HETEROCYCLES, Vol. 53, No11, 2000, pp. 2471 - 2485, Received, 1st August, 2000

A PRACTICAL PROCEDURE FOR PREPARATION OF *N*-(*endo*-8-(3-HYDROXY)PROPYL-8-AZABICYCLO[3.2.1]OCT-3-YL)-1-ISOPROPYL-2-OXO-1,2-DIHYDRO-3-QUINOLINE-CARBOXAMIDE (TS-951)

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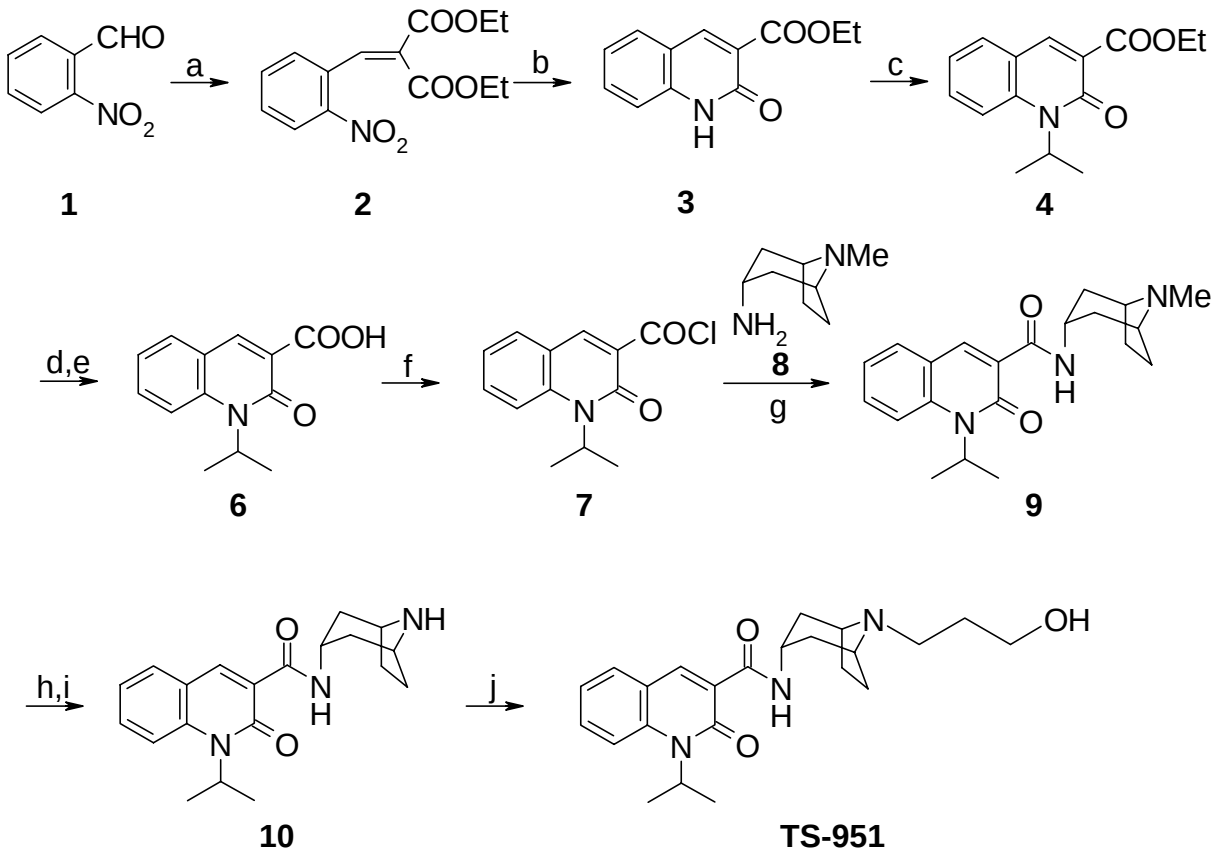
Abstract – Effective and convergent process for the preparation of a potent and selective 5-HT_4 receptor agonist, the title compound, by reaction of 1-isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxylic acid (**6**) with *endo*-3-amino-8-(3-hydroxypropyl)-8-azabicyclo[3.2.1]octane dihydrochloride (**20**) has been described. Furthermore, this process was developed to pilot plant scale. 1-Isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxylic acid (**6**) was prepared from 2-aminobenzyl alcohol (**12**) in 65.6% overall yield and *endo*-3-amino-8-(3-hydroxypropyl)-8-azabicyclo[3.2.1]octane dihydrochloride (**20**) was prepared from 2,5-dimethoxyfuran (**16**) in 43.4% overall yield.

Introduction

Serotonin (5-HT) is a neurotransmitter which is widely distributed in humans and has a remarkable variety of physiological effects.[1] Among them, the existence of 5-HT_4 receptor was reported by Dumuis.[2] In the gut,[3] it participates in the induction and maintenance of gastrointestinal motility, and its stimulants activate gastrointestinal motor function. We recently reported a potent and selective 5-HT_4 receptor agonist, (*N*-*endo*-8-(3-hydroxy)propyl-8-azabicyclo[3.2.1]oct-3-yl)-1-isopropyl-2-oxo-1,2-dihydro-3-quinoline-carboxamide (**TS-951**).[4] In the present paper, we describe an effective and convergent process for preparation of **TS-951** and development to its pilot plant scale.

Our initial approach to **TS-951** is outlined in Scheme 1. 2-Nitrobenzaldehyde (**1**) was condensed with diethyl malonate in acetic anhydride in the presence of $NaHCO_3$ at 100 ℃ to give diethyl benzylidenemalonate (**2**),[5] which was transformed into the quinoline-carboxylate (**3**) by reduction of nitro group and spontaneous cyclization. Alkylation of **3** with isopropyl iodide in the presence of sodium hydride in DMF led to a separable mixture

Scheme 1



Reagents: (a) diethyl malonate, $NaHCO_3$, Ac_2O; (b) Fe, AcOH; (c) i-PrI, NaH, DMF; (d) NaOH, EtOH, H_2O; (e) HCl; (f) $SOCl_2$, toluene; (g) NaOH, H_2O, toluene; (h) $ClCOOCH(Cl)Me$, $ClCH_2CH_2Cl$; (i) MeOH; (j) $BrCH_2CH_2CH_2OH$, K_2CO_3, EtOH

of *N*-isopropylquinolinecarboxylate (**4**) and *O*-isopropyl isomer (**5**). In the case of pyridine derivatives,[6] the ratio of *N*-isopropyl isomer vs *O*-isopropyl isomer was 1:1 to 1:2, while in this case, *O*-isopropylation proceeded predominantly to yield **4** in only 7%, although the reason is uncertain. Quinolinecarboxylate (**4**) was transformed into acid chloride (**7**) in a usual manner, which was condensed with 3**α**-aminotropane (**8**) [7] to give carboxamide (**9**). Furthermore, carboxamide (**9**) was demethylated by treatment with 1-chloroethyl chloroformate [8] followed by methanolysis to give demethylated product (**10**), from which **TS-951** was prepared by alkylation with 3-bromo-1-propanol under basic conditions. Although a sequence of the process mentioned above was sufficient for the supplies of modified derivatives of **TS-951**, it was undesirable to prepare their large amounts for the following problems; 1. The yield in the process from **3** to **4** is very low and it needs separation by column chromatography; 2. 8-Methyl group of 3**α**-aminotropane (**8**) has to be demethylated in two-step demethylation processes.

