Journal of Pharmaceutical Analysis 13 (2023) 403–411

Contents lists available at ScienceDirect

Journal of Pharmaceutical Analysis

journal homepage: www.elsevier.com/locate/jpa

Original article

Solriamfetol impurities: Synthesis, characterization, and analytical method (UPLC-UV) validation

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ARTICLE INFO

Article history:
Received 12 November 2022
Received in revised form
17 February 2023
Accepted 23 February 2023
Available online 1 March 2023

Keywords:
Solriamfetol
Impurity analysis
Impurity synthesis
UPLC
Method validation

ABSTRACT

Given that impurities may affect the quality and safety of drug products, impurity identification and profiling is an integral part of drug quality control and is particularly important for newly developed medications such as solriamfetol, which is used to treat excessive daytime sleepiness. Although the high-performance liquid chromatography analysis of commercial solriamfetol has revealed the presence of several impurities, their synthesis, structure elucidation, and chromatographic determination have not been reported yet. To bridge this gap, we herein identified, synthesized, and isolated eight process-related solriamfetol impurities, characterized them using spectroscopic and chromatographic techniques, and proposed plausible mechanisms of their formation. Moreover, we developed and validated a prompt impurity analysis method based on ultrahigh-performance liquid chromatography with UV detection, revealing that its selectivity, linearity, accuracy, precision, and quantitation limit meet the acceptance criteria of method validation stipulated by the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use. Thus, the developed method was concluded to be suitable for the routine analysis of solriamfetol substances.

1. Introduction

Solriamfetol hydrochloride (*R*-2-amino-3-phenylpropylcarbamate hydrochloride, Fig. 1) is a central nervous system drug that is used to treat excessive daytime sleepiness accompanied by narcolepsy or obstructive sleep apnea and has been marketed since late 2019 by Jazz Pharmaceuticals under the brand name Sunosi [1,2]. The action mechanism of solriamfetol is not yet fully understood and is thought to involve the inhibition of dopamine and norepinephrine reuptake [3–5].

Fig. 2A presents the method used to synthesize solriamfetol as an active pharmaceutical ingredient (API) according to a patent filed by SK Biopharmaceuticals [6]. This method involves the protection of the amino group of D-phenylalaninol followed by the introduction of a carbamate moiety at the hydroxyl group using phosgene and ammonia, with subsequent hydrogenation-induced deprotection and salt formation affording solriamfetol in the form of a hydrochloride. An alternative one-step synthesis of solriamfetol in high yield, which involves reacting D-phenylalaninol with sodium cyanate under acidic conditions [7], is described in Fig. 2B.

Patent WO2020035769A1 describes an improved high-yield synthesis of high-purity solriamfetol hydrochloride without forming any isomers and other process-related impurities [8]. In this patent, it is reported that solriamfetol free base can be reacted with an organic acid and then converted to the hydrochloride salt (Fig. 2C).

However, process-related impurities are commonly detected by high-performance liquid chromatography (HPLC) during the synthesis and purification steps. As these impurities may affect the quality and safety of drug products, impurity identification and profiling have received considerable attention from regulatory authorities [9]. The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) states that impurities present in quantities above the identification threshold should be identified and characterized [10]. All APIs used in human medication must meet the ICH quality guidelines. The quality of any API depends on its synthetic process, potential degradation

Peer review under responsibility of Xi'an Jiaotong University.
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https://doi.org/10.1016/j.jpha.2023.02.012

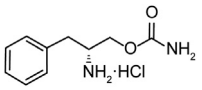


Fig. 1. Structure of solriamfetol hydrochloride.

pathway, and possible side reactions. Consequently, API manufacturers attempt to minimize impurity levels; nevertheless, the formation of impurities cannot be fully avoided. There have been many reports on the identification and characterization of unknown impurities formed in drug development processes [11–15]. If some of these characterized impurities are not readily available, appropriate synthetic procedures should be established to produce quantities sufficient for the development and validation of an analytical method and thus benefit pharmaceutical development teams worldwide.

The marketed solriamfetol drug is the *R*-enantiomer, while the *S*-enantiomer might exist as a chiral impurity [16]. Phenylalaninol enantiomers are also considered potential impurities of solriamfetol and can be present either as the residual starting material of the synthesis and/or as degradation products of solriamfetol [17]. Patent WO2020035769A1 reports nine process-related impurities of solriamfetol potentially produced during its synthesis [8] (Fig. S1). Moreover, patent WO2021250067A2 describing solriamfetol purification reports five most common and critical solriamfetol impurities (Fig. S1) and suggests mechanisms of their formation [18]. However, these patents do not deal with the syntheses, structure elucidation, or chromatographic determination of solriamfetol impurities.

Herein, we present a first-time account of the syntheses, identification, and characterization of eight potential process-related solriamfetol impurities (Table 1) [19–21] and discuss their formation mechanisms. Moreover, we describe the development and validation of a chromatographic method for analyzing solriamfetol impurities to facilitate their detection and quantitation in industrial settings.

2. Experimental

2.1. Materials and reagents

D-phenylalaninol (**I**, 98%), *N*-Cbz-D-phenylalanine (Z-D-Phe-OH) (**II**, 97%), L-phenylalaninol (**VII**, 97%), and biuret (**XI**, 98%) were purchased from AA Blocks (San Diego, CA, USA). Other chemicals and reagents were acquired from commercial sources including Merck (Darmstadt, Germany), Quality Reagent Chemicals (QReC; Auckland, New Zealand), and TEDIA (Fairfield, OH, USA). Silica gel (Geduran Si 60; 0.063–0.200 mm) from Merck was used for column chromatography. Ultrapure water (18.2 MΩ cm) was generated using a Millipore water purification system (Molsheim, France) and used to prepare mobile phases for HPLC.

2.2. HPLC

Chromatographic separation was achieved using an HPLC instrument consisting of an LC-40D XR pump, SIL-40C XR autosampler, CTO-40 S column oven, and SPD-M30A PDA detector and equipped with an 8-cm-path-length flow cell (Shimadzu, Kyoto, Japan). The detection wavelength was set to 210 nm. Separation was achieved at 30 °C and a flow rate of 0.4 mL/min using a Kinetex Polar C_{18} column (100 mm × 2.1 mm, 2.6 μm) manufactured by Phenomenex (Torrance, CA, USA). Elution was performed in gradient mode using mobile phases A (0.1% aqueous perchloric acid) and B (0.1 M aqueous perchloric acid:acetonitrile, 10:90, *V/V*). Mobile phase B was maintained at 3% for 13 min, changed to 20% from 13 to 16 min, and maintained at 20% for 6 min. The column was re-equilibrated at the initial ratio for 7 min. The injection volume equaled 1 μL. Data were processed using Lab Solution software version 6.106SP1 (Shimadzu).

