\underline{CH_3}$), 13.5 (C-5'''); **MS:***m/z* 610.0 $[M+H]^+$.

***Tert*-butyl-1-(2-(3-(9H-carbazol-4-yl-oxy)-2-hydroxypropyl)-2-(4-(pyridin-2-yl)benzyl) hydrazinyl)-1-oxopentan-2-ylcarbamate (9c):**

Anal. Calcd for **$C_{37}H_{43}N_5O_5$:** C, 69.68; H, 6.80; N, 10.98; O, 12.54 Found: C, 69.99; H, 6.55; N, 11.05; O, 12.19. **IR**(KBr cm^{-1}**)**: 3323 (NH); 1694 (C=O), 1164 and 1101 (C-O-C). **^{1}H NMR** (DMSO-d_6, 300 MHz): δ 0.59-0.67 (m, 3H), 1.08-1.14 (m, 2H),1.28-1.31 (m, 2H)1.38(s, 9H), 2.97-3.08 (m, 2H), 3.63-3.84 (m, 1H), 4.06-4.50 (m, 4H), 4.97-5.08 (m, 1H), 6.71-7.98 (m, 15H), 8.64 (s, 1H), 9.09 (s, 1H), 11.20 (s, 1H); **^{13}C NMR** (DMSO-d_6, 100 MHz): δ171.0 (C-1'''),155.9 (O-C= O), 155.1 (C-8'), 149.4 (C-1''), 141.1 (C-6''), 138.9 (C-5''), 138.6 (C-5'), 137.4 (C-12'), 137.1 (C-9') , 129.0 (C-11'), 126.4 (C-10'), 126.1 (C-2'), 124.4 (C-4', 6'), 122.5 (3', 7'), 122.3 (C-10''), 121.8 (C-8''), 119.9 (C-9''), 118.5 (C-3''), 117.2 (C-7''), 111.7 (C-11''), 110.2 (C-4''), 103.7 (C-2''), 100.5 (C-12''), 75.8 (O-$\underline{C}[CH_3]_3$), 70.3 (C-3), 66.9 (C-2), 60.8 (C-1'), 59.9 (C-1), 51.3 (C-2'''), 33.9 (C-3'''), 24.7 (O-C[$\underline{CH_3}]_3$), 18.3 (C-4'''), 13.5 (C-5''');**MS**: *m/z* 638.0 $[M+H]^+$.

Methyl-1-(2-(3-(9H-carbazol-4-yloxy)-2-hydroxypropyl)-2-(4-(pyridin-2-yl)benzyl) hydrazinyl)-1-oxo-3-phenylpropan-2-yl-carbamate (10a):

Anal. Calcd for **$C_{38}H_{37}N_5O_5$:** C, 70.90; H, 5.79; N, 10.88; O, 12.43 Found: C, 69.99; H, 5.55; N, 10.99; O, 12.25. **IR**(KBr cm^{-1}**)**: 3408 (NH); 3280 (OH); 1720 (C=O), 1612 (C=O), 1259 and 1103 (C-O-C). **^{1}H NMR** (DMSO-d_6, 300 MHz) δ2.50-2.73 (m, 2H),3.07-3.14 (m, 2H), 3.51 (s, 3H), 3.99-4.24 (m, 5H), 4.89-5.06 (m, 1H), 6.68-7.98 (m, 20H), 8.65 (s, 1H), 9.32 (s, 1H), 11.20 (s, 1H); **^{13}C NMR** (DMSO-d_6, 100 MHz): δ170.6 (C-1'''),155.9(O-C= O), 155.1 (C-8'), 155.0 (C-1''), 149.4 (C-6''), 141.1 (C-5''), 138.9 (C-5'), 138.5 (C-12'), 137.8 (C-9') , 137.4 (C-11'), 137.1 (C-10'), 137.0 (C-2'), 129.1 (C-4'''), 127.9 (C-4',6'), 126.4 (3',7'), 126.2 (5''', 9'''), 126.1 (C-10''), 126.0 (C-8''), 124.4 (C-9''), 122.5 (C-3''), 122.3 (C-7''), 121.9 (6''', 8'''), 121.8 (C-11''), 119.9 (7'''), 110.2 (C-4''), 103.7 (C-2''), 100.5 (C-12''), 70.2 (C-3), 67.1 (C-2), 66.8 (C-1'), 60.9 (C-1), 59.6 (OCH_3), 51.3 (C-2'''), 37.5 (C-3'''); **MS:***m/z* 644.0 $[M+H]^+$.

