

An Efficient, Commercially Viable, and Safe Process for Preparation of Losartan Potassium, an Angiotensin II Receptor Antagonist

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ABSTRACT: An efficient, commercially viable and safe process for the preparation of losartan potassium, an antihypertensive drug substance, with an overall yield of 55.5% and ~99.9% purity (including five chemical reactions and two recrystallizations) and meeting all other regulatory requirements is described. Formation and control of all the possible impurities are also described.

INTRODUCTION

The renin–angiotensin system (RAS) is known to play an important role in cardiovascular regulation and the maintenance of blood pressure.¹ Angiotensin II is the principal active hormone of this system and acts through the stimulation of specific receptors located on various organs.^{2,3} Angiotensin II antagonists are known medicaments used in the treatment of hypertension, anxiety, glaucoma, and cardiac events. One effect of angiotensin II production is vasoconstriction, resulting in an increase in systemic blood pressure. Interruption of the RAS has been shown to be an effective means of controlling hypertension as evidenced by the success of the angiotensin-converting-enzyme (ACE) inhibitors.^{4,5} The actions of angiotensin II are mediated by angiotensin receptors AT₁ and AT₂. Most of the known actions of angiotensin II are mediated through the AT₁ receptors, for example vasoconstriction, aldosterone release, renal sodium reabsorption, and vasopressin secretion. The AT₂ receptor actions are blood pressure regulation and renal function. However, an alternative and possibly superior approach to controlling the RAS activity is the use of specific, nonpeptide antagonists of angiotensin II.^{6,7} Among cardiovascular drugs, angiotensin II receptor antagonists such as losartan potassium (**1**) are prominently used as an active ingredient in the management of hypertension. **1** plays an effective role in patients having intolerance with ACE inhibitors.

In 1990, a group of Abbott scientists initiated an angiotensin II project using the Du Pont⁸ angiotensin II antagonist as the starting point. In 1995, losartan became the first nonpeptide AT₁ receptor antagonist⁹ approved by the U.S. Food and Drug Administration for clinical use. In particular, losartan is approved for the treatment of hypertension alone or in combination with other antihypertensive agents. Losartan is administered orally as its monopotassium salt. **1** is available by prescription in tablet form as a sole active ingredient (Cozaar: Merck) and as a coactive ingredient with hydrochlorothiazide (Hyzaar: Merck).

Reports are available in the literature regarding the various routes, methodologies, and processes that have been adopted

for the preparation of losartan. These processes have restricted application in the industry because of less overall yield,^{10,11} cumbersome workup process,^{12,13} and difficult post-treatment and recovery of excessive organotin reagent.¹⁴ To minimize the cost constraints and the number of steps, we avoided use of tributyltin azide and chose to replace tributyltin azide with sodium azide and triethylamine hydrochloride salt. A recently developed process¹⁵ for **1** describes sodium azide and triethylamine hydrochloride salt for the construction of a tetrazole ring from the cyano group. However, this process is also encumbered by disadvantages such as treatment with hydrochloric acid which poses safety concerns as it generates hydrazoic acid from the unreacted sodium azide present in the reaction mixture. Hydrazoic acid is present ~3.45% w/w in organic solution.¹⁶ Hydrazoic acid is toxic and extremely explosive in organic media.¹⁷ In view of high volume requirement, huge revenues associated with this molecule, and disadvantages from the reported processes, there arises a need to develop a safe process for losartan, meeting with all regulatory aspects.

