An efficient total synthesis of vilanterol: an inhaled drug

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This article is dedicated to Prof. Dr. Ahmad Kamal for his outstanding contribution to organic synthesis, chemical biology and medicinal chemistry

Received 12-24-2022 Accepted Manuscript 08-01-2023 Published on line 08-17-2023

Abstract

Total synthesis of vilanterol, a long-acting β2-adrenoceptor agonist and potent drug for chronic obstructive pulmonary disease & asthma is accomplished efficiently by a novel method. In this synthesis, the key intermediate oxazolidinone compound is prepared using convenient and efficient reaction methods including Friedel-Crafts acylation, chemo-selective reduction, Corey-Itsuno reduction and oxazolidinone ring formation. The oxazolidinone was coupled with an alkyl bromide and then selective de protections produced vilanterol in satisfactory yield.

Keywords: Vilanterol, salicylaldehyde, β2-adrenoceptor agonists drug, total synthesis
Introduction

Pulmonary infections caused by inflammatory responses are becoming a prominent cause of mortality across the globe; asthma and chronic obstructive pulmonary disease (COPD) are traditionally thought to be two different respiratory illnesses. β2-Adrenoceptor (β2-AR) agonists are indeed the main class of drugs used to treat both asthma and COPD by enhancing airflow into the lungs through regulating the airways. This class is further subdivided into long-acting and short-acting β2-AR agonists depending on the length of time and effect. All these β2-AR agonists show bronchodilating properties.

Vilanterol is a novel, ultra-long-acting β2-adrenoceptor agonist used as first-line therapy for asthma and COPD (chronic obstructive pulmonary disease). Its pharmacological effect is due to stimulation of β2-adrenoceptor in the lungs which triggers the enzyme adenylyl cyclase that catalyzes the reaction in the formation of cyclic adenosine monophosphate (cAMP) from adenosine triphosphate (ATP). These increased cAMP’s lead to relaxation of bronchial smooth muscle. Vilanterol demonstrated significant sub-nanomolar affinity for the β2-AR as good as salmeterol and superior to indacaterol, formoterol and olodaterol. Further, it shows higher intrinsic efficacy over salmeterol. Moreover, Vilanterol human recombinant β1/2/3-AR cAMP assays revealed that it has significantly greater β2-AR selectivity than formoterol, indacaterol and salbutamol. Vilanterol is an inhaled drug approved by FDA and used in combination with other drugs for the treatment of asthma & COPD patients.

More than one synthetic approach of Vilanterol was reported in the literature mainly in the public patents. However, the synthetic approach by Dammalapati et al is the most broadly used. There is still considerable need of research on novel drugs and also their synthetic approaches for the development of long acting β2-AR bronchodilators as there are challenges for better activity and higher selectivity. So we have been interested in synthesis of vilanterol because of its significance and high β2-AR potency and selectivity. Hence we attempted total synthesis of vilanterol in a novel and convenient way.

Scheme 1. Ashthma and COPD potent drugs.
Results and Discussion

Scheme 2 shows the retrosynthesis of vilanterol (1). Its structure has one chiral centre, a secondary amine linkage, two ether linkages, aromatic phenol, and aromatic dichloro moieties. Vilanterol (1) can be broken down into two parts: oxazolidinone 10 and alkyl bromide 11. The amino alcohol might be used to make chiral oxazolidinone 10 easily. The CBS reduction of 6, afterwards hydrogenation of the azide and subsequent protection of both the -NH2 and -OH groups, can yield the chiral center of the crucial intermediate 10. Compound 6 was easily made from commercially available salicylaldehyde (2) by Friedel–Crafts acylation, then reduction and 2,2-DMP protection of both -OH groups.

Scheme 2. Retrosynthesis of Vilanterol.