Ethyl-1-(2-(3-(9H-carbazol-4-yl-oxy)-2-hydroxypropyl)-2-(4-(pyridin-2-yl)benzyl) hydrazinyl)-1-oxo-3-phenylpropan-2-yl-carbamate (10b):

Anal. Calcd for **$C_{39}H_{39}N_5O_5$:** C, 71.21; H, 5.98; N, 10.65; O, 12.16 Found: C, 70.99; H, 5.59; N, 10.95; O, 12.35. **IR**(KBr cm^{-1}**)**: 3407 (NH); 3306 (OH); 1672 (C=O), 1262 and 1099 (C-O-C). **^{1}H NMR** (DMSO-d_6, 300 MHz): δ 1.01-1.08 (m, 3H),2.52-2.76 (m, 2H),2.98-3.16 (m, 2H), 3.81-3.98 (m, 2H), 4.04-4.34 (m, 5H), 4.89-5.08 (m, 1H), 6.70-8.00 (m, 20H), 8.63 (s, 1H), 9.29 (s, 1H), 11.21 (s, 1H); **^{13}C NMR** (DMSO-d_6, 100 MHz): δ 170.6 (C-1'''),155.9(O-C= O), 155.1 (C-8'), 155.0 (C-1''), 149.4 (C-6''), 141.1 (C-5''), 138.9 (C-5'), 138.5 (C-12'), 137.8 (C-9')

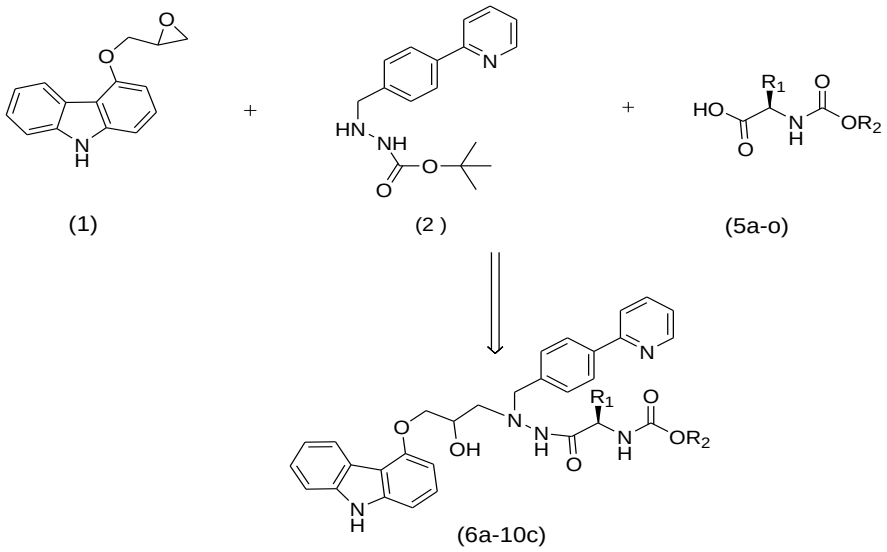
, 137.4 (C-11'), 137.1 (C-10'), 137.0 (C-2'), 129.1 (C-4'"), 127.9 (C-4',6'), 126.4 (3',7'), 126.2 (5'", 9'"), 126.1 (C-10"), 126.0 (C-8"), 124.4 (C-9"), 122.5 (C-3"), 122.3 (C-7"), 121.9 (6'", 8'"), 121.8 (C-11"), 119.9 (7'"), 110.2 (C-4"), 103.7 (C-2"), 100.5 (C-12"), 70.2 (C-3), 67.1 (C-2), 66.8 (C-1'), 64.3 (O$\underline{CH_2}CH_3$), 60.9 (C-1), 51.3 (C-2'"), 37.5 (C-3'"), 14.7 (OCH$_2\underline{CH_3}$); **MS:***m/z* 658.0 $[M+H]^+$.