2.3. Liquid chromatography-mass spectrometry (LC-MS)

MS/MS identification was conducted using a quadrupole time-of-flight mass spectrometer (Triple TOF 5600; AB Sciex, Foster City, CA, USA) equipped with an electrospray ionization (ESI) source. Scanning was performed within the *m/z* range of 100–1500. The pressures of ion source gases one and two were set to 379 kPa, and the curtain gas pressure was set to 241 kPa. The collision energy was set to 35 eV. Nitrogen was used as the collision cell, nebulizer and auxiliary gas. Data were acquired using the Analyst® TF 1.6 software (AB Sciex).

2.4. Nuclear magnetic resonance (NMR) spectroscopy

NMR spectra were recorded on a 400-MHz FT-NMR spectrometer (Avance-III, Bruker, Germany) using deuterated dimethyl

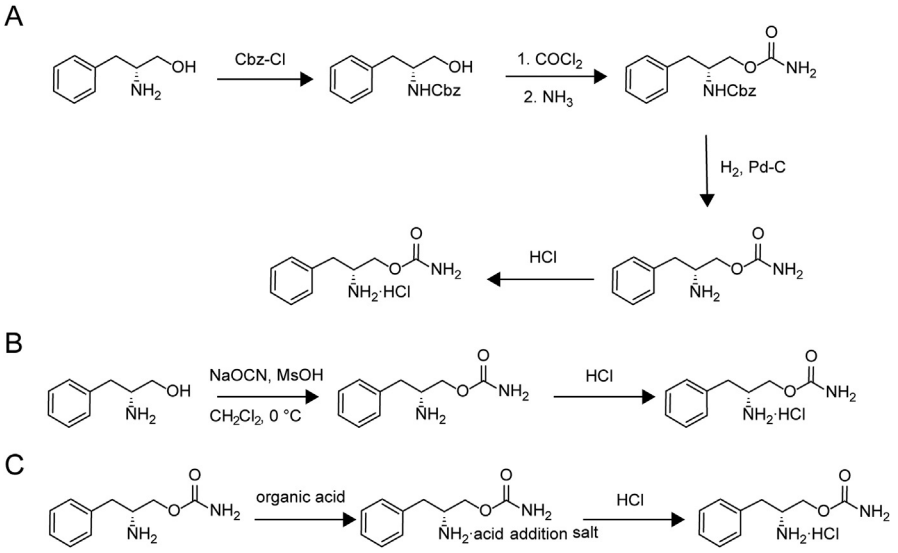
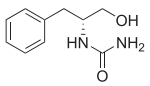
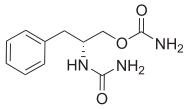
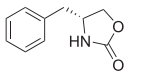
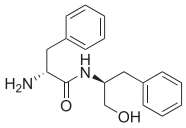
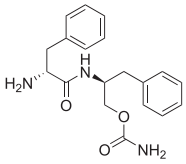
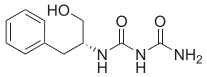
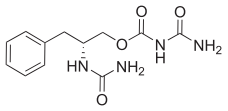
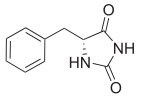


Fig. 2. Previously reported solriamfetol synthesis methods. (A) Patent US5955499 A [6], (B) patent WO2005033064 A1 [7], and (C) patent WO2020035769 A1 [8]. Cbz: benzyloxycarbonyl; Ms: mesyl.

Table 1
International Union of Pure and Applied Chemistry (IUPAC) names and structures of solriamfetol impurities investigated herein[a].

Impurity	Structure	IUPAC name
Imp. **1**		(*R*)-1-(1-hydroxy-3-phenylpropan-2-yl)urea
Imp. **2**		(*R*)-3-phenyl-2-ureidopropyl carbamate
Imp. **3**		(*R*)-4-benzyloxazolidin-2-one
Imp. **4**		(*R*)-2-Amino-*N*-((*S*)-1-hydroxy-3-phenylpropan-2-yl)-3-phenylpropanamide
Imp. **5**		(*S*)-2-((*R*)-2-amino-3-phenylpropanamido)-3-phenylpropyl carbamate
Imp. **6**		*N*-[(2*R*)-1-hydroxy-3-phenylpropan-2-yl]dicarbonimidic diamide
Imp. **7**		(2*R*)-2-(carbamoylamino)-3-phenylpropyl carbamoyl carbamate
Imp. **8**		(*R*)-5-benzylimidazolidine-2,4-dione

[a] Imps. **1** [19], **3** [20] and **8** [21] have been synthesized and characterized before (but not in a research related to solriamfetol) while the rest of impurities have not.

sulfoxide (DMSO-d_6) as the solvent and tetramethylsilane as the internal standard.

2.5. Fourier transform infrared (FTIR) spectroscopy

The spectra of neat samples were recorded in attenuated total reflectance mode on an FTIR-4X spectrometer (Jasco, Hachioji, Tokyo, Japan).

2.6. Synthesis and characterization of solriamfetol impurities

Imps. **1**–**8** were synthesized as described in Fig. 3.

2.6.1. (R)-1-(1-hydroxy-3-phenylpropan-2-yl)urea (imp. **1**)

I (0.500 g, 3.31 mmol) was dissolved in H_2O (20.0 mL) inside a 250 mL round-bottom flask (RBF), which was subsequently charged with a solution of sodium carbonate (0.250 g, 2.36 mmol) in H_2O (2.5 mL) and potassium cyanate (0.500 g, 6.16 mmol). The reaction mixture was stirred overnight at 80–90 °C and monitored using HPLC. After the reaction was complete, the mixture was extracted with methylene chloride, and the combined organic extracts were dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain imp. **1** (0.366 g, 57% yield, 99.3% purity by HPLC) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm = 7.28–7.17 (m, 5H, Ar), 5.85 (d, J = 7.6 Hz, 1H), 5.42 (d, J = 7.1 Hz, 2H), 4.81–4.77 (m, 1H), 3.70 (s, 1H), 3.29 (dt, J = 28.6, 5.6 Hz, 2H), 2.81–2.50 (m, 2H); ^{13}C NMR (101 MHz, DMSO-d_6): δ/ppm = 158.4 (C=O), 139.4 (C, Ar), 129.2 (2CH, Ar), 128.1 (2CH, Ar), 125.8 (CH, Ar), 62.7 (CH_2OH), 52.5 (CHNH), 37.3 ($PhCH_2$); HRMS (ESI+): calcd for $C_{10}H_{15}N_2O_2^+$: 195.11280 $[M+H]^+$; found 195.1123.