We chose to manufacture the vilanterol (1) molecule because of its biological potential. We synthesized it in a non-infringing manner using commercially accessible and inexpensive salicylaldehyde (2) as a starting material and adopted this in order to effectively overcome disadvantages of harsh reaction conditions and expensive reagents. We were able to synthesize alfa-azidomethyl ketone 6 from salicylaldehyde in a simple and convenient way and then performed reduction on that azide compound which different from previously reported methods. Friedel–Crafts acylation of salicylaldehyde (2) in the presence of AlCl₃ and chloroacetyl chloride in dichloromethane (DCM) solvent led to the acylated product 3 in 75% yield. Chemoselective reduction of the aldehyde group in 3 with NaBH₄ and acetic acid at 5 °C to room temperature gave 4 in 85% yield. Now to protect both the phenolic -OH group and the primary alcoholic -OH group with single protection group, treatment of 4 with 2,2-DMP in the presence of a catalytic amount of PTSA in dichloromethane furnished the acetonide protected compound 5 in 90% yield. Conversion of chlorido to azide by using sodium azide in DMF at RT gave 6 in 95% yield. Conversion of the keto group into a chiral alcohol succeeded by using chiral CBS-oxazaborolidine. Reduction of keto compound 6 with (R)-CBS and BH₃.DMS in tetrahydrofuran (THF) solvent at 0 °C to RT delivered chiral compound 7 in 68% yield and >98% enantiomeric excess.[7]
Reduction of azide 7 by using 10% Pd/C in methanol solvent at RT gave amino alcohol 8 in 80% yield. Protection of the amino group in compound 8 with (BOC)$_2$O by using the base DIPEA in DMF solvent yielded compound 9. Subsequent treatment with potassium tert-butoxide (KO$_3$Bu) in dimethylformamide yielded the oxazolidinone 10 in 70% yield. This intermediate proved extremely useful as it was a stable crystalline solid which could be alkylated very cleanly under mild conditions with a variety of electrophiles.


Thus, alkylation of 10 with bromide 11 in presence of KO$_3$Bu and DMF at 0 °C to room temperature gave the coupled product 12 in 90% yield. Now the deprotection of the oxazolidine group was performed by using potassium trimethylsilanolate (KOSiMe$_3$). Treatment of 12 with two equivalents of potassium trimethylsilanolate in THF solvent under reflux conditions furnished the amino alcohol 13 in 95% yield. Finally, deprotection the acetonide under mild acidic conditions succeeded by treatment of 13 with 1N HCl solution at 0°C to RT to give (R)-vilarterol 1 in 70% yield. Analytical data of the final compound vilarterol (1) matched the previously reported data and overall yield from 2 is 11.9%. 

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Scheme 4. Synthesis of vilanterol (1).

**Conclusion**

We report our efforts to develop a convenient and effective total synthesis of the β₂-adrenoceptor agonist drug (R)-vilanterol, which has a longer action and is a more potent drug for COPD & asthma. Our synthetic route has advantages like commercially accessible inexpensive starting materials and reagents, standard reaction conditions, simple and broadly used reactions and satisfactory yields. The total synthesis of vilanterol was achieved in 11 steps.

**Experimental Section**

**General.** All reagents and solvents were obtained from commercial suppliers and were used without further purification. Analytical thin-layer chromatography (TLC) was performed on MERCK precoated silica gel 60-F254 (0.5 mm) aluminium plates. Visualization of the spots on TLC plates was achieved by UV light. $^1$H and $^{13}$C NMR spectra were recorded on Bruker 500 and 125 MHz instruments, respectively by making a solution of samples in DMSO using tetramethylsilane (TMS) as the internal standard. Chemical shifts for $^1$H and $^{13}$C are reported in parts per million (ppm) downfield from tetramethylsilane. Spin multiplicities are described as s (singlet), brs (broad singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Coupling constant (J) values are reported
in Hertz (Hz). HRMS were determined with Agilent QTOF mass spectrometer 6540 series instrument. Wherever required, column chromatography was performed using silica gel (60-120). The reactions wherever anhydrous conditions were required were carried out under nitrogen positive pressure using freshly distilled solvents. All evaporation of solvents was carried out under reduced pressure using a rotary evaporator below 45 °C. Melting points were determined with an electrothermal digital melting point apparatus IA9100 and are uncorrected. The names of all the compounds given in the experimental section were taken from Chem Bio Draw Ultra, Version 12.0.