***Tert*-butyl-1-(2-(3-(9H-carbazol-4-yl-oxy)-2-hydroxypropyl)-2-(4-(pyridin-2-yl)benzyl) hydrazinyl)-1-oxo-3-phenylpropan-2-yl-carbamate (10c):**

Anal. Calcd for **$C_{41}H_{43}N_5O_5$:** C, 71.80; H, 6.32; N, 10.21; O, 11.66 Found: C, 70.99; H, 6.55; N, 10.19; O, 11.55. **IR**(KBr cm^{-1})**:** 3406 (NH); 3310 (OH); 1675 (C=O), 1262 and 1165 (C-O-C). **^{1}H NMR** (DMSO-d_6, 300 MHz) δ 1.29 (s, 9H),2.50-2.76 (m, 2H),3.02-3.26 (m, 2H), 3.80-4.26 (m, 5H), 4.88-5.11 (m, 1H), 6.71-8.01 (m, 20H), 8.65 (s, 1H), 9.28 (s, 1H), 11.22 (s, 1H); **^{13}C NMR** (DMSO-d_6, 100 MHz): δ170.6 (C-1'"),155.9(O-C= O), 155.1 (C-8'), 155.0 (C-1"), 149.4 (C-6"), 141.1 (C-5"), 138.9 (C-5'), 138.5 (C-12'), 137.8 (C-9') , 137.4 (C-11'), 137.1 (C-10'), 137.0 (C-2'), 129.1 (C-4'"), 127.9 (C-4',6'), 126.4 (3',7'), 126.2 (5'", 9'"), 126.1 (C-10"), 126.0 (C-8"), 124.4 (C-9"), 122.5 (C-3"), 122.3 (C-7"), 121.9 (6'", 8'"), 121.8 (C-11"), 119.9 (7'"), 110.2 (C-4"), 103.7 (C-2"), 100.5 (C-12"), 75.8 (O-$\underline{C}[CH_3]_3$), 70.2 (C-3), 67.1 (C-2), 66.8 (C-1'), 60.9 (C-1), 51.3 (C-2'"), 37.5 (C-3'"), 24.7 (O-C[$\underline{CH_3}]_3$); **MS:** *m/z* 686.0 $[M+H]^+$.