2.6.2. (R)-3-Phenyl-2-ureidopropyl carbamate (imp. **2**)

I (16.0 g, 105.8 mmol) was dissolved in methylene chloride (150 mL) inside a 250 mL RBF, and the solution was supplemented with sodium cyanate (17.0 g, 2611.49 mmol), cooled to 0 °C, and dropwise supplemented with methanesulfonic acid (23.68 g, 16 mL, 246.4 mmol) at 0 °C. After the addition was complete, the mixture was stirred overnight at room temperature, and the reaction was monitored by HPLC. When the reaction was complete, the solvent was concentrated under reduced pressure, the residue was dissolved in H_2O (~70 mL), and the mixture was sonicated for 10 min. The produced crude white solid was collected by filtration and dried (13.0 g, 52% yield). For purification, the crude product was refluxed in ethyl acetate:methanol (1:1, *V/V*, 30 mL) for 1 h, filtered, and dried to yield imp. **2** as a white solid (98.3% purity by HPLC). ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm = 7.31–7.19 (m, 5H, Ar), 6.53 (bs, 2H), 5.92 (d, J = 8.2 Hz, 1H), 5.45 (s, 2H), 3.94–3.88 (m, 1H), 3.83–3.74 (m, 2H), 2.78–2.65 (m, 2H); ^{13}C NMR (101 MHz, DMSO-d_6): δ/ppm = 158.0 (C=O), 156.7 (C=O), 138.5 (C, Ar), 129.1(2CH, Ar), 128.2 (2CH, Ar), 126.1 (CH, Ar), 64.9 (CH_2O), 49.8

(CHNH), 37.45 ($PhCH_2$); HRMS (ESI+): calcd for $C_{11}H_{16}N_3O_3^+$: 238.11662 $[M+H]^+$; found 238.1189.

*2.6.3. (R)-4-Benzyloxazolidin-2-one (imp. **3**)*

VI (1.18 g, 3.6 mmol) was dissolved in methanol (20.0 mL), 10% (*m/m*) Pd/C (120 mg) was added, and the mixture was stirred at room temperature under H_2 for 12 h. The mixture was filtered, and the filtrate was evaporated under reduced pressure. The residue was crushed with a spatula to give imp. **3** (0.367 g, 52% yield, 100% purity by HPLC) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm = 7.79 (s, 1H), 7.32–7.21 (m, 5H, Ar), 4.25 (t, J = 8.2 Hz, 1H), 4.08–4.02 (m, 1H), 3.98 (dd, J = 8.2, 5.4 Hz, 1H), 2.84–2.72 (m, 2H); ^{13}C NMR (101 MHz, DMSO-d_6): δ/ppm = 158.6 (C=O), 136.6 (C, Ar), 129.4 (2CH, Ar), 128.4 (2CH, Ar), 126.5 (CH, Ar), 68.0 (CH_2O), 52.5 (CHNH), 40.25 ($PhCH_2$); HRMS (ESI+): calcd for $C_{10}H_{12}NO_2^+$: 178.08626 $[M+H]^+$; found 178.0857.

*2.6.3.1. Preparation of methyl ((benzyloxy)carbonyl)-d-phenylalaninate (**III**).* **II** (3.0 g, 10.0 mmol) was dissolved in methanol (50.0 mL, 0.2 M) inside a 250 mL RBF. The solution was dropwise supplemented with thionyl chloride (1.7 g, 14.0 mmol) over 5 min at 0 °C upon stirring and further stirred for ~2 h at the same temperature. The reaction mixture was concentrated under reduced pressure, and the residue was treated with water and extracted with methylene chloride. The combined organic extracts were dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain **III** (3.550 g, 113% yield) as a colorless oil.

*2.6.3.2. Preparation of benzyl (R)-(1-hydroxy-3-phenylpropan-2-yl) carbamate (**IV**).* **III** (3.550 g, 11.3 mmol) was dissolved in methanol