RESULTS AND DISCUSSION

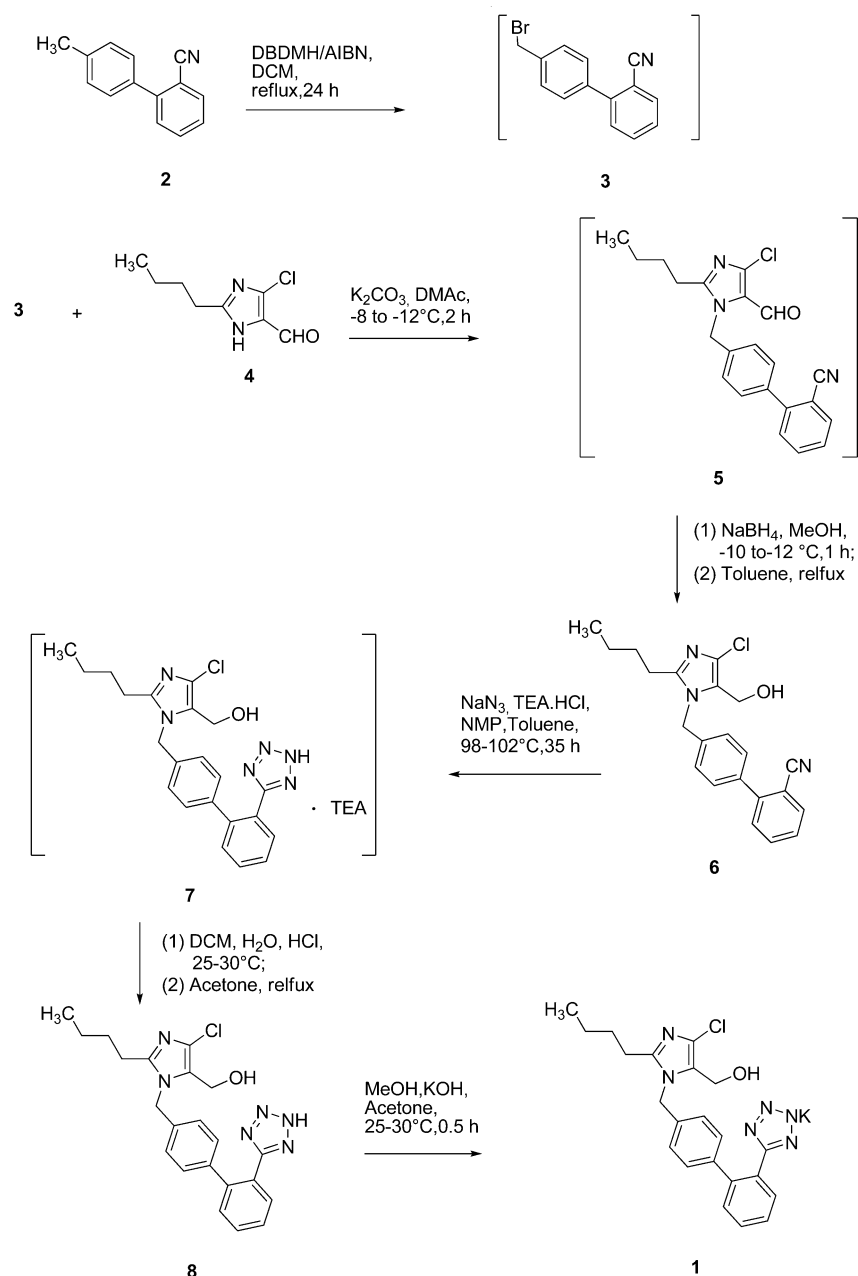
Our synthesis (Scheme 1) commenced from the commercially available *p*-tolyl benzonitrile (PTBN, **2**) and 2-*n*-butyl-4-chloro-1*H*-imidazole-5-carboxaldehyde (BCFI, **4**). Few synthetic processes for bromination of **2** with different brominating reagents are reported in the literature, such as *N*-bromosuccinamide/2,2-azobisisobutyronitrile (NBS/AIBN), NBS/benzoyl peroxide, Br₂/HOAc,¹⁸ and 1,3-dibromo-5,5-dimethylhydantoin (DBDMH)/AIBN. All NBS/AIBN and DBDMH/AIBN are commercially feasible and optimized in 79% and 80% isolated yield, after crystallization of the crude from methanol. Moreover, use of DBDMH/AIBN is cost-effective. The initial experiments carried out bromination of **2** in dichloromethane

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Scheme 1. Synthetic route for 1



in the presence of AIBN with DBDMH at reflux for 24 h. During this reaction, bromo-PTBN 3 is formed in 85%, with 8% dibromo-PTBN 9 (formed due to over bromination, Figure 1) and a remaining 7% unreacted PTBN 2. After achieving the unreacted PTBN limit, the dimethyl hydantoin was removed by

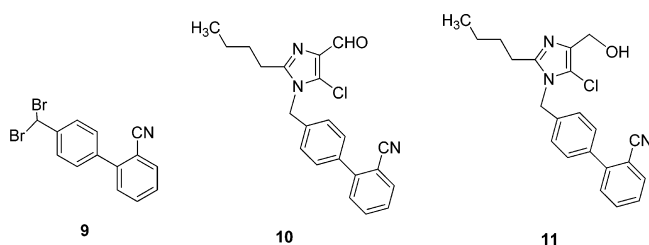


Figure 1. Structures of impurities 9, 10, and 11.