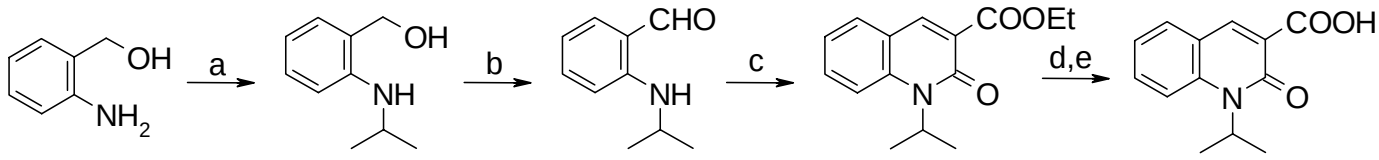
In order to solve the above problems, the following plans were made. 1. Increase the yield of **4**. 2. Develop newly direct syntheses of compound (**11**) as intermediate.

Results and discussion

Preparation of 6

In order to improve the yield in alkylation of **3**, we changed a sequence of alkylation and cyclization for preparation of **4**. The synthetic pathway to **6** was depicted in Scheme 2.

Scheme 2

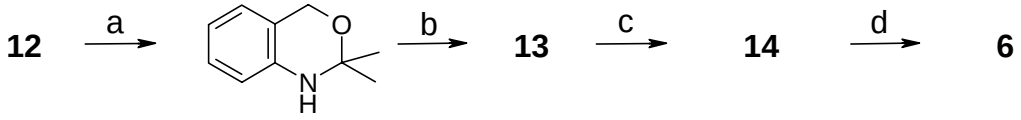


12 **13** **14** **4** **6**

Reagents: (a) acetone, $NaBH_4$, AcONa, AcOH, EtOH, H_2O; (b) PCC/Al_2O_3, benzene; (c) diethyl malonate, $NaHCO_3$, Ac_2O; (d) NaOH, EtOH, H_2O; (e) HCl

2-Aminobenzyl alcohol (**12**) reacted with acetone and $NaBH_4$ to give 2-isopropylaminobenzyl alcohol (**13**)[9]in 70.7% yield. In this reaction, 1,2-dihydro-2,2-dimethyl-4*H*-3,1-benzoxazine (**15**) was formed as a sideproduct and precipitated as a crystalline solid from the reaction mixture. Fortunately, we found that **15** led to **13** by $NaBH_4$ reduction in EtOH [10] or catalytic reduction with platinum carbon in MeOH. Therefore, *N*-alkylation route through benzoxazine (**15**) was tried (Scheme 3).

Scheme 3



15

Reagents: (a) acetone, AcOH, H_2O; (b) H_2/5%Pt-C, MeOH; (c) MnO_2, toluene; (d) Meldrum's acid, ethylenediamine, AcOH, MeOH

Namely, amino alcohol (**12**) reacted with acetone containing AcOH to give **15** as a solid, catalytic hydrogenation of which produced to 2-isopropylaminobenzyl alcohol (**13**). Although in this catalytic hydrogenation unchanged amino alcohol (**12**) was found to be removed by washing with water, at the same time some of **13** was transferred into aqueous layer by this washing process, and it caused somewhat decrease of yield of **13**. Oxidation of **13** to benzaldehyde (**14**) was carried out by using manganese dioxide (MnO_2).[11,12] Unexpectedly, commercially available MnO_2 did not give satisfactory results except for two companies. Finally, we could find preferable MnO_2 (CMD-100®) [13] for this oxidation. Furthermore, the oxidation in toluene, acetonitrile and hexane gave good results, while that in acetone and ether did not proceed. As a result, the oxidation was performed with CMD-

100® in toluene to give **14** in 62% yield. Reaction of **14** with diethyl malonate under basic conditions took place simultaneously to give quinolinecarboxylate (**4**), which was turned into carboxylic acid (**6**) by hydrolysis. However, the reaction of **14** with diethyl malonate requires long reaction time and high reaction temperature. Since unchanged **14** were still remained despite of long reaction time, it caused somewhat decrease of yield of **4**. Therefore, employment of more reactive malonate seemed to be required. Thus, the reaction of compound (**14**) with Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) instead of diethyl malonate was investigated. First, solvent and catalyst were examined. After several attempts, the reaction was found to proceed smoothly in the presence of ethylenediamine diacetate in MeOH. Next, we investigated combination of ethylenediamine diacetate / MeOH system (Table 1). As shown in Table 1, the condition of Run 16 resulted in the highest yield (92%). Based on these investigations, the pilot plant scale conditions

Table 1. The reaction of **14** with Meldrum's acid [a)]

Run	MeOH (vol.)	Ethylendiamine (eq)	AcOH (eq)	Meldrum's acid (eq)	(**6**) [b)] (%)
1	10	1.0	2.0	1.8	84
2	5	1.0	2.0	1.8	87
3	10	0.1	0.2	1.8	63
4	10	0.5	1.0	1.8	86
5	10	2.0	4.0	1.8	61
6	10	1.0	2.0	1.2	52
7	10	1.0	2.0	1.5	71
8	10	1.0	2.0	3.0	90
9 [c)]	10	1.0	2.0	1.8	85
10 [d)]	10	1.0	2.0	1.8	85
11 [e)]	10	1.0	2.0	1.8	84
12 [f)]	10	1.0	2.0	1.8	83
13 [g)]	10	1.0	2.0	1.8	85
14	5	0.5	1.0	1.8	90
15	5	0.5	1.0	1.5	86
16	5	0.5	1.0	2.0	92
17	5	0.5	1.0	2.2	92
18 [g)]	5	0.5	1.0	1.8	89