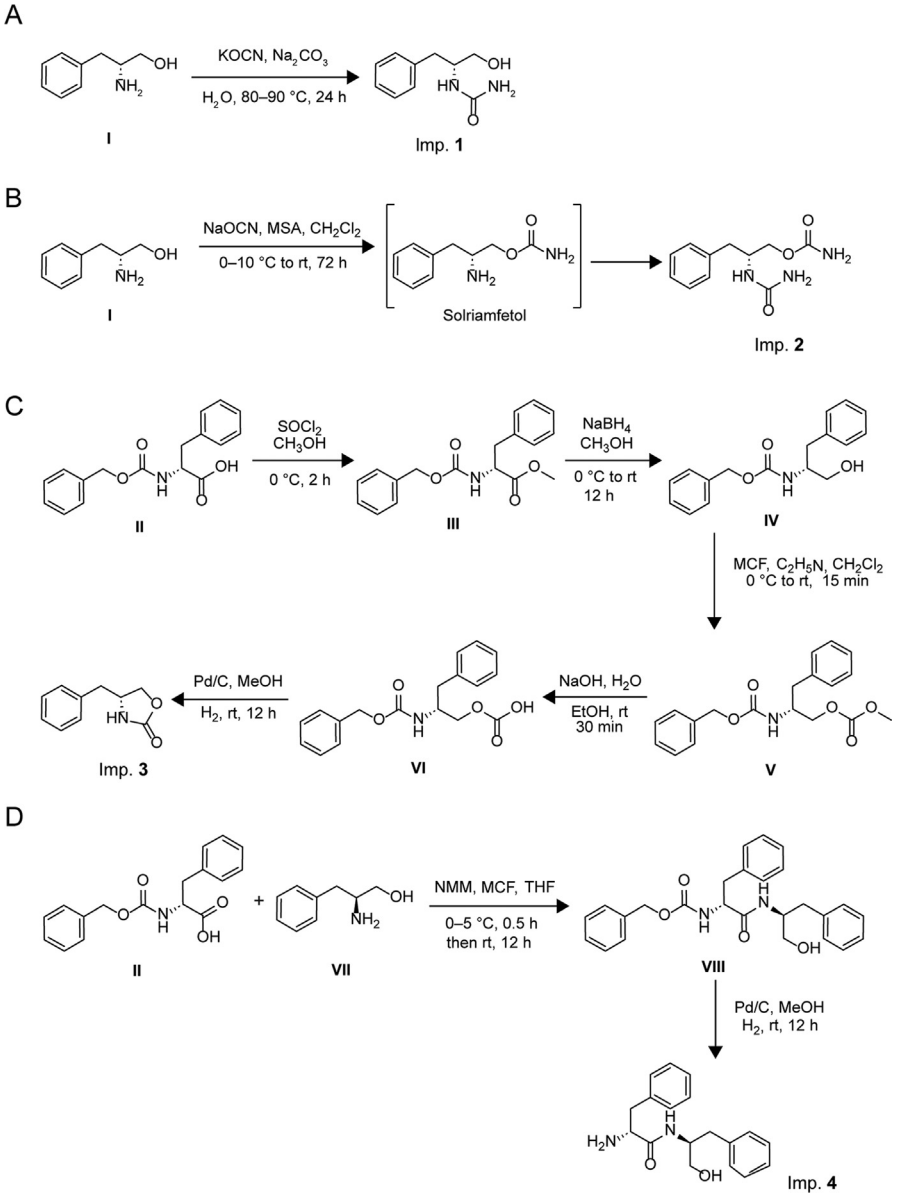


Fig. 3. Syntheses of imps. **1**–**8**. (A) Imp. **1** ((*R*)-1-(1-hydroxy-3-phenylpropan-2-yl)urea) from compound **I**, (B) Imp. **2** ((*R*)-3-phenyl-2-ureidopropyl carbamate) from compound **I**, (C) Imp. **3** ((*R*)-4-benzyloxazolidin-2-one) in five steps starting with compound **II**, (D) Imp. **4** ((*S*)-2-amino-*N*-((*R*)-1-hydroxy-3-phenylpropan-2-yl)-3-phenylpropanamide) in two steps starting with compounds **II** and **VII**, (E) Imp. **5** ((*R*)-2-((*R*)-2-amino-3-phenylpropanamido)-3-phenylpropyl carbamate) in three steps starting with compound **VII**, (F) Imp. **6** (*N*-[(2*R*)-1-hydroxy-3-phenylpropan-2-yl]dicarbonimidic diamide) in two steps starting with compound **XI**, (G) Imp. **7** ((2*R*)-2-(carbamoylamino)-3-phenylpropyl carbamoyl carbamate) from imp. **2**, and (H) Imp. **8** ((*R*)-5-benzylimidazolidine-2,4-dione) from compound **XIII**. MSA: methanesulfonic acid; MCF: methyl chloroformate; NMM: *N*-methylmorpholine.

(40 mL) inside a 250 mL RBF, and the solution was portionwise supplemented with sodium borohydride (2.95 g, 77.9 mmol) upon stirring in an ice bath. The mixture was further stirred for 12 h at room temperature, concentrated under reduced pressure, and the residue was treated with water and extracted with ethyl acetate. The combined organic extracts were dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain **IV** (2.495 g, 78% yield) as a white solid.

*2.6.3.3. Preparation of benzyl (R)-(1-((methoxycarbonyl)oxy)-3-phenylpropan-2-yl)carbamate (**V**).* **IV** (1.5 g, 5.3 mmol) was dissolved in methylene chloride (40.0 mL) inside a 250 mL RBF, and the solution was supplemented with pyridine (1.5 mL, 18.6 mmol). Subsequently, methyl chloroformate (2.43 mL, 31.5 mmol) was dropwise added upon cooling in an ice bath, and the reaction mixture was stirred for 15 min at room temperature and washed with water. The methylene chloride layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain crude **V** (1.5 g, 83% yield).

*2.6.3.4. Preparation of (R)-2-(((benzyloxy)carbonyl)amino)-3-phenylpropyl hydrogen carbonate (**VI**).* Crude **V** (1.5 g, 4.4 mmol) was dissolved in ethanol (20.0 mL) inside a 250 mL RBF, and the dispersion was charged with a solution of sodium hydroxide (1.3 g, 32.5 mmol) in water (10.0 mL) and ethanol (10.0 mL) upon stirring. After ~30 min stirring at room temperature, ethanol was removed under reduced pressure, water was added, and pH was adjusted to 3.0 with aqueous hydrochloric acid. The mixture was then extracted with methylene chloride, and the combined organic extracts were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The resulting product was purified by column chromatography using methylene chloride:methanol (50:1, *V/V*) as an eluent to afford **VI** (1.18 g, 81% yield) as a white solid.

*2.6.4. (R)-2-amino-N-((S)-1-hydroxy-3-phenylpropan-2-yl)-3-phenylpropanamide (imp. **4**)*

A dispersion of **VIII** (1.0 g, 2.3 mmol) in methanol (15.0 mL) was supplemented with 10% (*m/m*) Pd/C (250 mg), stirred at room temperature under H_2 for 12 h, and filtered through a filter paper. The filtrate was evaporated under reduced pressure to give imp. **4** (0.77 g, 81% yield, 99.4% purity by HPLC) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm = 7.77 (d, J = 8.3 Hz, 1H), 7.28–7.13 (m, 10H, Ar), 4.81 (t, J = 5.6 Hz, 1H), 3.91 (d, J = 5.6 Hz, 1H), 3.38–3.26 (m, 3H), 2.85–2.79 (m, 2H), 2.51–2.45 (m, 2H), 1.58 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6): δ/ppm = 174.3 (C=O), 139.5 (C, Ar), 139.2 (C, Ar), 129.8 (2CH, Ar), 129.6 (2CH, Ar), 128.6 (2CH, Ar),

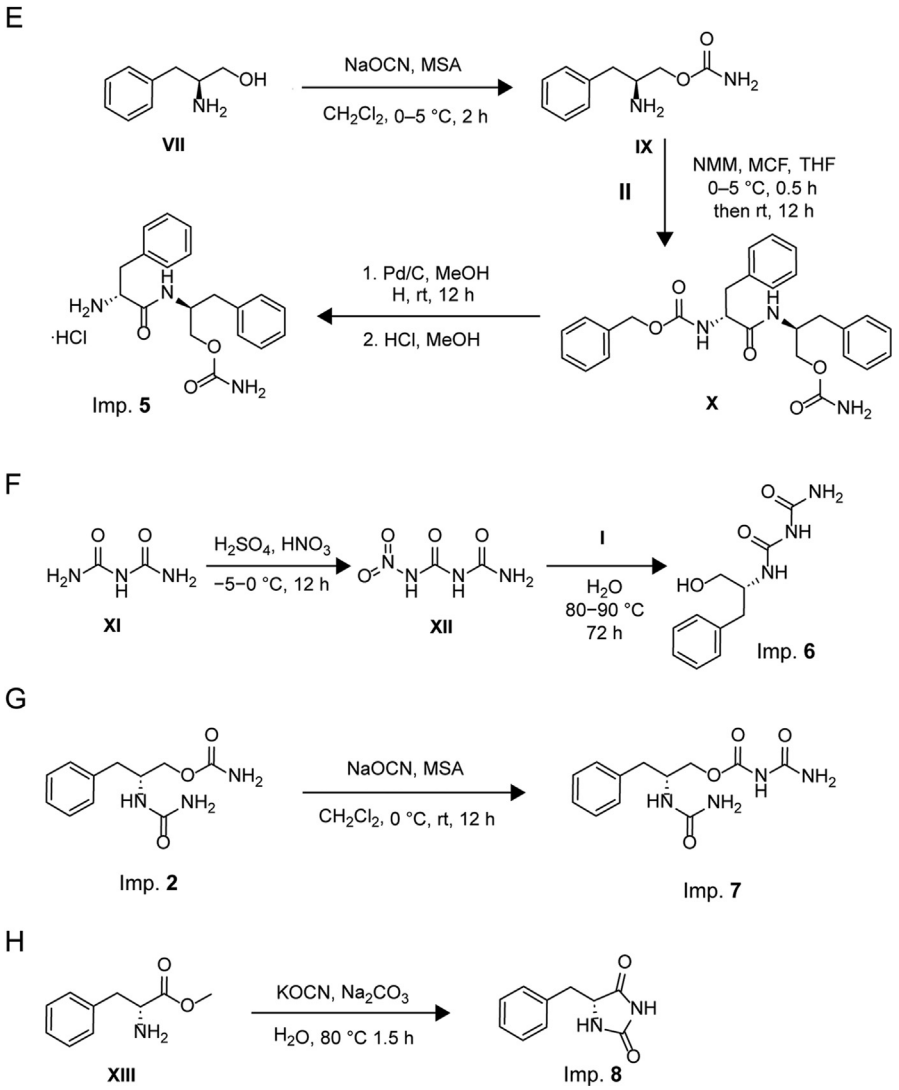


Fig. 3. (*continued*).

