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STRUCTURE MODIFICATION OF RITONAVIR WITH CARBAZOLE; SYNTHESIS AND CHARACTERIZATION

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ABSTRACT: The core moiety of ritonavir (2S, 3S, 5S)-5-(tert-butyloxycarbonyl)amino-2-amino-3-hydroxy-1,6-diphenylhexane **(7)** on condensation with oxirane of carbazole **(8)** in isopropyl alcohol at reflux and deprotected with mineral acid gave compound **10**. Coupling of compound **10** with carbamate amino acid **(11a-15c)** in the presence of EDAC.HCl and HOBt at room temperature gave ritonavir analogues containing carbazole (**16a-20c**) as a novel for the human immunodeficiency virus (HIV)-1. These compound were characterized by IR, ^{1}H NMR and Mass spectroscopic.

INTRODUCTION: Ritonavir {(2S, 3S, 5S)-[N-[N-[[N-methyl-N-[(2-isopropyl-4-thiazolyl)-methyl] amino] carbonyl]-L-valinyl]amino]-2-[N-[(5-thiazolyl)methoxycarbonyl]amino]-1,6-diphenyl-3-hydroxyhexane} is a human immuno-deficiency virus (HIV) [1].

Protease inhibitor is indicated for the treatment of acquired immunodeficiency syndrome (AIDS) [2]. Peptidomimetic inhibitor is based on hydroxyl ethylene dipeptide isosteres show great efficacy against HIV-PR. Ritonavir (**Fig. 1**) is practically insoluble in water and could potentially exhibit dissolution rate limited absorption.

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These difficulties have limited their usefulness as therapeutic agent [3-7]. In the search for new better anti-HIV drugs, commonly is found in literature compounds designated as analogs or derivatives of protease inhibitors already consecrated.

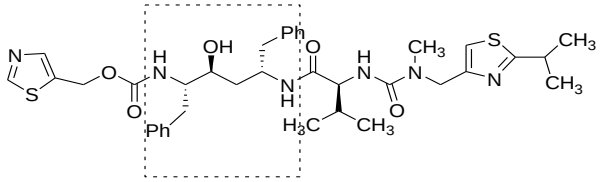


FIGURE 1: STRUCTURE OF RITONAVIR

Based on knowledge obtained from literature, we attempted to prepare ritonavir analogues by changing the left and right part of 1, 4-diamino-2-hydroxy butane in the structure of ritonavir. Left part of 1, 4-diamino-2-hydroxy butane was changed with active carbazole [8].

Right part of 1, 4-diamino-2-hydroxy butane was changed with carbamate amino acid (**11a-15c**).

Choice for carbazole is due to its bioactivity in many categories of drugs like carvedilol (**Fig. 2**). Structural modifications of ritonavir with carbazole resulted serious of analogues **(16a-20c)**, which may exhibit better activity profile.

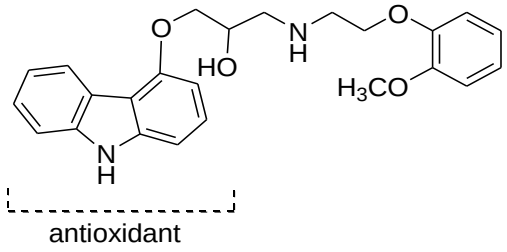


FIGURE 2: STRUCTURE OF CARVEDILOL

EXPERIMENTAL SECTION:

General experimental procedure: ^{1}H NMR were recorded on a Bruker 300 spectrometer at 300 MHz and the chemical shifts were reported as δ values in parts per million relative to TMS as an internal standard. Infrared spectra were recorded in the solid state as KBr dispersion using a PerkinElmer spectrophotometer. Mass spectra were recorded on API 2000 Perkin-Elmer PE-SCIEX mass spectrometer.

Synthesis of tert-butyl(*2S,4S,5S*)-5-(3-(9H-carbazol-4-yloxy)-2-hydroxypropylamino)-4-hydroxy-1,6-diphenylhexan-2-ylcarbamate (9): (*2S, 3S, 5S*)-5-(*tert*-butyloxycarbonyl)amino-2-amino-3-hydroxy-1,6-diphenylhexane (7) (24 gm, 0.0625 m), was dissolved in isopropyl alcohol (100 mL) and heated to 70-75°C. 4-Oxiranylmethoxy-9H-carbazole (8) (10 gm, 0.0418 m) was added slowly at 70-75°C and stirred at same temperature for 16 hr. The reaction mass was cooled to 20-30°C and concentrated under reduced pressure. The resulting residue was dissolved in ethyl acetate (200 mL) and washed water.

