

Electronic Supplementary Information (ESI)

Synthesis of ranitidine (Zantac) from cellulose-derived 5-(chloromethyl) furfural

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1. Materials

N-Acetylcysteamine (95%) and 1-methylthio-1-methylamino-2-nitroethylene **7** (98%) were purchased from Sigma-Aldrich Chemical Company. THF, CH₂Cl₂, CHCl₃, diethyl ether, MeOH, Me₂NH, NaH (95%) and KOH were purchased from Fischer Scientific and used as received. 5-(Chloromethyl)furfural (CMF) **12** was synthesized using a literature procedure.¹

2. Experimental Procedures

5-[[2-Acetamidoethyl]thio]methyl]furfural **14**

Sodium hydride (95%) (103 mg, 4.08 mmol) was added to a solution of N-acetylcysteamine (0.4051 g, 3.40 mmol) in dry THF (20 mL) under argon. The resulting suspension was stirred at RT for 30 min and a solution of CMF **12** (0.4912 g, 3.40 mmol) in dry THF (10 mL) was added dropwise over a 10 min period. The resulting light yellow solution was allowed to stir overnight at RT. The solvent was evaporated and saturated brine (50 mL) was added. The mixture was extracted with CH₂Cl₂ (2 × 50 mL) and the organic layers were combined and washed with saturated brine (100 mL). The organic layer was dried over Na₂SO₄. Charcoal (100 mg) was added and the mixture was stirred for 20 min and filtered. The solvent was evaporated to give **14** as a yellow liquid (0.7042 g, 91 %). ¹H NMR (CDCl₃, 300 MHz) 9.58 (1H, s), 7.21 (1H, d, *J* = 3.6 Hz), 6.48 (1H, s, br), 5.95 (1H, d, *J* = 3.6 Hz), 3.79 (2H, s), 3.45 (2H, q, *J* = 6.3 Hz), 2.72 (2H, t, *J* = 6.6 Hz), 2.00 (3H, s); ¹³C NMR (CDCl₃, 75 MHz) 23.1, 27.8, 31.7, 38.4, 110.7, 121.9, 152.2, 158.9, 170.7, 177.4; IR (neat) 3298, 3101, 1663, 1548, 1512, 1287, 1022, 772 cm⁻¹; HRMS (ESI): calculated for C₁₀H₁₄O₃NS: [M+H]⁺ 228.0694: found 228.0690.

5-[[2-Acetamidoethyl]thio]methyl]-N,N-dimethyl-2-furanmethanamine **15**

Me₂NH (1.0 mL) was added to a solution of **14** (0.2105 g, 0.926 mmol) in dry methanol (20 mL) and the mixture was stirred at RT for 1 h. The resulting red solution was cooled to 0 °C and NaBH₄ (98 %) (55 mg, 1.42 mmol) was added over a 5 min period. The mixture was allowed to come to RT and stirred for 30 min. The solvent was evaporated while keeping the bath temperature below 45 °C. The residue was dissolved in CH₂Cl₂

(50 mL) and filtered to remove inorganic impurities. The solvent was evaporated to give **15** (0.2145 g, 90 %) as a pale yellow oil. ^1H NMR (CDCl_3 , 300 MHz) 6.42 (1H, s, br), 6.09 (1H, s), 3.67 (2H, s), 3.37 (2H, s), 3.26 (2H, q, $J = 6.0$ Hz), 2.62 (2H, t, $J = 6.4$ Hz) 2.21 (6H, s), 1.93 (3H, s); ^{13}C NMR (CDCl_3 , 75 MHz) 23.5, 28.4, 31.9, 38.7, 45.4, 56.2, 108.4, 109.9, 151.4, 152.1, 170.5; IR (neat) 3273, 2944, 1656, 1545, 1291, 1019, 729 cm^{-1} ; HRMS (ESI): calculated for $\text{C}_{12}\text{H}_{21}\text{O}_2\text{N}_2\text{S}$: $[\text{M}+\text{H}]^+$ 257.1322: found 257.1323.