128.5 (2CH, Ar), 126.5 (CH, Ar), 126.4 (CH, Ar), 62.8 (CH_2OH), 56.5 (CHN), 52.5 (CHN), 41.6 (PhCH_2), 37.1 (PhCH_2); HRMS (ESI+): calcd for $C_{18}H_{23}N_2O_2^+$: 299.17540 $[M+H]^+$; found 299.1730.

*2.6.4.1. Preparation of benzyl ((R)-1-(((S)-1-hydroxy-3-phenylpropan-2-yl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (**VIII**).* **II** (3.0 g, 10.0 mmol) was dissolved in tetrahydrofuran (25.0 mL) inside a 250 mL RBF, and the solution was supplemented with *N*-methylmorpholine (1.1 mL, 10.0 mmol) and methyl chloroformate (770 μL, 10.0 mmol) upon stirring. The mixture was further stirred at 0–5 °C for 0.5 h, treated with **VII** (1.8 g, 12.0 mmol), and further stirred for 12 h at room temperature. Subsequently, tetrahydrofuran was removed under reduced pressure, and the crude product was taken up in methylene chloride. The solution was washed with 4 M hydrochloric acid and brine, and the organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give **VIII** (4.27 g, 99% yield).

*2.6.5. (S)-2-((R)-2-amino-3-phenylpropanamido)-3-phenylpropyl carbamate hydrochloride (imp. **5**)*

A dispersion of **X** (1.0 g, 2.1 mmol) in methanol (15.0 mL) was treated with 10% (*m/m*) Pd/C (200 mg) and stirred at 60–70 °C under H_2 for 2 h. Subsequently, heating was stopped, and the reaction mixture was stirred for another 12 h and filtered. The filtrate was evaporated under reduced pressure to give an oily material (0.620 g, 79.5% yield) that was dissolved in methanol. The solution was dropwise supplemented with aqueous hydrochloric acid (0.5 mL) until a precipitate was formed. The precipitate was filtered off and dried to afford imp. **5** (0.286 g, 36% yield, 95.3% purity by HPLC) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm = 8.82 (d, J = 8.3 Hz, 1H), 8.22 (s, 3H), 7.29–7.20 (m, 9H, Ar), 7.06–7.04 (m, 2H), 6.55 (bs, 2H), 4.14–4.13 (m, 1H), 3.98 (bs, 1H), 3.93–3.81 (m, 2H), 2.93 (dd, J = 13.9, 5.3 Hz, 1H), 2.81–2.72 (m, 2H), 2.62 (dd, J = 13.5, 9.1 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-d_6): δ/ppm = 167.7 (NC=O), 156.5 (OC=O), 138.1 (C, Ar), 134.8 (C, Ar), 129.5 (2CH, Ar), 129.2 (2CH, Ar), 128.4 (2CH, Ar), 128.3 (2CH, Ar), 127.0 (CH, Ar), 126.3 (CH, Ar), 64.4 (CH_2O), 53.3 (CHN), 50.0 (CHN), 36.7 (PhCH_2), 36.5 (PhCH_2); HRMS (ESI+): calcd for $C_{19}H_{24}N_3O_3^+$: 342.18120 $[M+H]^+$; found 342.1808.

*2.6.5.1. Preparation of (S)-2-amino-3-phenylpropyl carbamate (**IX**).* **VII** (1.0 g, 6.6 mmol) was dissolved in methylene chloride (25.0 mL) inside a 100 mL RBF, and the solution was sequentially supplemented with sodium cyanate (1.0 g, 15.4 mmol) and methanesulfonic acid (1.5 mL, 23.1 mmol; dropwise over 15 min at 0–5 °C). The mixture was stirred for 2 h at the same temperature and concentrated under reduced pressure. The residue was treated with water, and the mixture was pH-adjusted to 10.0 with 1 N sodium hydroxide and extracted with methylene chloride. The combined organic extracts were dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain an oily material (1.2 g, 93.8% yield). The crude product was purified by column chromatography using methylene chloride:methanol:ammonia (20:1:0.1, *V/V/V*) as an eluent to afford **IX** (0.800 g, 62.5% yield) as a yellow oil.

*2.6.5.2. Preparation of benzyl ((R)-1-(((R)-1-(carbamoyloxy)-3-phenylpropan-2-yl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (**X**).* **II** (1.7 g, 5.7 mmol) was dissolved in tetrahydrofuran (20.0 mL) inside a 250 mL RBF, and the solution was sequentially supplemented with *N*-methylmorpholine (960 μL, 8.7 mmol) and methyl chloroformate (410 μL, 5.3 mmol) upon stirring and further stirred at 0–5 °C for 0.5 h. Subsequently, **IX** (0.8 g, 4.1 mmol) was added, and the reaction mixture was stirred for 12 h at room temperature and then concentrated under reduced pressure. The residue was taken up in methylene chloride, and the solution was washed with 4 M hydrochloric acid and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to afford an off-white solid (4.4 g). The crude product was purified by column chromatography using methylene chloride:methanol:ammonia (30:1:0.1, *V/V/V*) as the eluent to obtain **X** (2.1 g, 77.8% yield) as a white solid.

*2.6.6. N-[(2 R)-1-Hydroxy-3-phenylpropan-2-yl]dicarbonimidic diamide (imp. **6**)*

I (1.0 g, 6.6 mmol) and **XII** (2.0 g, 13.5 mmol) were added to water (~20 mL) inside a 100 mL RBF, and the mixture was stirred at 80–90 °C for 72 h and then extracted with methylene chloride and ethyl acetate. The combined organic extracts were dried over anhydrous sodium sulfate and concentrated under reduced pressure to give an oily material (1.3 g, 83% yield), which was subjected to column chromatography using an ethyl acetate:*n*-hexane gradient of 1:1 to 5:1 (*V/V*) to afford imp. **6** (0.462 g, 29% yield, 95.0% purity by HPLC) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm = 8.48 (s, 1H), 7.55 (bs, 1H), 7.30–7.17 (m, 5H, Ar), 6.69 (s, 2H), 4.89 (t, J = 5.2 Hz, 1H), 3.82 (d, J = 6.8, 1H), 3.35–3.33 (m, 2H), 2.85–2.63 (m, 2H); ^{13}C NMR (101 MHz, DMSO-d_6): δ/ppm = 155.4 (C=O), 154.0 (C=O), 138.8 (C, Ar), 129.2 (2CH, Ar), 128.2 (2CH, Ar), 126.1 (CH, Ar), 61.9 (CH_2O), 52.4 (NCH), 37.0 (PhCH_2); HRMS (ESI+): calcd for $C_{11}H_{16}N_3O_3^+$: 238.11862 $[M+H]^+$; found 238.1185.