The organic layer was dried over anhydrous Na_2SO_4, concentrated under pressure and dried under vacuum to yield compound 9 (84%). Anal. Calcd for $C_{38}H_{45}N_3O_5$: C, 73.17; H, 7.27; N, 6.74; O, 12.82, found: C, 73.09; H, 7.24; N, 6.75; O, 12.80; IR (KBr cm^{-1}): 1714 (C=O); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.26 (s, 9H), 1.67-1.69 (m, 2H), 2.50-2.51 (m, 2H), 2.53- 2.58 (m, 2H), 2.97-3.05 (m, 2H), 3.47-3.51 (m, 2H), 3.67- 3.92 (m, 2H), 4.16-4.17 (m, 2H), 6.67-8.23 (m, 18H), 11.27 (s, 1H); MS: *m/z* 624.2 $[M+H]^+$.

Synthesis of (*2S,3S,5S*)-2-(3-(9H-carbazol-4-yloxy)-2-hydroxypropylamino)-5-amino-1,6-diphenylhexan-3-ol (10): Compound 9 (40 gm 0.0641 m) was dissolved in methylene chloride (200 mL) at 20-30°C. Conc. HCl (32.53 gm 0.3208 m) was added slowly at 20-30°C. The resulting mixture was stirred for 10 hr at 20-30°C. The aqueous layer was separated and washed with methylene chloride. The aqueous layer pH was adjusted to 9.0 with 10% w/w aqueous sodium carbonate and extracted with methylene chloride. Thereafter, the methylene chloride layer was concentrated completely at 40°C under pressure and dried under vacuum to yield 10. (78%) ; Anal.Calcd for $C_{33}H_{38}ClN_3O_3$: C, 70.76; H, 6.84; Cl, 6.33; N, 7.50; O, 8.57, found: C, 70.74; H, 6.85; Cl, 6.32; N, 7.51; O, 8.56; IR (KBr, cm^{-1}): 3403 (HO), 3058 (NH); ^{1}H NMR (300 MHz, DMSO-d_6, δ/ppm): 1.45-1.49 (m, 2H), 2.50-2.51 (m, 2H), 2.53-2.58 (m, 2H), 2.97-3.05 (m, 2H), 3.47 -3.51 (m, 2H), 3.87-3.92 (m, 2H), 4.08-4.13 (m, 1H), 4.86-4.97 (m, 1H), 6.65-8.23 (m, 18H), 11.23 (s, 1H); MS: *m/z* 524.3 $[M+H]^+$.

General procedure for the synthesis of compounds (16a): Compound (11a) (0.38 gm, 0.002 m) was dissolved in methylene chloride (10 mL) at 20-30°C. EDAC.HCL (0.39 gm, 0.0021 m), and HOBt (0.28 gm, 0.0021 m), were added at 20-30°C. The reaction mass was stirred at room temperature for 3 hr. Compound 10 (1 gm, 0.00191 m) was added and stirred for 8-10 hr at room temperature. After completion of reaction, DM water (5 mL) was added to reaction mixture and stirred for 5 min. Organic layer was separated and washed with 10%w/w aqueous sodium bicarbonate followed by brine solution (5 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under pressure to yield (16a) Yield= 1.03 gm (75.36 %).

Methyl-1-((*2S,4S,5S*)-5-(3-(*9H*-carbazol-4-yloxy)-2-hydroxypropylamino)-4-hydroxy-1,6-diphenyl- hexan-2-ylamino)-3,3-dimethyl-1-oxobutan-2-ylcarbamate (16a): Anal.Calcd for $C_{41}H_{50}N_4O_6$: C, 70.87; H, 7.25; N, 8.06; O, 13.82, found: C,70.69; H,7.23; N,8.05; O,13.83; IR (KBr, cm^{-1}): 1711 (C=O), 1657 (C=O). ^{1}H NMR (300 MHz, DMSO-d_6, δ/ppm): 0.82 (s, 9H), 1.55-1.62 (m, 2H), 2.66-2.73 (m, 7H), 3.55 (s, 3H), 3.57-3.62 (m, 1H), 3.76-4.11 (m, 4H), 4.87-4.92 (m, 1H),

6.61-8.22 (m, 19H), 11.22 (s, 1H); MS: *m/z* 695.2 $[M+H]^+$.