Results and Discussion

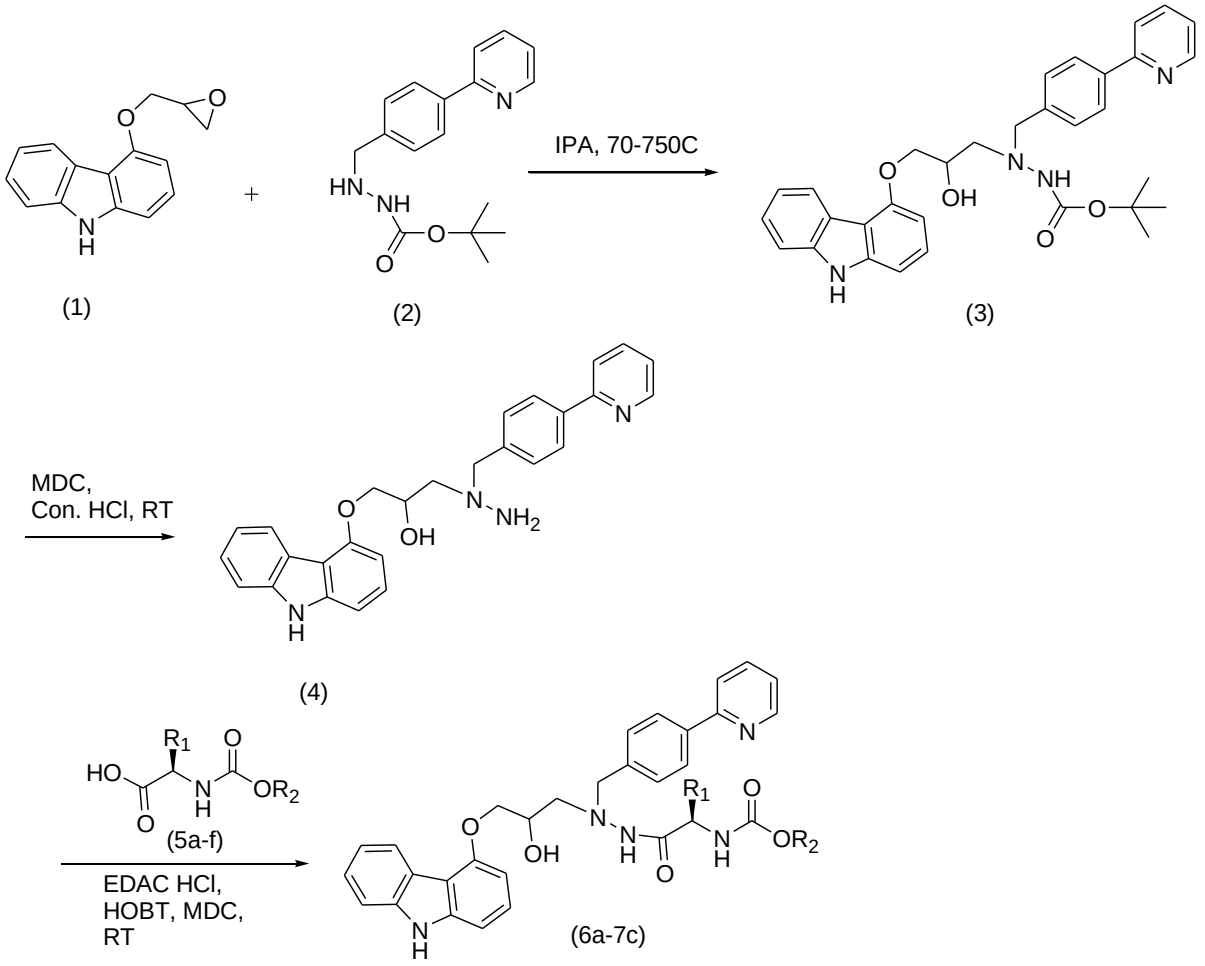
To incorporate the active moiety into the atazanavir, the right side part of the atazanavir structure (**Fig. 1**) was replaced with active carbazole, which results in structurally modified compounds (**6a-10c**) that may produce better activity than the parent compound (**Scheme 1**).



Scheme 1. Synthesis of atazanavir analogues(**6a-10c**)

We first focused on the synthesis of L-*tert*-leucine (**6a-6c**) and L-valine (**7a-7c**) analogues in three steps, where the starting compounds **1** and **2** were synthesized based on earlier literature protocols[16,17,18]. The first step involved ring opening of compound **1** with compound **2** (**Scheme 2**) in presence of isopropyl alcohol as solvent at 70-75 ^oC produing compound **3** in good yield (76.6 %). From the ^{1}H NMR spectra of compound **3**, we identified a singlet at δ 11.21 ppm that corresponds for the proton of NH of carbazole, a multiplet at δ 3.05-3.03 ppm for two protons of –CH_2N, a singletat δ 4.95 ppm for –CHOH and another singlet at δ 1.33 ppm for nine protons of the BOC group. The mass spectra of compound **3** gave the corresponding molecular ion peak [$[M+H]^+$: 539.2], which also confirms the

successful formation of desired compound **3**. The second step was the deprotection of the BOC group, which was carried out in a biphasic media at room temperature. Work-up of the reaction mixture was carried out using dichloromethane to remove unreacted starting reagents and process impurities, while the product was present in the aqueous layer as hydrochloride. pH of the aqueous layer was brought to 9.0 by addition of 10 % w/w aqueous sodium carbonate solution. The aqueous layer was treated with methylene chloride, the organic layers were collected and concentrated to yield compound **4** in 81.9 % isolated yield. The ^{1}H NMR spectra has a singlet at δ 3.64 ppm for NH_2 group and most importantly the proton singlet at δ 1.33 ppm proved the absence of the BOC group, indicating that the deprotection step was indeed successful. This was also confirmed by the molecular ion peak of $[M+H]^+$ at 439.2 (decrease of $[M+H]^+$: 100 corresponds to the missing BOC group) in the mass spectra.



