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Solid-phase parallel synthesis of 2-aminoimidazolidin-4-ones

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Abstract—The solid phase synthesis of 2-aminoimidazolidin-4-ones from resin-bound amino acids is described. Resin-bound thioureas were treated with Mukaiyama's reagent (2-chloro-1-methypyridinium iodide) to form, via intramolecular cyclization, resin-bound 2-iminoimidazolidin-4-ones. Following alkylation and cleavage, the corresponding 1,5-disubstituted 2-aminoimidazolidin-4-ones were provided in good yield and purity. © 2002 Elsevier Science Ltd. All rights reserved.

Solid-phase organic synthesis is a very efficient method for the production of combinatorial libraries and, with the implementation of high-throughput screening for biological evaluation, combinatorial methods continue to be a promising strategy for the discovery of new pharmaceutical lead compounds.[1] Low molecular weight heterocyclic compounds have received special attention in combinatorial synthesis due to their biologically relevant properties.[2]

The hydrogen-bonding acceptor and donor abilities of the guanidine group play important roles in supramolecule formation and in the active sites of various proteins, as well as in drug design in medicinal chemistry.[3] Guanidino compounds are reported as neuronal Na^+ and Ca^{2+} channel blockers,[4] glutamate release inhibitors, anti-ischemic agents,[5] antiseizure agents,[6] adrenergic neuron blocking agents,[7] HIV-1 protease inhibitors,[8] potassium/ATP channel openers, antitumor agents, NO sunthase inhibitors, influenza neuraminidase inhibitors,[9] cardiotonic agents,[10] histamine H_3 receptor antagonists,[11] H_2 receptor agonists/antagonists,[12] and antihistaminic, anti-inflammatory, antidiabetic, antibacterial agents, and antihypertensive drugs.[13] Imidazole-containing moieties are found in many biologically active compounds and are known to have useful therapeutic implications. Such compounds, which are conformationally constrained scaffolds, are quite common in nature and many imidazole-containing natural products have been isolated which encompass a wide range of biological activities.[14] Recent literature reports describe the application of carbodiimide chemistry to the synthesis of 2-aminoimidazolidin-4-ones from azidoesters[15] in solution or from polymer-supported carbodiimides.[16] However, both potential isomers derived from the intermediate guanidine are obtained when Wang resin is used.[16,17] As part of our ongoing efforts directed toward the solid phase synthesis of small molecule and heterocyclic compounds and the generation of combinatorial libraries of organic compounds,[18] we report here an efficient strategy for the solid-phase synthesis of 2-aminoimidazolidin-4-ones, which incorporates both the guanidine and imidazole functionalities.

The parallel solid-phase synthesis of 2-aminoimidazolidin-4-ones was carried out on the solid-phase using the 'tea-bag' methodology.[19] The reaction sequence is illustrated in Scheme 1. Starting from *p*-methylbenzhydrylamine (MBHA) resin, a Boc-L-amino acid was coupled to the resin. The Boc group was removed using 55% trifluoroacetic acid (TFA) in dichloromethane (DCM). The resin was neutralized with 5% diisopropylethylamine (DIEA) in DCM, dried and the resulting primary amine **2** was reacted with an isothiocyanate to provide the resin bound thiourea **3**. The reaction was monitored via the ninhydrin test.[20] Treatment of the resin-bound thiourea with Mukaiyama's reagent (2-chloro-1-methypyridinium iodide) in dichloromethane overnight resulted in the formation of carbodiimide intermediate **4**, which underwent intramolecular cyclization to give the corresponding resin-bound 2-iminoimidazolidin-4-ones **5**. The desired 2-aminoimidazolidin-4-ones **7** were readily obtained following cleavage from the resin using HF/anisole (95/5) for 1.5 h at 0°C in good yield and purity. It should be noted that these compounds might actually exist in different tautomeric forms depending on their substituents. The products were characterized by HRMS, as well as ^1H and ^{13}C NMR spectra. The results are summarized in Table 1. From these results, there appears to be no clear correlation between the electronic effects of the substituent of the ureas on the *N*-aryl group and final yields or purities. Thus, regardless of the electron-donating and electron-withdrawing groups on the *N*-phenyl substituents (H, CH_3, Cl, CN), similar results (entry **7b–f**) were obtained. In addition, no racemization was observed by ^1H NMR using two diasteriomeric analogues as described

Keywords: solid phase; 2-aminoimidazolidin-4-ones; organic synthesis.