Ethyl-1-((*2S,4S,5S*)-5-(3-(*9H*-carbazol-5-yloxy)-2-hydroxypropylamino)-4-hydroxy-1,6-diphenyl- hexan-2-ylcarbamoyl)-2,2-dimethyl propylcarbamate (16b): Anal.Calcd for $C_{42}H_{52}N_4O_6$: C, 71.16; H, 7.39; N, 7.90; O, 13.54, found: C, 71.14; H, 7.40; N, 7.88; O, 13.53; IR (KBr, cm^{-1}): 1705 (C=O),1657 (C=O); ^1H NMR (300 MHz, DMSO-d_6, δ/ppm): 0.82 (s, 9H), 1.15-1.18 (m, 3H), 1.55-1.62 (m, 2H), 2.66-2.73 (m, 7H), 3.57-3.62 (m, 1H), 3.76-4.11 (m, 6H), 4.87-4.92 (m, 1H), 6.61-8.22 (m, 19H), 11.22 (s, 1H); MS: (*m/z*) 709.2 $[M+H]^+$.

Tert-butyl-1-((*2S,4S,5S*)-5-(3-(*9H*-carbazol-5-yloxy)-2-hydroxypropylamino)-4-hydroxy-1,6-diphenyl hexan-2-ylcarbamoyl)-2,2-dimethylpropylcarbamate (16c): Anal.Calcd for $C_{44}H_{56}N_4O_6$: C, 71.71; H, 7.66; N, 7.60; O, 13.03, found: C, 71.70; H, 7.66; N, 7.58; O, 13.04; IR (KBr, cm^{-1}): 1697 (C=O),1657 (C=O); ^1H NMR (300 MHz, DMSO-d_6, δ/ppm): 0.82 (s, 9H), 1.39 (s, 9H), 1.55-1.62 (m, 2H), 2.66-2.73 (m, 7H), 3.57-3.62 (m, 1H), 3.76-4.11 (m, 4H), 4.87-4.92 (m, 1H), 6.61-8.22 (m, 19H), 11.22 (s, 1H); MS: (*m/z*) 737.2 $[M+H]^+$.

Methyl-1-((*2S,4S,5S*)-5-(3-(*9H*-carbazol-5-yloxy)-2-hydroxypropylamino)-4-hydroxy-1,6-diphenyl- hexan-2-ylcarbamoyl)-2-methylpropyl carbamate (17a): Anal.Calcd for $C_{40}H_{48}N_4O_6$: C, 70.56; H, 7.11; N, 8.23; O, 14.10, found: C, 70.55; H, 7.10; N, 8.24; O, 14.11; IR (KBr, cm^{-1}): 1696 (C=O),1650 (C=O); ^1H NMR (300 MHz, DMSO-d_6, δ/ppm): 0.70-0.76 (m, 6H), 1.55-1.62 (m, 2H), 1.80-1.85 (m, 1H), 2.66-2.73 (m, 7H), 3.55 (s, 3H), 3.57-3.62 (m, 1H), 3.76-4.11 (m, 4H), 4.87-4.92 (m, 1H), 6.61-8.22 (m, 19H), 11.22 (s, 1H); MS: *m/z* 681.2 $[M+H]^+$.

Ethyl-1-((*2S,4S,5S*)-5-(3-(*9H*-carbazol-5-yloxy)-2-hydroxypropylamino)-4-hydroxy-1,6-diphenyl -hexan-2-ylcarbamoyl)-2-methylpropyl carbamate(17b): Anal.Calcd for $C_{41}H_{50}N_4O$: C, 70.87; H, 7.25; N, 8.06; O, 13.82, found: C, 70.86; H, 7.23; N, 8.07; O, 13.81; IR (KBr, cm^{-1}): 1692 (C=O), 1648 (C=O); ^1H NMR (300 MHz, DMSO-d_6, δ/ppm): 0.70-0.76 (m, 6H), 1.15-1.18 (m, 3H), 1.55-1.62 (m, 2H), 1.80-1.85 (m, 1H), 2.66-2.73 (m, 7H), 3.57-3.62 (m, 1H), 3.76-4.11 (m, 6H), 4.87-4.92 (m, 1H), 6.61-8.22(m, 19H), 11.22(s, 1H); MS: *m/z* 695.2 $[M+H]^+$.