(6a) R1= C(CH3)3, R2= CH3 (7a) R1= CH(CH3)2, R2= CH3
(6b) R1= C(CH3)3, R2= CH2CH3 (7b) R1= CH(CH3)2, R2= CH2CH3
(6c) R1= C(CH3)3, R2= C(CH3)3 (7c) R1= CH(CH3)2, R2= C(CH3)3

Scheme 2. Synthesis of L-*tert*-leucine (**6a-6c**) and L-valine (**7a-7c**) analogue

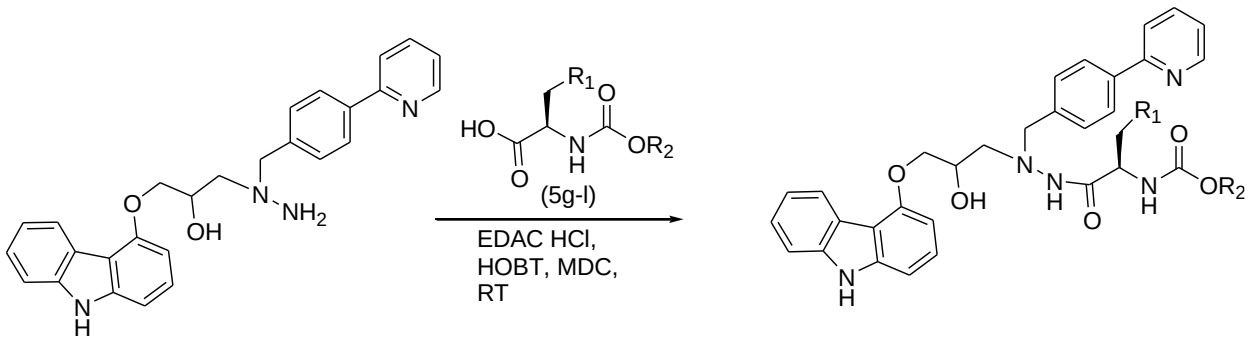
The third step involved the condensation of compound **4** with different carbamate amino acids **(5a-f)** to form a mono peptide bond ideally delivering compounds **6a-7c**. The reaction was carried out using two coupling agents *N*-hydroxybenzotriazole (HOBt) and 1-ethyl-3-(3-dimethylaminopropyl carbodiimide (EDAC.HCl) in presence of dichloromethane (MDC) at room temperature. Compounds **6a-7c** were obtained in moderate to good

yields (**Table-1**). From the ^{1}H NMR spectra, the disappearance of proton singlet at δ 3.64 ppm of NH_2 group and appearance of a new proton singlet (i.e. of NH carbazole group) in the range of δ 11.20-11.21 ppm for all the compounds (**6a-7c**) indicate that the reaction was successful. Apart from this, the ^{1}H NMR for compounds **6a-6c** has a singlet at δ 0.77 ppm for -CH_3 proton of *tert*-leucine and compounds **7a-7c** has a multiplet at δ 0.68-0.7 ppm for methyl protons of valine. The mass spectra of compounds **6a-7c** have the corresponding molecular ion peaks at [[M+H]$^+$: 610.0 (**6a**); 624.0 (**6b**); 652.0 (**6c**); 596.0 (**7a**); 610.0 (**7b**) and 638.0 (**7c**) respectively. Both these data confirm the formation of the desired compounds **6a-7c**.

Table 1. Reaction conditions and yields for the synthesis of compounds**6a-7c**

Entry	Carbamate amino acids	Time (h)	Product	Yield (%)
01	**5a**	10	**6a**	74.0
02	**5b**	9	**6b**	53.5
03	**5c**	9	**6c**	81
04	**5d**	8	**7a**	53.8
05	**5e**	10	**7b**	74.8
06	**5f**	8	**7c**	81.4