water washing, evaporated dichloromethane, and isolation of bromo-PTBN 3 from methanol to afford pure product 3 ($\geq 98.5\%$, by HPLC). The overall yield of isolated compound 3 is very low due to the solubility of the product in methanol. On the basis of experimental data, it was observed that bromo-PTBN 3 does not make any effect in the next step without isolation, and 10% yield increase realized in the isolated product. Further study regarding carry-over impact of dibromo-PTBN 9 on the product profile was conducted. During the *N*-alkylation reaction of BCFI 4 with a mixture of bromo-PTBN 3 and dibromo-PTBN 9 (30:70), it was observed that dibromo-PTBN 9 was not reacted with 4 and remained as such up to losartan cyanoalcohol 6 and was eliminated during the isolation of 6. Thereafter, to reduce the cost of the losartan, bromination was carried out in 2 volumes dichloromethane instead of 10 without significant change in the reaction rate or handling feasibilities (Table 1) and was fixed in a mole ratio of 0.54 mol

DBDMH and 5% AIBN for reaction consistency on the basis of the experimental data.

Table 1. Screening of brominating agent, AIBN, and dichloromethane

entry	brominating reagent	mol ratio	AIBN (%)	DCM (vol)	reaction time (h)	purity by HPLC (%) ^a	yield (%) ^b
1	NBS	1.10	2	10	22	84	70.5
2	NBS	0.95	3	5	22	85	71.0
3	DBDMH	1.10	2	10	22	85	71.2
4	DBDMH	0.75	3	5	24	84	71.2
5	DBDMH	0.54	5	2	24	85	71.2
6	Br ₂	1.10	2	10	18	80	68.0
7	Br ₂	0.75	3	5	20	78	67.1
8	Br ₂	0.54	5	2	20	75	65.5

^aIs it reaction conversion during monitoring. ^bIsolated yields of losartan cyanoalcohol.

Reported processes¹⁹ are available for *N*-alkylation in biphasic systems using PTC with sodium hydroxide and potassium hydroxide as bases; however, the reaction required 30 h to complete. To minimize the reaction time we evaluated the reaction in a single solvent such as dimethylacetamide, dimethylformamide, acetonitrile, or *N*-methyl-2-pyrrolidone (NMP) with potassium carbonate as base. Other than dimethylacetamide, all other solvents furnished either lower yield or lower-purity product. Experimental results are presented in Table 2. Moreover, *N*-alkylation is completed in 2 h. Hence, the

Table 2. Screening of solvents for the *N*-alkylation

entry	solvent	temperature (°C)	time (h)	purity by HPLC (%) ^a	yield (%) ^b
1	dimethylacetamide	-8 to -12	2	80	71.2
2	dimethylformamide	-5 to -10	3	65	50.9
3	acetonitrile	-5 to -10	4	62.5	45.8
4	NMP	-5 to -10	4	69	61.0

^aIt is reaction conversion during monitoring. ^bIsolated yields of losartan cyanoalcohol.

use of dimethylacetamide would be appropriate for the reaction of 3 with 4. After selecting dimethylacetamide as the solvent for *N*-alkylation, another key parameter, the potassium carbonate mole ratio, was studied. On the basis of the results, it was observed that a minimum of 0.86 mol is required for *N*-alkylation and more than 0.86 mol has no significant advantage (table 3).

After fixing the potassium carbonate mole ratio, it was also observed that the effect of temperature on *N*-alkylation resulted in formation of losartan cyanoaldehyde isomer 10 (Figure 1). During *N*-alkylation, the “N-1” atom of BCFI 4 will attack the

Table 3. Screening of K₂CO₃ mole ratio (m/r) for the *N*-alkylation

entry	K ₂ CO ₃ (m/r)	purity By HPLC (%) ^a	time (h)
1	0.52	70	4
2	0.70	72	4
3	0.86	80	2
4	1.0	80	2

^aIt is reaction conversion during monitoring.

carbonium ion of bromo-PTBN 3 to form the desired product 5. Similarly, the “N-3” atom of BCFI 4 can attack the carbonium ion of bromo-PTBN 3 to form losartan cyanoaldehyde isomer, 10. On the basis of experimental data (Table 4), it was found that the temperature of -8 to -12 °C would be the optimum condition for *N*-alkylation to control the losartan cyanoaldehyde isomer, 10.