Tert-butyl-1-((*2S,4S,5S*)-5-(3-(*9H*-carbazol-5-yloxy)-2-hydroxypropylamino)-4-hydroxy-1,6-diphenylhexan-2-ylcarbamoyl)-2-methylpropylcarbamate (17c): Anal.Calcd for $C_{43}H_{54}N_4O$: C, 71.44; H, 7.53; N, 7.75; O, 13.28, found: C, 71.42; H, 7.52; N, 7.75; O, 13.29; IR (KBr, cm^{-1}): 1683 (C=O), 1652 (C=O); ^1H NMR (300 MHz, DMSO-d_6, δ/ppm): 0.70-0.76 (m, 6H), 1.39 (s, 9H), 1.55-1.62 (m, 2H), 1.80-1.85 (m, 1H), 2.66-2.73 (m, 7H), 3.57-3.62 (m, 1H), 3.76-4.11 (m, 4H), 4.87-4.92 (m, 1H), 6.61-8.22 (m, 19H), 11.22 (s, 1H); MS: *m/z* 723.2 $[M+H]^+$.

Methyl-1-((*2S,4S,5S*)-5-(3-(*9H*-carbazol-5-yloxy)-2-hydroxypropylamino)-4-hydroxy-1,6-diphenyl- hexan-2-ylcarbamoyl)-3-methylbutylcarbamate (18a): Anal.Calcd for $C_{41}H_{50}N_4O_6$: C, 70.87; H, 7.25; N, 8.06; O, 13.82, found: C, 70.86; H, 7.23; N, 8.07; O, 13.83; IR (KBr, cm^{-1}): 1705 (C=O),1650 (C=O); ^1H NMR (300 MHz, DMSO-d_6, δ/ppm): 0.83-0.79 (m, 6H), 1.25-1.52 (m, 2H), 1.55-1.62 (m, 2H), 1.80-1.85 (m, 1H), 2.66-2.73 (m, 7H), 3.55 (s, 3H), 3.57-3.62 (m, 1H), 3.76-4.11 (m, 4H), 4.87-4.92 (m, 1H), 6.61-8.22 (m, 19H), 11.22 (s, 1H); MS: *m/z* 695.2 $[M+H]^+$.

Ethyl-1-((*2S,4S,5S*)-5-(3-(*9H*-carbazol-5-yloxy)-2-hydroxypropylamino)-4-hydroxy-1,6-diphenyl- hexan-2-ylcarbamoyl)-3-methylbutyl carbamate (18b): Anal.Calcd for $C_{42}H_{52}N_4O_6$: C, 71.16; H, 7.39; N, 7.90; O, 13.54, found: C, 71.14; H, 7.40; N, 7.91; O, 13.56; IR (KBr, cm^{-1}): 1705 (C=O), 1650 (C=O); ^1H NMR (300 MHz, DMSO-d_6, δ/ppm): 0.83-0.79 (m, 6H), 1.15-1.18 (m, 3H), 1.25-1.52 (m, 2H), 1.55-1.62 (m, 2H), 1.80-1.85 (m, 1H), 2.66-2.73 (m, 7H), 3.57-3.62 (m, 1H), 3.76-4.11 (m, 6H), 4.87-4.92 (m, 1H), 6.61-8.22 (m, 19H), 11.22 (s, 1H); MS: *m/z* 709.2 $[M+H]^+$.

Tert-butyl-1-((*2S,4S,5S*)-5-(3-(*9H*-carbazol-5-yloxy)-2-hydroxypropylamino)-4-hydroxy-1,6-diphenylhexan-2-ylcarbamoyl)-3-methylbutyl carbamate (18c): Anal.Calcd for $C_{44}H_{56}N_4O_6$: C, 71.71; H, 7.66; N, 7.60; O, 13.03, found: C, 71.70; H, 7.67; N, 7.58; O, 13.02; IR (KBr, cm^{-1}): 1683 (C=O), 1655 (C=O); ^1H NMR (300 MHz, DMSO-d_6, δ/ppm): 0.83-0.79 (m, 6H), 1.25-1.36 (m, 2H), 1.39 (s, 9H), 1.55-1.62 (m, 2H), 1.80-1.85 (m, 1H),

2.66-2.73 (m, 7H), 3.57-3.62 (m, 1H), 3.76-4.11 (m, 4H), 4.87-4.92 (m, 1H), 6.61-8.22 (m, 19H), 11.22 (s, 1H); MS: *m/z* 737.2 $[M+H]^+$.

Methyl-1-((*2S,4S,5S*)-5-(3-(*9H*-carbazol-5-yloxy)-2-hydroxypropylamino)-4-hydroxy-1,6-diphenyl- hexan-2-ylcarbamoyl)-2-phenylethyl carbamate (19a): Anal.Calcd. for $C_{44}H_{48}N_4O_6$: C, 72.50; H, 6.64; N, 7.69; O, 13.17, found C, 72.49; H, 6.65; N, 7.68; O, 13.16; IR (KBr, cm^{-1}): 1707 (C=O), 1658 (C=O); ^{1}H NMR (300 MHz, DMSO-d_6, δ/ppm): 1.55-1.62 (m, 2H), 2.66-2.73 (m, 9H), 3.55 (s, 3H), 3.57-3.62 (m, 1H), 3.76-4.11 (m, 4H), 4.87-4.92 (m, 1H), 6.61-8.22 (m, 22H), 11.22 (s, 1H), MS *m/z* 729.2 $[M+H]^+$.

