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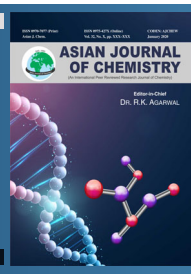

Synthesis and Characterization of Novel Analogues of Cefpodoxime Proxetil

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The present work describes the origin, identification, synthesis, characterization and control of four novel analogues of cefpodoxime proxetil, which are ethyl, methyl, propyl and *N*-propyl analogues of cefpodoxime proxetil.

Keywords: Cefpodoxime proxetil, Cephlosporin, Novel analogues.

INTRODUCTION

Cefpodoxime proxetil is a potent antibiotic and is of great therapeutic interest in the treatment of acute bronchitis, exacerbations, pneumonia, sinusitis, recurrence of chronic tonisillitis, pharyngitis and acute otitis media. Cefpodoxime proxetil (**1**) is chemically known as 1-(isopropoxycarbonyl-oxy)ethyl (*6R,7R*)-7-[(*Z*)-2-(2-amino-4-thiazolyl)-2-(methoxy-imino)acetamido]-3-methoxymethyl-3-cephem-4-carboxylate.

The presence of impurities in an Active Pharmaceutical Ingredient (API) drug substance will influence the quality and safety of the drug product. As per the regulatory guidelines of the International Conference on Harmonization (ICH), it is recommended that impurities more than 0.1% [1] should be identified and characterized. Impurities are required to check the analytical performance characteristics such as specificity, linearity, range, accuracy, precision, limit of detection (LOD), limit of quantification (LOQ), robustness, system suitability testing and relative retention factor [2].

In view of regulatory importance of the related substances in the API, a detailed study on all possible analogues in cefpodoxime proxetil was conducted. During the process development of cefpodoxime proxetil in the laboratory, we prepared possible, novel analogues of cefpodoxime proxetil. In the present work, the novel analogues of cefpodoxime proxetil were synthesized and characterized by spectroscopic techniques. The structures of four novel analogues of cefpodoxime proxetil *viz*. 1-(ethoxycarbonyloxy)ethyl-(*6R,7R*)-7-[(*Z*)-2-(2-amino-4-thiazolyl)-2-(methoxyimino)acetamido]-3-methoxymethyl-3-cephem-4-carboxylate (ethyl analogue of cefpodoxime proxetil), 1-(methoxycarbonyloxy)ethyl (*6R,7R*)- 7-[(*Z*)-2-(2-amino-4-thiazolyl)-2-(methoxyimino)aceta-mido]-3-methoxymethyl-3-cephem-4-carboxylate (methyl analogue of cefpodoxime proxetil, 1-(isopropooxycarbonyloxy)-ethyl-(*6R, 7R*)-7-[(*Z*)-2-(2-amino-4-thiazolyl)-2-(methoxyimino)-acetamido]-3-methoxymethyl-3-cephem-4-carboxylate (propyl analogue of cefpodoxime proxetil) and 1-(propoxy-carbonyloxy)ethyl (*6R,7R*)-7-[(*Z*)-2-(2-amino-4-thiazolyl)-2-(methoxyimino)acetamido]-3-methoxymethyl-3-cephem-4-carboxylate (*N*-propyl analogue of cefpodoxime proxetil).

A number of impurities and analogues of cefpodoxime proxetil were also reported in literature [3-9]. To the best of our knowledge identification, synthesis and characterization of these four novel analogues are not reported in the literature.

EXPERIMENTAL

Solvents and reagents were obtained from commercial sources and used without purification. ^{1}H and ^{13}C NMR spectral data were performed on Bruker-Avance 300-MHz, 500 MHz spectrometer in DMSO-d_6 & $CDCl_3$. The chemical shift values reported on the δ scale in parts per million (ppm), downfield from tetramethylsilane (TMS) as an internal standard. IR spectra

were recorded in the solid state as KBr pellet using a Perkin-Elmer FT-IR spectrophotometer. Mass spectrum was recorded by using a Perkin-Elmer PE SCIEX-API 2000, equipped with ESI source used online with a HPLC system after the ultraviolet (UV) detector.

