PRAVADOLINE SYNTHESIS USING AN IMIDAZOLIUM-BASED IONIC LIQUID AS A GREEN SOLVENT

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(Manuscript Received on May 13th, 2011, Manuscript Revised November 01st, 2011)

ABSTRACT: *An easily accessible ionic liquid, 1-butyl-3-methylimidazolium hexafluorophosphate ([BMIM][PF_6]) was synthesized, and characterized using ^1H and ^{13}C NMR, and MS. The ionic liquid was demonstrated to be an efficient green solvent for the synthesis of pravadoline, one of non-steroidal drugs. High yield was achieved without the presence of an anhydrous Lewis acid catalyst. The reaction was also successfully carried out using other imidazolium-based ionic liquids, including 1-hexyl-3-methylimidazolium hexafluorophosphate ([HMIM][PF_6]), and 1-octyl-3-methylimidazolium hexafluorophosphate ([OMIM][PF_6]). To our best knowledge, this is the first report in Viet Nam on the synthesis of a pharmaceutical chemical in ionic liquids as green solvents.*

Key words:

1. INTRODUCTION

Pravadoline, being commercialized under the name of Win 48098 by Sterling Drug (Sterling Research Group, Rensselaer, New York), was developed as a new antiinflammatory and prostaglandin synthesis inhibitor, acting through inhibition of the enzyme cyclooxygenase [1]. Pravadoline and more importantly some of its analogues have also been used as a probe for neurochemical receptors, since it has been found to be an agonist of the cannabinoid receptor [1,2]. Ionic liquids have been considered as green alternatives to conventional organic solvents because their non-volatile nature can reduce the emission of toxic organic compounds and facilitate the separation of products from the reaction mixtures [3,4].

A variety of ionic liquids have been investigated, in which dialkylimidazolium-based ionic liquids exhibit several advantages such as keeping the liquid condition under a wide range of temperature and having excellent solubility for many substrates and molecular catalysts [5,6]. We recently reported the use of an imidazolium-based ionic liquid as a green solvent for the reaction between 1-(*N*-morpholino)-2-chloroethane hydrochloride and 2-methylindole to form 1-(2-(*N*-morpholino)ethyl)-2-methylindole as the principal product [8,9]. In this paper, we wish to report *for the first time in Viet Nam*, to our best knowledge, the synthesis of pravadoline using imidazolium-based ionic liquids as green solvents.

2. EXPERIMENTAL

2.1. Materials and instrumentation

Chemicals were purchased from Sigma-Aldrich and Merck, and used as received without further purification. ^{1}H and ^{13}C NMR spectra were recorded using a Bruker AV 500 spectrometer. MS spectra were recorded using a Thermo Finigan TSQ7000 triple quadrupole. GC analyses were performed using a Shimadzu GC-17A equipped with a FID detector and a 30 m x 0.25 mm x 0.25 µm DB-5 column. GC-MS analyses were performed using a Hewlett Packard GC-MS 5972 with a RTX-5MS column (length = 30 m, inner diameter = 0.25 mm, and film thickness = 0. 5 µm). The temperature program for GC-MS analysis heated samples from 40 to 300 ^{o}C at 10^{o}C/min and held them at 300 ^{o}C for 5 min. Inlet temperature was set constant at 280 ^{o}C. MS spectra were compared with the spectra gathered in the NIST library. HPLC-MS was conducted on a P4000/Spectra physic HPLC coupled with a TSQ7000/ Thermo Finnigan MS.

2.2. Synthesis of the ionic liquid

In a typical reaction, *N*-methylimidazole (20.68 g, 0.252 mol) and *n*-butyl bromide (38.13 g, 0.278 mol) were added to a 500 ml round-bottom flask equipped with a Dimroth condenser. The mixture was heated intermittently in a modified household microwave oven (Whirlpool M541-800W) at 200 W. After the first heating for 5 s, the irradiation was paused for 1 min, and the reaction mixture was then heated at the same power level for an additional 5 s. The procedure was repeated for a total irradiation time of 1 min. The resulting ionic liquid was then cooled, triturated and washed with diethyl ether (6 x 50 ml) to remove unreacted starting materials. The solvent residue was then removed by a rotovap at 30 ^{o}C, affording 52.93 g of 1-butyl-3-methylimidazolium bromide ([BMIM][Br]) (95% yield).