After successful synthesis of L-*tert*-leucine (**6a-6c**) and L-valine (**7a-7c**) analogues, we further went on to synthesize L-leucine (**8a-8c**) and L-norvaline (**9a-9c**) analogues as shown in **scheme 3**. Under similar reaction conditions, condensation of compound **4** with different carbamate amino acids **(5g-l)** in the presence of coupling agents (HOBt and EDAC.HCl) in methylene chloride at room temperature gave compounds **8a-9c** (**Scheme 3**) in good yields (**Table 2**). The presence of carbazole moiety in compounds **8a-9c** was confirmed by ^{1}H NMR spectra with the appearance of a singlet peak in the range at δ 11.20-11.21 ppm. Apart from this, the ^{1}H NMR of compound **8a-8c** has a multiplet at δ 0.68-0.71 ppm for methyl protons of leucine. Further, ^{1}H NMR spectrum of compound **8a** has a singlet at δ 3.49 ppm for the methoxy proton; compound **8b** has a multiplet at δ 1.04-1.09 ppm for the methyl protons and another multiplet at δ 4.07 ppm for OCH_2 protons and compound **8c** has a singlet peak at δ 1.32 ppm for $C(CH_3)_3$ protons. In case of ^{1}H NMR of compound **9a-9c**, we identified one multiplet at δ 0.68 ppm and another multiplet at δ 0.84-1.16 ppm for methyl protons of L-norvaline. Further ^{1}H NMR of compound **9a** has a singlet peak at δ 3.48 ppm for the methoxy proton; compound **9b** has a multiplet at δ 1.10 ppm for methylprotons and another multiplet at δ 4.01 for OCH_2 protons and **9c** has a singlet peak at δ 1.38 ppm for $C(CH_3)_3$ protons. The mass spectra of compound **8a-9c** were found to contain the molecular ion peaks at [[M+H] $^+$: 610.0 (**8a)**; 624.0 (**8b**); 652.0 (**8c**); 596.0 (**9a**); 610.0 (**9b**) and 638.0 (**9c**) respectively. Both ^{1}H NMR and MS data indicate the successful formation of the desired analogues.



(8a) R1= CH(CH3)2, R2= CH3
(8b) R1= CH(CH3)2, R2= CH2CH3
(8c) R1= CH(CH3)2, R2= C(CH3)

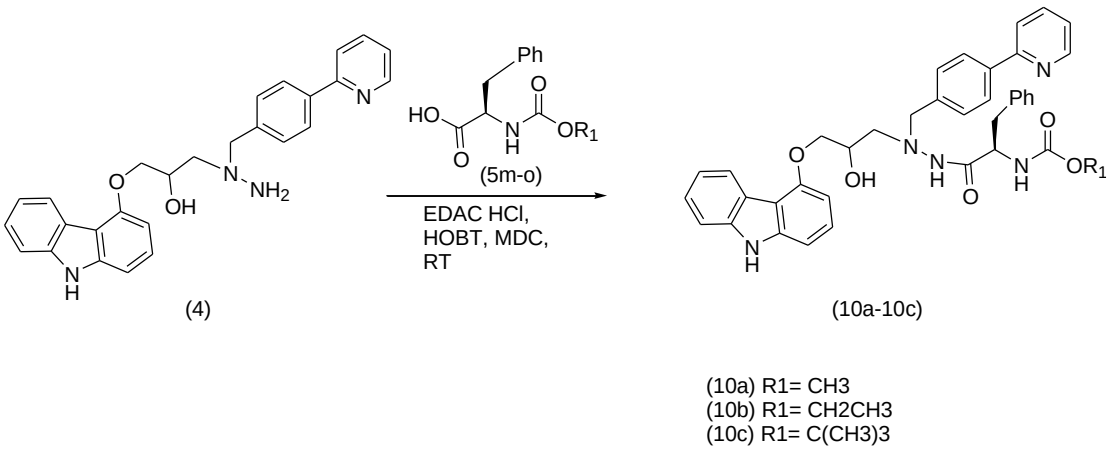
(9a) R1=CH2CH3, R2=CH3
(9b) R1=CH2CH3, R2=CH2CH3
(9c) R1=CH2CH3, R2=C(CH3)3

Scheme 3. Synthesis ofL-leucine (**8a-8c**) and L-norvaline (**9a-9c**) analogue

Table 2. Reaction conditions and yields for the synthesis of compounds **8a-9c**

Entry	Carbamate amino acids	Time (h)	Product	Yield (%)
01	**5g**	9	**8a**	79.1
02	**5h**	10	**8b**	77.5
03	**5i**	8	**8c**	79
04	**5j**	9	9a	43.8
05	**5k**	10	**9b**	72.7
06	**5**l	9	**9c**	64.1