Synthesis of 1-(ethoxycarbonyloxy)ethyl (*6R*,*7R*)-7-[(*Z*)-2-(2-amino-4-thiazolyl)-2-(methoxyimino)acetamido]-3-methoxymethyl-3-cephem-4-carboxylate (ethyl analogue of cefpodoxime proxetil) (10): To a suspension of sodium iodide (10.26 g, 68.4 mmol) in toluene (50 mL), added 18-crown-6 (0.2 g, 2% w/w) followed by 1-chloroethyl ethyl carbonate (10 g. 65.14 mmol) at room temperature. The suspension was heated to 105-110 ºC and stirred for 2h to complete the reaction. Cooled the reaction mass to 0-5 ºC and filtered the unreacted sodium iodide and sodium chloride byproducts. Toluene filtrate containing 1-iodoethyl ethyl carbonate is washed with 1% aqueous sodium thiosulfate and used as such in the further process.

To a solution of cefpodoxime acid (20 g, 46.83 mmol) in *N*,*N*-dimethylacetamide (100 mL), added 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU,6.90 g, 45.39 mmol) at room temperature and stirred the reaction mass for about 30 min. This solution is cooled to -20 ºC and added above prepared toluene solution of 1-iodoethyl ethyl carbonate in 30 min at -20 to -15 ºC. Further, stirred the reaction mass for 2 h at -20 to -15 ºC to complete the esterification reaction. After completion of reaction by HPLC, poured the reaction mass into mixture of water (800 mL) and cyclohexane (400 mL) at 20-25 ºC to precipitate the product. Adjusted pH of the slurry mass to 6.0 with aqueous Na_2CO_3 solution and isolated the product by filtration. Wet material after washing with water dried at 45-50 ºC to obtain 20 g (79%) of white colored ethyl analogue of cefpodoxime proxetil. HPLC purity: 99.15%; IR (KBr pellet, cm^{-1}): 3436, 3332, 3211, 2987, 2939, 2823, 1778, 1769, 1681, 1620, 1537, 1447, 1374, 1349, 1301, 1270, 1219, 1181, 1149, 1130, 1076, 1055, 786, 740, 691; ^{1}H NMR (DMSO-d_6, 500 MHz): 1.246-1.205 (t, *J* = 7.0, 6.5 Hz, 3H), 1.504-1.488 (d, *J* = 3.0 Hz, 3H), 3.207 (s, 3H) , 3.645-3.550 (m, 2H), 3.833 (s, 3H), 4.195-4.144 (m, 4H), 5.198-5.171 (m, 1H), 5.847-5.793 (m,1H), 6.870-6.725 (m, 2H), 7.206 (brs, 2H), 9.620-9.593 (m, 1H). MS *m/z*: 544.1 [(M+H)$^+$].

Synthesis of 1-(methoxycarbonyloxy)ethyl (*6R*,*7R*)-7-[(*Z*)-2-(2-amino-4-thiazolyl)-2-(methoxyimino)acetamido]-3-methoxymethyl-3-cephem-4-carboxylate (methyl analogue of cefpodoxime proxetil) (13): To a suspension of sodium iodide (11.29 g, 75.26 mmol) in toluene (50 mL), added 18-crown-6 (0.2 g, 2% w/w) followed by 1-chloroethyl methyl carbonate (10 g. 71.68 mmol) at room temperature. The suspension was heated to 105-110 ºC and stirred for 2 h to complete the reaction. Cooled the reaction mass to 0-5 ºC and filtered the unreacted sodium iodide and sodium chloride byproducts. Toluene filtrate containing 1-iodoethyl methyl carbonate is washed with 1% aqueous sodium thiosulfate and used as such in the further process.