Ethyl-1-((*2S,4S,5S*)-5-(3-(*9H*-carbazol-5-yloxy)-2-hydroxypropylamino)-4-hydroxy-1,6-diphenyl- hexan-2-ylcarbamoyl)-2-phenylethyl carbamate (19b): Anal.Calcd for $C_{45}H_{50}N_4O_6$: C, 72.75; H, 6.78; N, 7.54; O, 12.92, found: C, 72.74; H, 6.77; N, 7.55; O, 12.93; IR (KBr, cm^{-1}): 1692 (C=O), 1649 (C=O); ^{1}H NMR (300 MHz, DMSO-d_6, δ/ppm): 1.15-1.18 (m, 3H), 1.55-1.62 (m, 2H), 2.66-2.73 (m, 9H), 3.57-3.62 (m, 1H), 3.76-4.11 (m, 6H), 4.87-4.92 (m, 1H), 6.61-8.22 (m, 22H), 11.22 (s, 1H); MS: *m/z* 743.2 $[M+H]^+$.

Tert-butyl-1-((*2S,4S,5S*)-5-(3-(*9H*-carbazol-5-yloxy)-2-hydroxypropylamino)-4-hydroxy-1,6-diphenylhexan-2-ylcarbamoyl)-2-phenylethylcarbamate (19c): Anal.Calcd for $C_{47}H_{54}N_4O_6$: C, 73.22; H, 7.06; N, 7.27; O, 12.45, found: C, 73.23; H, 7.05; N, 7.25; O, 12.46; IR (KBr, cm^{-1}): 1689 (C=O), 1651(C=O); ^{1}H NMR (300 MHz, DMSO-d_6, δ/ppm): 1.39 (s, 9H), 1.55-1.62 (m, 2H), 2.66-2.73 (m, 9H), 3.57-3.62 (m, 1H), 3.76-4.11 (m, 4H), 4.87-4.92 (m, 1H), 6.61-8.22 (m, 22H), 11.22 (s, 1H); MS: *m/z* 771.2 $[M+H]^+$.

Methyl-1-((*2S,4S,5S*)-5-(3-(*9H*-carbazol-5-yloxy)-2-hydroxypropylamino)-4-hydroxy-1,6-diphenyl- hexan-2-ylcarbamoyl)butylcarbamate (20a): Anal.Calcd for $C_{40}H_{48}N_4O_6$: C, 70.56; H, 7.11; N, 8.23; O, 14.10, found: C, 70.55; H, 7.11; N, 8.22; O, 14.09; IR (KBr, cm^{-1}): 1692 (C=O), 1650 (C=O); ^{1}H NMR (300 MHz, DMSO-d_6, δ/ppm): 0.79-0.81 (m, 3H), 1.15-1.23 (m, 4H), 1.55-1.62 (m, 2H), 2.66-2.73 (m, 7H), 3.55 (s, 3H), 3.57-3.62 (m, 1H), 3.76-4.11 (m, 4H), 4.87-4.92 (m, 1H), 6.61-8.22 (m, 19H), 11.22 (s, 1H); MS: *m/z* 681.6 $[M+H]^+$.

