An Alternate Synthesis of Bosentan Monohydrate, an Endothelin Receptor Antagonist[1]

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Received: 16.08.2013; Accepted after revision: 14.10.2013

Abstract: An alternate synthesis of an endothelin receptor antagonist bosentan monohydrate is reported. This new synthetic route involves the coupling of *p-tert*-butyl-*N*-[6-chloro-5-(2-methoxyphenoxy)(2,2′-bipyrimidin)-4-yl]benzene sulfonamide with commercially available raw material (2,2-dimethyl-1,3-dioxolan-4-yl)methanol as the key step. Attractive features of this approach are its versatileness, commercial availability of raw materials, usage of eco-friendly reagents, and it efficiently provides the desired bosentan monohydrate free from reported impurities such as dimer, N-alkylated, and pyrimidinone impurities.

Key words: alternate synthesis, bosentan monohydrate, eco-friendly reagents, dimer impurity, N-alkylated, pyrimidinone

Pulmonary hypertension is an increase in blood pressure in the pulmonary artery, pulmonary vein, or pulmonary capillaries. There are many pathways to control the pulmonary hypertension, of which three are important because they have been targeted with drugs like endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, and prostacyclin derivatives. Bosentan monohydrate (**1**, Figure 1) is the first approved endothelin receptor antagonist for endothelin receptor type A and type B in 2001 and marketed as Tracleer.

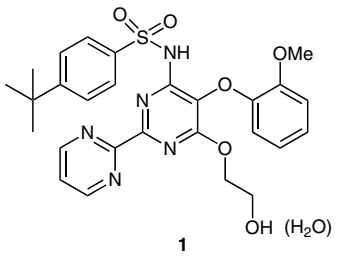

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Figure 1 Structure of bosentan monohydrate (**1**)

The preparation of bosentan monohydrate (**1**) has been reported by many authors using different methodologies. The first-generation process reported by K. Burri et al.[2] using genotoxic ethylene glycol and the highly pyrophoric base sodium metal which are not very conducive for a large-scale commercial synthesis of bosentan monohydrate. By use of excess ethylene glycol a huge amount of toxic aqueous ethylene glycol effluent is generated and also predominant dimer impurity is formed. The crude bosentan formed requires more than three purifications to wash out dimer **2** and pyrimidinone **3** impurities (which are formed during the synthesis) and to provide International Conference on Harmonization (ICH) grade quality of bosentan. Finally, the process provides bosentan monohydrate (**1**) in very poor yields.

P. J. Harrington et al.[3] developed a new (second-generation) process for the synthesis of bosentan monohydrate (**1**). In this process ethylene glycol was replaced with mono-*tert*-butyl-protected ethylene glycol to eliminate dimer impurity **2** (Figure 2). During the deprotection of bosentan *tert*-butyl ether using formic acid gave bosentan formate, which on hydrolysis with sodium hydroxide provides bosentan along with thermally degraded N-alkylated impurity **4** and pyrimidinone impurity **3**, which are difficult to wash out during a single purification step. To get high-purity bosentan a greater number of recrystallizations is required, which decreases the yield of bosentan monohydrate (**1**).

In all the above previously reported commercial processes for the preparation of bosentan monohydrate (**1**), formation of impurities like dimer **2**, pyrimidinone **3**, and N-alkylated impurity **4** are playing a crucial role on quality and yield of the bosentan. Several other methods[4–9] have been reported, which have their own disadvantages like formation of prior reported impurities and provides bosentan in less yields. To overcome these disadvantages we recently reported two new approaches for the preparation of bosentan.[10] The process involved the conversion of chloro compound **5** into the corresponding hydroxy compound and condensing it with either chloro acetonitrile or α-halo esters, converting the intermediates formed into bosentan monohydrate (**1**) with an overall yield of 62–65%.