5-[[2-(2-aminoethyl)thio]methyl]-N,N-dimethyl-2-furanmethanamine 5

A solution of **15** (0.2473 g, 0.965 mmol) in freshly prepared 2N aq NaOH (10 mL) was heated at reflux for 2 h. The mixture was cooled to RT and extracted with CH_2Cl_2 (3×30 mL). The organic layers were combined and washed with saturated brine, dried over Na_2SO_4 , and evaporated to give **5** (0.1934 g, 94 %) as a pale yellow oil. ^1H NMR (CDCl_3 , 300 MHz) 6.02 (2H, s), 3.61 (2H, s), 3.33 (2H, s), 2.74 (2H, t, $J = 6.3$ Hz), 2.52 (2H, t, $J = 6.6$ Hz), 2.16 (6H, s); ^{13}C NMR (CDCl_3 , 75 MHz) 28.2, 35.9, 40.9, 45.1, 55.9, 108.1, 109.5, 151.4, 152.1; IR (neat) 3359 cm^{-1} , 2947, 2769, 1559, 1459, 1015, 797 cm^{-1} ; HRMS (ESI): calculated for $\text{C}_{10}\text{H}_{19}\text{ON}_2\text{S}$: $[\text{M}+\text{H}]^+$ 215.1212: found 215.1218.

N-[2-[[[5-[(dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1-Ethenediamine (Ranitidine) 1

The experimental procedure is modified from existing literature:² A solution of **5** (0.1501 g, 0.700 mmol) in distilled water (10 mL) was added dropwise over a period of 10 min to a suspension of 1-methylthio-1-methylamino-2-nitroethylene **7** (0.1041 g, 0.703 mmol) in distilled water (5 mL) with stirring. The resulting light yellow solution was placed in an oil bath at 55 °C and the mixture was stirred at that temperature overnight. Saturated brine (30 mL) was added and the mixture was extracted with CHCl_3 (3×20 mL). The combined organic layer was dried over Na_2SO_4 . Evaporation of the solvent gave **1** as a pale yellow oil (0.1935 g, 88 %). ^1H NMR (CDCl_3 , 300 MHz, 56 °C) 10.23-10.15 (1H, br, NH), 6.57 (1H, s), 6.13 (2H, d, 6.0 Hz), 5.04 (1H, br, NH), 3.73 (2H, s), 3.41 (4H, s), 2.92 (2H, s), 2.76 (2H, t, 6.0 Hz), 2.24 (6H, s); ^{13}C NMR (CDCl_3 , 75 MHz, 56 °C) 28.2, 30.6, 40.7, 44.6, 55.6, 97.9, 108.1, 109.1, 150.4, 152.1, 156.6; IR (neat) 3209, 2944,

2815, 2776, 1620, 1574, 1384, 1230, 1019, 761 cm^{-1} ; HRMS (ESI): calculated for $\text{C}_{13}\text{H}_{23}\text{O}_3\text{N}_4\text{S}$: $[\text{M}+\text{H}]^+$ 315.1491: found 315.1497.

3. Atom Economy Calculation

Reagent	FW	utilized atoms	FW utilized	unutilized atoms	FW unutilized
CMF	144.5557	$\text{C}_6\text{H}_5\text{O}$	93.1033	ClO	51.4524
$\text{HSCH}_2\text{CH}_2\text{NHAc}$	119.1854	$\text{C}_2\text{H}_5\text{NS}$	75.1328	$\text{C}_2\text{H}_4\text{O}$	44.0526
NaH	23.9977		0	NaH	23.9977
Me_2NH	45.0837	$\text{C}_2\text{H}_6\text{N}$	44.0757	H	1.0079
NaBH_4	37.8325	H	1.0079	NaBH_3	36.8246
NaOH	39.9971		0	NaOH	39.9971
$\text{C}_4\text{H}_8\text{N}_2\text{O}_2\text{S}$	148.1835	$\text{C}_3\text{H}_5\text{N}_2\text{O}_2$	101.084	MeS	47.0995
Total	558.8356	$\text{C}_{13}\text{H}_{22}\text{N}_4\text{O}_3\text{S}$	314.4037	$\text{C}_3\text{H}_{13}\text{BClNa}_3\text{O}_3\text{S}$	244.4318
				% atom economy	56.26

