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Research Article

An Efficient Total Synthesis of N-2-mono-N-desmethyl Nizatidine[1]

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Abstract: N-2-mono-N-desmethyl Nizatidine, a metabolite exhibiting H_2-blocking activity is synthesized in eight steps, starting from commercially available Glycine. The Synthesis is simple and involves non hazardous chemicals.

Introduction

Nizatidine (1), (N-[2-[[[2-[(dimethylamino) methyl]-4-thiazolyl]-methyl] thio] ethyl]-N"-methyl-2-nitro-1,1-ethenediamine) is a specific and potent H_2-receptor antagonist that blocks gastric acid production. Also Nizatidine decreases basal, nocturnal, food-stimulated, and chemically stimulated gastric acid production[2-5]. N-2-mono-N-desmethyl Nizatidine (N-2-MDMN, 2) is a metabolite and exhibits H_2-blocking activity, like parent drug[6]. NDM also facilitates gastric emptying probably direct or/and indirect (acetyl cholinesterase inhibition) cholinergic mechanism[7]. Literature describes synthesis of (1)[8], starting from expensive N-methyl N-benzoylthioacetamide via the formation of ethyl-2- (methylbenzoylaminomethyl) - 4 - thiazolecarboxylate. However rest of the steps to make TM, starting from this intermediate is not high yielding and also involves tedious work-ups.

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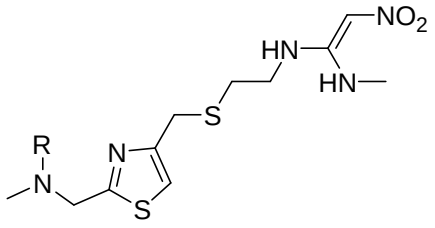
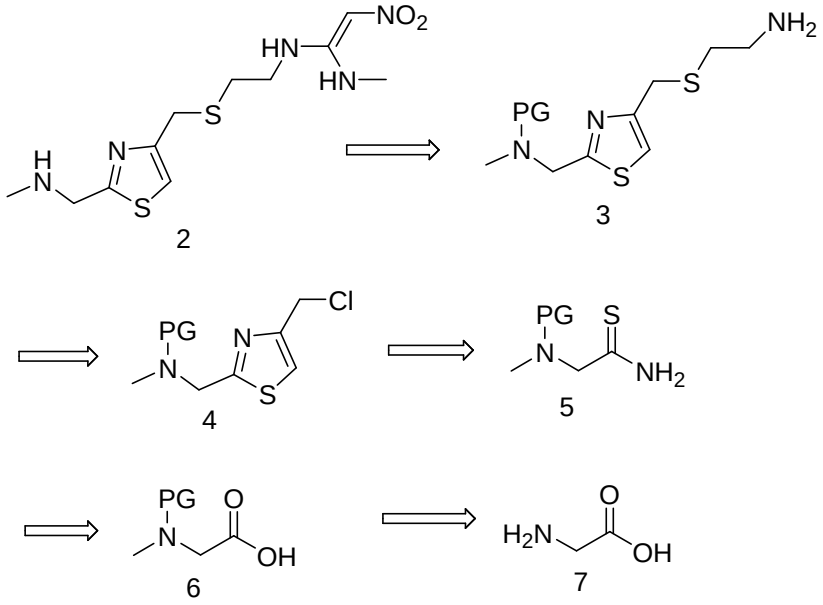


R = CH3, Nizatidine, **1**
R = H, N-Desmethyl Nizatidine, **2**

Figure 1. Structure of Nizatidine and N-Desmethyl Nizatidine

There is no direct literature available for the synthesis of N-desmethyl Nizatidine, herein we describe an efficient synthesis of N-2-MDMN starting from an easily accessible starting material Glycine.

Retro synthetically, we envisaged that (2) could be derived from protected tert-butyl-(4-(chloromethyl) thiazole-2-yl) methyl (methyl) carbamate (4) by condensation with amino ethylthiol through intermediate (3). Thiazole (4) would be prepared from protected thioamide, obtained from glycine (7) through intermediate (6) (Scheme 1).