As a part of our ongoing studies on the development of new and efficient syntheses of active pharmaceutical ingredients, we have explored an alternate synthesis of bosentan monohydrate (**1**) as shown in Scheme 1. The key features of this approach include the use of (2,2-dimethyl-1,3-dioxolan-4-yl)methanol[11] (**6**) in place of ethylene glycol; on coupling with chloro compound **5**, **6** provides pro-

SYNLETT 2014, 25, 0265–0269
Advanced online publication: 02.12.2013
DOI: 10.1055/s-0033-1340281; Art ID: ST-2013-B0747-L

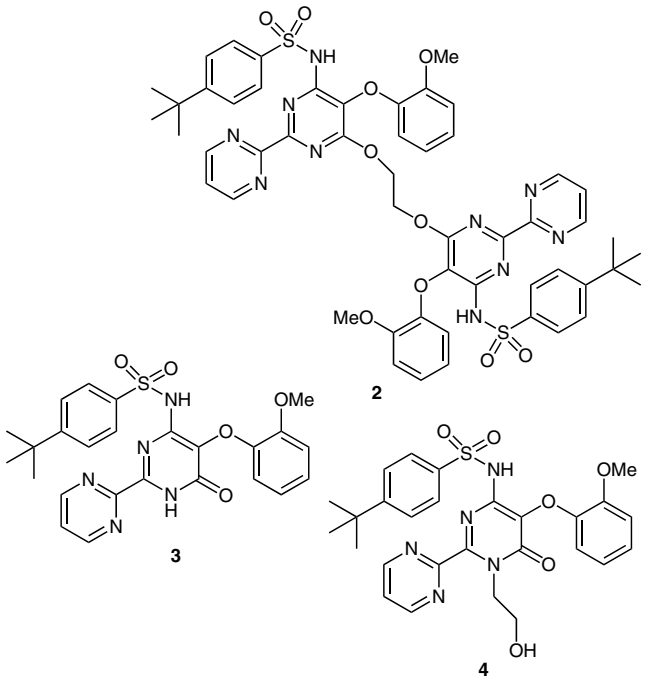


Figure 2 Structures of dimer impurity **2**, pyrimidinone impurity **3**, and N-alkylated impurity **4**

tected diol compound **7**, which on deprotection followed by oxidation gives aldehyde compound **9**. The subsequent reduction of the aldehyde compound and purification of crude bosentan provides high pure bosentan monohydrate (**1**) with an average step yield of 87% and free of impurities such as dimer impurity **2**, pyrimidinone impurity **3**, and N-alkylated impurity **4**.

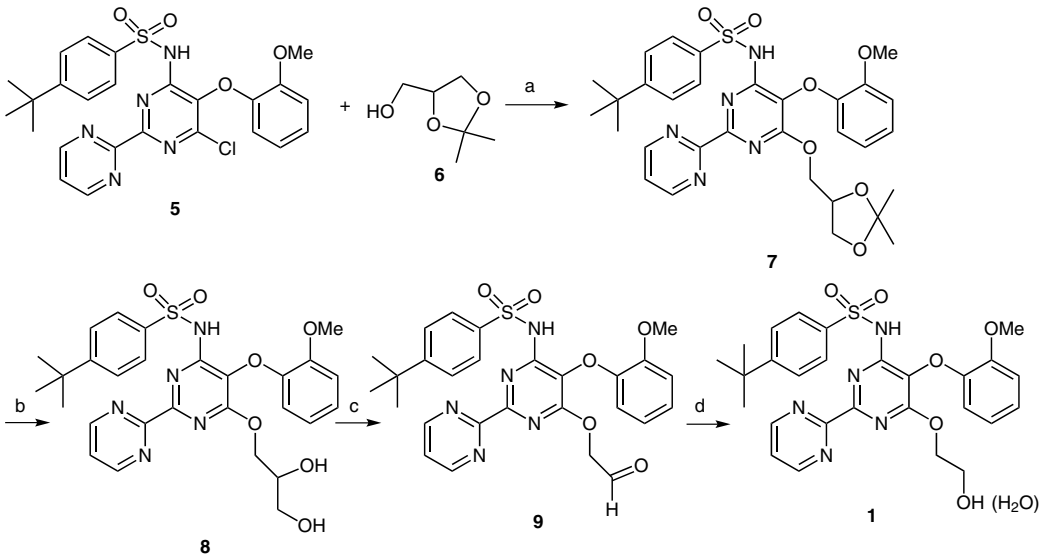
The key step in this approach is the coupling of chloro compound **5** with (2,2-dimethyl-1,3-dioxolan-4-yl)methanol (**6**) in the presence of a base. In the initial phase of this study we investigated this condensation step using sodium hydroxide in toluene under heating for ten hours which yielded the required compound **7** in 65% yield (Table 1, entry 1). Further optimization results are presented in Table 1.