5-(2-Chloroacetyl)-2-hydroxybenzaldehyde (3). Chloroacetyl chloride (55.5 g) was added to a solution of AlCl$_3$ (133 g, 1 mol) in dry DCM (200 mL) over 30 min. Salicylaldehyde (2) (12.2 g, 0.1 mol) in dry DCM was added to the above mixture which was stirred at reflux temperature. After completion of reaction, it was poured onto crushed ice and extracted with ethyl acetate and then washed with brine. Concentration of the organic layer and recrystallization (hexane - ethyl acetate mixture) gave the pure compound 3 in 75% yield. $^1$H NMR (CDCl$_3$, 300 MHz): δ 2.78 (s, 3H), 5.50 (s, 1H), 6.40-6.53 (m, 3H), 6.86-7.01 (m, 3H), 7.03-7.35 (m, 8H), 7.44 (t, 2H, J 7.5 Hz), 7.69 (s, 1H) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$): δ 192.1, 165.8, 139.2, 131.7, 129.3, 128.8, 117.6, 45.3 ppm; IR (KBr): v$_{\text{max}}$3414, 3055, 2925, 1611, 1454, 1217, 746, 705 cm$^{-1}$; ESI-MS: m/z 199[M+H]$^+$. 

2-Chloro-1-(4-hydroxy-3-(hydroxymethyl)phenyl)ethan-1-one (4). Sodium borohydride (294 mg, 7.8 mmol) was added portionwise to a solution of 5-(chloroacetyl)-2-hydroxybenzaldehyde 3 (1.50 g, 7.5 mmol) in acetic acid (38 mL) stirred at 5 °C (ice/water bath) under nitrogen. The mixture was stirred at rt. After completion of the reaction, water (40 mL) was added and the mixture was neutralized with saturated Na$_2$CO$_3$ solution. The mixture was extracted with ethyl acetate (4 × 50 mL). The combined organic phases were washed with brine, dried over MgSO$_4$, filtered and concentrated to give a light red oil that turned solid upon standing. The crude residue was purified by column chromatography (silica gel, pentane-ethyl acetate, gradient from 9:1 to 2:8) and afforded a light pink solid product 4 (1.33 g, 6.6 mmol, 85% yield). $^1$H NMR (DMSO-d$_6$, 400 MHz): δ 10.53 (s, 1H (OH)); 7.97 (d, 1H, J 2.0); 7.76 (dd, 1H, J 8.4, 2.4); 6.87 (d, 1H, J 8.4); 5.15 (br s, 1H(OH)); 5.04 (s, 2H (CH$_2$OH)); 4.50 (s, 2H (CH$_2$Cl)) ppm; $^{13}$C NMR (125 MHz, DMSO-d$_6$): δ 190.3, 159.9, 129.7, 129.6, 128.5, 126.0, 114.8, 58.2, 47.5 ppm; IR (KBr): v$_{\text{max}}$3414, 3055, 2925, 1611, 1454, 1217, 746, 705 cm$^{-1}$; ESI-MS: m/z 201[M+H]$^+$. 

2-Chloro-1-(2,2-dimethyl-4H-benzo[d][1,3]dioxin-6-yl)ethan-1-one (5). To a suspension of 2-chloro-1-(4-hydroxy-3-(hydroxymethyl)phenyl)ethanone (4) (1.33 g, 6.6 mmol) and p-toluenesulfonic acid (0.0061 g, 0.035 mmol) in 33 mL of dichloromethane was added dropwise 2,2-dimethoxypropane (0.763 g, 7.3 mmol) in dichloromethane (17 mL). The suspension was stirred vigorously until it became homogeneous (light yellow). The reaction mixture was washed with saturated NaHCO$_3$ solution. The organic phase was separated and dried over MgSO$_4$. The solvent was evaporated under reduced pressure to give 5 as a solid (1.35 g, 5.6 mmol, 90% yield). $^1$H NMR (CDCl$_3$, 300 MHz): δ 7.79 (dd, 1H, J 8.6, 2.2); 7.68 (d, 1H, J 2.0); 6.88 (d, 1H, J 8.8); 4.89 (s, 2H (CH$_2$O)); 4.63 (s, 2H (CH$_2$Cl)); 1.57 (s, 6H (C(CH$_3$)$_2$)) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$): δ 189.7, 156.4, 129.2, 126.7, 126.2, 119.6, 117.4, 100.8, 60.6, 45.5, 24.8 ppm; IR (KBr): v$_{\text{max}}$3414, 3055, 2925, 1611, 1454, 1217, 746, 705 cm$^{-1}$; ESI-MS: m/z 263[M+Na]$^+$; HRMS: calcd for C$_{24}$H$_{24}$ClO$_5$Na, 263.0445, found: 263.0445.