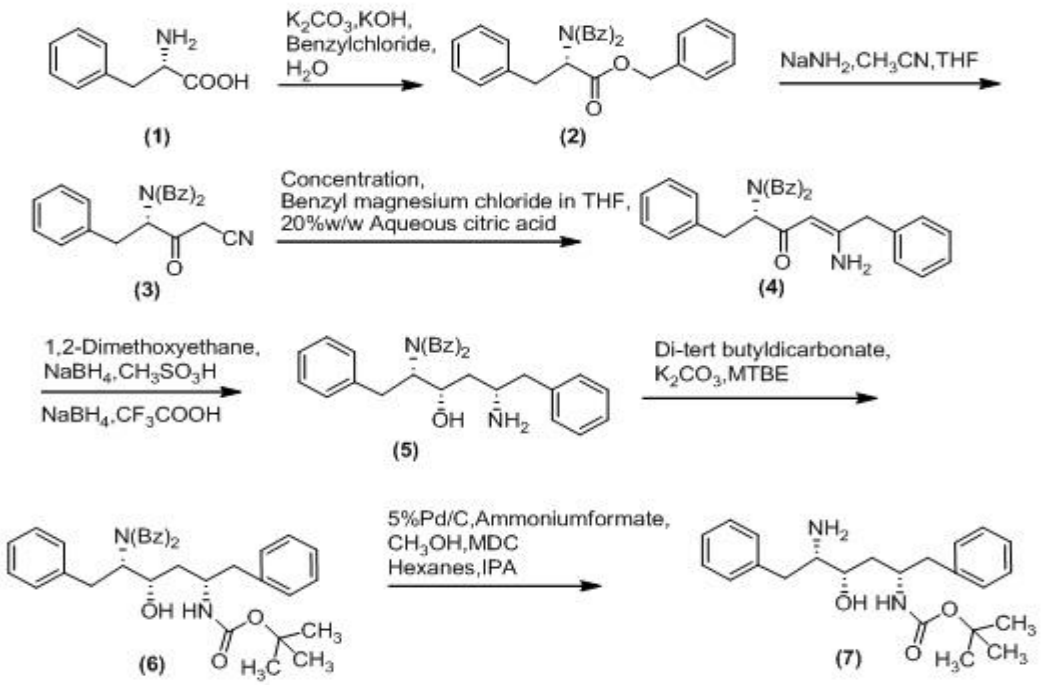
Ethyl-1-((*2S,4S,5S*)-5-(3-(*9H*-carbazol-5-yloxy)-2-hydroxypropylamino)-4-hydroxy-1,6-diphenyl hexan-2-ylcarbamoyl)butylcarbamate (20b): Anal.Calcd for $C_{41}H_{50}N_4O_6$: C, 70.87; H, 7.25; N, 8.06; O, 13.82, found: C, 70.86; H, 7.24; N, 8.05; O, 13.82; IR (KBr, cm^{-1}): 1691 (CO), 1650 (CO); ^{1}H NMR (300 MHz, DMSO-d_6, δ/ppm): 0.79-0.81 (m, 3H). 1.15-1.34 (m, 7H), 1.55-1.62 (m, 2H), 2.66-2.73 (m, 7H), 3.57-3.62 (m, 1H), 3.76-4.11 (m, 6H), 4.87-4.92 (m, 1H), 6.61-8.22 (m, 19H), 11.22 (s, 1H); MS: *m/z* 695.6 $[M+H]^+$.

Tert-butyl-1-((*2S,4S,5S*)-5-(3-(*9H*-carbazol-5-yloxy)-2-hydroxypropylamino)-4-hydroxy-1,6-diphenylhexan-2-ylcarbamoyl)butylcarbamate (20c): Anal.Calcd for $C_{43}H_{54}N_4O_6$: C, 71.44; H, 7.53; N, 7.75; O, 13.28, found: C, 71.43; H, 7.52; N, 7.73; O, 13.28; IR (KBr, cm^{-1}): 1684 (C=O), 1655 (CO); ^{1}H NMR (300 MHz, DMSO-d_6, δ/ppm): 0.79-0.81 (m, 3H), 1.15-1.23 (m, 4H), 1.39 (s, 9H), 1.55-1.62 (m, 2H), 2.66-2.73 (m, 7H), 3.57-3.62 (m, 1H), 3.76-4.11 (m, 4H), 4.87-4.92 (m, 1H), 6.61-8.22 (m, 19H), 11.22 (s, 1H); MS: *m/z* 723.2 $[M+H]^+$.

RESULTS AND DISCUSSION: Initially, we have developed a process for preparation of compound 7 for commercial purpose. Process critical parameter to prepare the compound 7 is described (**Scheme 1**) in this paper.

Benzylation of L-phenylalanine **(1)** with benzyl chloride, in the presence potassium carbonate and potassium hydroxide in aqueous medium at 105°C gave compound **2**. The unreacted L-phenylalanine (**1)** was achieved less than 0.5% by HPLC in 4 hr. Thereafter, the reaction mass was cooled to room temperature and extracted with toluene.

The toluene layer containing product was washed with a mixture of water and methanol till the aqueous layer pH 7.0-8.0 was achieved. During washing, the toluene layer was separated at bottom due to higher density and aqueous layer was separated in top.