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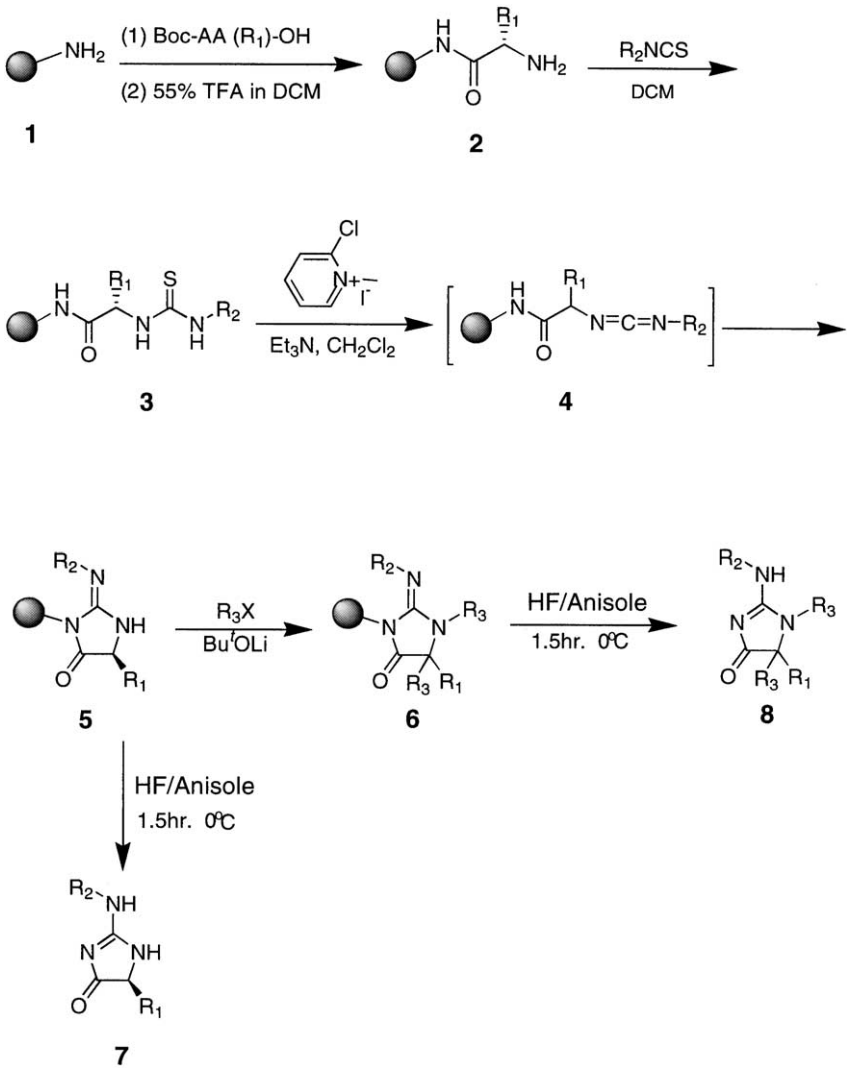

Scheme 1. Solid-phase synthesis of 2-aminoimidazolidin-4-ones.

previously.[21] Fig. 1 illustrates a typical LC–MS spectra of the 2-aminoimidazolidin-4-ones **7b** derived from phenylalanine and phenylisothiocyanate.

In order to increase the diversity around the 2-aminoimidazolidin-4-ones template, alkylation of the resin-bound 2-iminoimidazolidin-4-one **5** was also examined. When Bu^{t}OK, NaH or NaOMe were used as the base, the dialkylation product **6** as well as *N*-alkylation products (depending on the substitution of R_1) were found as determined by LC–MS. The conversion of resin-bound **5** into the corresponding resin-bound dialkylation product **6** was accomplished by treatment with Bu^{t}OLi, followed by alkylation with alkyl halides. The desired product **8** was cleaved from