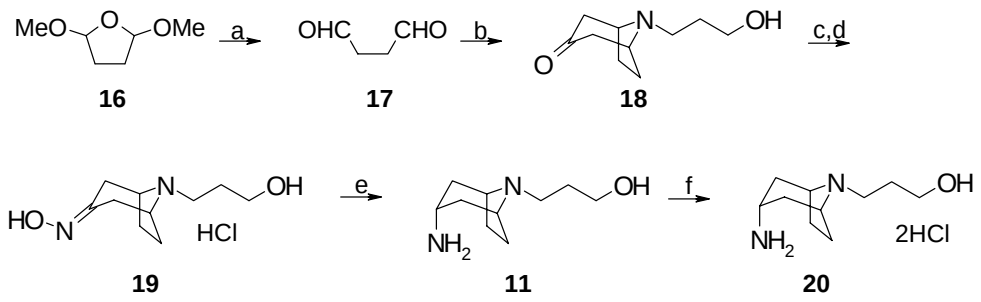
a) The reaction was carried out at 0 ℃ for 2 h and then at rt overnight, unless otherwise noted.
b) Purity of **6** is >99% by HPLC analysis.
c) at rt overnight.
d) at 40 ℃ for 2 h and at rt overnight.
e) at reflux for 2 h and then at rt overnight.
f) at 0 ℃ for 2 h and then at rt for 2 d.
g) at 0 ℃ for 0.5 h and reflux for 1 h.

were determined. This reaction has 3 advantages. 1) This reaction undergoes at room temperature to give carboxylic acid (**6**) directly. 2) Carboxylic acid (**6**) is crystallized from reaction mixture because of its insolubility in the used solvent. So that work-up is performed only by filtration. 3) The product is obtained in high yield (92%) and high purity (>99% by HPLC). Therefore, no purification step is required. Thus, we could develop synthetic route of **6** fitting for scale-up as depicted in Scheme 3.

Synthesis of compound 11

In the original route, 8-methyl group in **8** had to be removed for preparation of **11**. Consequently, direct synthesis of 8-(3-hydroxy)propyl-3α-aminotoropane (**11**) was required (Scheme 4). A solution of **17** in water, 3-amino-1-propanol and acetonedicarboxylic acid was

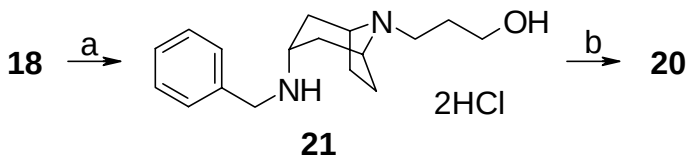
Scheme 4



Reagents: (a) HCl; (b) 3-amino-1-propanol, acetonedicarboxylic acid, pH 5;
(c) H_2NOH, EtOH; (d) HCl; (e) H_2-PtO_2, AcOH; (f) HCl

reacted at pH4-5 to give tropinone (**18**).[14] Also dimethyl acetonedicarboxylate could be used instead of acetonedicarboxylic acid. Tropinone (**18**) reacted with hydroxylamine in EtOH followed by treatment in a usual manner to lead to HCl salt (**19**) of tropinone oxime. The reduction of **19** to amine (**11**) was accomplished by the catalytic reduction [3]using Adams catalyst. This reduction was sensitive to the reaction temperature. The reaction did not start under 35 ℃ and hydrolysis of oxime function occurred over 50 ℃. Consequently, the yield was less than 60% because of hydrolysis of **19** to tropinone (**18**). Since amine (**11**) from oxime (**19**) was not obtained in high purity, purification step was required. For this aim, conversion of **11** to the oxalate appeared to be preferable because of its facile recrystallization. However, in the reaction of oxalate of **11** with acid chloride (**7**), neutralization process was needed to remove oxalic acid, because oxalic acid reacts with **7**. From the above reasons, we gave up a route through oxime (**19**) as a procedure for scale-up. A route by reductive amination of **18** was examined (Scheme 5). Tropinone (**18**) reacted with benzylamine under reductive conditions to give amino product, which was converted into HCl salt (**21**). Debenzylation reaction of **21** produced. Aminotropane (**20**) which hydroxypropyl chain was introduced in advance was synthesized, so that demethylation and

Scheme 5



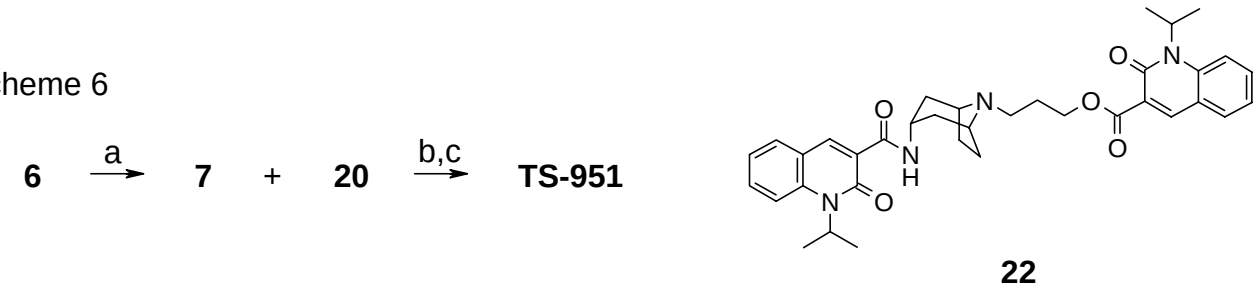
Reagents: (a) benzylamine, H_2-5%Pt/C, MeOH; (b) H_2-5%Pd/C, MeOH

alkylation steps could be taken off. Therefore, a manufacturing process to **TS-951** in 2 steps shorter than the original route was accomplished.

Preparation of TS-951

Condensation reaction of **20** with acid chloride (**7**) was performed in a two-phase system using toluene and aqueous NaOH solution. The reaction produced **TS-951** accompanied with a little amount of diacylated product (**22**), which increased at elevated reaction temperature.

Scheme 6



Reagents: (a) $SOCl_2$, toluene; (b) NaOH, H_2O, toluene; (c) NaOH, EtOH, H_2O

Fortunately, **22** was removed effectively by hydrolysis of the reaction mixture with 10% aqueous NaOH solution in EtOH. After the hydrolysis, the product was precipitated by addition of water to the reaction mixture and collected by filtration. Thus, **TS-951** was obtained as crystals from the reaction mixture without any separation process.