*2.6.6.1. Preparation of nitrobiuret (**XII**).* **XI** (5.0 g, 48.5 mmol) was portionwise added to a mixture of concentrated sulfuric (12.5 mL, 233.2 mmol) and nitric (3.3 mL, 73.9 mmol) acids at −5 to 0 °C inside a 250 mL RBF, and the mixture was stirred under N_2 at the same temperature for 12 h, poured into ice water, and stirred for 5 min. The precipitate was filtered off and dried to give **XII** (6.4 g, 89% yield) as a white solid.

*2.6.7. (2 R)-2-(carbamoylamino)-3-phenylpropyl N-carbamoyl carbamate (imp. **7**)*

Imp. **2** (1.4 g, 5.9 mmol) was dissolved in methylene chloride (30 mL) inside a 250 mL RBF, and the solution was supplemented with sodium cyanate (1.42 g, 21.8 mmol) upon stirring, cooled to 0 °C, and dropwise treated with methanesulfonic acid (2.36 g, 3.5 mL, 24.6 mmol). After the addition was completed, the reaction mixture was warmed to room temperature and stirred overnight at this temperature. The reaction was monitored using HPLC. After the reaction was complete, the solvent was removed under reduced pressure, the residue was dissolved in H_2O (50 mL), and the mixture was sonicated for 10 min to give a white solid that was filtered off, dried (1.25 g), treated with refluxing acetonitrile for 1 h, filtered, and dried (690 mg). The dried solid was treated with refluxing ethyl acetate:methanol (9:1, *V/V*, 30 mL) for 1 h, filtered, and dried to afford imp. **7** (550 mg, 33.3% yield, 97.5% purity by HPLC) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm = 9.89 (s, 1H), 7.29–7.21 (m, 7H), 5.98 (s, 1H), 5.49 (s, 2H), 3.99–3.87 (m, 3H), 2.75 (d, J = 28.6 Hz, 2H); ^{13}C NMR (101 MHz, DMSO-d_6): δ/ppm = 158.1 (C=O), 154.4 (C=O), 153.6 (C=O), 138.4 (C, Ar), 129.2 (2CH, Ar), 128.3 (2CH, Ar), 126.2 (CH, Ar), 66.2 (OCH_2), 49.5 (NCH), 37.1 (PhCH_2); HRMS (ESI$^+$): calcd for $C_{12}H_{17}N_4O_4^+$: 281.12443 $[M+H]^+$; found 281.1264.

*2.6.8. (R)-5-Benzylimidazolidine-2,4-dione (imp. **8**)*

D-phenylalaninol methyl ester (1.0 g, 5.6 mmol) was dissolved in water (20.0 mL) inside a 100 mL RBF, and the reaction mixture was sequentially treated with a solution of sodium carbonate (0.5 g, 4.7 mmol) in water (5.0 mL) and potassium cyanate (1.0 g, 12.3 mmol), stirred at 80 °C for 1.5 h, and extracted with ethyl acetate. The combined organic extracts were dried over anhydrous sodium sulfate and concentrated under reduced pressure to give imp. **8**

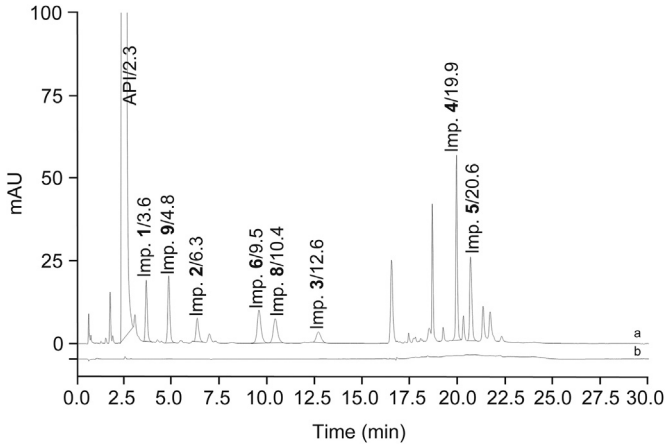


Fig. 4. Results of high-performance liquid chromatography with ultraviolet (HPLC-UV) analysis. Chromatograms of a 1 mg/mL solution of solriamfetol spiked with all impurities (1 μg/mL each) (a) and a blank solution (b). API: active pharmaceutical ingredient.

(0.44 g, 35% yield, 99.7% purity by HPLC) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm = 10.42 (s, NH), 7.91 (s, NH), 7.29–7.17 (m, 5H), 4.32 (t, 1H, J = 4.8 Hz), 3.14–3.00 (m, 2H) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): δ/ppm = 175.3 (CH_2C=O), 157.3 (NHC=ONH), 135.8 (C, Ar), 129.9 (2CH, Ar), 128.2 (2CH, Ar), 126.8 (CH, Ar), 58.55 (CHNH), 36.59 (PhCH_2); HRMS (ESI+): calcd for $C_{10}H_{11}N_2O_2^+$: 191.08150 $[M+H]^+$; found 191.0823.

3. Results and discussion

3.1. Impurity detection and identification

Fig. 4 presents a representative analytical HPLC chromatogram of solriamfetol spiked with eight impurities that had been detected in crude solriamfetol during process development studies and identified by LC-MS. Consequently, these impurities were herein synthesized in quantities sufficient for full characterization and analytical (HPLC) method validation. All synthesized impurities were co-injected with solriamfetol to confirm their identity based on retention time matching (Fig. 4). The high-performance liquid chromatography with ultraviolet detection (HPLC-UV) chromatograms of each impurity separately are given in Figs. S2–S9. Figs. S10–S17, S18–S33, and S34–S41 present the Fourier transform infrared spectra, original ^{1}H and ^{13}C NMR spectra, and high-resolution mass spectra of imps. **1**–**8**, respectively. The assignments corresponding to ^{1}H and ^{13}C NMR spectra are presented in Section 2. All spectral data confirmed the structures of the synthesized impurities.

3.2. Elucidation of impurity structure and formation mechanism

The positive ionization mode mass spectrum of the impurity at a relative retention time (RRT) (relative to API peak) of 1.6 showed a molecular ion ($[M+H]^+$, m/z = 195.1123) corresponding to a molecular weight of 194 amu, which agreed with the structure of imp. **1**. This impurity was prepared by heating a basic aqueous solution of **I** to 80–90 °C in the presence of potassium cyanate and was fully characterized and standardized for advanced analytical studies. For all prepared impurities, the used precursors are enantiomerically pure isomers, and given that the reactions do not involve the chiral centers, the products (i.e., impurities) are pure isomers, as indicated by their names in Table 1.