2-Azido-1-(2,2-dimethyl-4H-benzo[d][1,3]dioxin-6-yl)ethan-1-one (6). A suspension of chloroketone 5 (52 g, 181 mmol) in DMF (300 mL) was treated with sodium azide (12.24 g, 188 mmol) and the mixture was stirred at 20 °C for 2 h, by which time the mixture became homogeneous and red coloured. To the reaction mixture was added water, and a solid was formed. Filtrate the solid compound and washing with water gave the required azide 6 as a pale yellow solid (41.0 g, 95%). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.68 – 7.60 (m, 1H), 7.59 – 7.49 (m, 1H), 6.80 (t, J 8.8 Hz, 1H), 4.81 (s, 2H), 2.12 (s, 2H), 1.49 (s, 6H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 191.69, 156.52,
(R)-2-Azido-1-(2,2-dimethyl-4H-benzo[d][1,3]dioxin-6-yl)ethan-1-ol (7). (R)-Tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaborolidine in toluene (1 M, 7.5 mL) was added to THF (75 mL) and the solution was cooled to 0 °C. BH₃·DMS complex (1 M solution in DMS, 125 mL) was added and the mixture was stirred under nitrogen for 15 min. A solution of 6 (24.7 g, 0.1 mol) in THF (250 mL) was added dropwise over 1.5 h at 5 °C. The mixture was stirred for a further 1h and then cautiously treated with 2 M HCl (100 mL). The reaction mixture was extracted with ether and the organic layer was washed with 2M HCl, saturated NaHCO₃, brine and dried over MgSO₄. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel column eluting with EtOAc–petroleum ether (10:90) to give 7 (16.99 g, 68%) as a white solid: ¹H NMR (500 MHz, CDCl₃) δ 7.14 (dd, J 8.4, 1.9 Hz, 1H), 7.06 (d, J 1.5 Hz, 1H), 6.78 (d, J 8.4 Hz, 1H), 4.85 (s, 2H), 4.40 (dt, J 23.0, 11.5 Hz, 1H), 2.65 (ddd, J 20.6, 12.8, 6.0 Hz, 2H), 1.50 (s, 6H). ¹³C NMR (101 MHz, CDCl₃) δ 150.67, 134.39, 125.80, 122.21, 119.34, 117.01, 99.58, 74.02, 60.98, 49.24, 24.86, 24.76.; ESI-MS: m/z 250[M+H]+.

(tert-Butyl (R)-(2-(2,2-dimethyl-4H-benzo[d][1,3]dioxin-6-yl)-2-hydroxyethyl)carbamate (9). To a stirred solution of 8 (12.40 g, 55.61 mmol) in dimethylformamide (150 mL) was added N,N-diisopropylethylamine (11.8 mL, 66.73 mmol) at 5 °C under nitrogen atmosphere and followed by (BOC)₂O (12.12 g, 55.61 mmol). The mixture was stirred at 20 °C for 3 h. The mixture was re-cooled to 0°C and quenched by the addition of 2M hydrochloric acid. The mixture was partitioned between ethyl acetate (1 L) and water (1 L) and the organic layer washed with brine and dried. The solvent was removed by distillation to give compound 9 (15.1 g, 96%) as a white solid: ¹H NMR (400 MHz, CDCl₃) δ 7.11 (d, J 8.4 Hz, 1H), 6.99 (s, 1H), 6.79 (d, J 8.4 Hz, 1H), 4.84 (s, 2H), 4.53 (dd, J 7.7, 3.8 Hz, 1H), 2.97 (dd, J 12.6, 3.6 Hz, 1H), 2.77 (dd, J 12.7, 7.9 Hz, 1H), 1.53 (s, 6H); ¹³C NMR (101 MHz, CDCl₃) δ 150.65, 134.47, 125.80, 122.22, 119.33, 116.99, 99.58, 73.97, 60.97, 49.23, 24.76. IR (KBr): 3414, 3247, 3121, 2925, 1792, 1717, 1650, 1510, 1370, 1285, 1215, 1050, 1000, 760 cm⁻¹; ESI-MS: m/z 224[M+H]+.