Under similar reaction conditions (**Scheme 4**) as described above, we finally worked on the synthesis of D-phenyl alanine analogs (**10a-c**), which resulted in the desired compounds in good yields (**Table 3**). The ^{1}H NMR spectra of compounds **10a-10c** has a singlet peak in the range at δ 11.20-11.21 ppm for NH of carbazole like other compounds along with a multiplet at δ 2.52-2.76 ppm for the two protons of CH_2Ph. The ^{1}H NMR of compound **10a** has a singlet peak at δ 3.51 ppm for the methoxy proton; compound **10b** showed a multiplet peak in the range of δ 1.01-1.08 ppm for methyl protons and another multiplet at δ 3.81-3.98 ppm for OCH_2 protons and compound **10c** has a singlet at δ 1.29 ppm for $C(CH_3)_3$ protons. The mass spectra of compound **10a**, **10b** and **10c** gave the corresponding molecular ion peaks at $[M+H]^+$: 644.0; 658.0 and 686.0 respectively.



Scheme 4. Synthesis of D-phenyl alanine (**10a-10c**) analogs

Table 3. Reaction conditions and yields forcompounds**10a-10c**

Entry	Carbamate amino acids	Time (h)	Product	Yield (%)
01	**5m**	10	**10a**	75.5
02	**5n**	9	**10b**	81.4
03	**5o**	10	**10c**	46.6

Conclusion:

In this study, we have successfully modified the structure of atazanavir with active carbazole moieties and obtained new series of atazanavir analogues **6a-10c** in good yields. Currently, further work is in progress to study the anti-HIV activity of these new series of compound **6a-10c**.

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References:

1. Clemente, J. C.; Coman, R. M.; Thiaville, M.M.; Janka, L. K.; Jeung, J. A.; Nukoolkarn, S.; Govindasamy, L.; Agbandje-McKenna, M.; McKenna, R.; Leelamanit, W.; Goodenow, M. M.; Dunn, B. M. 2006. Analysis of HIV-1 CRF_01 A/E protease inhibitor resistance: structural determinants for maintaining sensitivity and developing resistance to atazanavir. *Biochemistry*. **45**: 5468-5477.
2. Michael, D. A.; Akbar, A.; Kiran Kumar Reddy, G. S.; Madhavi, N. L. N.; Saima, G. A.; Hong. C.; Sripriyam, C.; Visvaldas, K.; Miguel, X. F.; Michael, K. G.; Celia, A. S.; Tariq, M .R.; Bruce, T. 2008. HIV-1 protease inhibitors from inverse design in the substrate envelope exhibit subnanomolar binding to drug-resistant variants. *J. Am. Chem. Soc*. **130**: 609-613.