Table 1. Individual 2-aminoimidazolidin-4-ones on solid-phase

Entry	Product	R_1	R_2	R_3	Yield[a]	Purity[b]	M_W (expected)	M_W (found)[c]
1	**7a**	$(CH_3)_2CH$	C_6H_5	H	92	92	217.3	218.1($[M+H]^+$)
2	**7b**	$C_6H_5CH_2$	C_6H_5	H	88	91	265.3	266.1($[M+H]^+$)
3	**7c**	$C_6H_5CH_2$	3-CH_3–C_6H_4	H	90	88	279.3	280.0($[M+H]^+$)
4	**7d**	$C_6H_5CH_2$	4-Cl–C_6H_4	H	91	91	299.1	300.0($[M+H]^+$)
5	**7e**	$C_6H_5CH_2$	4-F–C_6H_4	H	93	92	283.1	284.1($[M+H]^+$)
6	**7f**	$C_6H_5CH_2$	4-CN–C_6H_4	H	90	90	290.1	291.1($[M+H]^+$)
7	**7g**	$(CH_3)_2CH_2CH$	C_6H_5	H	89	89	231.1	232.0($[M+H]^+$)
8	**8a**	$C_6H_5CH_2$	C_6H_5	CH_3	87	76	293.3	294.0($[M+H]^+$)
9	**8b**	$C_6H_5CH_2$	C_6H_5	$C_6H_5CH_2$	89	73	445.6	446.2($[M+H]^+$)
10	**8c**	CH_3	C_6H_5	$C_6H_5CH_2$	85	75	293.3	294.0($[M+H]^+$)

[a] Yields (in %) are based on the weight of crude material and are relative to the initial loading of the resin. The isolated yields are listed in Section 2.
[b] The purity of the crude material was estimated from analytical RP-HPLC traces at λ=214 nm.
[c] Confirmed by mass spectra (ESI).

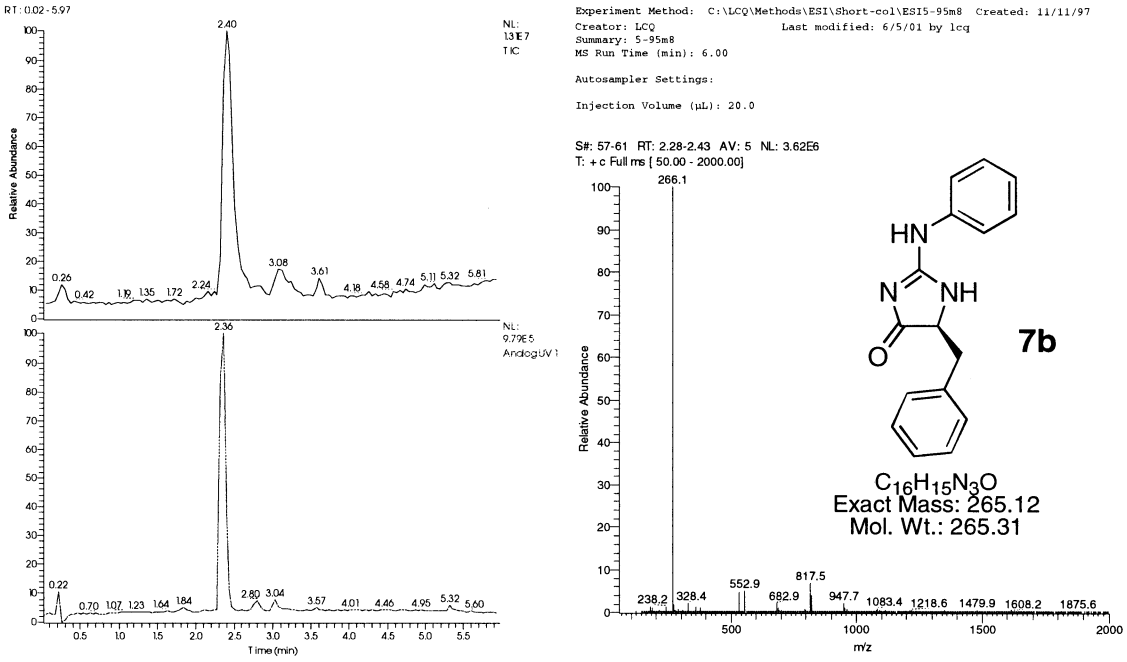

Figure 1. LC–MS of (5*S*)-2-anilino-5-benzyl-1,5-dihydro-4*H*-imidazol-4-one (**7b**).

the resin by treatment with HF for 1.5 h at 0°C and yielded the desired product in good purity and yield. LC–MS of alkylated product **8a** showed the purity of the major product to be 76%. Based on a structure similar to compound **5** in a related methylation reaction,[22] we deduced that the alkylation occurred at the internal nitrogen to give **8a**.