Table 1 Effect of Reaction Conditions on the Coupling of **5** with (2,2-Dimethyl-1,3-dioxolan-4-yl)methanol (**6**)

Entry	Base	Solvent	Temp (°C)[a]	Time (h)	Yield (%)[b]
1	NaOH	toluene	110	10	65
2	NaOH	THF	65	10	75
3	NaOH	MeCN	80	10	90
4	Na_2CO_3	MeCN	80	10	45
5	K_2CO_3	MeCN	80	10	55
6	NaOMe	MeCN	80	10	58
7	NaOH	MeCN	80	9	88
8	NaOH	MeCN	80	8	90

[a] Reaction temperature.
[b] Isolated yield of **7**.

Replacement of toluene with acetonitrile caused a sharp increase in the yield (to 90%) of this reaction (Table 1, entry 3). On the other hand, replacement of sodium hydroxide with other bases such as sodium carbonate (Table 1, entry 4), potassium carbonate (Table 1, entry 5), and sodium methoxide (Table 1, entry 6) substantially reduced the yield of the reaction. The solvent and base used were found to have a dramatic impact on the efficiency of this reaction. Thus among the combination of solvents and bases screened, only the sodium hydroxide in acetonitrile provided the required product **7** in high yield within a short reaction time (Table 1, entry 8).



Scheme 1 Alternate synthesis of bosentan monohydrate (**1**). *Reagents and conditions*: (a) NaOH, MeCN, 80–85 °C, 12 h; (b) 2 M HCl, MeCN, r.t., 5 h; (c) $NaIO_4$, acetone, H_2O, 0 °C to r.t., 3 h; (d) $NaBH_4$, MeOH, 0 °C to r.t., 4 h.

The condensed product **7** on deprotection using 2 M HCl in acetonitrile afforded the desired diol intermediate **8** in almost quantitative yield (92%). The diol intermediate **8** was converted into the corresponding aldehyde **9** by oxidizing with sodium periodate. The effect of temperature and nature of solvent on the yields of the reaction were investigated, and the results are tabulated in Table 2. The preliminary study was conducted using toluene (Table 2, entry 1) as a solvent at 0–5 °C for nine hours, but the yield of the desired product **9** was only 45%. Replacement of toluene with acetone at 0–5 °C (Table 2, entry 3) provided the required aldehyde **9** in 75% yields.

Table 2 Effect of Solvent and Reaction Conditions on the Cleavage of Diol Intermediate **8** Using Sodium Periodate

Entry	Solvent	Temp (°C)[a]	Time (h)	Yield (%)[b]
1	toluene	0–5	13	45
2	toluene	30	9	50
3	acetone	0–5	8	75
4	acetone	30	2.5	89
5	CH_2Cl_2	30	8	45
6	MeCN	30	8	58
7	THF	30	8	65

[a] Reaction temperature.
[b] Isolated yield of **9**.

Increasing the reaction temperature to room temperature resulted in the highest yield (89%) within a short time (Table 2, entry 4). Next the reaction was carried out using various solvents, and the results are shown in Table 2 (entries 5–7). Finally, we have concluded that using acetone at room temperature was the most suitable method for the conversion of diol intermediate **8** into aldehyde intermediate **9**.

The aldehyde compound **9**,[12] on reduction using sodium borohydride, provided the crude bosentan monohydrate (**1**) using methanol as solvent. This conversion does not give any scope for the formation of prior known impurities. There is only a scope for the formation of acid impurity **10** (Figure 3), which may be due to overoxidation of compound **9**. This impurity was completely washed out (<0.15% impurity in the final product) during the isolation process of bosentan monohydrate. For commercial synthesis the isolation of pure bosentan from crude bosentan at low production cost by minimizing the yield loss during the purification is a very challenging task.