4. Spectral Data

^1H NMR spectra were recorded using a Varian Mercury 300 NMR spectrometer operating at 300 MHz. ^{13}C NMR spectra were recorded on the same instrument with an operating frequency of 75 MHz. The data were processed using MestReNova (version 6.2.0) desktop NMR data processing software.³

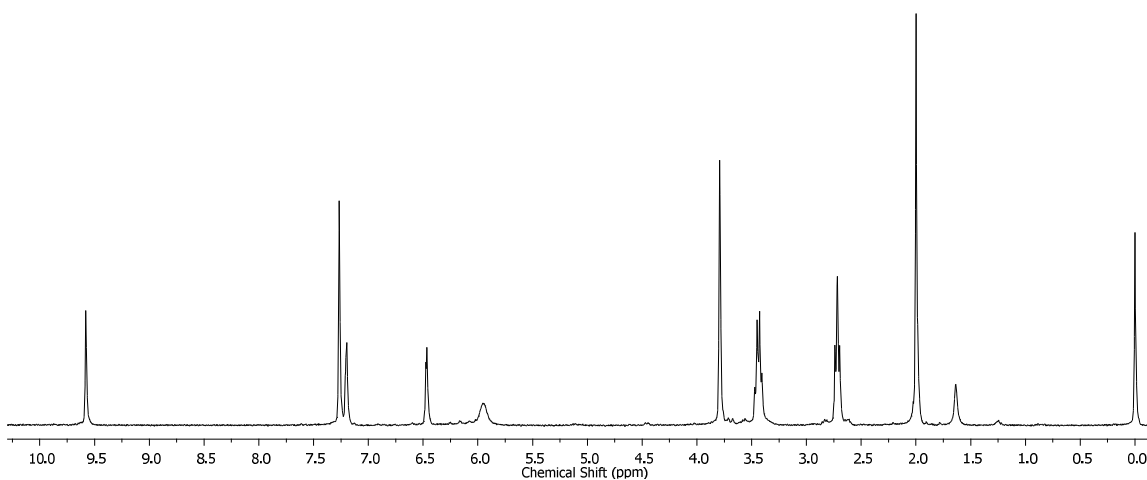


Fig. S1. ^1H NMR spectrum of **14** in CDCl_3 .

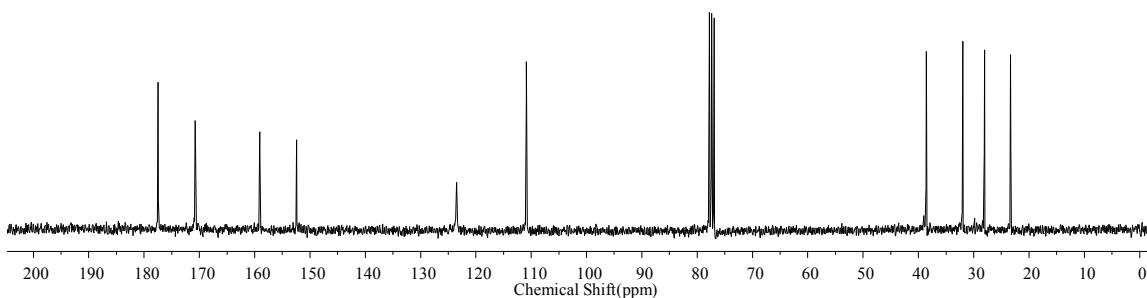


Fig. S2. ^{13}C NMR spectrum of **14** in CDCl_3 .