The impurity at RRT 2.1 was observed in crude solriamfetol during process development studies. The corresponding positive ionization mode mass spectrum revealed a molecular ion ($[M+H]^+$, m/z = 191.0823) corresponding to a molecular weight of 190 amu, which agreed with the structure of imp. **8**. To validate this assignment, we synthesized imp. **8** by reacting D-phenylalaninol methyl ester (**XIII**) with potassium cyanate in the presence of sodium carbonate and the result showed that its RRT matched that of the corresponding impurity found in the API. Imp. **8** was purified, characterized, and scaled up for analytical studies.

The positive ionization mode mass spectrum of the impurity with RRT 2.7 revealed a molecular ion ($[M+H]^+$, m/z = 238.1189) corresponding to a molecular weight of 238 amu, which was slightly higher than that of solriamfetol and agreed with the structure of imp. **2**. Substantial amounts of imp. **2** were obtained by reacting **I** with sodium cyanate in the presence of methanesulfonic acid. This transformation was assumed to proceed via the formation of solriamfetol as an intermediate.

The positive ionization mode mass spectrum of the impurity with RRT 4.1 showed a molecular ion ($[M+H]^+$, m/z = 238.1185) corresponding to a molecular weight of 237 amu, which agreed with the structure of imp. **6**. This impurity was synthesized by reacting **XII** with **I**.

The positive ionization mode ESI mass spectrum of the impurity with RRT 4.5 showed a molecular ion ($[M+H]^+$, m/z = 281.1264) corresponding to a molecular weight of 280 amu, which agreed with the structure of imp. **7**. This impurity was synthesized by reacting imp. **2** with excess cyanate and methanesulfonic acid.

The positive ionization mode mass spectrum of the impurity with RRT 5.5 showed a molecular ion ($[M+H]^+$, m/z = 178.0857) corresponding to a molecular weight of 177 amu, which was 17 amu lower than that of solriamfetol and complied with the structure of imp. **3**. This impurity was synthesized in five steps starting from carbamate **II**. In the first step, the carboxylic acid group was converted to the corresponding acid chloride, which was then reacted with methanol to form the corresponding ester **III**. The subsequent reduction of **III** with sodium borohydride yielded the primary alcohol **IV**, which was then reacted with methyl chloroformate in the presence of pyridine to give **V**. After that, **V** was hydrolyzed to afford **IV**, which was catalytically hydrogenated to give the desired 5-membered ring product, i.e., imp. **3**.

The positive ionization mode mass spectrum of the impurity with RRT 8.7 showed a molecular ion ($[M+H]^+$, m/z = 299.1730) corresponding to a molecular weight of 298 amu, which agreed with the structure of imp. **4**. This impurity was synthesized by reacting carbamate **II** with **VII** in the presence of methyl chloroformate and *N*-methylmorpholine to give **VIII**, which was then catalytically hydrogenated to produce imp. **4** in quantitative yield.

The positive ionization mode mass spectrum of the impurity with RRT 9.0 showed a molecular ion ($[M+H]^+$, m/z = 342.1808) corresponding to a molecular weight of 298 amu, which agreed with the structure of imp. **5**. This impurity was synthesized in three steps. **VII** was carbamoylated to produce **IX**, which was subsequently reacted with **II** and methyl chloroformate in the presence of *N*-methylmorpholine to give **X**. Finally, dehydrogenation followed by salt formation afforded imp. **5**.

3.3. Proposed formation mechanisms of the identified impurities

The *N*-carbamoylation-derived imp. **1** is a process-related impurity that can be formed during API manufacturing. In the API production process disclosed in patent US5955499A [6], a carbamate moiety is introduced to protect the amino group of D-phenylalaninol. Traces of unprotected D-phenylalaninol may react with phosgene and ammonia at the amino group (and not at the hydroxyl group) to produce imp. **1**. In patent WO202150067A2, this impurity was denoted as a *urea* impurity and was suggested to form

Table 2
Results of linearity, limit of quantitation (LOD), limit of detection (LOQ), relative retention time (RRT), relative response factor (RRF), and resolution evaluation obtained for the high-performance liquid chromatography (HPLC) analysis method ($n = 3$).

Compound	Linearity equitation	r	RRT[a]	RRF	LOD (ng/mL)	LOQ (ng/mL)	Resolution
Solriamfetol	$y = 173x + 60.5$	0.9999	1.0	1.00	–	–	–
Imp. **1**	$y = 667x + 2580$	0.9963	1.6 ± 0.1	3.84 ± 0.10	6.7 ± 2.0	20.0 ± 2.0	5.3
Imp. **2**	$y = 390x - 343$	0.9998	2.7 ± 0.2	2.24 ± 0.05	20.0 ± 6.2	62.0 ± 6.1	6.5
Imp. **3**	$y = 494x + 250$	0.9999	5.5 ± 0.7	2.84 ± 0.05	19.0 ± 5.8	58.0 ± 5.9	5.4
Imp. **4**	$y = 498x - 1250$	0.9999	8.7 ± 0.6	2.87 ± 0.03	0.9 ± 0.3	2.7 ± 0.3	–
Imp. **5**	$y = 49.9x - 130$	0.9968	9.0 ± 0.7	0.29 ± 0.01	0.4 ± 0.1	1.1 ± 0.1	–
Imp. **6**	$y = 606x - 1030$	0.9999	4.1 ± 0.4	3.49 ± 0.13	29.0 ± 8.9	89.0 ± 9.1	10.0
Imp. **7**	$y = 357x + 175$	0.9983	4.5 ± 0.3	2.05 ± 0.04	28.0 ± 8.5	85.0 ± 8.2	2.3
Imp. **8**	$y = 759x - 859$	0.9999	2.1 ± 0.1	4.37 ± 0.06	5.9 ± 1.8	18.0 ± 1.7	6.3

[a] Relative to the retention time of the solriamfetol peak.

via the migration of the carbamoyl group from the oxygen to the nitrogen of the API under basic conditions [18].

The bicarbamate imp. **2** was presumably formed through the reaction of *N*-unprotected API traces with phosgene and ammonia according to the process disclosed in patent US5955499A [6].

Patent WO202150067A2 denoted the cyclic imp. **3** as a *cycle* impurity and suggested that it was formed by the loss of ammonia from the API at low pH followed by the intermolecular formation of a five-membered cycle [18].

According to the API production process disclosed in patent US5955499A [6], phosgene can catalyze the conversion of traces of D-phenylalanine in D-phenylalaninol to the corresponding acid chloride, which directly reacts with the amino functional group of phenylalaninol to form imp. **4**.

If imp. **4** is present in the API, it can react with phosgene and ammonia used for carbamoylation to give imp. **5**. Fig. S42 summarizes the proposed pathways for the formation of imps. **1**–**5** in solriamfetol.

The *N*-dicarbonimidic diamide imp. **6** can be formed under conditions similar to those affording imp. **1**, that is, the amino group of *N*-unprotected D-phenylalaninol traces can repeatedly react with phosgene and ammonia to produce imp. **6**.