To a solution of cefpodoxime acid (20 g, 46.83 mmol) in *N*,*N*-dimethylacetamide (100 mL), added 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU, 6.90 g, 45.39 mmol) at room temperature and stirred the reaction mass for about 30 min. This solution is cooled to -20 ºC and added above prepared toluene solution of 1-iodoethyl methyl carbonate in 30 min at -20 to -15 ºC. Further, stirred the reaction mass for 2h at -20 to -15 ºC to complete the esterification reaction. After completion of reaction by HPLC, poured the reaction mass into mixture of water (800 mL) and cyclohexane (400 mL) at 20-25 ºC to precipitate the product. Adjusted pH of the slurry mass to 6.0 with aqueous sodium bicarbonate solution and isolated the product by filtration. Wet material after washing with water dried at 45-50 ºC to obtain 20.5 g (82%) of white coloured methyl analogue of cefpodoxime proxetil. HPLC purity : 96.72%; IR (KBr, ν_{max}, cm^{-1}): 3438, 3340, 2940, 2824, 1769, 1677, 1619, 1535, 1445, 1379, 1280, 1220, 1181, 1077, 1055, 787, 742, 691; ^{1}H NMR (DMSO-d_6, 500 MHz): 1.491-1.502 (d, *J* = 5.5 Hz, 3H), 3.212 (s, 3H), 3.645-3.552 (m, 2H), 3.746 (s, 3H), 3.833 (s, 3H), 4.178-4.122 (m, 2H), 5.197-5.170 (m, 1H), 5.837-5.790 (m, 1H), 6.893-6.739 (m, 1H), 7.204 (brs, 2H), 9.619-9.593 (m, 1H). MS *m/z*: 530.1 [(M+H)$^+$].

Synthesis of 1-(isopropoxycarbonyloxy)ethyl (6*R*,7*R*)-7-[(*Z*)-2-(2-amino-4-thiazolyl)-2-(methoxyimino)acetamido]-3-methoxymethyl-3-cephem-4-carboxylate (propyl analogue of cefpodoxime proxetil) (18): To a suspension of sodium iodide (21.7 g, 144.6 mmol) in toluene (250 mL), added 18-crown-6 (0.5 g, 2% w/w) followed by 1-chloropropyl isopropyl carbonate (25 g, 137.7 mmol) at room temperature. The suspension was heated to 105-110 ºC and stirred for 2 h to complete the reaction. Cooled the reaction mass to 0-5 ºC and filtered the unreacted sodium iodide and sodium chloride byproducts. Toluene filtrate containing 1-iodoethyl ethyl carbonate is washed with 1% aqueous sodium thiosulfate and used as such in the further process.

To a solution of cefpodoxime acid (50 g, 117 mmol) in *N*,*N*-dimethylacetamide (250 mL), added 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU, 17.26 g, 113.5 mmol) at room temperature and stirred the reaction mass for about 30 min. This solution is cooled to -20 ºC and added above prepared toluene solution of 1-iodopropyl isopropyl carbonate in 30 min at -20 to -15 ºC. Further, stirred the reaction mass for 2h at -20 to -15 ºC to complete the esterification reaction. After completion of reaction by HPLC, poured the reaction mass into mixture of water (2000 mL) and cyclohexane (1000 mL) at 20-25 ºC to precipitate the product. Adjusted pH of the slurry mass to 6.0 with aqueous sodium bicarbonate solution and isolated the product by filtration. Wet material after washing with water dried at 45-50 ºC to obtain 52 g (78%) of white colored propyl analogue of cefpodoxime proxetil. HPLC purity: 96.27%; IR (KBr, ν_{max}, cm^{-1}): 3742, 3110, 2984, 2939, 2823, 1760, 1680, 1617, 1535, 1465, 1453, 1376, 1350, 1275, 1219, 1182, 1147, 1099, 1076, 788, 741, 692; ^{1}H NMR (DMSO-d_6, 500 MHz): 0.913-0.873 (t, *J* = 7.5, 12.5 Hz, 3H), 1.234-1.206 (d, *J* = 3.0 Hz, 3H), 1.776-1.761 (m, 2H), 3.128 (s, 3H) , 3.323 (m, 2H), 3.587 (s, 3H), 4.104 (s, 2H), 4.752 (s, 2H), 5.170-5.142 (m, 1H), 5.782 (m, 1H), 6.749 (m, 2H), 7.178 (brs, 2H), 9.569-9.553 (d, *J* = 8.0 Hz, 1H). MS *m/z*: 558.1 [(M+H)$^+$].