Pilot Plant Result

Carboxylic acid (**6**) was synthesized according to synthetic route developed as depicted in Scheme 3. Both cyclization of **12** to **15** and catalytic hydrogenation of **15** to **13** were performed similar to laboratory examination. Oxidation of **13** to **14** was performed in higher yield than that in laboratory examination. In laboratory, some of **14** were lost in filtration and purification processes. Also condensation step to **6** performed higher yield. We used centrifugal separator in pilot plant, which required very little amount of solvent for washing crystals and free from loss of product. It was confirmed from the HPLC analysis that some of product was transferred to mother liquid in laboratory examination. According to developed synthetic route, carboxylic acid (**6**) was synthesized from **12** in 4 steps (65.6% overall yield). Compound (**20**) was synthesized according to synthetic route developed as

depicted in Scheme 5. Reductive amination of **18** to **21** and reductive debenzylation of **21** to **20** were performed under higher hydrogen pressure (4.0-5.0 Mpa) than that (0.5 Mpa) in laboratory procedure, which did not result in unpreferable difference in reaction. Thus, compound (**20**) was synthesized in 3 steps and 43.4% yield. Carboxylic acid (**6**) was turned into acid chloride (**7**) with $SOCl_2$ in toluene. The reaction mixture was vigorously bubbled even if $SOCl_2$ was added slowly. The reaction proceeded very clearly and **7** was obtained in >99% purity by HPLC analysis. The acid chloride solution was added to a solution of NaOH and **20** in water over 1 h to prevent rising of reaction temperature. After work-up, **TS-951** was prepared in 92.6% yield as crystals. It was result similar to that obtained in laboratory examination.

Conclusions

Effective and convergent process for the preparation of **TS-951** has been examined. Synthesis of 1-isopropyl-2-oxo-3-quinolinecarboxylic acid (**6**) by a sequence containing reductive cleavage of oxazine ring, oxidation using MnO_2, and condensation with Meldrum's acid was accomplished. Also HCl salt (**20**) of 8-(3-hydroxypropyl)-3α-aminotropane was synthesized effectively through reductive amination. Compounds (**6**) and (**20**) were condensed under phase-transfer conditions to produce **TS-951** in good yield. This process could be developed to a pilot plant scale.

EXPERIMENTAL

Melting points were determined by a Buchi 535 melting point apparatus and are uncorrected. IR spectra (KBr) were taken on a Perkin-Elmer 1760 spectrometer. ^{1}H-NMR spectra were recorded on a Varian VXL-200 spectrometer in $CDCl_3$, unless otherwise noted. Chemical shifts are reported in ppm (δ) values, based on tetramethylsilane as an internal standard. MS were taken on a JEOL JMS-SX102 spectrometer. Elemental analyses were taken on a Perkin-Elmer 2400. TLC was performed on silicagel pre-coated plates (Merck, Kieselgel 60F-254). Column chromatography was carried out over silicagel (Asahi glass, M. S. GEL. SIL.)

Diethyl (2-nitrobenzylidene)malonate (2) [5]

To a solution of 2-nitrobenzaldehyde (**1**) (70.0 g, 0.46 mol) in acetic anhydride (175 mL) were added diethyl malonate (70.3 mL, 0.46 mol) and $NaHCO_3$ (58.4 g, 0.70 mol). The reaction mixture was heated at 100 ℃ for 6 h. After being cooled, the reaction mixture was partitioned between AcOEt and water. The organic layer was washed successively with water, 5% Na_2CO_3 and brine, and dried over Na_2SO_4. The solvent was removed *in vacuo* to give a residue, which was triturated with EtOH to give 77.1 g (56.7%) of **2** as a pale yellow solid: mp 49-51 ℃ (recrystallized from EtOH). ^{1}H-NMR δ: 1.02 (3H, t, *J* = 7.2 Hz), 1.36 (3H, t, *J* = 7.2 Hz), 4.08 (2H, q, *J* = 7.2 Hz), 4.35 (2H, q, *J* = 7.2 Hz), 7.39-7.48 (1H, m), 7.50-7.70 (2H, m), 8.20 (1H, s), 8.16-8.26 (1H, s). MS *m/z*: 293 (M^+).

Ethyl 2-oxo-1,2-dihydro-3-quinolinecarboxylate (3)

To a pre-heated (80 ℃) solution of **2** (46 g, 0.15 mol) in acetic acid (500 mL) was added iron powder (53 g, 0.95 mol). The reaction mixture was heated at 80 ℃ for 6.5 h and then cooled and filtered through a Celite pad. The filtrate was evaporated *in vacuo* to leave a residue, which was purified by column chromatography using $CHCl_3$/MeOH 10:1, to give 21.3 g (62.5%) of **3** as a yellow solid: mp 175-179 ℃ (recrystallized from AcOEt-hexane). ^{1}H-NMR δ: 1.45 (3H, t, *J* = 7.2 Hz), 4.46 (2H, q, *J* = 7.2 Hz), 7.20-7.30 (1H, m), 7.50 (1H, d, *J* = 7.8 Hz), 7.61 (1H, ddd, *J* = 1.4, 7.0, 8.4 Hz), 7.65 (1H, d, *J* = 8.0 Hz), 8.56 (1H, s), 12.51 (1H, s). IR cm^{-1}: 3009, 2901, 1732, 1641, 1211. MS *m/z*: 217 (M^+). *Anal.* Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.11; H, 5.24; N, 6.20.

Ethyl 1-isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxylate (4)

To a suspension of sodium hydride (60% mineral oil suspension, 8.9 g, 0.38 mol) in DMF (200 mL) was added ethyl 2-oxo-1,2-dihydro-3-quinolinecarboxylate (**3**) (40 g, 0.18 mol) and isopropyl iodide (62.6 g, 0.36 mol). The reaction mixture was heated at 70 ℃ for 8 h. It was then diluted with water and extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4 and evaporated *in vacuo* to afford a residue, which was purified by column chromatography using AcOEt/hexane 1:4, to give 3.1 g (6.5%) of **4** as a yellow solid: mp 54-57 ℃ (recrystallized from AcOEt-hexane). ^{1}H-NMR δ: 1.42 (3H, t, *J* = 7.2 Hz), 1.66 (6H, d, *J* = 7.2 Hz), 4.41 (2H, q, *J* = 7.2 Hz), 5.15-5.80 (1H, br), 7.17-7.27 (1H, m), 7.54-7.69 (3H, m), 8.30 (1H, s). IR cm^{-1}: 3454, 1732, 1646. MS *m/z*: 259 (M^+). *Anal.* Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.28; H, 6.72; N, 5.18.

1-Isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxylic acid (6)

To a mixture of ethylenediamine (0.41 mL, 6.1 mmol), acetic acid (0.70 mL, 12.2 mmol), **14** (1.00 g, 6.1 mmol) and MeOH (10 mL) was added meldrum's acid (1.59 g, 11.0 mmol) at 0 ℃ and the mixture was stirred for 2 h at same temperature. The reaction mixture was stirred at rt overnight. The resulting precipitates was filtered and washed with MeOH to give 1.17 g (84%) of **6** as a yellow solid: mp 167-169 ℃ (recrystallized from acetone-H_2O). ^{1}H-NMR δ: 1.71 (6H, d, *J* = 7.2 Hz), 5.25-5.75 (1H, br), 7.36-7.45 (1H, m), 7.69-7.85 (3H, m), 8.88 (1H, s), 14.76 (1H, s). IR cm^{-1}: 2535, 1734, 1631. MS *m/z*: 231 (M^+). *Anal.* Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.42; H, 5.54; N, 6.07.

