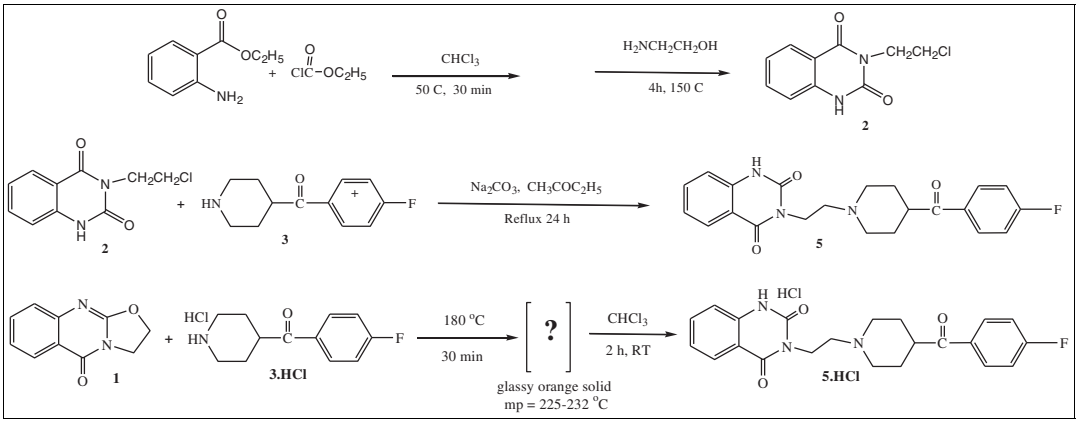
Reinvestigation of the Synthesis of Ketanserin (**5**) and its Hydrochloride Salt (**5.HCl**) via 3-(2-Chloroethyl)-2,4-(1*H*,3*H*)-quinazolinedione (**2**) or Dihydro-5*H*-oxazole(2,3-*b*)quinazolin-5-one (**1**)

Hossein Fakhraian* and Mehdi Heydary

Department of Chemistry, Imam Hossein University, Tehran, Iran
*E-mail: fakhraian@yahoo.com

Received September 1, 2012
DOI 10.1002/jhet.1897
Published online 00 Month 2013 in Wiley Online Library (wileyonlinelibrary.com).



The synthesis of ketanserin (**5**) and its hydrochloride salt (**5.HCl**) using respectively equimolar amounts of 3-(2-chloroethyl)-2,4-(1*H*,3*H*)-quinazolinedione (**2**) with 4-(parafluorobenzoyl)piperidine (**3**) and dihydro-5*H*-oxazole(2,3-*b*)quinazolin-5-one (**1**) with hydrochloride salt of 4-(parafluorobenzoyl)piperidine (**3.HCl**) is reinvestigated. The one-pot reaction of ethyl-2-aminobenzoate with ethyl chloroformate and ethanol amine has afforded 3-(2-chloroethyl)-2,4-(1*H*,3*H*)-quinazolinedione (**2**) (86%) that was then refluxed with 4-(parafluorobenzoyl)piperidine (**3**) in ethyl methyl ketone in the presence of sodium carbonate to obtain free base of ketanserin (87%). In another attempt, a very pure hydrochloride salt of ketanserin (**5.HCl**) was synthesized using equimolar amounts of dihydro-5*H*-oxazole(2,3-*b*)quinazolin-5-one (**1**) and hydrochloride salt of 4-(parafluorobenzoyl) piperidine (**3.HCl**) by a solvent-less fusion method. Thus, under optimized conditions, 180°C and a reaction time of 30 min, the powder mixture was transformed into glassy crystals that were initially readily soluble in chloroform but were transformed afterwards over time (2 h) to white precipitates (**5.HCl**) suspended in chloroform with a yield of 72%.

INTRODUCTION

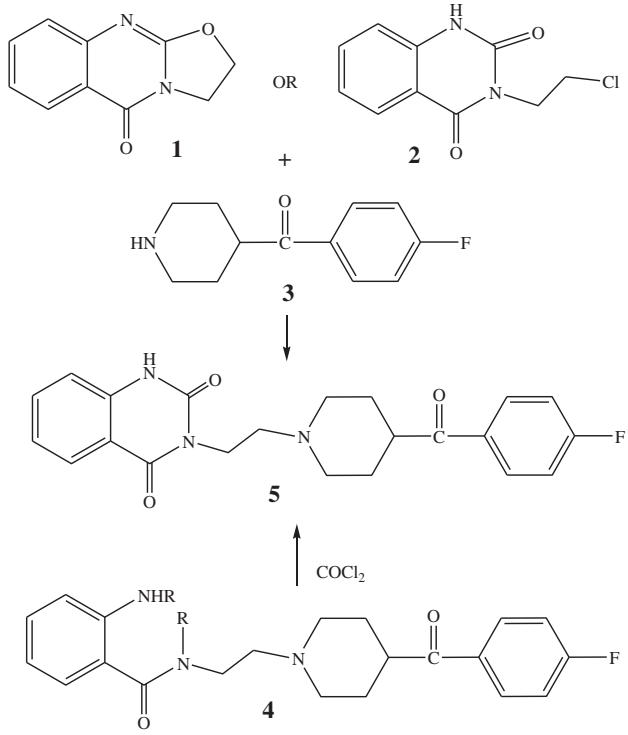
Ketanserin (**5**), a drug with affinity for multiple G protein-coupled receptors, especially serotonin receptors, was discovered at Janssen Pharmaceutical in 1980 and classified as an antihypertensive by the World Health Organization. It has been used to reverse hypertension caused by protamine (which, in turn, was administered to reverse the effects of heparin overdose) and in cardiac surgery. [1,2] Tritium (^{3}H) radioactively labeled **5** was used as a radioligand for the serotonin 5-HT_{2A} receptor, for example, in receptor binding assays and autoradiography.[3–6] This radiolabeling enables the study of the serotonin-2A receptor distribution in the human brain.