Synthesis of 1-(Propoxycarbonyloxy)ethyl (*6R*,*7R*)-7-[(*Z*)-2-(2-amino-4-thiazolyl)-2-(methoxyimino)acetamido]-3-

methoxymethyl-3-cephem-4-carboxylate (*N*-propyl analogue of cefpodoxime proxetil) (21): To a suspension of sodium iodide (9.45 g, 63 mmol) in toluene (50 mL), added 18-crown-6 (0.2 g, 2% w/w) followed by 1-chloroethyl propyl carbonate (10 g, 60 mmol) at room temperature. The suspension was heated to 105-110 ºC and stirred for 2 h to complete the reaction. Cooled the reaction mass to 0-5 ºC and filtered the unreacted sodium iodide and sodium chloride byproducts. Toluene filtrate containing 1-iodoethyl propyl carbonate is washed with 1% aqueous sodium thiosulfate and used as such in the further process.

To a solution of cefpodoxime acid (20 g, 46.83 mmol) in *N*,*N*-dimethylacetamide (100 mL), added 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU, 6.90 g, 45.39 mmol) at room temperature and stirred the reaction mass for about 30 min. This solution is cooled to -20 ºC and added above prepared toluene solution of 1-iodoethyl propyl carbonate in 30 min at -20 to -15 ºC. Further, stirred the reaction mass for 2 h at -20 to -15 ºC to complete the esterification reaction. After completion of reaction by HPLC, poured the reaction mass into mixture of water (800 mL) and cyclohexane (400 mL) at 20-25 ºC to precipitate the product. Adjusted pH of the slurry mass to 6.0 with aqueous sodium bicarbonate solution and isolated the product by filtration. Wet material after washing with water dried at 45-50 ºC to obtain 20.5 g (82%) of white coloured *N*-propyl analogue of cefpodoxime proxetil. HPLC purity: 98.48%; IR (KBr pellet, cm^{-1}): 3851, 3630, 3323, 3203, 2971, 2939, 2901, 2824,1765, 1678, 1618, 1535, 1461, 1450, 1380, 1360, 1350, 1272, 1219, 1181, 1149, 787, 738, 692; ^{1}H-NMR (DMSO-d_6, 500 MHz): 0.898-0.869 (t, J = 7.0, 7.5 Hz, 3H), 1.501-1.490 (d, J = 35.5 Hz, 3H),1.648-1.592 (m, 2H), 3.206 (s, 3H) , 3.643-3.550 (m, 2H), 3.83 (s, 3H), 4.089-4.066 (m, 2H), 5.198-5.181 (d, J = 8.5 Hz, 1H), 5.847-5.810 (m,1H), 6.871-6.788 (m, 2H), 7.208 (brs, 2H), 9.619-9.592 (m, 1H). MS *m/z*: 558.1 [(M+H)$^+$].