(R)-5-(2,2-Dimethyl-4H-benzo[d][1,3]dioxin-6-yl)oxazolidin-2-one (10). Potassium tert-butoxide (KOtBu) (2.65 g, 66.2 mmol) was added to a stirred solution of 9 (16.40 g, 50.71 mmol) in dimethylformamide (150 mL) at 5 °C under nitrogen atmosphere. The mixture was stirred at 20 °C for 3 h. The mixture was cooled to 0 °C and quenched by the addition of 2M hydrochloric acid. The mixture was partitioned between ethyl acetate (1000 mL) and water (1000 mL). The organic phase was washed with brine (250mL), dried and evaporated. The solid was triturated with diethyl ether to give 10 (8.84 g, 70%) as a white crystalline solid: [α]D²⁰c 1.379 in CHCl₃; Chiral HPLC on a Whelk-O1 column (25 cm ×0.46 cm) eluting with ethanol–heptane (35 : 65) at a flow rate of 1 mL min⁻¹ and detecting at 215 nm: tR 8.11 min, 0.9%; tR 10.38min, 99.1% (racemate: tR 7.99 min and 10.50 min). ¹H NMR (400 MHz, CDCl₃) δ 7.18 – 7.12 (m, 1H), 7.05 – 7.00 (m, 1H), 6.88 – 6.79 (m, 1H), 5.54 (q, J 8.1 Hz, 1H), 5.40 (s, 1H), 4.89 – 4.79 (s, 2H), 3.96 – 3.87 (m, 1H), 3.57 – 3.46 (m, 1H), 1.55 – 1.53 (s, 6H). ¹³C NMR (126 MHz, CDCl₃) δ 162.67, 159.96, 151.85, 130.13, 125.98, 122.59, 119.87, 117.57, 99.89, 77.91, 60.80, 48.31,
24.74.; IR (KBr): $\nu_{\text{max}}$ 3274.64, 2994.28, 2849.32, 1719.62, 1502.09, 1438.54, 1267.33, 1130.90 ,1077.58, 868.59, 821.14, 694.24 cm$^{-1}$; ESI-MS: $m/z$ 250[M+H]$^+$. HRMS: calcld for C$_{13}$H$_{16}$NO$_4$, 250.10854, found: 250.10738.

(R)-3-{6-(2-(2,6-Dichlorobenzyl)oxy)ethoxy}hexyl)-5-(2,2-dimethyl-4H-benzo[d][1,3]dioxin-6-yl)oxazolidin-2-one (12). Potassium tert-butoxide (KO$^t$Bu) (4.72g, 4.216 mmol) was added to the solution of oxazolidine compound 10 (10 g, 4.016 mmol) in DMF at room temperature. The mixture was stirred for 1 h at room temperature. Bromide 11 (16.8 g, 4.417 mmol) in DMF was added and stirring was continued at RT. After completion of the reaction, cold water was added and the mixture was extracted with ethyl acetate. The separated organic layer was washed with brine and dried on Na$_2$SO$_4$. Removal of the organic layer afforded the title compound 12 as a pale-yellow oil in 90% Yield. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.22 (t, J 7.7 Hz, 2H), 7.12 – 7.00 (m, 2H), 6.93 (dd, J 10.6, 1.8 Hz, 1H), 6.77 (dd, J 12.5, 8.4 Hz, 1H), 5.30 (dt, J 12.0, 8.2 Hz, 1H), 4.74 (t, J 9.6 Hz, 4H), 3.76 (dt, J 11.3, 8.7 Hz, 1H), 3.65 – 3.61 (m, 2H), 3.53 (dd, J 7.4, 2.6 Hz, 2H), 3.39 – 3.15 (m, 5H), 2.10 (s, 3H), 1.53 – 1.43 (m, 7H), 1.27 (m, 4H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 157.88, 151.73, 136.96, 133.43, 130.56, 129.98, 128.42, 125.70, 122.32, 119.86, 117.58, 99.87, 74.26, 71.20, 70.00, 67.56, 60.82, 52.19, 44.20, 29.60, 28.03, 27.36, 26.52, 25.81, 24.81, 24.70. IR (KBr): $\nu_{\text{max}}$ 3446.58, 3349.63, 2996.59, 2944.82, 2878.42, 2215.32, 2101.99, 1681.71, 1609.77, 1583.91, 1497.28, 1317.47, 1118.78, 1059.37 cm$^{-1}$; ESI-MS: $m/z$ 552[M+H]$^+$. HRMS: calcld for C$_{28}$H$_{36}$Cl$_2$NO$_{16}$, 552.19179, found: 552.1918.