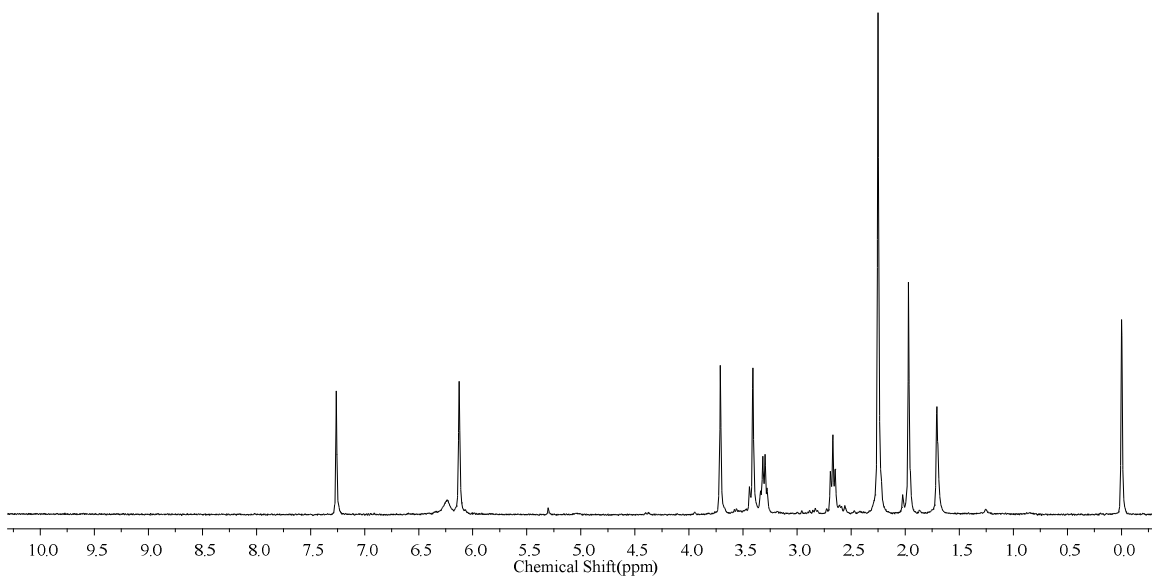


Fig. S3. ^1H NMR spectrum of **15** in CDCl_3 .

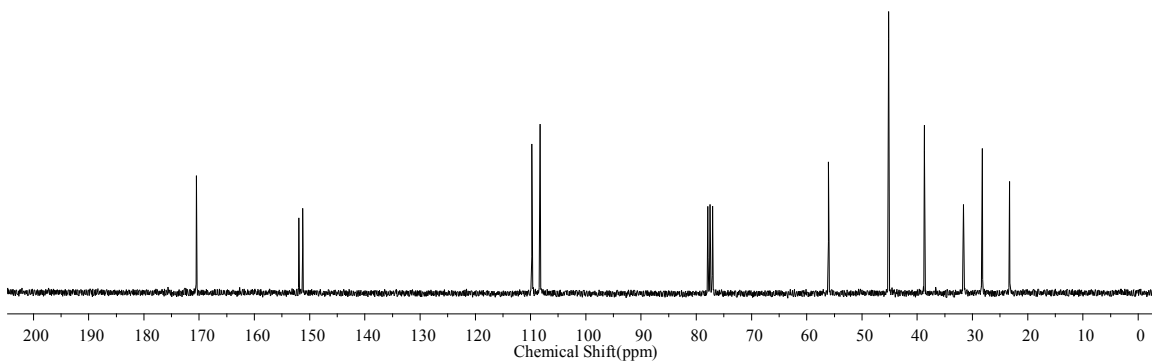


Fig. S4. ^{13}C NMR spectrum of **15** in CDCl_3 .