So we have attempted several purifications using different solvents such as methanol, isopropyl alcohol, ethanol, ethyl acetate, isopropyl acetate, *tert*-butyl acetate, and combinations of these solvents. Optimization results are presented in Table 3. Initially, the purification was attempted using a single solvent (Table 3, entries 1–5), but the purity of compound **1** is less. So we turned to attempt

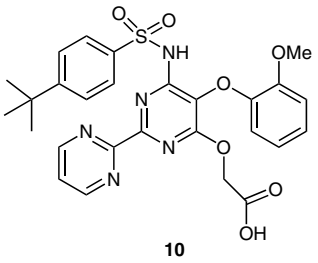


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Figure 3 Structure of acid impurity

this purification using a mixture of solvents. When we used a mixture of methanol and ethyl acetate (Table 3, entry 6), the purity of compound **1** increased gradually to 99.82%, but the obtained yield decreased. On the other hand, replacement of ethyl acetate with cyclohexane (Table 3, entry 7) increases the yield, but the quality of the product decreased. Finally, we concluded that the high-purity bosentan could be obtained using the combination of methanol and ethyl acetate as solvent. Surprisingly, a mixture of methanol and ethyl acetate (1:1) in combination with 1% water (Table 3, entry 9) provided pure bosentan monohydrate (**1**) having HPLC[13] purity of 99.8% in 85% yield. The results of the optimization studies are tabulated in Table 3.

Table 3 Effect of Solvent on the Quality and Yield of Bosentan Monohydrate (**1**)

Entry	Solvent	Solvent volume[a]	Yield (%)[b]	Purity by HPLC (%)[c]
1	EtOAc	4×	71	97.5
2	MeOH	3×	69	98.25
3	*t*-BuOAc	3×	74	98.1
4	2-PrOH	3×	72	96.7
5	EtOH	3×	70	98.3
6	MeOH–EtOAc	4:4	68	99.82
7	MeOH–cyclohexane	3:3	74	97.3
8	MeOH–EtOAc	2:2	76	99.65
9	MeOH–EtOAc (1% H_2O)	1:1	85	99.8

[a] Solvent volume is with respect to input quantity.
[b] Isolated yield of **1** from crude bosentan.
[c] Purity of bosentan monohydrate.

The residual solvents present in the final purified bosentan monohydrate (**1**) were analyzed using the described GC method,[14] and it was found that all the solvents were well within the specified ICH limits as shown in Table 4.

In conclusion, an alternate, improved, efficient, and industrially scalable synthetic route was developed for the endothelin receptor antagonist bosentan monohydrate (**1**). A further feature of this sequence was involving of novel intermediates **7** and **8** and finally provided bosentan

Table 4 Trend Data for Residual Solvents Present in the Bosentan Monohydrate (**1**)

Entry	Solvent	ICH limit (ppm)	Residual solvents trend data for batch 1	Residual solvents trend data for batch 2
1	MeCN	410	n.d.[a]	n.d.
2	CH_2Cl_2	600	n.d.	n.d.
3	MeOH	3000	174	260
4	acetone	5000	n.d.	n.d.
5	cyclohexane	3880	n.d.	n.d.
6	EtOAc	5000	566	510
7	toluene	890	n.d.	n.d.

[a] n.d. = not detected.

monohydrate (**1**) free of dimer **2**, pyrimidinone **3**, and N-alkylated **4** impurities. The new process reduces the number of hazardous reagents and the amount of hazardous waste generated, which was making the process more environmentally friendly. The quality of the final active pharmaceutical ingredient (API) easily meets the specifications approved by ICH guidelines.

4-*tert*-Butyl-*N*-{6-[(2,2-dimethyl-1,3-dioxolan-4-yl)methoxy]-5-(2-methoxyphenoxy)-2,2′-bipyrimidin-4-yl}benzenesulfonamide (7)