^{1}H NMR (500 MHz, DMSO-d6): δ = 0.887 (t, 3H; CH_3), 1.256 (m, 2H; CH_2CH$_3$), 1.770 (m, 2H; CH_2CH$_2$CH$_3$), 3.882 (s, 3H; N-CH_3), 4.204 (m, 2H; N-CH_2), 7.778 (t, 1H; N-C*H*=C), 7.856 (t, 1H; N-C*H*=C), 9.340 (s, 1H, N-*CH*=N). ^{13}C NMR (125 MHz, DMSO-d6): δ = 13.173 (C-*C*H$_3$), 18.652 (*C*H$_2$), 31.279 (*C*H$_2$), 35.693 (N-*C*H$_3$), 48.357(N-*C*H$_2$), 122.172 (*C*=C-N), 123.461 (C=*C*-N), 136.435 (N-*C*=N). MS (ESI): *m*/*z* 139 [BMIM]$^{+}$, 357 [(BMIM)$_2$Br]$^{+}$.

A plastic conical flask containing a mixture of [BMIM][Br] (25.10 g, 0.115 mol) and distilled water (50 ml) was immersed in an ice bath for 30 min. Hexafluorophosphoric acid (HPF_6) 60% (20 ml, 0.147 mol) and water (50 ml) were then added dropwise to prevent the temperature from rising significantly. After stirring for 12 h at room temperature, the upper acidic aqueous layer was separated by decantation and the lower ionic liquid portion was washed with cold water (10 x 50 ml) until the washings were no longer acidic. The ionic liquid was then heated under vacuum at 60 °C to remove any excess water, affording 27.32 g of 1-butyl-3-methylimidazolium

hexafluorophosphate ([BMIM][PF_6]) (83 % yield).

^{1}H NMR (500 MHz, DMSO-d6): δ = 0.905 (t, 3H; C*H*$_3$), 1.262 (m, 2H; C*H*$_2$CH$_3$), 1.771 (m, 2H; C*H*$_2$CH$_2$CH$_3$), 3.846 (s, 3H; N-C*H*$_3$), 4.157 (m, 2H; N-C*H*$_2$), 7.668 (t, 1H; N-C*H*=C), 7.733 (t, 1H; N-C*H*=C), 9.071 (s, 1H, N-*CH*=N). ^{13}C NMR (125 MHz, DMSO-d6): δ = 13.141 (C-*C*H$_3$), 18.711 (*C*H$_2$), 31.276 (*C*H$_2$), 35.651 (N-*C*H$_3$), 48.509 (N-*C*H$_2$), 122.193 (*C*=C-N), 123.542 (C=*C*-N), 136.444 (N-*C*=N). MS (ESI): *m*/*z* 139 [BMIM]$^+$, 423 [(BMIM)$_2$PF$_6$]$^+$.

1-Hexyl-3-methylimidazolium hexafluorophosphate ([HMIM][PF_6]), and 1-octyl-3-methylimidazolium hexafluorophosphate ([OMIM][PF_6]) were synthesized in a yield of 83% and 85%, respectively, using a similar procedure.

^{1}H NMR (500 MHz, DMSO-d6) for [HMIM][PF_6]: δ = 0.873 (t, 3H; C*H*$_3$), 1.272 (m, 6H; C*H*$_2$C*H*$_2$C*H*$_2$), 1.783 (m, 2H; C*H*$_2$), 3.846 (s, 3H; N-C*H*$_3$), 4.149 (m, 2H; N-C*H*$_2$), 7.7665 (t, 1H; N-C*H*=C), 7.734 (t, 1H; N-C*H*=C), 9.069 (s, 1H, N-*CH*=N). ^{13}C NMR (125 MHz, DMSO-d6): δ = 13.708 (C-*C*H$_3$), 21.799 (*C*H$_2$), 25.085 (*C*H$_2$), 29.266 (*C*H$_2$), 30.487 (*C*H$_2$), 35.651 (N-*C*H$_3$), 48.789 (N-*C*H$_2$), 122.191 (*C*=C-N), 123.540 (C=*C*-N), 136.436 (N-*C*=N). MS (ESI): *m*/*z* (%) 167 [HMIM]$^+$, 479 [(HMIM)$_2$PF$_6$]$^+$.