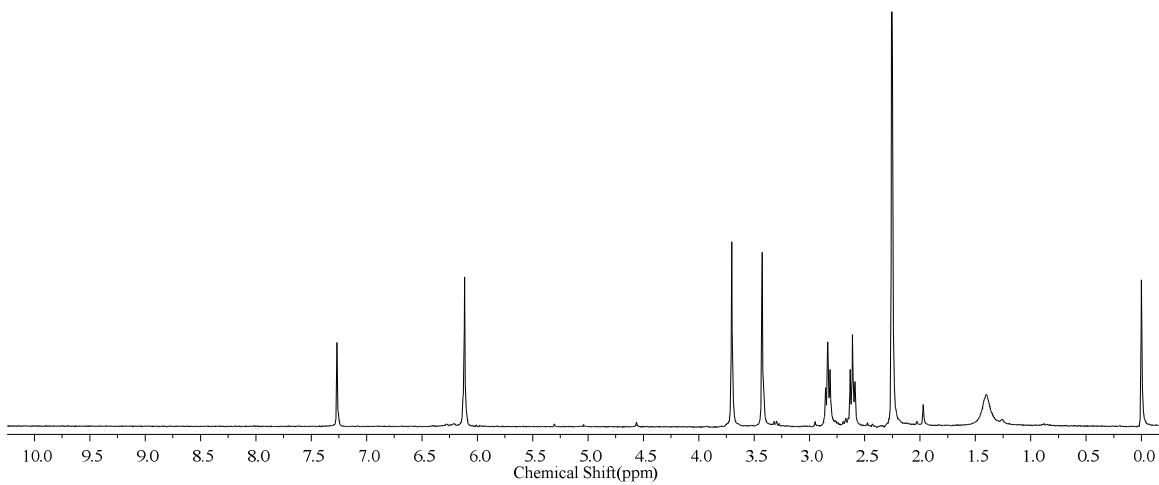


Fig. S5. ^1H NMR spectrum of **5** in CDCl_3 .

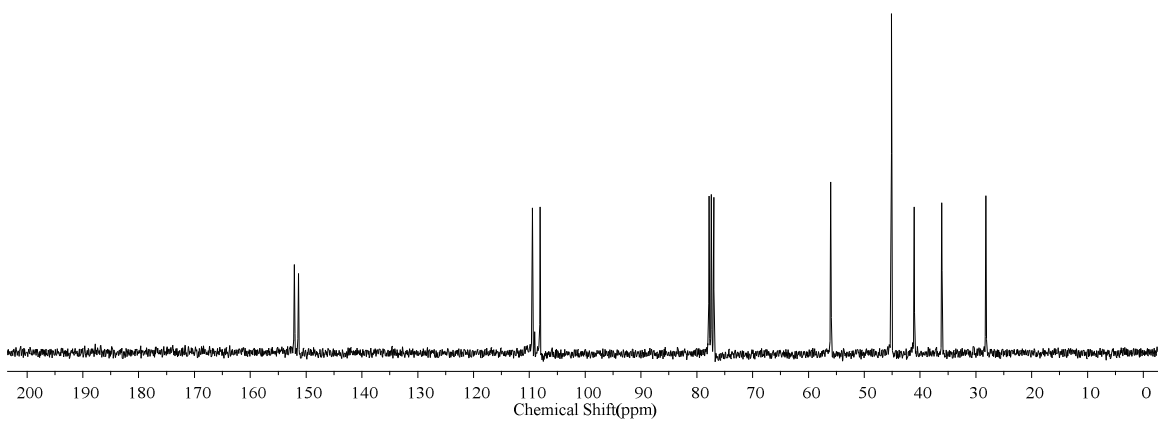


Fig. S6. ^{13}C NMR spectrum of **5** in CDCl_3 .