1-Isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxylic acid chloride (7)

3-Quinolinecarboxylic acid (**6**) (10.0 g, 43.2 mmol) was dissolved in thionyl chloride (20mL, 274 mmol) and the mixture was heated at reflux for 4 h. It was evaporated *in vacuo* to leave a residue, which was dissolved in toluene (30 mL). It was evaporated *in vacuo* again to give 10.6 g of crude **7** as a pale yellow solid.

***N*-(*endo*-8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-1-isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxamide (9)**

To a solution of crude **7** (540 mg) obtained above in toluene (2 mL), 3α-aminotropane (**8**) (404 mg, 2.8 mmol) in toluene (3 mL) was added and the whole was stirred at rt for 1 h. The reaction mixture was then poured into 5%$NaHCO_3$ and extracted with $CHCl_3$. The

organic layer was washed with brine, dried over Na_2SO_4 and evaporated under vacuum. The residue was purified by column chromatography using $CHCl_3$ to give a solid, which was recrystallized from AcOEt to give 391 mg (51%) of **9** as a colorless solid: mp 173-177 ℃. ^{1}H-NMR δ: 1.68 (6H, d, *J* = 7.2 Hz), 1.76-1.83 (2H, m), 2.00-2.40 (6H, m), 2.34 (3H, s), 3.10-3.28 (2H, m), 4.30 (1H, q, *J* = 7.0 Hz), 5.40-5.90 (1H, br), 7.22-7.33 (1H, m), 7.55-7.70 (2H, m), 7.75 (1H, d, *J* = 7.8 Hz), 8.83 (1H, s), 10.48 (1H, d, *J* = 7.2 Hz). IR cm^{-1}: 3263, 2961, 1673, 1616, 1585, 1568, 1528. MS *m/z*: 353 (M^+). *Anal.* Calcd for $C_{21}H_{27}N_3O_2$: C, 71.36; H, 7.70; N, 11.88. Found: C, 71.21; H, 7.67; N, 11.84.

_N_-(_endo_-8-Azabicyclo[3.2.1]oct-3-yl)-1-isopropyl-2-oxo-1,2-dihydro-3-quinoline-carboxamide (10)

To a solution of **9** (1.0 g, 2.8 mmol) in 1,2-dichloroethane (10 mL) was added 1-chloroethyl chloroformate (0.41 g, 2.8 mmol) at 0 ℃. The mixture was stirred at 0 ℃ for 0.5 h and refluxed for 1 h. It was evaporated *in vacuo* and the residue was dissolved in MeOH (10 mL). The solution was stirred at reflux for 1 h and was then evaporated *in vacuo*. The residue was purified by column chromatography using $CHCl_3$/MeOH (saturated with NH_3) 20:1 to leave a solid, which was recrystallized from AcOEt to give 530 mg (55%) of **10** as a colorless solid: mp 202-203 ℃. ^{1}H-NMR δ: 1.69 (6H, d, *J* = 7.2Hz), 1.78-2.40 (9H, m), 3.55-3.68 (2H, m), 4.38 (1H, q, *J* = 7.0 Hz), 5.40-5.82 (1H, br), 7.23-7.35 (1H, m), 7.56-7.70 (2H, m), 7.75 (1H, d, *J* = 7.8 Hz), 8.83 (1H, s), 10.54 (1H, d, *J* = 7.2 Hz). IR cm^{-1}: 3257, 2971, 1674, 1622, 1569, 1531. MS *m/z*: 339 (M^+). *Anal.* Calcd for $C_{20}H_{25}N_3O_2$: C, 70.77; H, 7.42; N, 12.38. Found: C, 70.57; H, 7.49; N, 12.44.

1,2-Dihydro-2,2-dimethyl-4_H_-3,1-benzoxadine(15)

To a mixture of 2-aminobenzyl alcohol (**12**) (500 g, 4.63 mol), acetic acid (8.3 g, 0.14 mol) and water (4000 mL) was added acetone (509 mL, 6.94 mol). The reaction mixture was stirred at rt for 1 h and was then stirred at 0 ℃ for 1 h. Resulting precipitates were filtered, washed with water and dried to give 700 g (93%) of **15** as a yellow solid: mp 119-121 ℃ (recrystallized from acetone-H_2O). ^{1}H-NMR δ: 1.48 (6H, s), 3.97 (1H, s), 4.83 (2H, s), 6.64 (1H, d, *J* = 7.0 Hz), 6.79 (1H, t, *J* = 7.0 Hz), 6.95 (1H, d, *J* = 7.0 Hz), 7.08 (1H, t, *J* = 7.0 Hz). IR cm^{-1}: 3310, 1612, 1592. MS *m/z*: 163 (M^+). *Anal.* Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.40; H, 7.97; N, 8.64.

2-Isopropylaminobenzyl alcohol (13)

From **12**: To a mixture of **12** (150 g, 1.22 mol), acetic acid (850 mL), sodium acetate hydrate (300 g), acetone (500 mL), EtOH (275 mL) and water (950 mL) was added a solution of sodium borohydride (140 g, 3.68 mol) in 5% NaOH aqueous solution (500 mL) at 0-5 ℃ over a period of 2 h. The reaction mixture was stirred for 1 h and basified with K_2CO_3. The mixture was extracted with hexane. The organic layer was washed with water, and brine. The solvent was evaporated *in vacuo* and the resulting oily residue was distilled under reduced pressure to give 142 g (70.7%) (bp 114 ℃ / 4 mmHg) of **13** as a yellow oil:^{1}H-

NMR δ : 1.24 (6H, d, *J* = 7.2 Hz), 3.78 (1H, sept, *J* = 7.2 Hz), 4.62 (2H, s), 6.57-6.72 (2H, m), 7.02-7.05 (1H, m), 7.15-7.27 (1H, m). IR cm^{-1}: 3391, 1608, 1587. MS *m/z*: 165 (M^+). *Anal.* Calcd for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.30; H, 9.33; N, 8.88.

From **15**: A mixture of **15** (7.0 g, 43 mmol), 5%Pt-C (0.14 g) and MeOH (70 mL) was heated at 40 ℃ for 15 h under hydrogen pressure of 0.5 MPa. The reaction mixture was filtered and filtrate was concentrated *in vacuo*. The residue was dissolved in toluene and washed with water repeatedly. The solvent was evaporated *in vacuo* to give 5.6 g of crude **13** as a yellow oil.