^{1}H NMR (500 MHz,DMSO-d6) for [OMIM][PF_6] : δ = 0.860 (t, 3H; C*H*$_3$), 1.265 (m, 10H; C*H*$_2$C*H*$_2$C*H*$_2$C*H*$_2$C*H*$_2$), 1.780 (m, 2H; C*H*$_2$), 3.845 (s, 3H; N-C*H*$_3$), 4.145 (m, 2H; N-C*H*$_2$), 7.674 (t, 1H; N-C*H*=C), 7.741 (t, 1H; N-C*H*=C), 9.076 (s, 1H, N-*CH*=N). ^{13}C NMR (125 MHz, DMSO-d6): δ = 13.870 (C-*C*H$_3$), 22.390 (*C*H$_2$), 26.085 (*C*H$_2$), 28.772 (*C*H$_2$), 28.841 (*C*H$_2$), 30.137 (*C*H$_2$), 31.495 (*C*H$_2$), 36.642 (N-*C*H$_3$), 50.003 (N-*C*H$_2$), 121.860 (*C*=C-N), 123.641 (C=*C*-N), 137.076 (N-*C*=N). MS (ESI): *m*/*z* 195 [OMIM]$^+$, 535 [(OMIM)$_2$PF$_6$]

2.3. The synthesis of pravadoline

In the first step, 1-(*N*-morpholino)-2-chloroethane hydrochloride was dissolved into the ionic liquid (solution A). KOH was added to the solution of 2-methylindole in the ionic liquid, and the mixture was magnetically stirred to dissolve the base (solution B). After that, solution A was added dropwise to solution B, and the resulting mixture was then magnetically stirred for 7 h at room temperature. The 1-(2-(*N*-morpholino)ethyl)-2-methylindole product was extracted into *n*-hexane, and the solvent was then removed by a rotovap at 30 ^{o}C. The product was purified by recrystalization to achieve isolated yield, and analyzed by GC-MS, ^{1}H and ^{13}C NMR.

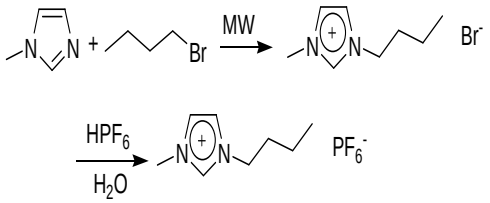
^{1}H NMR (500 MHz, acetone-d6): δ = 2.459 (m, 4H, (C*H*$_2$)$_2$N), 2.467 (s, 3H; C*H*$_3$), 2.643(m, 2H, C*H*$_2$N), 3.590 (m, 4H, (C*H*$_2$)$_2$O), 4.249 (t, 2H, C*H*$_2$N), 6.183 (s, 1H, C*H*=C-N), 6.979 (m, 1H, ArH), 7.070 (m, 1H, ArH), 7.342 (m, 1H, ArH), 7.426 (m, 1H, ArH). ^{13}C NMR (125 MHz, acetone-d6): δ = 12.798 (*C*H$_3$), 41.694 (*C*H$_2$N), 54.972 (*C*H$_2$)$_2$N), 58.754 (*C*H$_2$N), 67.475 (C*H*$_2$)$_2$O), 100.615 (*C*H=C-N), 109.851 (ArC), 119.794 (ArC), 120.198 (ArC),

120.970 (ArC), 129.264 (ArC), 137.30 (ArC), 137.697 (CH=*C*-N). MS (EI): *m*/*z* 244 $[M]^+$.

In the second step, 1-(2-(*N*-morpholino)ethyl)-2-methylindole was dissolved into the ionic liquid and the solution was heated to 150 ^oC for 10 min. 4-Methoxybenzoyl chloride was then introduced to the solution and the reaction mixture was heated under an argon atmosphere at 150 ^oC with vigrous magnetic stirring for 20 min. After cooling down to room temperature, the reaction mixture was washed with diethyl ether, neutralized using aqueous KOH solution. The pravadoline product was extracted into toluene, dried over Na_2SO_4. Toluene and any ether residue was removed by a rotovap at 30 ^oC. The product was dried under vacuum at room temperature for 24 h, purified by recrystalization to achieve isolated yield, and analyzed by HPLC-MS, ^1H and ^{13}C NMR.