SCHEME 1

The separated toluene layer was concentrated at 60°C under vacuum to afford compound **2** in 97.5% theory yield and purity ~ 94% by HPLC. Compound **2** was converted to compound **3** by reacting with acetonitrile in THF in the presence of sodamide. Optimization of solvent and mole equivalent of reagent is given in **Table 1**. As the cost of THF very high and recovery not feasible, we have chosen the MTBE as an alternative solvent. The advantage of MTBE is less cost and recoverable. However, the isolated product yield from MTBE reaction was very low and not satisfactory.

TABLE 1: OPTIMIZATION OF SOLVENT, SODAMIDE, AND ACETONITRILE

Entry	Solvent	Sodamide (m. eq)	Acetonitrile (m. eq)	Yield (%)	Purity (%, by HPLC)
1	THF	2.21	1.33	67	79.20
2	MTBE	2.63	1.16	74	65.86
3	MTBE	2.37	1.16	69	90.21
4	MTBE	2.63	1.16	70	79.60
5	THF	2.4	1.16	84	92.11
6	THF	2.34	1.16	82	87.32

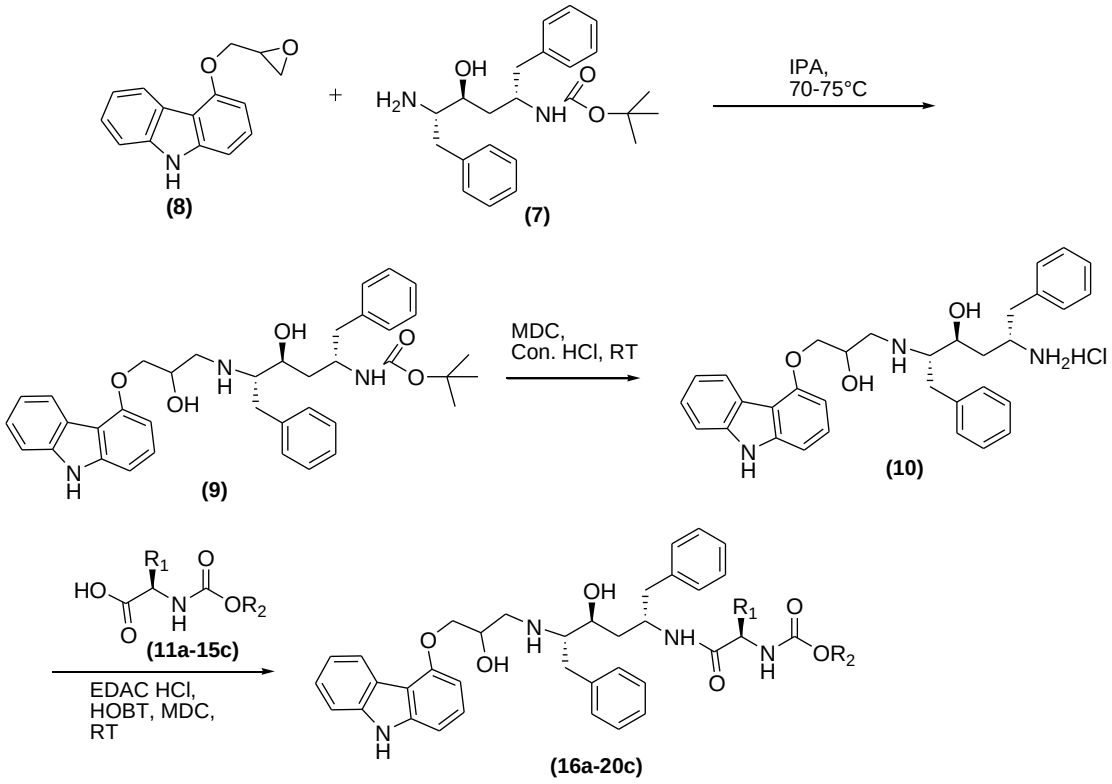
From table 1, it was clear that 2.4 m.eq. of sodamide was required to get compound **3** in 84% theory yield. As the mole equivalent of sodamide decrease, the product conversion was decrease from 84% to 67%. Grignard reaction of compound **3** with benzyl magnesium chloride (RMgX) gave compound **4**. Optimization of mole equivalent and assay of RMgX is given in Table-2. The rate of reaction was depends upon mole equivalent of RMgX as well as concentration of RMgX. In our hand, 1.8 mole equivalent of RMgX with 28.5% assay was required to prepare compound **4.** As the concentration of RMgX reduces, the yield of product **4** was reduced drastically.