To a solution of (2,2-dimethyl-1,3-dioxolan-4-yl)methanol (**6**, 62.7 g, 0.47 mol) in MeCN (1000 mL), NaOH (20.9 g, 0.52 mol) was added and heated to 80–85 °C for 4 h. To this *p-tert*-butyl-*N*-{6-chloro-5-(2-methoxyphenoxy)[2,2′-bipyrimidin]-4-yl}benzene sulfonamide (**5**, 50 g, 0.1 mol) was added, and the mixture was agitated for 8 h. MeCN was distilled off from the reaction mixture, and MeOH (100 mL) was added to it. To this clear solution H_2O (1000 mL) was slowly added and stirring continued for 1 h. The resulting precipitate was filtered, washed with H_2O (50 mL) and dried in oven at 65 °C to afford **7** (53.5 g, 90%); mp 185–188 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.20 (s, 9 H), 1.27 (s, 6 H), 3.53–3.82 (m, 2 H), 3.85 (s, 3 H), 4.52–4.57 (m, 1 H), 6.68–6.98 (m, 4 H), 7.10–7.25 (m, 5 H), 8.81 (s, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.05, 30.41, 34.27, 55.52, 62.98, 73.65, 77.16, 111.82, 118.23, 120.19, 122.39, 123.87, 125.66, 125.85, 127.69, 128.19, 135.71, 144.56, 149.18, 152.79, 155.11, 156.1, 156.91, 160.86, 162.36. MS: *m/z* = 622.3 [M + H]. IR (KBr): ν_{max} = 3467.57 (NH), 1368.4 (SO_2) cm^{-1}. Anal. Calcd (%) for $C_{31}H_{35}N_5O_7S$: C, 59.89; H, 5.67; N, 11.26. Found: C, 59.77; H, 5.71; N, 11.16.

4-*tert*-Butyl-*N*-[6-(2,3-dihydroxypropoxy)-5-(2-methoxyphenoxy)-2,2′-bipyrimidin-4-yl]benzenesulfonamide (8)

The solution of 4-*tert*-butyl-*N*-{6-[(2,2-dimethyl-1,3-dioxolan-4-yl)methoxy]-5-(2-methoxy phenoxy)-2,2′-bipyrimidin-4-yl}benzenesulfonamide (**7**, 50 g, 0.08 mol) in MeCN (250 mL), 2 M HCl (250 mL) was added slowly for 20–30 min and stirring continued for 5 h at ambient conditions. Then reaction mass was extracted twice with CH_2Cl_2 (2 × 250 mL). The organic solvent was evaporated, and the residue was dissolved in MeOH (50 mL). The MeOH solution was added slowly to H_2O (250 mL) for 45 min. The resulting precipitate was filtered, washed with H_2O (50 mL) and dried in oven at 60 °C for 6 h to provide **8** (43 g, 92%) as a yellow color solid; mp 100–103 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.29 (s, 9 H), 3.51–3.53 (d, *J* = 1.4 Hz, 2 H), 3.81–3.88 (m, 1 H), 3.92 (s, 3 H), 4.60–4.71 (m, 2 H), 6.88–6.90 (d, *J* = 2.7 Hz, 1 H), 6.97–7.06 (m, 2 H), 7.10–7.15 (t, 1 H), 7.44–7.54 (m, 3 H), 8.40–8.43 (d, *J* = 2.2 Hz, 2 H), 9.08–9.10 (d, *J* = 1.5 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.14, 34.31, 55.73, 62.37, 69.63, 71.93, 113.9, 117.92, 120.92, 123.52, 123.59, 124.89, 128.11, 129.15, 135.84, 144.29, 149.04, 152.06, 153.62, 156.55, 156.93, 160.96, 162.35. MS: *m/z* = 582.3 [M + H]. IR (KBr): ν_{max} = 3364.54 (NH), 3184.34 (OH), 1384.67 (SO_2) cm^{-1}. Anal. Calcd (%) for $C_{28}H_{31}N_5O_7S$: C, 57.82; H, 5.37; N, 12.04. Found: C, 57.75; H, 5.25; N, 12.17.

4-*tert*-Butyl-*N*-[5-(2-methoxyphenoxy)-6-(2-oxoethoxy)-2,2′-bipyrimidin-4-yl]benzenesulfonamide (9)