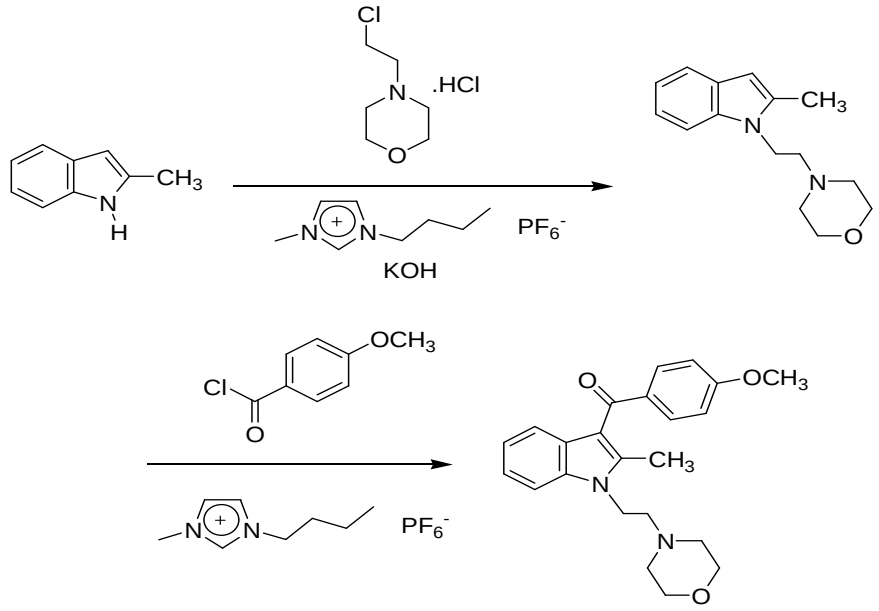
^1H NMR (500 MHz, acetone-d6): δ = 2.480 (m, 4H, (C*H*$_2$)$_2$N), 2.570 (s, 3H; C*H*$_3$), 2.724 (m, 2H, C*H*$_2$N), 3.594 (m, 4H, (C*H*$_2$)$_2$O), 3.887 (s, 3H, C*H*$_3$O), 4.365 (t, 2H, C*H*$_2$N), 7.021 (m, 3H, ArH), 7.168 (m, 1H, ArH), 7.397 (m, 1H, ArH), 7.487 (m, 1H, ArH), 7.726 (m, 2H, ArH). ^{13}C NMR (125 MHz, acetone-d6): δ = 12.676 (*C*H$_3$), 41.903 (*C*H$_2$N), 54.915 (*C*H$_2$)$_2$N), 55.807 (*C*H$_2$N), 58.294 (*C*H$_3$O) 67.443 (C*H*$_2$)$_2$O), 100.585 (*C*H=C-N), 114.216 (ArC), 114.430 (ArC), 121.329 (ArC), 121.677 (ArC), 122.504 (ArC), 128.241 (ArC), 132.003 (ArC), 134.927 (ArC), 136.844 (ArC), 144.282 (CH=*C*-N), 163.474 (ArC-O), 191.380 (C=O). MS (ESI): *m*/*z* 378 $[M]^+$.

3. RESULTS AND DISCUSSION



Scheme 1. Synthesis of the1-butyl-3 methylimidazolium hexafluorophosphate ([BMIM][PF_6]) ionic liquid.

The ionic liquid was synthesized according to a previously reported procedure [10]. In view of the green chemistry, it was decided to explore the synthesis of 1-butyl-3-methylimidazolium bromide ([BMIM][Br]) using microwave irradiation under solvent-free condition. The anion metathesis reaction of 1-butyl-3-methylimidazolium bromide with hexafluorophosphoric acid was then carried out to prepare 1-butyl-3-methylimidazolium hexafluorophosphate ([BMIM][PF_6]), according to a literature procedure (Scheme 1) [11,12]. 1-Hexyl-3-methylimidazolium hexafluorophosphate ([HMIM][PF_6]), and 1-octyl-3-methylimidazolium hexafluorophosphate ([OMIM][PF_6]) were also synthesized using similar procedure. The ionic liquids were characterized using ^1H and ^{13}C NMR, and MS, which were in good agreement with the literature [10,11].