Scheme 1. Retro synthesis of N-Desmethyl Nizatidine

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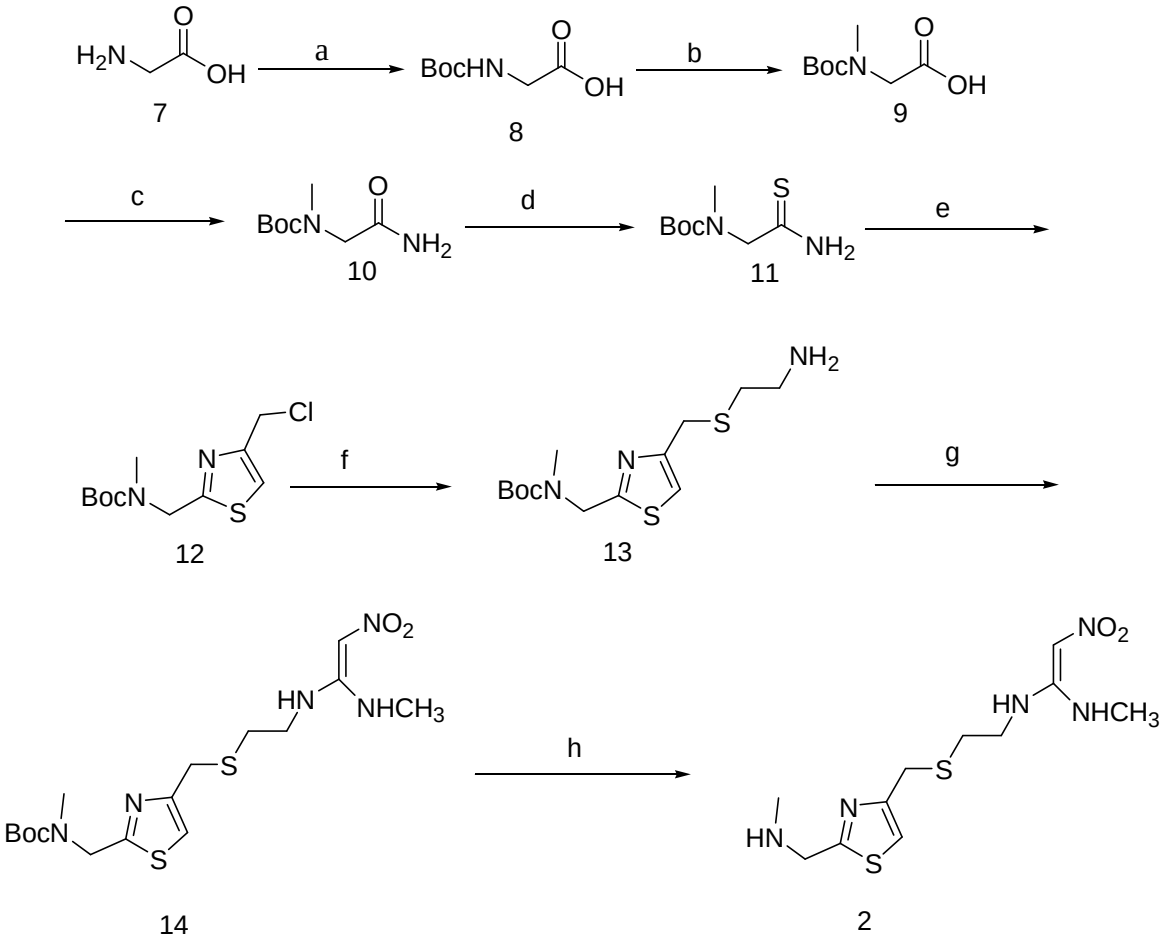

Scheme 2. Reagents & conditions: (a) $(Boc)_2O$, THF, Aq. NaOH, 0^oC to r.t.15h, 93%;

(b) MeI, NaH, THF, 0^oC to r.t. 15h, 92%; (c) Ethyl chloro formate, THF, 0^oC to 5^oC, 1h; NH_4OH, r.t., 72.5%; (d) P_2S_5, Na_2CO_3, DME, 0^oC to r.t. 48h, 52%; (e) 1,3-dichloroacetone, Na_2CO_3, Toluene, 70-80^oC, 14h, 34%; (f) Cysteamine.HCl, KOH, IPA, r.t. 2h, 69.5%; (g) 2-methyl amino-2-methyl thio-1-nitroethylene, H2O, r.t. 48h, 56%; (h) IPA.HCl, r.t. 15h, 44%.