2-Isopropylaminobenzaldehyde (14)

To a solution of crude **13** (33.62 g) in toluene (300 mL) was added MnO_2(CMD-100®) (44.12 g, 0.51 mol) and the mixture was stirred at reflux for 2 h. The reaction mixture was filtered and filtrate was evaporated *in vacuo*. The residue was purified by column chromatography using hexane/AcOEt = 10:1 to give 20.59 g of **14** as a yellow oil: ^{1}H-NMR δ : 1.28 (6H, d, *J*= 6.4 Hz), 3.75 (1H, sept, *J* = 6.4 Hz), 6.61-6.72 (2H, m), 7.33-7.47 (2H, m), 8.28 (1H, br), 9.80 (1H, s). IR cm^{-1}: 3317, 1652, 1610, 1579. MS *m/z*: 163 (M^+). *Anal.* Calcd for $C_{10}H_{13}NO \cdot 0.25H_2O$: C, 71.61; H, 8.11; N, 8.35. Found: C, 71.64; H, 7.92; N, 8.65.

To a solution of **14** (1.00 g, 6.13 mmol) in AcOEt (5 mL) was added 4 mol/L HCl in AcOEt (1.5 mL) and the mixture was stirred at 0 ℃ for 2 h. The resulting precipitates was filtered and washed with AcOEt to give 1.02 g of 2-isopropylaminobenzaldehyde hydrochloride as a orange prism: mp 133-136 ℃ (recrystallized from IPA-AcOEt). ^{1}H-NMR δ : 1.45 (6H, d, *J* = 7.0 Hz), 3.74 (1H, sept, *J* = 7.0 Hz), 7.48 (1H, dt, *J* = 1.5, 7.0 Hz), 7.60-7.95 (5H, m), 10.00 (1H, s). IR cm^{-1}: 3372, 2980, 2630, 1692, 1610, 1588. MS *m/z*: 163 (M^+). *Anal.* Calcd for $C_{10}H_{13}NO \cdot HCl \cdot 0.1H_2O$: C, 59.61; H, 7.10; N, 6.95. Found: C, 59.65; H, 6.91; N, 6.91.

8-(3-Hydroxypropyl)-8-azabicyclo[3.2.1]octan-3-one (18)

To a stirred mixture of 2,5-dimethoxytetrahydrofuran **16** (120 mL, 0.93 mol) and water (300 mL) was added concentrated HCl (45 mL) at rt. After 20 min, the reaction mixture became homogeneous. Thereafter, water (450 mL), a solution of 3-amino-1-propanol (105 mL,1.37 mol) and concentrated HCl (138 mL) in water (600 mL), a solution of 1,3-acetonedicarboxylic acid (150 g, 1.03 mol) in water (700 mL), and a solution ofNa_2HPO_4 (66 g) in water (300 mL) were successively added to the homogeneous reaction mixture. Furthermore, pH of the resulting solution was then adjusted to the range of 4 to 5 with 40% aqueous NaOH solution (215 mL). After bubbling of carbon dioxide (CO_2) was confirmed, the mixture was stirred at rt overnight. Then concentrated HCl was added to adjust pH of the reaction mixture to 3. The reaction mixture was heated to 80 ℃ and stirring was continued until bubbling of CO_2 was not observed. After completion of the reaction, the reaction mixture was cooled and 20% aqueous NaOH solution was added thereto to render alkaline. Thereafter sodium chloride was added, and the mixture was extracted with $CHCl_3$. The organic layer was washed with water and dried over Na_2SO_4. The organic layer was

evaporated *in vacuo* to give **18** (178.1 g) as a crude product: mp 42-43 ℃. (recrystallized from acetone-hexane) ^{1}H-NMR δ: 1.57-1.68 (2H, m), 1.73-1.83 (2H, m), 2.00-2.17 (4H,m), 2.20-2.29 (2H, m), 2.66 (2H, dd, *J* = 4.4, 16.1 Hz), 2.84 (2H, t, J = 5.7 Hz), 3.62-3.66 (2H, m), 3.90 (2H, t, *J* = 5.7 Hz), 5.12 (1H, brs). IR cm^{-1}: 1714. MS *m/z*: 183 (M^+). *Anal.* Calcd for $C_{10}H_{17}NO_2$ 0.1H_2O: C, 64.91; H, 9.37; N, 7.57. Found: C, 64.53; H, 9.40; N,7.57.

8-(3-Hydroxypropyl)-8-azabicyclo[3.2.1]octan-3-one oxime hydrochloride (19)

A crude product of **18** (178.1g) obtained above was dissolved in EtOH (1200 mL) and 50% aqueous hydroxylamine solution (72.9 g, 1.10 mol) was added to the solution at rt. The reaction mixture was stirred at rt overnight. The reaction mixture was evaporated *in vacuo* and toluene was added to the residue. The solvent was again evaporated *in vacuo* and the residue was dissolved in EtOH. To a solution was added concentrated HCl and the crystalline precipitates were filtered to give 161 g (73.9% from **16**) of **19** as a colorless solid: mp 239-242 ℃ (decomp, recrystallized from MeOH-EtOH). ^{1}H-NMR(MeOH-d_4) δ: 1.75-2.08 (4H, m), 2.21-2.56 (4H, m), 2.83-2.93 (1H, m), 3.19-3.45 (3H, m), 3.73 (2H, t, *J* = 5.7 Hz), 4.14-4.20 (2H, m). IR cm^{-1}: 1658. MS *m/z*: 198 (M^+). *Anal.* Calcd for $C_{10}H_{19}N_2O_2Cl$: C, 51.17; H, 8.16; N, 11.93. Found: C, 51.17; H, 8.15; N, 11.93.

***endo*-3-Amino-8-(3-hydroxypropyl)-8-azabicyclo[3.2.1]octane (11)**

To a solution of **19** (100 g, 0.43 mol) in AcOH (500 mL) was added platinum oxide (5.0 g) and the whole was stirred at 45 ℃ for 18 h under hydrogen pressure of 0.5 MPa. To the reaction mixture was added water and the mixture was filtered. The filtrate was evaporated *in vacuo*. The residue was dissolved in water (50 mL) and MeOH (100 mL). To asolution was added a solution of oxalic acid (38.4 g) in MeOH (200 mL) and further MeOH (200 mL) was added. The mixture was stirred at rt overnight. The precipitated crystals were filtered to give 71.3 g (53.9%) of *endo*-3-amino-8-(3-hydroxypropyl)-8-azabicyclo[3.2.1]octane hydrochloride oxalate as a colorless solid: mp 230-233 ℃ (decomp, recrystallized from MeOH). ^{1}H-NMR(DMSO-d_6) δ 1.66-1.94 (6H, m), 1.94-2.25 (6H, m), 2.38-2.63 (2H, m), 2.71-3.10 (3H, m), 3.35-3.61 (3H, m), 3.63-4.00 (3H, m). IR cm^{-1}: 3414, 2115, 1634. MS *m/z*: 184 (M^+). *Anal.* Calcd for $C_{12}H_{23}N_2O_4Cl$: C, 48.89; H, 7.86; N, 9.50. Found: C, 48.59; H, 8.10; N, 9.77.