RESULTS AND DISCUSSION

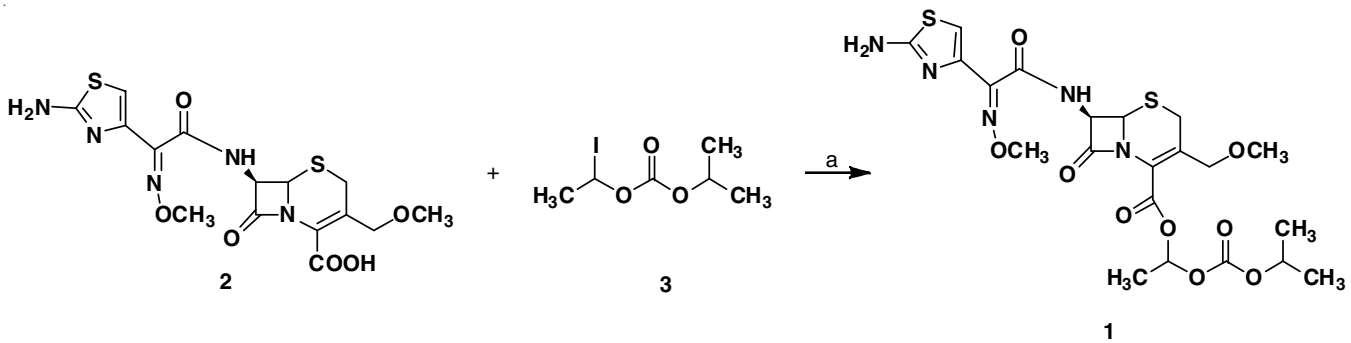
Cefpodoxime proxetil has been synthesized by known literature methods [10-18]. Present route of synthesis of cefpodoxime proxetil is shown in **Scheme-I**. Cefpodoxime proxetil was prepared by reacting (*6R*,*7R*)-7-[(*Z*)-2-(2-amino-4-thiazolyl)-2-(methoxyimino)acetamido]-3-methoxy methyl-3-cephem-4-carboxylic acid (cefpodoxime acid, **2)** with 1-iodo-ethylisopropyl carbonate (**3**) to produce cefpodoxime proxetil (**1**).

1-Iodoethyl isopropyl carbonate (**3**) is prepared from acetaldehyde [13-15]. Acetaldehyde reacted with phosgene to produce 1-chloroethyl chloroformate (**6**). 1-Chloroethyl chloroformate (**6**) is reacted with isopropyl alcohol in presence of pyridine to produce 1-chloroethyl isopropyl carbonate (**7**). Further, 1-chloroethyl isopropyl carbonate (**7**) on treated with sodium iodide results 1-iodoethyl isopropyl carbonate (**3**) as shown in **Scheme-II**.

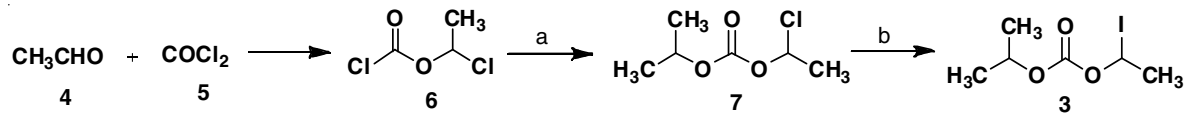
Ethyl analogue of cefpodoxime proxetil (10): 1-Chloroethyl isopropyl carbonate (**7**) is a key raw material for the synthesis of cefpodoxime proxetil (**1**). 1-Chloroethyl chloroformate reacted with isopropanol to produce compound **7**. Ethanol is a contaminant in isopropanol also reacted with 1-chloroethyl chloroformate would give 1-chloroethyl ethyl carbonate (**9**). 1-Chloroethyl ethyl carbonate was reacted in the subsequent steps of cefpodoxime proxetil synthesis to give ethyl analogue of cefpodoxime proxetil (**Scheme-III**).

Methyl analogue of cefpodoxime proxetil: 1-Chloroethyl isopropyl carbonate (**7**) is a key raw material for the preparation of cefpodoxime proxetil (**1**). 1-Chloroethyl chloroformate was reacted with isopropanol to produce compound **7**. Methanol is a contaminant in isopropanol also react with 1-chloroethyl chloroformate would give 1-chloroethyl methyl carbonate. 1-Chloroethyl methyl carbonate reacted in the subsequent steps of cefpodoxime proxetil synthesis to give methyl analogue of cefpodoxime proxetil (**13**) (**Scheme-IV**).