Scheme 2. The synthesis of pravadoline in the [BMIM][PF_6] ionic liquid.

The [BMIM][PF_6] ionic liquid was evaluated for their suitability as reaction solvent for the synthesis of pravadoline. The first step of the process was the reaction between 1-(*N*-morpholino)-2-chloroethane hydrochloride and 2-methylindole to form 1-(2-(*N*-morpholino)ethyl)-2-methylindole as the principal product. The second step was the Friedel-Crafts acylation of 4-methoxybenzoyl chloride with the intermediate product from the first step (Scheme 2). The first reaction was normally carried out in DMF or DMSO, in the presence of a strong base such as NaH, $NaNH_2$, CH_3ONa, KOH, or NaOH, respectively [13,14]. These conventional processes suffer from the disadvantage that the solvent is difficult to separate from the product, is usually lost to the environment, is noxious (in the case of DMSO), and has an unpleasant odor [2]. Using the [BMIM][PF_6] ionic liquid as solvent for the reaction in conjunction with KOH as a base, 1-(2-(*N*-morpholino)ethyl)-2-methylindole was achieved in an isolated yield of 80%. The product was fully characterized using ^{1}H and ^{13}C NMR, and MS. Full investigation of the first step was previously published by our research group [8,9].

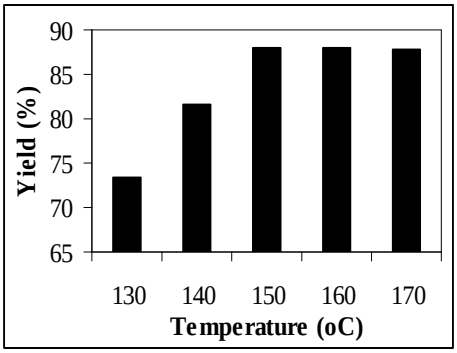


Figure 1. Effect of reaction temperature on reaction yield

The work in this paper focused on the synthesis of pravadoline using the Friedel-Crafts acylation reaction between 1-(2-(*N*-morpholino) ethyl)-2-methylindole and 4-methoxybenzoyl chloride in ionic liquids. Initial investigation addressed the effect of temperature on reaction yield, have carried out the reaction in [BMIM][PF_6] in 20 min at 130 ^oC, 140 ^oC, 150 ^oC, 160 ^oC, and 170 ^oC, respectively. It was observed that the temperature had a significant effect on the reaction yield. The reaction carried out at 150 ^oC proceeded readily, with a yield of 88% being obtained. As expected, decreasing the temperature to 130 ^oC resulted in a significant drop in reaction yield (73%). The reaction carried out at 140 ^oC could afford a yield of 81%. Interestingly, it was found that the reaction yield remained almost unchanged when the temperature increased from 150 ^oC to 160 ^oC and 170 ^oC, respectively (Figure 1).

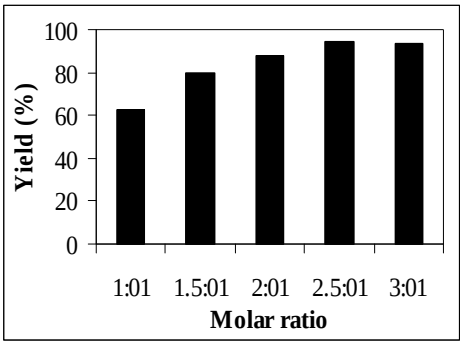


Figure 2. Effect of reagent molar ratio on reaction yield

It was therefore decided to carry out the Friedel-Crafts acylation reaction in the ionic liquid at 150 ^oC in further studies. With this result in mind, we then investigated the effect of the 4-methoxybenzoyl chloride: 1-(2-(*N*-morpholino) ethyl)-2-methylindole molar ratio on the reaction yield. It was observed that the reaction using one equivalent of 4-methoxybenzoyl chloride produced the pravadoline product in a yield of only 62%. As expected, increasing the reagent molar ratio of the reagents led to an enhancement in the reaction yield. The reaction using the molar ratio of 1.5:1 afforded the pravadoline in a yield of 79%, while 88% yield was achieved at the molar ratio of 2:1. It was found that the reaction yield could be improved to 94% at the reagent molar ratio of 2.5:1. However, increasing the ratio to higher than 2.5:1 was found to be unnecessary as the pravadoline yield was not improved any further (Figure 2).