Our approach to the synthesis of the N-2-mono-N-desmethyl Nizatidine (2) is described in scheme 2. With the aim of achieving a quick synthesis of N-2, we focused our attention to synthesis of tert-butyl-(4-(chloromethyl) thiazole-2-yl) methyl (methyl) carbamate (4) intermediate starting from Glycine.

Materials & Methods

N-Boc glycine (tert–butoxycarbonyl amino- acetic acid)[1] (8)

To a solution of glycine (30.0 g, 0.4 mol) in THF (300 mL) was added an aq 10 % NaOH solution (300 mL). The clear solution was cooled to 0^oC. Di tert-butyl dicarbonate (87.2g, 0.4 mol, 1.0 equiv) was added slowly over the period of 1h, stir reaction mixture at room temperature for overnight. The progress of the reaction was

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monitored by TLC. The pH of reaction mixture was adjusted to 2-3 using 2N HCl (300 mL) and extracted with Ethyl acetate (3×500 mL). The combined organic extracts were washed with water (2×400 mL), brine(2×200 mL), dried(anhydrous Na_2SO_4) and concentrated in vacuo to give **8** (65.0 g, 93% Yield) as a white crystalline solid.

N-(tert-Butoxycarbonylmethyl) amino acetic acid[2] (9)

To a cooled (0ºC) solution of **8** (50 g, 0.28 mol) and Methyl iodide (72 mL, 1.14 mol, 4.0 equiv) in dry THF (1600 mL), was added NaH (37.4 g, 0.85 mol, 3.0 equiv, 55% in mineral oil) in portions cautiously and the mixture was stirred gently for overnight at room temperature. The progress of the reaction was monitored by TLC. To destroy the excess NaH added H_2O slowly (100 mL) under ice cooling followed by Ethyl acetate (500 mL) and water (400 mL). Ethyl acetate layer Separated and acidified aqueous layer to pH 2 with 2N HCl under ice cooling. The product was then extracted into Ethyl acetate (3×500mL). The extracted organic layer was washed with water (100 mL), 5% aq sodium thiosulfate (2×100 mL) and brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to give **9** (49.9g, 92.4% Yield) as a pale yellow oil.

Carbamoylmethyl-methyl-carbamic acid tert-butyl ester (10)

A solution of **9** (28 g, 0.15 mol), N-methylmorpholine (18.0 g, 0.18 mol, 1.2 equiv) in THF (280 mL) was cooled to 0-5ºC. Ethylchloroformate (19.3 g, 0.18 mol, 1.2 equiv) was added slowly drop wise at the same temperature. After stirring for 1.0 h at the same temperature, NH3 solution (81 mL, 25%soln) was added and stirred for 4 h at room temperature. The THF was removed under vacuo. The Ethyl acetate (280 mL) and saturated $NaHCO_3$ (100 mL) was added to the reaction mixture. Seperated organic layer and the aq layer was extracted with Ethyl acetate (2×280 mL). The combined organic layer was washed with water (100 mL), brine (100 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to give 3 as a white solid. The obtained solid was triturated in Hexane (55 mL) to give **10** (20.2g, 72.5% Yield) as a pure solid.

Methyl-thiocarbamoylmethyl-carbamic acid tert-butyl ester (11)

A solution of **10** (23.5 g, 0.125 mol) in dimethoxy ethane (450 mL) was added Na_2CO_3 (53.0 g, 0.5 mol, 4.0 equiv) at room temperature. Cooled the reaction mixture to 0-5ºC. Added P_2S_5 (55.5 g, 0.25 mol, 2.0 equiv) to reaction mixture in portion wise at same temperature. The reaction mixture was stirred at room temperature for 48 h. The progress of the reaction was monitored by TLC. Filtered the reaction mass over celite bed and washed with Ethyl acetate (235 mL) and evaporated solvent (filtrate) under vacuo. 10% aq solution of $NaHCO_3$ (100 mL) was added to the reaction mixture and extracted with ethyl acetate (2×500 mL). The combined organic extracts were washed with 10% aq solution of $NaHCO_3$ (2×100 mL), water (2×100 mL), brine (2×100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuo to obtain solid. The obtained solid was further purified by column chromatography over silica (eluent: 40%Ethyl acetate in hexane) to give **11** (13.2g, 52% Yield) as a white solid after evaporation under vacuo.