To a solution of 4-*tert*-butyl-*N*-{6-[(2,2-dimethyl-1,3-dioxolan-4-yl)methoxy]-5-(2-methoxy phenoxy)-2,2′-bipyrimidin-4-yl}benzenesulfonamide (**8**, 40 g, 0.07 mol) in acetone (200 mL), $NaIO_4$ (36.8 g, 0.17 mol) in H_2O (200 mL) was added slowly for 30 min at 0–5 °C. The reaction mixture was further stirred for 2–3 h at ambient conditions. The reaction mixture was extracted twice with CH_2Cl_2 (2 × 200 mL), and washed with H_2O (160 mL). The organic solvent was evaporated under reduced pressure. Cyclohexane (200 mL) was added to the obtained residue and stirred for 30–45 min. The precipitated solid was filtered and washed with cyclohexane (40 mL) and dried in oven at 60 °C to afford **9** (33.5 g, 89%); mp 208–210 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (s, 9 H), 3.98 (s, 3 H), 5.15 (s, 2 H), 6.85–7.6 (m, 7 H), 8.42–8.45 (s, 2 H), 9.0 (d, 2 H), 9.72 (s, 1 H). MS: *m/z* = 550.5 [M + H]. IR (KBr): ν_{max} = 1720 (C=O stretching) cm^{-1}.

4-*tert*-butyl-*N*-[6-(2-hydroxyethoxy)-5-(2-methoxy phenoxy)-2,2′-bipyrimidin-4-yl]benzenesulfonamide, Bosentan Monohydrate (1)

A solution of **9** (100 g, 0.18 mol) in MeOH (500 mL) was cooled to 0–5 °C and $NaBH_4$ (6.91 g, 0.18 mol) was slowly added in portions. The reaction mixture was stirred for 2–3 h, and MeOH was distilled off. Then the mixture was quenched with ice-cold H_2O, and the pH value was adjusted to 2–3 using 6 M HCl. Afterwards the reaction mixture was extracted with EtOAc. The EtOAc layer was washed with 5% brine solution (2 × 500 mL) and concentrated under reduced pressure to obtain the residue. The obtained residue was dissolved in MeOH (120 mL) and reprecipitated with H_2O (240 mL). The precipitated solid was filtered, washed with H_2O (100 mL). The resultant solid dissolved in EtOAc (100 mL), MeOH (100 mL), and H_2O (1 mL), heated to 65–70 °C for 1 h, cooled to 30 °C, and maintain for 4–5 h. The solid was filtered and washed with cyclohexane (25 mL), dried under vacuum at 30–35 °C for 3–4 h to get high-purity bosentan monohydrate (**1**, 79.6 g, 80%) as a white to pale yellow solid; mp 138–140 °C. ^{1}H NMR (300 MHz, $CHCl_3$): δ = 1.29 (s, 9 H), 3.86 (s, 2 H), 4.0 (s, 3 H), 4.57–4.60 (m, 2 H), 4.88 (s, 1 H), 6.85–7.15 (m, 4 H), 7.41–7.45 (m, 3 H), 8.42–8.45 (d, *J* = 8.5 Hz, 2 H), 8.8 (br s, 1 H), 9.00–9.10 (d, *J* = 4.9 Hz, 2 H). MS: *m/z* = 552 [M + H]. IR (KBr): ν_{max} = 3437.4 (NH), 1342 (SO2) cm^{-1}. HPLC purity: 99.8%; water content: 3.2% (w/w).

Acknowledgement

One of the author (Pradeep Rebelli) thanks to the HOD's Osmania university and JNTU Hyderabad for giving opportunity to pursue PhD studies. Our sincere thanks to Dr. M. S. N. Reddy and Dr. Ch. Nagaraju for providing infrastructural facilities to carry out the research work and also be indebted to S. Eswaraiah, S. T. Rajan, and Dr. M. Srinivas for their continuous guidance and support.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(12) Aldehyde intermediate **9** was found to be stable at r.t. in airtight polythene bags. Hence special storage and packing conditions are not required.
(13) **HPLC Method**
Column: BDS Hypersil C_{18}, 250 × 4.6 mm, 5 μm; UV, λ = 220 nm; temp: 30 °C; load: 20 μL; elution: gradient; buffer: dipotassium hydrogen orthophosphate; diluent: mobile phase A + mobile phase-B; mobile phase A: 95% buffer + 5% MeOH; mobile phase B: 95% MeOH + 5% H_2O.
(14) **GC Method for Residual Solvents**
Column: DB-624; length: 30 m; film thickness: 30 μm; injector temp: 140 °C; split: 1:5; detector temp: 260 °C (FID); carrier gas: helium; load: 1.0 μL; diluent: DMSO; oven temp: 40 °C; program to 130 °C at 6 °C per min; hold for 5 min; then again raised to 240 °C at 35 °C per min.