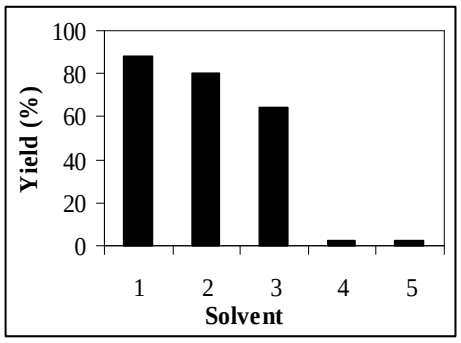


Figure 3. Effect of solvents on reaction yield: [BMIM][PF_6] (1), [HMIM][PF_6] (2), [OMIM][PF_6] (3), DEF (4), and DMSO (5)

Indoles are known to be fairly reactive in the Friedel-Crafts reaction, and the use of strong Bronsted or Lewis acids is known to polymerize indoles. For example, indole readily dimerizes to 3'-indoyl-2,3-dihydroindole in the presence of a catalytic

quantity of acid [2,15]. The significant advantage of the pravadoline synthesis using ionic liquids as solvents was that no acid catalyst was required for the Friedel-Crafts acylation reaction. Indeed, Yeung and co-wokers previously reported that when the Friedel-Crafts acylation of indoles were carried out in acidic ionic liquids containing aluminum chloride, the reaction could occur at room temperature within 18 h [15]. Other imidazolium-based ionic liquids, including [HMIM][PF_6], and [OMIM][PF_6], were also used as solvents for the reaction. The reaction was carried out in 20 min at 150 ^{o}C, using the reagent molar ratio of 2.5 : 1. It was found that increasing the alkyl chain resulted in a drop in reaction yield, with 80% yield and 65% yield being achieved for the case of [HMIM][PF_6] and [OMIM][PF_6], respectively. It should be noted that the acylation reaction carried out in DEF and DMSO failed completely under similar reaction conditions (Figure 3). These results emphasized the advantages of the ionic liquids over conventional organic solvents in the synthesis of pravadoline.

4. CONCLUSIONS

In conclusion, an easily accessible ionic liquid, [BMIM][PF_6], was synthesized and characterized using ^{1}H and ^{13}C NMR, and MS. It was found that the ionic liquid could be used as a green solvent for the synthesis of pravadoline, one of non-steroidal drugs. The reaction was also successfully carried out using other imidazolium-based ionic liquids, including [HMIM][PF_6], and [OMIM][PF_6]. The significant advantage of the process was that the ionic liquid offered easy product separation. Furthermore, the Friedel-Craft acylation reaction in the second step could be successfully carried out without the need of an anhydrous Lewis acid catalyst. Our results here demonstrate the feasibility of applying ionic liquids as green solvents in the field of organic synthesis. Current research in our laboratory has been directed to the design and the synthesis of several ionic liquids for a wide range of organic transformations, and results will be published in due course.

NGHIÊN CỨU SỬ DỤNG CHẤT LỎNG ION HỌ IMIDAZOLIUM LÀM DUNG MÔI XANH CHO PHẢN ỨNG TỔNG HỢP PRAVADOLINE

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TÓM TẮT: *Các chất lỏng ion 1-butyl-3-methylimidazolium hexafluorophosphate ([BMIM][PF_6]) đã được điều chế và nhận danh bằng phương pháp ^1H và ^{13}C-NMR kết hợp với phương pháp MS. Chất lỏng ion ([BMIM][PF_6] đã được sử dụng làm dung môi xanh cho phản ứng tổng hợp pravadoline, một loại thuốc kháng viêm không chứa steroid, với hiệu suất cao mà không cần xúc tác acid Lewis. Phản ứng cũng được thực hiện thành công trong các chất lỏng ion họ imidazolim khác, bao gồm 1-hexyl-3-methylimidazolium hexafluorophosphate ([HMIM][PF_6]) và 1-octyl-3-methylimidazolium hexafluorophosphate ([OMIM][PF_6]). Theo hiểu biết của chúng tôi, đây là lần đầu tiên ở Việt Nam, quá trình tổng hợp pravadoline được nghiên cứu và tiến hành trong dung môi xanh là chất lỏng ion.*

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