TABLE 2: OPTIMIZATION OF ASSAY AND MOLE EQUIVALENT OF RMgX

Entry	Assay of RMgX (% w/w)	m. eq. of RMgX	Yield (%)
1	8.7	3.51	41.6
2	16.5	4.5	79.44
3	27	2.13	74.74
4	27	2.15	78.55
5	29	2.15	80.84
7	28.5	1.8	88.46

Reduction of double bond and keto group of compound **4** in monoglyme with $NaBH_4$/ methanesulfonic acid and $NaBH_4$/TFA respectively gave compound **5.** This is well known reaction which gives predominantly (S, S, S) isomer only. [8] The amino group of compound **5** was protected with BOC in presence of aqueous K_2CO_3 to yield compound **6**. Hydrogenation of compound **6** for debenzylation using 5% Pd/C ammonium format in methanol gave compound **7** [9, 12].

Oxirane **(8)** was prepared according to the method described in the literature [13, 14]. Ring opening of compound **8** with compound **7** (Scheme-2) in isopropyl alcohol at 70-75°C gave compound **9** in 84% yield. The ^{1}H-NMR spectrum of compound **9** in DMSO-d_6 showed a singlet at δ 11.27 for NH of carbazole, a multiplet at δ 2.50-2.51 for two proton of $–CH_2NH$ and another multiplet as 4.08-4.13 for singlet proton of –CHOH. The mass spectra of compound **9** gave the corresponding molecular ion peak [[M+H] $^+$: 624.2] which confirmed the product formation.



(16a) R_1= $C(CH_3)_3$, R_2= CH_3
(16b) R_1= $C(CH_3)_3$, R_2= CH_2CH_3
(16c) R_1= $C(CH_3)_3$, R_2= $C(CH_3)_3$

(17a) R_1= $CH(CH_3)_2$, R_2= CH_3
(17b) R_1= $CH(CH_3)_2$, R_2= CH_2CH_3
(17c) R_1= $CH(CH_3)_2$, R_2= $C(CH_3)_3$

(18a) R_1= $CH_2CH(CH_3)_2$, R_2= CH_3
(18b) R_1= $CH_2CH(CH_3)_2$, R_2= CH_2CH_3
(18c) R1= $CH_2CH(CH_3)_2$, R_2= $C(CH_3)$

(19a) R_1= CH_2Ph, R_2= CH_3
(19b) R_1= CH_2Ph, R_2= CH_2CH_3
(19c) R_1= CH_2Ph, R_2= $C(CH_3)_3$

(20a) R_1=$CH_2CH_2CH_3$, R_2=CH_3
(20b) R_1=$CH_2CH_2CH_3$, R_2=CH_2CH_3
(20c) R_1=$CH_2CH_2CH_3$, R_2=$C(CH_3)_3$

SCHEME 2

Deprotection of BOC group of compound **9** in biphasic media with concentrated hydrochloric acid at room temperature gave compound **10**. The aqueous layer containing product as hydrochloride was separated and washed with methylene chloride to remove unreacted and process impurity. The aqueous layer pH was adjusted to 9.0 with 10% w/w aqueous sodium carbonate, extracted with methylene chloride and concentrated to yield compound **10** in 78% theory yield.

The molecular ion peak observed in the mass spectra of compound **10** of [[M+H] $^+$: 524.3], proved the product formation. Condensation of compound **10** with different carbamate amino acids **(11a-15c)** for formation of mono peptide bond using 1-hydroxybenzotriazole (HOBt), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydro chloride (EDAC.HCl) as coupling agent in methylene chloride at room temperature gave compounds (**16a-20c**) (**Table 3**).

The ^{1}H-NMR spectrum of compound **16a** in DMSO-d_6 showed a singlet at δ 11.22 for NH of carbazole, a singlet at δ 0.82 for methyl proton of tert-leucine and singlet at δ 3.55 for methoxy proton. The mass spectra of compound **16a** gave the corresponding molecular ion peak at [[M+H]$^{+}$: 695.2].

TABLE 3: REACTION CONDITION AND YIELD FOR 16A-20c

Entry	Time (hr)	Compound	Yield (%)
11a	8	16a	75.36
11b	7	16b	72.35
11c	8	16c	68.88
12a	10	17a	38.43
12b	10	17b	49.71
12c	9	17c	62.26
13a	9	18a	70.04
13b	9	18b	69.40
13c	9	18c	64.62
14a	10	19a	35.90
14b	10	19b	30.29
14c	10	19c	43.44
15a	10	20a	21.52
15b	10	20b	73.06
15c	10	20c	78.20

CONCLUSION: We have successfully modified the structure of ritonavir with active carbazole and obtained a new series of compounds (**16a-20c**). Further work is in progress to study the anti HIV activity of these new series of compound (**16a-20c**).

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