(4-Chloromethyl-thiazol-2-ylmethyl)-methyl-carbamic acidtert-butyl ester (12)

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A mixture of **11** (10 g, 0.05 mol), 1, 3-dichloroacetone (7.5 g, 0.06 mol, 1.2 equiv) and sodium carbonate (11.5 g, 0.107 mol, 2.2 equiv) in 200 mL of toluene was stirred at 70-80ºC for 14 h. The progress of the reaction was monitored by TLC. Then cooled the reaction mixture to room temperature and filtered salts which had precipitated during the reaction and washed with toluene (100 mL). Toluene filtrate was washed with water (100 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuo. The crude product was further purified by column chromatography over silica (eluent: 20% ethyl acetate and hexane) to give **12** (4.6g, 34% Yield) as a thick red liquid.

[4-(2-Amino-ethylsulfanylmethyl)-thiazol-2-ylmethyl]-Methyl-carbamic acid tert-butyl ester (13)

The solution of **12** (4.0g, 0.0145 mol) in isopropanol (10 mL) was added to the solution of KOH (2.4 g, 0.043 mol, 3.0 equiv), cysteamine hydrochloride (3.3 g, 0.0292 mol, 2.0 equiv) and isopropanol (30 mL) at room temperature. The resulting suspension was stirred at room temperature for 2h. The progress of the reaction was monitored by TLC. Organic layer (reaction mixture) was concentrated in vacuo. To the obtained residue added water (40 mL) and extracted into Ethyl acetate (2×50 mL). The combined organic layer was washed with water (40 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The viscous liquid **13** (3.2g, 69.5% Yield) which obtained is substantially pure and directly used for next step.

Methyl-{4-[2-(1-methylamino-2-nitro-vinylamino)-ethylsulfanylmethyl]-thiazol-2- ylmethyl}-carbamic acid tert-butyl ester (14)

To a solution of **13** (2.1g, 0.0066 mol) in water (20 mL) was added 2-methyl amino-2-methyl thio-1-nitroethylene (1.2g, 0.0081 mol, 1.2 equiv). The suspension was stirred at room temperature for 48h. The progress of the reaction was monitored by TLC. Reaction mixture was extracted with Ethyl acetate (1×50 mL & 1×25 mL). Both the organic layers combined and washed with water (25 mL), brine (25 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was further purified by column chromatography over silica (eluent: 1% methanol in chloroform) to give **14** (1.5 gm, 56% Yield) as a red thick liquid.

N-2-[[2-(methylaminomethyl)-1,3-thiazol-4-yl]ethylsulfanylmethyl]-N'-methyl-2-nitroethene-1,1-diamine (2)

To a solution of **14** (1.5g, 0.0036 mol) in isopropanol (2 mL) was added 15 mL of Isopropanol Hydrochloride. The solution was stirred at room temperature for overnight. The progress of the reaction was monitored by TLC. Solvent was removed under vacuo. To the residue thus obtained added water (20 mL) and 10% aq $NaHCO_3$ solution. Extract the reaction mixture with Ethyl acetate(3×100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to give **2** (0.5g, 44% Yield) as a residue.

Results

N-Bocglycine(tert -butoxycarbonylamino-acetic acid) [1] (8)

Obtained **8** in 93% Yield. Its Melting Point is 87-88ºC; IR (KBr) γmax: 3407 & 3344(NH),3120(COOH),2979,1750(COOH), 1683(CONH), 1535(NH), 1411, 1369, 1215, 1198, 1170, 1056.5, 958.9, 859.5cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ ppm = 1.45 (s, 9H, CH_3), 3.9 (d, J=5.2Hz, 2H,

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CH_2), 5.16 & 6.7(s, 1H, NH), 8.6(s); MS: m/z =174.1 ([M-H] +).

N-(tert-Butoxycarbonylmethyl) amino acetic acid[2] (9)

Obtained **9** in 92.4% Yield. IR (Neat) γmax: 3423(COOH), 2979, 1677(C=O),1152 cm-1; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 3.99 (d, J = 30 Hz, 2H, CH_2), 2.94 (s, 3H, CH_3), 1.43-1.47 (m, 9H); MS: m/z = 188.1([M-H] +).