To a solution of oxalate obtained above (30.0 g, 0.097 mol) in water (300 mL) was added $KHCO_3$ (48.3 g) and stirring was continued at rt for 4 h. Then, EtOH (300 mL) was added. After stirring for 1 h, the precipitated matters were filtered off and the filtrate was concentrated. Again EtOH (300m L) was added to the residue. The precipitated matters were filtered off and the filtrate was concentrated. The residue was dissolved in $CHCl_3$ (300 mL). After drying over Na_2SO_4, the solvent was evaporated *in vacuo* to give 18.5 g of crude **11** as a colorless oil: ^{1}H-NMR δ: 1.43-1.50 (2H, m), 1.54-1.71 (2H, m), 1.85-2.14 (6H, m), 2.60 (2H, t, *J* = 5.6 Hz), 3.19-3.37 (3H, m), 3.85 (2H, t, *J* = 5.2 Hz).

***endo*-3-Amino-8-(3-hydroxypropyl)-8-azabicyclo[3.2.1]octane dihydrochloride (20)**

To a solution of oxime hydrochloride (**19**) (100 g, 0.43 mol) in AcOH (500 mL) was added

platinum oxide (5.0 g) and the reaction mixture was stirred at 45 ℃ for 18 h under hydrogen pressure of 0.5 MPa. Water was added to the reaction mixture and the mixture was filtered. Concentrated HCl was added to the filtrate and the mixture was evaporated *in vacuo*. The residue was recrystallized from MeOH-EtOH to give 66.4 g (50.2%) of **20** as a colorless solid: mp >270℃. ^{1}H-NMR (D_2O) δ: 1.95-2.03 (2H, m), 2.03-2.35 (4H, m), 2.35-2.58 (2H, m), 2.58-2.75 (2H, m), 3.10-3.25 (2H, m), 3.70 (2H, t, *J* = 6.0 Hz), 3.80 (1H, t, *J* = 5.4 Hz), 4.05-4.25 (2H, m). IR cm^{-1}: 3408, 2989, 2849, 1597, 1505. MS *m/z*: 185 (M^+). *Anal.* Calcd for $C_{10}H_{22}N_2OCl_2$: C, 46.70; H, 8.62; N, 10.89. Found: C, 46.70; H, 8.77; N, 10.85.

_N_-(_endo_-8-(3-Hydroxy)propyl-8-azabicyclo[3.2.1]oct-3-yl)-1-isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxamide (TS-951)

From **10**: To a solution of **10** (2.00 g, 5.9 mmol) in EtOH (50 mL) were added3-bromo-1-propanol (0.53 mL, 5.9 mmol) and K_2CO_3 (0.81 g, 5.9 mmol). The reaction mixture was stirred at reflux for 10 h and was then evaporated *in vacuo*. To the residue was added water and the mixture was extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified by column chromatography using $CHCl_3$/MeOH (saturated with NH_3) 40:1, to afford a solid, which was recrystallized from AcOEt to give 510 mg (21.8%) of **TS-951** as a colorless solid.

From **6** and **20**: To a solution of **6** (0.99 g, 4.3 mmol) in toluene (10 mL) was added thionyl chloride (0.77 g, 6.5 mmol) and the whole was stirred at 80 ℃ for 1 h. The reaction mixture was used in next step without purification.

To a solution of NaOH (0.93 g, 23.3 mmol) and **20** (1.00 g, 3.89 mmol) in water (10 mL) was added a solution of acid chloride at 5-15 ℃. After being stirred for 0.5 h, the reaction mixture was concentrated *in vacuo*. To the resulting residue were added EtOH (10 mL) and 10% aqueous NaOH solution (10 mL), and the whole was stirred at rt for 0.5 h. Additional water (20 mL) was added to the reaction mixture. The resulting precipitates was filtered to give 1.44 g (93%) of **TS-951** as a colorless solid: mp 171-172 ℃ (recrystallized from EtOH-H_2O). ^{1}H-NMR δ: 1.68 (6H, d, *J* = 7.2 Hz), 1.62-1.78 (2H, m), 1.80-196 (2H, m), 2.00-2.38 (6H, m), 2.72 (2H, t, *J* = 7.0 Hz), 3.32-3.52 (2H, m), 3.88 (2H, t, *J* = 7.0 Hz), 4.30 (1H, q, *J* = 7.0 Hz), 5.45-5.80 (1H, br), 7.23-7.33 (1H, m), 7.56-7.70 (2H, m), 7.75 (1H, d, *J* = 7.8 Hz), 8.83 (1H, s), 10.51 (1H, d, *J* = 7.2 Hz). IR cm^{-1}: 3431, 3240, 1669. MS *m/z*: 397 (M^+). *Anal.* Calcd for $C_{23}H_{31}N_3O_3$: C, 69.49; H, 7.86; N, 10.57. Found: C, 69.22; H, 7.90; N, 10.43.

A procedure for pilot plant scale

1,2-Dihydro-2,2-dimethyl-4*H*-3,1-benzoxadine (15)

To a mixture of 2-aminobenzyl alcohol (**12**) (49.5 kg, 402 mol), acetic acid (0.73 kg, 12.1 mol) and water (360 kg) was added acetone (35.0 kg, 603 mol). The reaction mixture was stirred at rt for 1 h and the whole was stirred at 5 ℃ for overnight. Resulting precipitates was filtered, washed with water and dried, to give 62.2 kg (purity 98.9%, yield 94.8%) of **15** as a brown solid.

2-Isopropylaminobenzyl alcohol (13)

A mixture of **15** (31.1 kg, 191 mol), 5%Pt-C (wet) (1.2 kg as dry weight) and MeOH (160kg) was stirred at 35 ℃ for 5 h under hydrogen pressure of 3.0 MPa. The reaction mixture was filtered. This reaction was repeated twice and combined filtrate was concentrated *in vacuo*. The residue was dissolved in toluene (250 kg) and washed three times with water (130 kg). This toluene solution was estimated including 49.3 kg of **13** by GC, which was advanced directly to next oxidation step.