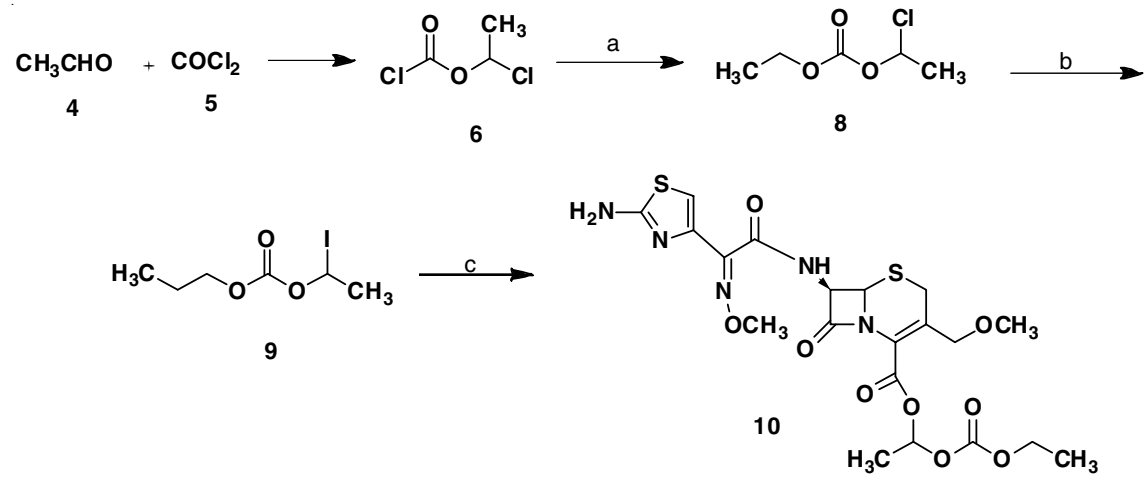
Propyl analogue of cefpodoxime proxetil: 1-Chloroethyl isopropyl carbonate (**7**) is a key raw material for the preparation of cefpodoxime proxetil (**1**)**.** The presence of propanaldehyde (**14**) in acetaldehyde (**4**) used in the synthesis of 1-chloroethyl chloroformate (**6**) reacts with phosgene produces 1-chloropropyl chloroformate (**15**). Further 1-chloropropyl chloroformate (**15**) reacted with isopropanol gives 1-chloropropyl



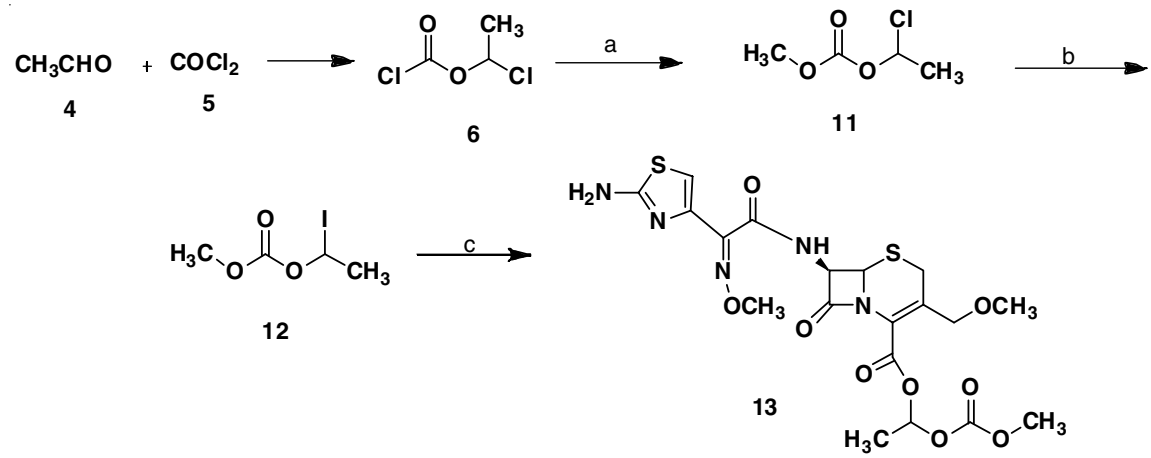
Scheme-I: Synthetic route of cefpodoxime proxetil (**1**); Reagents: (a) DBU, DMAC, toluene and cyclohexane