Table 4. Experimental results for formation of 10

entry	temperature (°C)	time (h)	purity by HPLC (%) ^a	10 (%)
1	-20 to -25	4	81.5	5.0
2	-8 to -12	2	81.0	4.9
3	0-5	2	78	7.0
4	25-30	1.5	72	9.5

^aIt is *N*-alkylated product conversion during monitoring.

The inorganic salts were filtered after completion of *N*-alkylation and filtrate was used in situ for next reduction reaction. This reduction reaction was carried out using methanol and sodium borohydride. Addition of sodium borohydride is highly exothermic. This issue was overcome by introducing lot wise addition at lower temperature (-8 to -12 °C) over a period of 30-45 min by maintaining temperature. After complete reduction, excess sodium borohydride was decomposed with aqueous acetic acid. Losartan cyanoalcohol 6 is precipitated after decomposition of excess sodium borohydride by addition of water and with ≥96% purity, PTBN 2, dibromo-PTBN 9 and losartan cyanoalcohol isomer 11. All of these impurities (Figure 1) were removed from toluene by dissolving crude material at 108-110 °C followed by cooling at 23-30 °C to obtain losartan cyanoalcohol 6 pure (HPLC purity~99.8%).

Construction of the tetrazole ring was accomplished following the widely practiced protocol by mildly refluxing the mixture of losartan cyanoalcohol 6 and hydrazoic acid triethylamine complex²⁰ (generated in situ from sodium azide and triethylamine hydrochloride) in toluene and NMP. During the study, it was found that the mole ratios of triethylamine hydrochloride and sodium azide have significant impact on the reaction rate and impurity profile. The tetrazole formation reaction proceeded smoothly in a shorter period (35 h) when 2.7 mol triethylamine hydrochloride and 3.0 mol sodium azide were utilized; however, at the stoichiometric ratio where one impurity due to traces of free hydrochloric acid, losartan azide 13 (Scheme 2), is formed >1%, it proved difficult to remove. Further increasing the mole ratio beyond this limit proved futile as there was no significant reduction in the reaction time. Further decreasing the mole ratio, thus taking a longer reaction time, increased the levels of the impurities. The quantities of 2.7 mol triethylamine hydrochloride and 3.0 mol sodium azide were optimal to result in intermediate 7 with not more than 0.5% losartan azide 13 impurity during reaction monitoring.

For the completion of the reaction, more than an equivalent of an amine salt to the cyano group is required. If the produced tetrazole triethylamine salt acts as a catalyst instead of triethylamine hydrochloride, a decrease in the amount of triethylamine hydrochloride should be possible; however, amine salts only react with one equivalent of the substrate²¹ because the amine is stable as a tetrazole triethylamine complex and cannot be recycled in the system.

After reaction completion, workup was complicated because the reaction mass contained hydrazoic acid. Addition of