1. Summary

In summary, we have successfully carried out the parallel synthesis of 2-aminoimidazolidin-4-ones from resin-bound amino acids. Reaction of resin-bound L-amino acids with isothiocyanates yielded resin-bound thioureas that, when reacted with Mukaiyama's reagent, yielded resin-bound 2-aminoimidazolidin-4-ones via intramolecular cyclization. The dialkylation of the resin-bound 2-aminoimidazolidin-4-ones was accomplished by treatment with Bu^{t}OLi followed by reaction with alkyl halides. The desired products were readily obtained following cleavage from the resin in good yield and purity by treatment with HF/anisole (95/5) for 1.5 h at 0°C.

2. Experimental

p-Methylbenzhydrylamine (MBHA) resin, 1% divinylbenzene, 100–200 mesh, 1 mequiv./g substitution, and *N*,*N*′-diisopropylcarbodiimide (DIC) were purchased from Chem Impex Intl. (Wood Dale, IL). Boc-amino acid derivative and *N*-hydroxybenzotriazole (HOBt) were purchased from Calbiochem–Novabiochem Corp. (San Diego, CA) and Bachem Bioscience Inc. (Philadelphia, PA). Trifluoroacetic acid (TFA) and HF were purchased from Halocarbon (River Edge, NJ) and Air Products (San Marcos, CA), respectively. All other reagents and anhydrous solvents were purchased from Aldrich Chemical Co. (Milwaukee, WI). Analytical RP-HPLC was performed on a Beckman System Gold Instrument (Fullerton, CA). Samples were analyzed using a Vydac 218TP54 C18 column (0.46×25 cm^2). LC–MS (ESI) was recorded on a Finnigan Mat LCQ mass spectrometer (ThermoQuest Corporation, CA) at 214 nm using a Betasil C18, 3 μm, 100 Å, 3×50 mm^2 column. Preparative RP-HPLC was performed on a Waters DeltaPrep preparative HPLC (Millipore) using a Vydac 218TP1022 C18 column (2.2×25 cm^2). High-resolution mass spectra (HRMS) were recorded at The Scripps Research Institute. NMR spectra were recorded on a Bruker AM 500 instrument at 500 and 125 MHz for ^{1}H and ^{13}C NMR, respectively. NMR chemical shifts are expressed in ppm relative to the internal solvent peak. Coupling constants were calculated in hertz.

2.1. Typical procedure for the synthesis of 2-aminoimidazolidin-4-ones (7)

A polypropylene mesh packet was sealed with 50 mg of MBHA resin (1 mequiv./g, 100–200 mesh).[19] Reactions were carried out in polypropylene bottles. The resin was washed with dichloromethane (DCM, 3 times) followed by neutralization with 5% diisopropylethylamine (DIEA) in DCM and washed with DCM (3 times). The first Boc-L-amino acid (6 equiv., 0.1 M) was coupled using DIC and HOBt (6 equiv., 0.1 M each) in anhydrous dimethylformamide (DMF) for 2 h. Following washes with DMF (6 times), Boc deprotection was performed using 55% TFA in DCM for 30 min, followed by washing with DCM (2 times), 2-propanol (IPA) (2 times), and DCM (2 times). Following neutralization, the resin was treated with isothiocyanate (6 equiv., 0.1 M) in anhydrous DCM overnight to yield the thioureas **3**. Completeness of the coupling was verified by the ninhydrin test. The resin was washed with DCM (2 times), IPA (2 times), and DCM (2 times). The resin-bound thiourea was reacted

with Mukaiyama's reagent (2-chloro-1-methypyridinium iodide) (6 equiv., 0.1 M) in the present of the Et_3N (6 equiv., 0.1 M) in anhydrous DCM overnight to afford resin-bound 2-iminoimidazolidin-4-ones **5**. After washing with DMF (3 times), MeOH (3 times), CH_2Cl_2 (3 times), the resin was cleaved by anhydrous HF in the presence of anisole at 0°C for 1.5 h.[19] and the product **7** was extracted with 95% acetic acid in H_2O and lyophilized. Following purification by RP-HPLC, the identity of the compounds was confirmed by HRMS, ^1H and ^{13}C NMR.