Carbamoylmethyl-methyl-carbamic acid tert-butyl ester (10)

Obtained **10** in 72.5% Yield.IR (KBr) γ_{max}: 3363($CONH_2$), 3172, 1697 &, 1659(C=O) , 1403, 1245, 1145 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 6.0 (b, 2H, NH2), 3.86 (s, 2H, CH_2), 2.95 (s, 3H, CH_3), 1.47 (s, 9H); ^{13}C NMR (100MHz,$CDCl_3$): δ ppm =172.32 ,155.93, 80.50, 52.49, 35.58, 28.16; MS: m/z =211.1([M +Na] $^+$).

Methyl-thiocarbamoylmethyl-carbamic acid *tert*-butyl ester (11)

Obtained **11** in 52% Yield. IR (KBr) γ_{max}: 3363.5($CSNH_2$), 3254, 2925, 1694.5, 1666, 1396, 1156 cm^{-1}; ^{1}H NMR (400 MHz, DMSO): δ ppm = 9.58 (b, 1H, CSNHH), 9.07 (b, 1H, CSNHH), 4.01 (s, 2H, CH_2), 2.81 (s, 3H, CH_3), 1.35-1.40 (m, 9H); MS: m/z = 203 ([M-H] $^+$); HRMS (M-H) + in TOF MS ES- shows mass (m/z) = 203.08 and Molecular Formula is $C_8H_{15}N_2O_2S$.

(4-Chloromethyl-thiazol-2-ylmethyl)-methyl-carbamic acidtert-butyl ester (12)

Obtained **12** in 34% Yield. IR (Neat) γmax: 3105, 2976, 2932, 1696, 1391, 1157 cm-1; ^{1}H NMR (400 MHz, DMSO): δ ppm = 7.69 (s, 1H, CH), 4.79 (s, 2H, CH_2), 4.62 (s, 2H, CH_2), 2.88 (s, 3H, CH_3), 1.38-1.42 (m, 9H, $C(CH_3)_3$); MS: m/z = 299 ([M+Na]+); HRMS (M+H) + in TOF MS ES+ shows mass (m/z) = 277.07 and Molecular Formula is $C_{11}H_{18}ClN_2O_2S$.

[4-(2-Amino-ethylsulfanylmethyl)-thiazol-2-ylmethyl]-Methyl-carbamic acid tert- butyl ester (13)

Obtained **13** in 69.5% Yield. IR(Neat) γmax: 3551, 3353, 3098, 2975, 2930, 1693($CONCH_3$), 1391, 1160 cm-1; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.07 (s, 1H, CH), 4.66 (s, 2H), 3.82 (s, 2H), 2.95 (s, 3H), 2.87 (m, 2H), 2.63 (m, 2H), 1.48 (s, 9H); MS: m/z = 318.1([M+H]+); HRMS (M+H) + in TOF MS ES+ shows mass(m/z)= 318.13 and Molecular Formula is $C_{13}H_{24}N_3O_2S_2$.

Methyl-{4-[2-(1-methylamino-2-nitro-vinylamino)-ethylsulfanylmethyl]-thiazol-2- ylmethyl}-carbamic acid tert-butyl ester (14)

Obtained **14** in 56% Yield. IR (Neat) γmax: 3688(NH), 3094, 2975, 2925, 1693($CONCH_3$), 1614, 1574, 1390, 1244, 1161 cm-1; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.1 (s, 1H, CH), 6.6 (s, 1H), 4.64 (s, 2H), 3.83 (s, 2H), 3.35 (b, 2H), 2.96 (s, 6H), 2.81 (t, J = 7Hz, 2H), 1.25 (s, 9H); MS: m/z = 418 ([M+H] +); HRMS (M-H)+ in TOF MS ES- mass(m/z)= 416.14 and Molecular Formula is $C_{16}H_{26}N_5O_4S_2$.