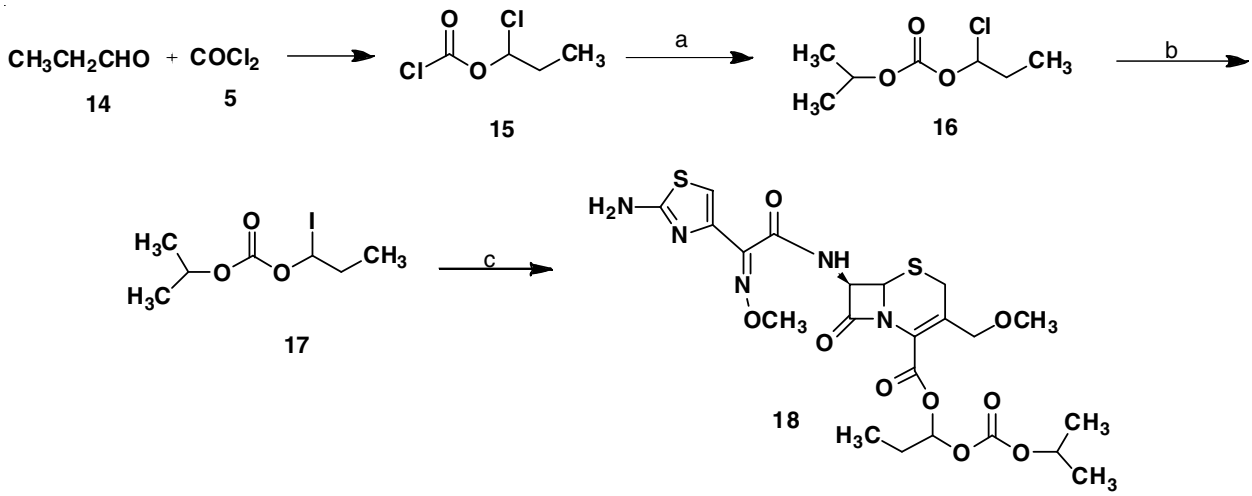
Scheme-II: Synthetic route of 1-iodoethyl isopropyl carbonate (**3**); Reagents: (a) isopropanol, pyridine (b) sodium iodide, toluene



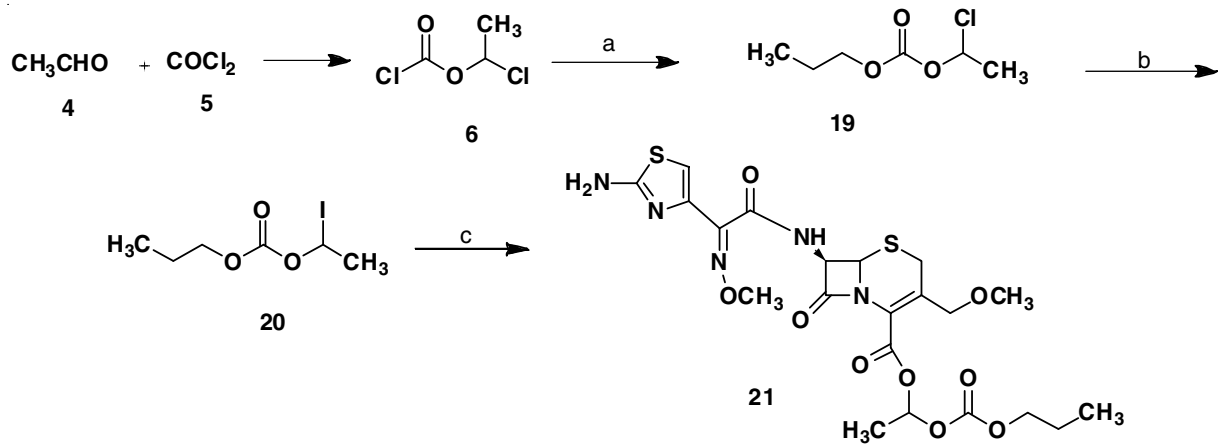
Scheme-III: Synthetic route of ethyl analogue of cefpodoxime proxetil (**10**); **Reagents:** (a) ethanol, pyridine (b) sodium iodide, toluene (c) cefpodoxime acid, DBU, DMAc, toluene, cyclohexane, water; **Origin:** Presence of ethanol in isopropanol used during the preparation of 1-chloroethyl isopropyl carbonate (**7**) may give ethyl analogue of cefpodoxime proxetil (**10**) in the subsequent steps of cefpodoxime proxetil; **Control:** Ethanol should be controlled to not detected level in isopropanol used during the preparation of 1-chloroethyl isopropyl carbonate (**7**)