2.2. Typical procedure for the alkylation of 2-amino-imidazolidin-4-ones (8)

To the resin **5** was added 1 M lithium *t*-butoxide in THF (10 equiv., 0.1 M). After shaking 30 min, excess base was removed by decantation. The individual alkylating agent (5 equiv., 0.1 M) in DMSO was then added. The solution was vigorously shaken for 4 h at room temperature. After washing with DMF (3 times), DCM (3 times), MeOH (3 times), the resin was cleaved by anhydrous HF at 0°C for 1.5 h and the product **8** extracted with 95% acetic acid in H_2O and lyophilized. Following purification by RP-HPLC, the product was characterized by HRMS, ^1H and ^{13}C NMR.

2.2.1. (5*S*)-2-Anilino-5-isopropyl-1,5-dihydro-4*H*-imidazol-4-one (7a). Isolated yield 58%. ^1H NMR (500 MHz, DMSO): δ 0.91 (d, J=6.8 Hz, 3H), 0.97 (d, J=6.8 Hz, 3H), 2.12 (m, 1H), 4.16 (d, J=3.6 Hz, 1H), 7.33–7.50 (m, 5H). ^{13}C NMR (125 MHz, DMSO): δ 17.0, 18.7, 30.8, 65.3, 125.0, 128.5, 130.8, 135.2. HRMS (MALDI) *m/z* calcd for $C_{12}H_{16}N_3O$ (M+H) 218.1293, found 218.1286.

2.2.2. (5*S*)-2-Anilino-5-benzyl-1,5-dihydro-4*H*-imidazol-4-one (7b). Isolated yield 54%. ^1H NMR (500 MHz, DMSO): δ 3.02–3.11 (m, 2H), 4.55 (brs, 1H), 7.01–7.35 (m, 10H). ^{13}C NMR (125 MHz, DMSO): δ 36.2, 60.7, 124.9, 128.1, 128.5, 129.1, 130.4, 130.7, 135.1. HRMS (MALDI) *m/z* calcd for $C_{16}H_{16}N_3O$ (M+H) 266.1293, found 266.1266.

2.2.3. (5*S*)-5-Benzyl-2-[(3-methylphenyl)amino]-1,5-dihydro-4*H*-imidazol-4-one (7c). Isolated yield 59%. ^1H NMR (500 MHz, DMSO): δ 2.34 (s, 3H), 3.08–3.11 (m, 2H), 4.58 (brs, 1H), 7.01–7.35 (m, 9H). ^{13}C NMR (125 MHz, DMSO): δ 21.0, 35.7, 59.9, 120.9, 124.4, 127.1, 127.7, 128.3, 129.5, 129.7, 134.9, 139.3. HRMS (MALDI) *m/z* calcd for $C_{17}H_{18}N_3O$ (M+H) 280.1450, found 280.1449.

2.2.4. (5*S*)-5-Benzyl-2-[(4-chlorophenyl)amino]-1,5-dihydro-4*H*-imidazol-4-one (7d). Isolated yield 52%. ^1H NMR (500 MHz, DMSO): δ 3.04–3.06 (m, 2H), 4.61–4.62 (t, J=4.8 Hz, 1H), 7.17–7.58 (m, 9H). ^{13}C NMR (125 MHz, DMSO): δ 35.8, 59.7, 127.0, 127.9, 128.3, 128.5, 128.9, 129.8, 130.2, 134.7. HRMS (MALDI) *m/z* calcd for $C_{16}H_{15}ClN_3O$ (M+H) 300.0904, found 300.0899.

2.2.5. (5*S*)-5-Benzyl-2-[(4-fluorophenyl)amino]-1,5-dihydro-4*H*-imidazol-4-one (7e). Isolated yield 56%. ^1H NMR (500 MHz, DMSO): δ 3.00–3.12 (m, 2H), 4.53 (brs, 1H), 7.05–7.50 (m, 9H). ^{13}C NMR (125 MHz, DMSO): δ 35.9, 60.0, 110.4, 110.6, 112.9, 119.2, 126.9, 128.2, 129.6, 131.2, 131.3, 135.3, 137.5, 161.3, 163.3. HRMS (MALDI) *m/z* calcd for $C_{16}H_{15}FN_3O$ (M+H) 284.1199, found 284.1196.