N-2-[[2-(methylaminomethyl)-1,3-thiazol-4-yl]ethylsulfanylmethyl]-N'-methyl-2-nitroethene-1,1-diamine (2)

Obtained **2** in 44% Yield. IR (KBr) γ_{max}: 3401, 2963, 1622, 1574, 1441, 1393 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.07 (s, 1H), 6.58 (s, 1H), 4.03 (s, 2H), 3.83 (s, 2H), 3.34 (b, 2H), 2.95 (s, 2H), 2.87 (s, 2H), 2.8 (t, J=6HZ, 3H), 2.53 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ ppm = 172.294, 156.555, 152.702, 115.703, 98.122, 52.688, 36.112, 31.509, 30.766, 29.506; MS: m/z = 318 ([M+H] $^+$); HRMS

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$(M+H)^+$ in TOF MS ES+ shows mass(m/z)= 318.1 and Molecular Formula is $C_{11}H_{20}N_5O_2S_2$.

Discussion

Glycine was converted to Boc protected glycine (8) as per previously described[9]. Boc protected glycine (8) was obtained in 93% yield. N-methylation was affected in presence of NaH and MeI to furnish (9) in good yield[10]. Before the introduction of mercapto group N-methylated glycine was converted into the amide. The carboxylic acid was activated with ethyl chloroformate which was subsequently converted to amide in presence of aq. Ammonium hydroxide to furnish amide (10) in good yield. Thionation was affected in presence of P_2S_5 and anhydrous dimethoxyethane at r.t. to get thioamide (11) as a white solid in 52% yield[11]. The next challenge was the formation of five membered thiazole in presence of N-Boc protection. tert-Butyl (4-chloromethyl) thiazole-2-yl) methyl methylcarbamate (12) was obtained directly from (11) without isolation of hydroxy compound which is forming as an intermediate. Methyl-thiocarbamoylmethyl-carbamic acid tert-butyl ester (11) and 1,3-dichloroacetone was heated at 60^{o}C in presence of sodium carbonate over a period of 24 h to obtain tert-Butyl (4-chloromethyl) thiazole-2-yl) methyl methylcarbamate (12). The thio amino chain was introduced by reaction of (12) with cysteamine hydrochloride in the presence of base yielding directly [4-(2-Amino-ethylsulfanylmethyl)-thiazol-2-ylmethyl]-Methyl-carbamic acid tert-butyl ester (13). The thiol compound (13) was fused with 2-methyl amino-2-methyl thio-1-nitroethylene to yield the boc protected N-2-mono-N-desmethyl Nizatidine (14). Boc protection was removed in IPA·HCl to get desired N-2-mono-N-desmethyl Nizatidine (2). All the products were characterized by IR, ^{1}H NMR, and Mass.

Conclusion

We have reported simple and efficient total synthesis of N2-mono-N-desmethyl Nizatidine (2), in 8 steps starting from readily available Glycine (7).

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References

[1] DRL-IPD communication Number: IPDO IPM 00224

[2] Fullarton, G. M.; Macdonald, A. M.; McColl, K. E. Aliment Pharmacol Ther, 1991, 5,391.

[3] Bertaccini, G.; Scarpignato, C. Br J Pharmacol, 1982, 77, 443.

[4] Kounenis, G.; Voutsas, D.; Koutsoviti Papadopoulou, M.; Elezoglou, V. J. Pharmacodyn, 1988, 11, 767.

[5] Takeuchi, K.; Kawauchi, S.; Araki, H.; Ueki, S.; Furukawa, O. World J. Gastroentero, 2000, 6, 651.

[6] Knadler, M. P.; Bergstrom, R. F.; Callaghan, J. T.; Rubin, A. Drug Metab. Dispos, 1986, 14, 175.

[7] Kaneo, H; Mitsuma, T; Uchida, K; Nagai, H; Harada, M; Kotera, H. Digestive diseases and sciences, 1995, 40, 2043.

[8] Pioch, R. US Patent 4,904,792, 1990.

[9] XU, Y.; Chen, L.; Duan, X.; Meng, Y.; Jiang, L.; Li, M.; Zhao, G.; Li, Y. Tetrahedron Lett. 2005, 46, 4377-4379.

[10] Xu, Y. ; Duan, X.; Li, M.; Jiang, L.; Zhao, G.; Meng, Y.; Chen, L. Molecules 2005, 10, 259-264.

[11] Harnett, J. J.; Roubert, V.; Dolo, C.; Charnet, C.; Spinnewyn, B.; Cornet, S.; Rolland, A.; Marin, J.; Bigg, D.; Chabrier, P. Biorg. Med. Chem. Lett. 2004, 14, 157.