The *O*-dicarbonimidic diamide imp. **7** can be formed under conditions similar to those affording imp. **2** via the further carbamoylation of the carbamate imp. **7** at its NH_2 group.

The D-phenylalanine-cyclized imp. **8** can be formed in the presence of phosgene and ammonia via the intramolecular carbamoylation of the acid chloride traces of D-phenylalanine found in D-phenylalaninol. Fig. S43 summarizes the proposed pathways for the formation of imps. **6**–**8** in solriamfetol.

3.4. Validation of the HPLC method

The chromatographic method was developed by testing different stationary phases and mobile phase compositions and validated according to the ICH Q2 (R1) guidelines [22] for system suitability, selectivity, linearity, recovery, precision, limit of quantitation (LOD), and limit of detection (LOQ). The concentration of the solriamfetol test solution equaled 1 mg/mL, and the impurity concentration was set to 0.1% of this value, i.e., 1 μg/mL.

3.4.1. Selectivity

Selectivity was evaluated by injecting a blank solution and a 1 mg/mL solution of solriamfetol spiked with eight impurities (1 μg/mL each) and was verified by the absence of interference between blank peaks and analyte peaks as well as by the proper separation between the peaks of solriamfetol and those of the eight impurities (Fig. 4). The corresponding resolutions ranged from 2.3 to 10. (Table 2).

The stability-indicating power of the developed method was tested by a stress testing (also called forced degradation) study according to ICH guidelines for stability (Q1A). The results (Table S1) indicate that solriamfetol was significantly degraded under basic conditions with a total degradation degree of 23%, while the degradation in response to acidic, oxidative, and thermal stresses was moderate (4.9%, 7.3%, and 2.0%, respectively). In all stress conditions, proper mass balance, calculated by adding the values of %assay to the %degradation, was achieved (>95% in all conditions). The mass balance results prove the selectivity and the stability-indicating power of the developed method as the loss of the drug substance accompanied by almost the same extent of degradation products peaks.

3.4.2. System suitability

System suitability was evaluated by injecting five replicates of a 1 mg/mL solriamfetol solution spiked with all impurities (1 μg/mL each). The relative standard deviations (%RSDs) of peak areas and retention times ranged from 0.26% to 0.91% and were therefore less than 2.0%, the generally accepted criterion. The resolution between adjacent analyte peaks (2.3–10.0, Table 2) exceeded the minimum value (~1.5) required for baseline separation.

Table 3
Result of recovery and precision evaluation obtained for the high-performance liquid chromatography (HPLC) analysis method.

Compound	Recovery						Precision (%RSD)		
	500 ng/mL		1000 ng/mL		1500 ng/mL		500 ng/mL	1000 ng/mL	1500 ng/mL
	%Avg	%RSD	%Avg	%RSD	%Avg	%RSD			
Solriamfetol	–	–	–	–	–	–	0.29	0.92	0.90
Imp. **1**	99.85	0.94	101.5	1.93	95.18	0.95	0.94	1.79	0.95
Imp. **2**	86.84	0.43	91.89	1.95	90.98	2.94	0.18	1.74	2.94
Imp. **3**	108.3	1.59	86.28	0.45	87.84	0.69	1.59	0.44	0.69
Imp. **4**	96.03	2.03	106.4	1.32	88.66	3.04	2.38	2.05	2.29
Imp. **5**	111.1	0.41	109.6	2.22	91.88	0.65	2.04	2.10	0.65
Imp. **6**	98.15	2.99	99.73	1.14	94.45	1.21	2.79	2.46	3.02
Imp. **7**	96.25	2.22	98.20	1.98	96.84	0.42	2.17	1.91	1.09
Imp. **8**	96.32	1.58	103.0	1.89	98.78	1.09	1.61	2.89	1.17

Avg: average recovery; RSD: relative standard deviation.

3.4.3. Linearity, range, accuracy, precision, and robustness

Linearity was studied at 50–3000 ng/mL using nine different concentrations (each prepared in triplicate). The average peak area was plotted versus concentration, and the plot was fitted using the least squares method to obtain the corresponding linearity equation and correlation coefficient (r). The above range corresponds to 0.003%–0.3% of the nominal concentration of solriamfetol (1 mg/mL). The obtained r values (0.9963–0.9999, Table 2) indicated good linear correlation.

Accuracy and precision were studied by spiking 1 mg/mL solriamfetol with impurities at individual impurity concentrations of 500, 1000, and 1500 ng/mL and calculating %recovery using impurity standards of the same concentration. Accuracy was investigated in terms of %recovery for triplicate samples at each level. The results (86.28%–111.1%, Table 3) indicated proper analyte recovery, as the numbers were within the accepted range of 85%–115%. Precision was studied by preparing six replicates for each level. The %RSD was in the range of 0.18%–3.02% (Table 3), less than the generally accepted limit (10%).

3.4.4. Sensitivity (LOD and LOQ)

LODs and LOQs were calculated from the slope (b) and the standard deviation (SD) of the y-intercept of the regression line at low analyte concentrations (50–150 ng/mL) as LOD = 3.3SD/b and LOQ = 10SD/b. The obtained LODs and LOQs were in the ranges of 0.4–29.0 ng/mL and 1.1–89.0 ng/mL, respectively (Table 2). These values were less than 0.003% (LOD) and 0.009% (LOQ) of the nominal concentration of solriamfetol. The value of 0.009% obtained for LOQs was much less than the ICH guideline Q3A–stipulated threshold of 0.05% [10].

Relative response factors (RRFs) were calculated from linear fits as the ratio of the slope observed for a given impurity to the slope observed for solriamfetol and can be used to calculate impurity concentrations when no standards are available.

Thus, the developed method was concluded to be selective, precise, accurate, and suitable for the assaying of solriamfetol batches.

4. Conclusion

Eight process-related solriamfetol impurities were identified, synthesized, and characterized, and plausible mechanisms of their formation were proposed to shed light on the critical steps of API synthesis. Impurity structures were elucidated using ^{1}H and ^{13}C NMR spectroscopy, infrared spectroscopy, and LC-MS. This characterization resulted in compliance with regulatory requirements, and the prepared impurity standards were used to develop and validate a chromatographic method of impurity analysis and thus enable efficient solriamfetol quality control in industrial settings.

CRediT author statement

Nafisah Al-Rifai: Conceptualization, Methodology, Writing - Original draft preparation; **Anas Alshishani**: Validation, Resources, Writing - Original draft preparation; **Fouad Darras**: Supervision, Project administration; **Ola Taha**: Investigation. **Shereen Abu-Jalloud**: Investigation; **Lena Shaghlil**: Validation, Investigation; **Yousef Al-Ebini**: Writing - Reviewing and Editing.

Declaration of competing interest

The authors declare that there are no conflicts of interest.

Acknowledgments

This research was funded by the Deanship of Scientific Research at the German-Jordanian University and the Deanship of Scientific Research at Zarqa University. The graphical abstract was created with BioRender software.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpha.2023.02.012.

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