(R)-2-[(6-(2-(2,6-Dichlorobenzyl)oxy)ethoxy)hexyl]amino)-1-(2,2-dimethyl-4H-benzo[d][1,3]dioxin-6-yl)ethan-1-ol (13). Potassium trimethylsilylanolate (KOSiMe$_3$) was added to the compound 12 in THF at room temperature. Then the mixture was stirred at reflux temperature until completion of reaction. The mixture was cooled the RM to 0°C to 5°C and the pH was adjusted 6 – 7 with sodium phosphate solution before work up with ethyl acetate. Then separated organic layer was washed with brine and then dried on Na$_2$SO$_4$. Removal of the solvent to afforded the title compound 13 as a pale-yellow oil in 95% yield. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.32 – 7.28 (m, 2H), 7.20 – 7.11 (m, 2H), 7.01 (s, 1H), 6.78 (dd, J 8.3, 2.9 Hz, 1H), 4.85 – 4.81 (m, 4H), 4.68 (d, J 6.3 Hz, 1H), 3.76 (s, 1H), 3.73 – 3.68 (m, 2H), 3.61 (dt, J 6.5, 4.4 Hz, 2H), 3.49 – 3.43 (m, 2H), 2.88 (dd, J 12.2, 3.4 Hz, 1H), 2.74 – 2.61 (m, 3H), 1.60 – 1.51 (m, 10H), 1.37 – 1.29 (m, 4H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 150.96, 136.97, 133.81, 133.14, 130.29, 128.40, 125.57, 121.71, 119.21, 117.65, 99.56, 71.31, 70.84, 70.07, 70.01, 67.57, 61.12, 56.76, 49.21, 29.73, 27.09, 25.98, 24.89, 24.65. IR (KBr): $\nu_{\text{max}}$ 3457.53, 3380.39, 2981.77, 2856.91, 1698.01, 1604.50, 1510.80, 1378.49, 1255.48, 1148.13, 1051.10, 954.96, 842.2, 751.81, 575.01 cm$^{-1}$; ESI-MS: $m/z$ 526[M+H]$^+$. HRMS: calcld for C$_{27}$H$_{36}$Cl$_2$NO$_{14}$, 526.2127, found: 526.21165.

(R)-4-(2-[[6-(2-(2,6-Dichlorobenzyl)oxy)ethoxy)hexyl]amino]-1-hydroxyethyl)-2-(hydroxymethyl)phenol (1). Acetonide compound 13 dissolved in aceton and cooled to 0 °C to 5 °C. Then slowly 1N HCl solution was added and the mixture was stir for 1h at the same temperature. After completion of reaction dichloromethane and water were added. Then separated red organic layer was washed with NaHCO$_3$ solution and brine solution and then dried on Na$_2$SO$_4$. Removal of the organic layer and purification by column chromatography afforded the title compound as a pale-yellow oil in 70% yield.

$^1$H NMR (400 MHz, DMSO) $\delta$ 9.44 (s, 1H), 8.71 (s, 1H), 7.51 – 7.47 (m, 2H), 7.42 – 7.36 (m, 1H), 7.32 (d, J 2.0 Hz, 1H), 7.05 (dd, J 8.2, 2.2 Hz, 1H), 6.78 (d, J 8.2 Hz, 1H), 5.94 (s, 1H), 5.03 (t, J 5.1 Hz, 1H), 4.84 (d, J 8.1 Hz, 1H), 4.69 (s, 2H), 4.48 (d, J 4.3 Hz, 1H), 3.64 – 3.58 (m, 2H), 3.51 (dd, J 5.8, 3.7 Hz, 2H), 3.37 (dd, J 11.7, 5.2 Hz, 3H), 3.03 – 2.85 (m, 4H), 1.63 (d, J 5.9 Hz, 2H), 1.52 – 1.44 (m, 2H), 1.34 – 1.25 (m, 4H).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 154.44, 135.88, 132.25, 130.10, 128.96, 127.38, 125.99, 125.65, 114.88, 70.11, 68.93, 67.74, 66.47, 53.27, 46.95, 28.41, 25.53, 25.22, 24.64, 22.79. IR (KBr) $\nu_{\text{max}}$ 3444.16, 2936.99, 2876.71
Acknowledegements

The authors are thankful to the Department of Chemistry, Telangana University and Osmania University, Telangana, India.

Supplementary Material

Supplementary data associated with this article is available in the Supplementary Material.

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13. https://www.drugbank.ca/drugs/DB09082


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