was stirred for 2 h at -8 to -12 °C under nitrogen; thereafter, the contents were maintained at room temperature for 2 h. The inorganic salts were filtered and washed with *N,N*-dimethylacetamide (75 L). The filtrate contains losartan cyanoaldehyde **5** (having HPLC purity $\sim 80\%$; losartan cyanoaldehyde isomer $\sim 5\%$; PTBN $\sim 7\%$; dibromo-PTBN $\sim 8\%$). The filtrate was cooled to -8 to -12 °C under nitrogen. Methanol (150 L) was added followed by slow, lotwise addition of sodium borohydride (7.5 kg, 0.198 kmol) in 30–45 min, maintaining temperature at -8 to -12 °C under nitrogen. After addition, the contents stirred at room temperature for 1 h. Aqueous acetic acid (50% w/w, 24 kg, 0.199 kmol) was added in 15–20 min to quench the excess sodium borohydride; this mixture was stirred for 1 h, water (345 L) was added, and the resultant reaction mixture was stirred for 2–3 h at 5 – 10 °C. The precipitated solid was filtered, washed with water (2×190 L), and then with toluene (2×150 L) to obtain crude losartan cyanoalcohol (**6**) (~ 300 kg). The crude **6** was dissolved in toluene (1800 L) at reflux and then cooled to room temperature. The resultant reaction mixture was stirred for 2 h, and the crystallized solid was filtered, washed with toluene (300 L), and dried under vacuum at 50 – 60 °C to furnish 210 kg (71.2%) of the title compound **6**. Purity by HPLC:²⁵ 99.8%; MR: 159 – 160 °C; IR (KBr, cm^{-1}): 3273.54, 2962.98, 2940.70, 2872.71, 2222.89, 1593.91, 1575.05, 1481.13, 1465.20, 1424.29, 1251.40, 1011.63, 999.23, 821.70, 777.44, 767.96; ¹H NMR (DMSO, 500 MHz, δ): 0.79 (t, 3H), 1.20 and 1.27 (m, 2H), 1.46 (q, 2H), 2.53 (t, 2H), 4.40 (d, 2H), 5.30 (t, 1H), 5.36 (s, 2H), 7.25 (d, 2H), 7.56 and 7.77 (m, 4H), 7.77 and 7.94 (m, 1H), 7.95 (d, 1H); ¹³C NMR and DEPT (DMSO, 500 MHz, δ): 13.54 (CH₃), 21.59 (CH₂), 25.79 (CH₂), 29.07 (CH₂), 46.43 (CH₂), 51.39 (CH₂), 110.15 (C), 118.42 (C), 125.33 (C), 125.68 (C), 126.62 (CH, CH), 128.21 (CH), 129.0 (CH, CH), 130.01 (CH), 133.47 (CH), 133.81 (CH), 136.91 (C), 137.66 (C), 143.98 (C), 147.34 (C); MS *m/z* (ESI): 380.15 [(MH)⁺].

2-*n*-Butyl-4-chloro-5-hydroxymethyl-1-[[2¹-(1*H*-tetrazol-5-yl)[1,1¹-biphenyl]-4-yl]-methyl]-1*H*-imidazole (Losartan) **8.** To a solution of losartan cyanoalcohol (**6**) (100 kg, 0.263 kmol) in a mixture of toluene (200 L) and NMP (58 kg, 0.586 kmol) at 70 – 75 °C was added sodium azide (51.4 kg, 0.790 kmol) and triethylamine hydrochloride (98.6 kg, 0.717 kmol). The resultant mixture was heated to 98 – 102 °C for 35 h and cooled to room temperature. Water (800 L) was charged, and losartan was extracted as triethylamine salt **7** with dichloromethane (1×700 L; 1×300 L). The aqueous layer containing sodium azide was safely decomposed by adding sodium nitrite (35.8 kg, 0.519 kmol) and hydrochloric acid (~ 71.6 kg, 0.685 kmol) at 4 – 10 °C in 1 h (maintaining pH at ~ 2.5), and the aqueous layer was drained. The dichloromethane layer was treated with carbon and washed with dichloromethane (100 L). Water (1200 L) was charged into the organic layer, and the pH was adjusted to 4.0 – 4.3 with a solution of hydrochloric acid (assay 35%, 21.6 kg, 0.205 kmol). The resultant reaction mixture was stirred at room temperature for 2 h and then for 2 h at 2 – 5 °C; the precipitated solid was filtered, washed with dichloromethane (2×50 L; 2 – 5 °C), and then washed with water (2×50 L; 2 – 5 °C) to obtain losartan **8**, crude (~ 220 kg). The crude was dissolved in acetone (500 L) at room temperature, then heated to reflux for 1 h, and thereafter cooled to room temperature. The resultant reaction mixture was stirred at room temperature for 2 h and then 2 h at 2 – 5 °C; the crystallized solid was filtered, washed with acetone