2.2.6. (5*S*)-5-Benzyl-2-[(4-cyanophenyl)imino]imidazolidin-4-one (7f). Isolated yield 55%. ^1H NMR (500 MHz, DMSO): δ 3.95–2.99 (dd, J=6.8, 6.5 Hz, 1H), 3.06–3.10 (dd, J=4.8, 4.9 Hz, 1H), 4.41–4.43 (t, J=5.0 Hz, 1H), 7.22–7.84 (m, 9H). ^{13}C NMR (125 MHz, DMSO): δ 35.2, 60.1, 106.5, 118.8, 122.4, 126.8, 128.8, 129.6, 133.4, 133.6, 135.8. HRMS (MALDI) *m/z* calcd for $C_{17}H_{15}N_4O$ (M+H) 291.1246, found 291.1244.

2.2.7. (5*S*)-2-Anilino-5-[(1*S*)-1-methylpropyl]-1,5-dihydro-4*H*-imidazol-4-one (7g). Isolated yield 51%. ^1H NMR (500 MHz, DMSO): δ 0.85–0.93 (m, 6H), 1.27–1.47 (m, 2H), 1.86–1.90 (m, 1H), 4.19 (brs, 1H), 7.32–7.49 (m, 5H). ^{13}C NMR (125 MHz, DMSO): δ 12.6, 15.8, 25.8, 34.2, 62.8.3, 118.9, 122.4, 129.7, 133.8. HRMS (MALDI) *m/z* calcd for $C_{13}H_{18}N_3O$ (M+H) 232.1450, found 232.1444.

2.2.8. 2-Anilino-5-benzyl-1,5-dimethyl-1,5-dihydro-4*H*-imidazol-4-one (8a). Isolated yield 42%. ^1H NMR (500 MHz, DMSO): δ 1.51 (s, 3H), 2.97–3.00 (d, J=14.8 Hz, 1H), 3.18–3.20 (d, J=14.8 Hz, 1H), 3.21 (s, 1H), 7.12–7.35 (m, 10H). ^{13}C NMR (125 MHz, DMSO): δ 19.9, 27.7, 69.0, 124.2, 126.7, 127.2, 128.3, 129.3, 129.4, 129.9, 134.6, 135.6, 157.8. HRMS (MALDI) *m/z* calcd for $C_{18}H_{20}N_3O$ (M+H) 294.1606, found 294.1620.

2.2.9. 2-Anilino-1,5,5-tribenzyl-1,5-dihydro-4*H*-imidazol-4-one (8b). Isolated yield 39%. ^1H NMR (500 MHz, DMSO): δ 3.07–3.10 (d, J=14.2 Hz, 2H), 3.33–3.36 (d, J=14.2 Hz, 2H), 5.09 (s, 2H), 6.80–7.34 (m, 20H). ^{13}C NMR (125 MHz, DMSO): δ 44.6, 73.6, 124.3, 126.9, 127.2, 128.1, 128.4, 129.1, 129.9, 130.1, 134.2. HRMS (MALDI) *m/z* calcd for $C_{30}H_{28}N_3O$ (M+H) 446.2232, found 446.2233.

2.2.10. 5-Benzyl-1,5-dimethyl-2-(phenylimino)imidazolidin-4-one (8c). Yield 41%. ^1H NMR (500 MHz, DMSO): δ 1.51 (s, 3H), 2.97–3.00 (d, J=14.8 Hz, 1H), 3.18–3.20 (d, J=14.8 Hz, 1H), 3.21 (s, 1H), 7.12–7.35 (m, 10H). ^{13}C NMR (125 MHz, DMSO): δ 19.9, 27.7, 69.0, 124.2, 126.7, 127.2, 128.3, 129.3, 129.4, 129.9, 134.6, 135.6, 157.8. HRMS (MALDI) *m/z* calcd for $C_{18}H_{20}N_3O$ (M+H) 294.1606, found 294.1620.

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