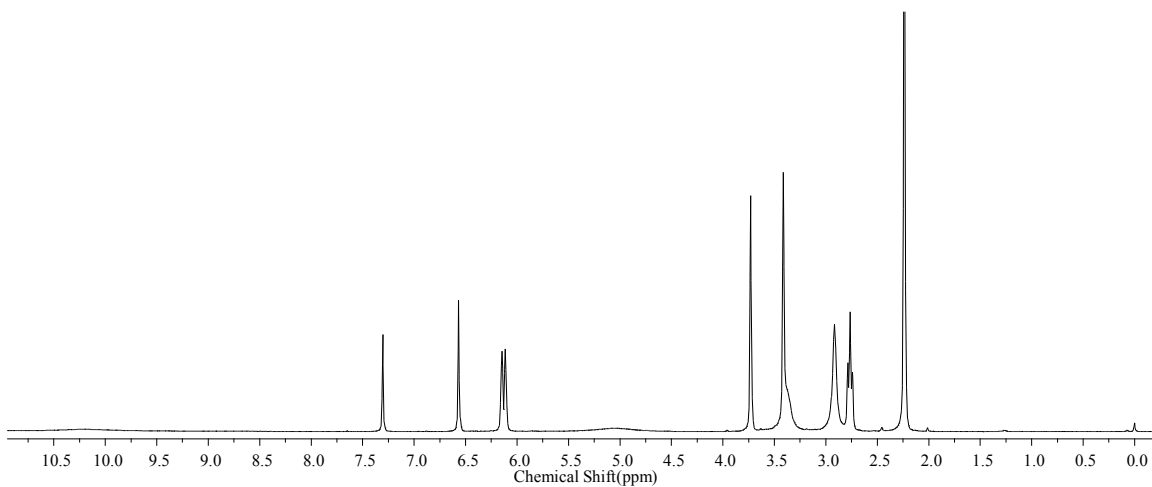


Fig. S7. ^1H NMR spectrum of **1** in CDCl_3 at $56\text{ }^\circ\text{C}$.

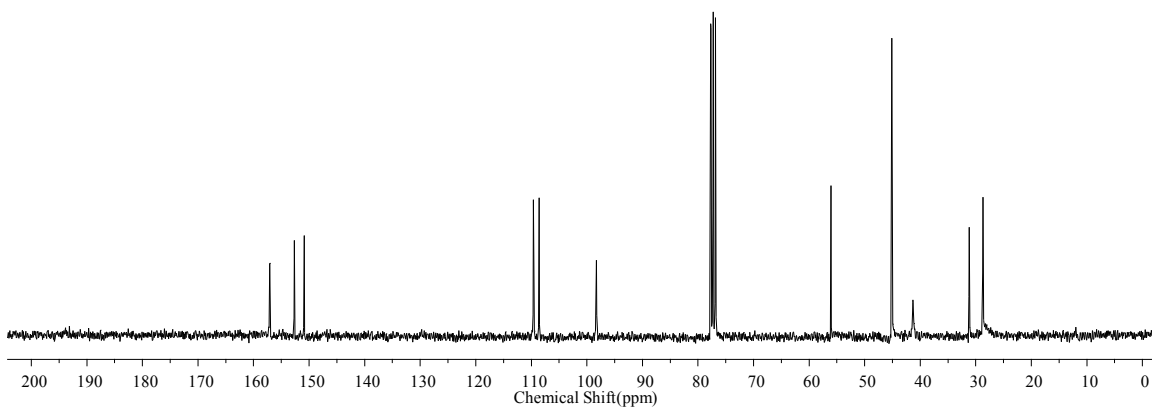


Fig. S8. ^{13}C NMR spectrum of **1** in CDCl_3 at $56\text{ }^\circ\text{C}$.

4. References

- 1 M. Mascal and E. B. Nikitin, *ChemSusChem*, 2009, **2**, 859.
- 2 J. M. Khanna, N. Kumar and B. Khera, P. C. Ray, *US Patent* 5696275, 1997.
- 3 MestReNova (Mnova), version 6.2.0, Mestrelab Research, SL, Santiago de Compostela, Spain