(100 L; 2 – 5 °C), and dried under vacuum at 50 – 60 °C to furnish 91 kg (81.7%) of the title compound **8**. Purity by HPLC:²⁵ 99.8%; MR: 184.3 – 186 °C; IR (KBr, cm^{-1}): 3374.23, 2952.47, 2926.14, 2867.82, 1973.78, 1579.25, 1468.81, 1436.75, 1411.42, 1358.06, 1322.74, 1263.54, 1230.22, 1191.20, 1087.22, 1034.89, 1008.04, 996.08, 763.45; ¹H NMR (DMSO, 500 MHz, δ): 0.80 (t, 3H), 1.21 and 1.26 (m, 2H), 1.42 and 1.48 (m, 2H), 2.45 and 2.48 (m, 2H), 4.34 (s, 2H), 5.25 (s, 2H), 7.03 and 7.10 (m, 4H), 7.52 and 7.59 (m, 2H), 7.66 and 7.69 (m, 2H); ¹³C NMR and DEPT (DMSO, 500 MHz, δ): 13.59 (CH₃), 21.60 (CH₂), 25.78 (CH₂), 28.99 (CH₂), 46.41 (CH₂), 51.34 (CH₂), 123.59 (C), 125.25 (C), 125.64 (C, C), 126.25 (CH, CH), 127.80 (CH), 129.11 (CH, CH), 130.54 (CH), 130.57 (CH), 131.00 (CH), 136.17 (C), 138.44 (C), 141.01 (C), 147.38 (C); MS *m/z* (ESI): 423.17 [(MH)⁺].

2-*n*-Butyl-4-chloro-5-hydroxymethyl-1-[[2¹-(1*H*-tetrazol-5-yl)[1,1¹-biphenyl]-4-yl]-methyl]-1*H*-imidazole, Potassium Salt (1**).** Losartan **8** (70 kg, 0.165 kmol) was dissolved in preheated methanol (834 L) at 40 – 45 °C and cooled to room temperature, treated with carbon (10%), and washed with methanol (70 L). To this filtrate was added a solution of potassium hydroxide (assay 85%, 10.58 kg, 0.161 kmol) in methanol (175 L) at room temperature; the mixture was stirred for 30 min and filtered through 0.22 μm . The methanol was evaporated completely under vacuum at 35 – 45 °C to form a residue which was stripped out with acetone (2×140 L) to remove the last traces of methanol. Acetone (210 L) was added, and this mixture was heated to 58 – 60 °C for 15–20 min. The resultant reaction mixture was stirred at room temperature for 2 h and then 2 h at 2 – 5 °C; the solid was filtered, washed with acetone (117 L; 2 – 5 °C), and dried under vacuum at 50 – 60 °C to furnish 72.8 kg (95.3%) of the title compound **1**. Purity by HPLC:²⁵ 99.9%; Potassium content: 8.47% w/w (by IC); IR (KBr, cm^{-1}): 3374.23, 2957.18, 2930.14, 2871.51, 1982.46, 1579.66, 1471.86, 1459.70, 1358.05, 1260.03, 1188.45, 1094.05, 1008.31, 996.87, 764.02; ¹H NMR (DMSO, 300 MHz, δ): 0.81 (t, 3H), 1.22 and 1.29 (m, 2H), 1.43 and 1.53 (m, 2H), 2.47 and 2.52 (m, 2H), 4.32 (d, 2H), 5.21 (s, 2H), 5.30 (t, 1H), 6.90 (d, 2H), 7.10 (d, 2H), 7.26 and 7.36 (m, 3H), 7.54 (m, 1H); ¹³C NMR and DEPT (DMSO, 300 MHz, δ): 13.7 (CH₃), 21.7 (CH₂), 25.8 (CH₂), 29.1 (CH₂), 46.5 (CH₂), 51.3 (CH₂), 125.3 (C), 125.3 (CH, CH), 125.6 (C), 126.7 (CH), 127.3 (CH), 129.4 (CH, CH), 130.1 (CH), 130.5 (CH), 132.5 (C), 134.6 (C), 139.9 (C), 141.1 (C), 147.3 (C), 160.7 (C); MS *m/z* (ESI): 423.17 [(MH)⁺], 461.1 [(MH)⁺K].

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Notes

The authors declare no competing financial interest.

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- (25) HPLC Method: Hypersil BDS C₁₈, 250 mm × 4.6 mm, 5 μm; flow: 1.5 mL/min; eluent A: Buffer, preparation: Dissolve 2.03 g of sodium dihydrogen orthophosphate dehydrate in 1000 mL of water. Adjust pH to 2.45 ± 0.05 using orthophosphoric acid. Filter through 0.45 μ; eluent B: water and acetonitrile in the ratio of 20:80 (v/v); Gradient: 0 min: 67% A, 33% B; 6 min: 67% A, 33% B; 40 min: 20% A, 80% B; 50 min: 20% A, 80% B; 55 min: 67% A, 33% B; 65 min: 67% A, 33% B. UV detection at 230 nm.