Scheme-IV: Synthetic route of methyl analogue of cefpodoxime proxetil (**13**); **Reagents:** (a) ethanol, pyridine (b) sodium iodide, toluene (c) cefpodoxime acid, DBU, DMAc, toluene, cyclohexane, water; **Origin:** Presence of methanol in isopropanol used during the preparation of 1-chloro ethyl isopropyl carbonate (**7**) may give methyl analogue of cefpodoxime proxetil (**13**) in the subsequent steps of cefpodoxime proxetil; **Control:** Methanol should be controlled to not detected level in isopropanol used during the preparation of 1-chloroethyl isopropyl carbonate (**13**)



Scheme-V: Synthetic route of propyl analogue of cefpodoxime proxetil (**18**); **Reagents:** (a) isopropanol, pyridine (b) sodium iodide, toluene (c) cefpodoxime acid, DBU, DMAc, toluene, cyclohexane, water; **Origin:** Presence of propanaldehyde in acetaldehyde used during the preparation of 1-chloroethyl chloroformate (**6**) may give propyl analogue of cefpodoxime proxetil (**18**) in the subsequent steps of cefpodoxime proxetil; **Control:** Propanaldehyde should be controlled to not detected level in acetaldehyde used during the preparation of 1-chloroethyl chloroformate (**6**)



Scheme-VI: Synthetic route of *N*-propyl analogue of cefpodoxime proxetil (**21**); **Reagents:** (a) *N*-propanol, pyridine (b) sodium iodide, toluene (c) cefpodoxime acid, DBU, DMAc, toluene, cyclohexane, water; **Origin:** Presence of *N*-propanol in isopropanol used during the preparation of 1-chloro ethyl isopropyl carbonate (**7**) may give *N*-propyl analogue of cefpodoxime proxetil (**21**) in the subsequent steps of cefpodoxime proxetil; **Control:** *N*-propanol should be controlled to not detected level in isopropanol used during the preparation of 1-chloroethyl isopropyl carbonate (**7**)

isopropyl carbonate, which in turn compound **16** reacted in the subsequent steps of cefpodoxime proxetil synthesis to give propyl analogue of cefpodoxime proxetil (**18**) (**Scheme-V**).

***N*-Propyl analogue of cefpodoxime proxetil:** 1-Chloroethyl isopropyl carbonate (**7**) is a key raw material for the preparation of cefpodoxime proxetil. 1-Chloroethyl chloroformate reacted with isopropanol to produce compound **7**. *N*-propanol is a contaminant in isopropanol also reacted with 1-chloroethyl chloroformate would give 1-chloroethyl propyl carbonate. 1-Chloroethyl propyl carbonate was reacted in the subsequent steps of cefpodoxime proxetil synthesis to give *N*-propyl analogue of cefpodoxime proxetil (**21**) (**Scheme-VI**).

Conclusion

In view of regulatory importance of the analogues in the API, a detailed study on various analogues in cefpodoxime proxetil was conducted. Different process related analogues of cefpodoxime proxetil were identified, synthesized and characterized by using various spectroscopic techniques like liquid chromatography-mass spectrometry (LC-MS), mass, ^{1}H NMR and FT-IR. These efforts to synthesize and characterize the analogues of cefpodoxime proxetil effectively have proved to be beneficial.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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