3. Silke, K.; Richard, M.; Fabian, D.; Gilles, D.; Sophie, L.; Masoud, R.; Mohammad, J. H.; Patrick, G. K.; Morteza, M. 2013. Therapeutic Benefits from Nanoparticles: The Potential Significance of Nanoscience in Diseases with Compromise to the Blood Brain Barrier. *Chem. Rev*. **113**: 1877–1903.
4. Javier, M.;Joshua, R. D. 2012. Large-scale carbonyl reductions in the pharmaceutical Industry. *Org. Process Res. Dev*. **16**: 1156–1184.
5. Arun, K. G.; Sofiya, L. Y.; David, D. A.; Abigail, B.; Marcus, N.; Heather, B. M.; Yunfeng, T.; Yuan-Fang, W.; Yasuhiro, K.; Irene, T. W.; Hiroaki, M. 2009**.** Design and Synthesis of Potent HIV-1 Protease Inhibitors Incorporating Hexahydrofuropyranol-Derived High Affinity P_2 Ligands: Structure−Activity Studies and Biological Evaluation. *J. Med. Chem.* **52**: 3902–3914.
6. Xing, F.;Yan-Li, S.;Ya-Qiu, L. 2008. An Efficient and Practical Synthesis of the HIV Protease Inhibitor atazanavir via a Highly diastereoselective Reduction Approach. *Org. Process Res. Dev*. **12**: 69–75.
7. David, A. D.; David, J. G.; Hui-Ju, C.; William, J. F.; Larry, L. K.; Tatyana, D.; Vincent, S.; Mulugeta, M.; Akhteruzzaman, M.; Dale, J. K. 2011. P1-Substituted Symmetry-Based Human Immunodeficiency Virus Protease Inhibitors with Potent Antiviral Activity against Drug-Resistat Viruses**.** *J. Med. Chem.* **5***:* 7094–7104.
8. Yoshimura, K.; Kato, R.; Kavlick, M. F.; Nguyen, A.; Maroun, V.; Maeda, K.; Hussain, K. M.; Ghosh, A. K.; Gulnik, S. V.; Erickson, J. W.; Mitsuya, H.A. 2002. Potent Human Immunodeficiency Virus Type 1 Protease Inhibitor, UIC-94003 (TMC-126), and Selection of a Novel (A28S) Mutation in the Protease Active Site.*J. vi.* **76**: 1349-1358.
9. Hoetelmans, R. M. W.; Meenhorst, P.L.; Mulder, J. W.; Burger, D. M.; Koks ,C. H.; Beijnen, J. H. 1997. Clinical pharmacology of HIV protease inhibitors: focus on saquinavir, indinavir, and ritonavir.*Pharm .World Sci.* **19**: 159-75.
10. Prasad, J. V. N. V.; Lunney, E. A.; Para, K. S.; Tummino , P. J.; Ferguson, D.; Hupe, D.; Domagala, J. M.; Erickson, J. W. 1996. Nonpeptidic potent HIV-1 protease inhibitors. 1 *Drug Des. Dis.* **13**: 15-28.
11. Tomasselli, A. G.; Thaisrivongs, S.; Heinrikson, R. L. 1996. Discovery and design of HIV protease inhibitors as drugs for treatment of aids Original Research Article. *Adv. in Ant. Drug Des*. **2**: 173-228.
12. Kageyama, S.; Hoekzema, D. T.; Murakawa, Y.; Kojima, E.; Shirasaka, T.; Kempf, D. J.; Norbeck, D. W.; Erickson, J.; Mitsuya, H.A 1994. C2 symmetry-based HIV protease inhibitor, A77003, irreversibly inhibits infectivity of HIV-1 in vivo.*AIDS Res. Hum. Ret.* **10**: 735-43.
13. Fässler, A.; Bold, G.; Capraro, H. G.; Cozens, R.; Mestan, J.; Poncioni, B.; Rösel, J.; Tintelnot-Blomley, M.; Lang, M. 1996. Aza-Peptide Analogs as Potent Human Immunodeficiency Virus Type-1 Protease Inhibitors with Oral Bioavailability. *J. Med. Chem.* **39**: 3203-3216.
14. Geetha Bhavani K., Bala Murali Krishna K.,, Srinivasu N.,, Ramachandran D.,, Raman N.V.V.S.S., Hari Babu B. 2017. Determination of genotoxic impurity in Atazanavir sulphate drug substance by LC–MS, *Journal of Pharmaceutical and Biomedical Analysis*, **132**: 156–158,
15. Venkata Siva Sri Nalini M., Hari Babu B., Rama Krishna Veni P. 2016. Stability Indicating RP-HPLC Method for Simultaneous Estimation of Atazanavir and Cobicistat in Tablets, *British Journal of Pharmaceutical Research,* **11(6)**: 1-10.
16. Lauer, K.; Kiegel, E. 1981. Process for the preparation of 4-hydroxycarbazole.*U.S. Pat.*4273711,
17. Kankan, N. R.; Ramachandrarao Rao, D. 2008. Process for the preparation of Carvedilol*U.S. Pat.* 0234492.
18. Zhongmin Xu.; Janak Singh.; Mark D. Schwinden.; Bin Zheng.; Thomas P. Kissick.;Bharat Patel.; Michael J. Humora.; Fernando Quiroz.;Lin Dong.;Dau-Ming Hsieh.;James E. Heikes.;Madhusudhan Pudipeddi.;Mark D. Lindrud.;Sushil K. Srivastava.; David R. Kronenthal.;Richard H. 2002**.** Mueller.Process Research and Development for an Efficient Synthesis of the HIV Protease Inhibitor BMS-232632. *Org. Proc. Res. Dev.*, **6**: 323–328.