2-Isopropylaminobenzaldehyde (14)

To a solution of **13** (estimated 49.3 kg by GC) in toluene (250 kg) was added MnO_2 (CMD-100®) (66 kg, 759 mol) and the mixture was stirred at reflux for 5 h. Additional MnO_2 (CMD-100®) (14 kg, 161 mol) and toluene (50 kg) were added to the reaction mixture and the reaction mixture was then heated at reflux for 2 h. The reaction mixture was filtered and filtrate was evaporated *in vacuo* to give 45.9 kg of crude **14**.

1-Isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxylic acid (6)

To a solution of crude **14** (45.9 kg) in MeOH (184 kg) were added ethylenediamine (8.5 kg, 141 mol), acetic acid (16.9 kg, 281 mol) and meldrum's acid (73.0 kg, 507 mol) at 0-10 ℃. After the reaction mixture was stirred at room temperature overnight, it was cooled to 5 ℃. The resulting precipitates was filtered, washed with MeOH (10 kg) and dried, to give 61.0 kg (purity: 99.7%, yield: 65.6% from **12**) of **6** as a yellow solid.

8-(3-Hydroxypropyl)-8-azabicyclo[3.2.1]octan-3-one (18)

To a cooled solution of 3-amino-1-propanol (56.3 kg, 750 mol) in water (330 kg) was added 36% HCl (91.2 kg, 900 mol). To a stirred mixture of 2,5-dimethoxytetrahydrofuran (**16**) (66.1 kg) in water (230 kg) was added 36% HCl (30.4 kg) at rt. After 20 min, 3-amino-1-propanol hydrochloride solution obtained above, water (180 kg), dimethyl acetonedicarboxylate (100 kg, 574 mol) in water (390 kg), Na_2HPO_4 $12H_2O$ (90 kg) solution in water (100 kg) were added to the reaction mixture. After addition was completed, pH of the resulting solution was then adjusted to the range of 4 to 5 with 25 kg of 48% aqueous NaOH solution. After the mixture was stirred for overnight, 188 kg of 48% aqueous NaOH solution was added and heated at 80 ℃ for 2 h. The mixture was cooled and 36% HCl (235 kg) was added. The mixture was stirred at 80 ℃ for 1 h, then cooled to rt. 110 kg of 48% aqueous NaOH solution was added thereto to render alkaline. Thereafter NaCl (325 kg) was added, and the mixture was extracted with CH_2Cl_2. The organic layer was washed with 25% aqueous NaCl solution and dried over Na_2SO_4 (30 kg). The organic layer was evaporated *in vacuo*, and the resulting residue was dissolved in MeOH (480 kg). The solution was evaporated *in vacuo* again, and the residue was dissolved in MeOH (640 kg). The solution was estimated including 63.2 kg of **18** by GC.

***endo*-3-Benzylamino-8-(3-hydroxypropyl)-8-azabicyclo[3.2.1]octane dihydrochloride (21)**

To a solution of **18** (estimated 63.2 kg by GC) in MeOH (640 kg), benzylamine (56.7 kg, 524

mol), 5%Pt-C (wet) (9.2 kg as dry weight) and MeOH (120 kg) were added. The reaction mixture was stirred for 18 h at 45 ℃ under hydrogen pressure of 4.0 MPa. The reaction mixture was filtered and the filtrate was evaporated *in vacuo*. To the residue was added 8.4% HCl in MeOH (567 kg), and then diisopropyl ether (329 kg) was added. The mixture was cooled to 0 ℃ and stirred for overnight. Resulting precipitates were filtered to give 83.3 kg of wet **21**: mp 246-249 ℃ (recrystallized from MeOH-diisopropyl ether). ^{1}H-NMR (DMSO-d_6) δ : 1.64-2.00 (2H, m), 2.05-2.46 (6H, m), 2.67-2.90 (2H, m), 2.90-3.12 (2H, m), 3.23-3.60 (3H, m), 3.80-4.05 (2H, m), 4.25 (2H, s), 7.37-7.52 (3H, m), 7.60-7.78 (2H, m), 9.43-9.80 (2H, br), 10.50-10.80 (1H, br). IR cm^{-1}: 3302, 1590. MS *m/z*:274 (M^+). *Anal*. Calcd for $C_{17}H_{28}N_2OCl_2$: C, 58.79; H, 8.13; N, 8.07. Found: C, 58.50; H, 8.21; N, 8.02.

***endo*-3-Amino-8-(3-hydroxypropyl)-8-azabicyclo[3.2.1]octane dihydrochloride (20)**

The mixture of wet **21** (83.3 kg), 5%Pd-C (wet) (9.3 kg as dry weight), 36% HCl (11.4 kg), MeOH (640 kg) and water (200 kg) was stirred for 3.5 h under hydrogen pressure of 5.0 Mpa at 60 ℃. The reaction mixture was filtered and the filtrate was evaporated *in vacuo*. To the residue were added water (6.3 kg) and EtOH (160 kg). The mixture was refluxed to dissolve a solid and then additional EtOH (200 kg) was added. It was cooled to 0 ℃ and stirred for overnight. Resulting precipitates were filtered and dried *in vacuo* to give 55.9kg (purity 100%, yield 43.4% from **16**) of **20** as a colorless solid. mp >270℃.

***N*-(*endo*-8-(3-Hydroxy)propyl-8-azabicyclo[3.2.1]oct-3-yl)-1-isopropyl-2-oxo-1,2-dihydro-3-quinolinecarboxamide (TS-951)**

To a mixture of **6** (13.0 kg, 56.2 mol) and toluene (56.2 kg) were added thionyl chloride (10.0 kg, 84.3 mol) and the mixture was stirred at 80 ℃ for 3 h. The reaction mixture bubbled vigorously in early stage of reaction. After the reaction was completed by HPLC analysis, it was cooled to rt. The acid chloride solution was used in following condensation step without work-up. To a solution of NaOH (12.3 kg, 307 mol) and **20** (13.2 kg, 51.1 mol) in water (132 kg), above obtained acid chloride solution was added under 15 ℃. The reaction mixture was stirred at rt overnight. The reaction mixture was heated to 70 ℃ and the organic layer was separated from aqueous layer. The organic layer was concentrated *in vacuo*. To the resulting residue were added EtOH (72.2 kg), 45.1 kg of 14% aqueous NaOH solution, and water (20.0 kg). The mixture was stirred at 38 ℃ for 1 h. After hydrolysis was completed by HPLC analysis, additional water (237 kg) was added. The resulting precipitates was filtered and dried to give 18.8 kg (purity 99.8%, yield 92.6%) of **TS-951** as a pale yellow solid.

ACKNOWLEDGEMENTS

The authors wish to thank Mr. Kyoichi Hasegawa and Mr. Masato Ito for their technical assistance.

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