There are different methods for the preparation of **5** (Scheme 1).[7–11] The earliest one consists of reacting 3-(2-chloroethyl)-2,4-(1*H*,3*H*)-quinazolinedione (**2**) with 4-(parafluorobenzoyl)piperidine (**3**) in the presence of Na_2CO_3 in a solvent such as isobutyl methyl ketone. Following this method, the product **5** was obtained in a low yield, approximately 20%.[7,8] Another approach consists of the reaction of $^{11}COCl_2$ with **4** for preparing ^{11}C-labeled ketanserin.[9]

Another process using equimolar quantities of 2,3-dihydro-5*H*-oxazole(2,3-*b*)quinazolin-5-one (**1**) and **3** for preparation of **5** has been reported.[11,12] The reaction of **1** with **3** was carried out in solvent-less conditions by mixing the two reagents in powder form and heating the mixture at 100°C until fusion takes place. Maintaining this temperature for a certain time has enabled the reaction to go to completion. The reaction product was in the form of a solid microcrystalline mass, from which the product was obtained with a high degree of purity by dissolving it in a solvent followed by recrystallization. Another approach is to carry out the reaction in an inert solvent, such as toluene, in the presence of a small quantity of acid acting as a catalyst. In both cases, the product was formed in high yields.

Two reagents (**1** and the hydrochloride salt of **3**) used in the synthesizing procedure are known compounds and

Scheme 1



commercially available, although they can be prepared by the methods described in the literature.[12–16]

Compound **2** is not commercial and should be prepared. There are different reports concerning the preparation of quinazolin-2,4(1*H*,3*H*)-diones.[17–19]

In this contribution, we propose a one-pot method for high-yield preparation of 3-(2-chloroethyl)-2,4-(1*H*,3*H*)-quinazolinedione and reinvestigate the synthesis of ketanserin and its hydrochloride salt via dihydro-5*H*-oxazole (2,3-*b*)quinazolin-5-one or 3-(2-chloroethyl)-2,4-(1*H*,3*H*)-quinazolinedione.

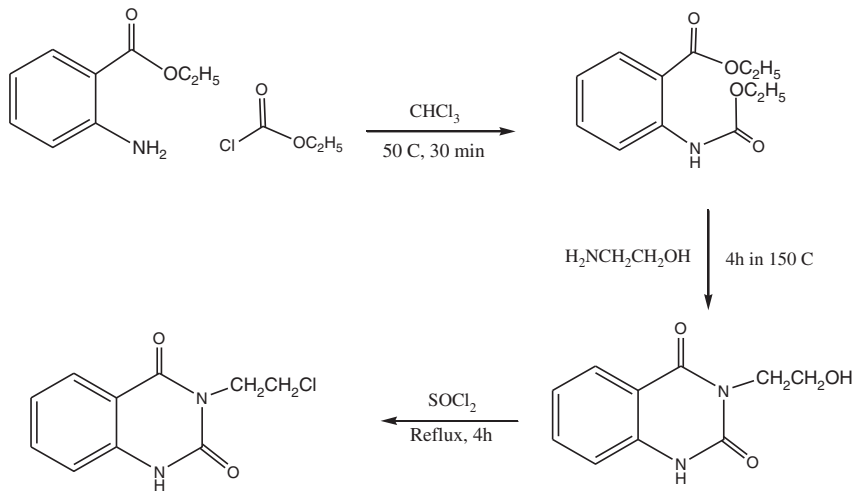
RESULTS AND DISCUSSION

We have firstly tried the synthesis of **2** via a three-step method starting with ethyl 2-aminobenzoate (Scheme 2, experimental part).

The first step of the reaction was very exothermic accompanied by rapid apparition of white precipitate soluble in 1-propanol and dichloromethane and insoluble in chloroform. This reaction was performed under different reaction conditions (solvent-less or in the presence of chloroform, at RT or at 50°C, at different reactant addition order). Under solvent-less condition and using 110 mol% of ethyl 2-chloroformate, the apparition of white precipitate was instantaneous preventing the stirring of the reaction mixture, and the yield was ~50%. The presence of a solvent in the reaction medium is necessary because of the exothermic nature of the reaction and volatility of ethyl chloroformate (bp 93°C) causing increase of yield to 68%. Order of reactant addition does not affect the yield of the product. GC–MS analysis of the product and the presence of fragment with *m/z* of 238, 165, and 119 attributed respectively to the MH^+, M – COOEt, and M – COOEt&OEt was conformed to the structure of ethyl (2-ethoxycarbonyl)phenylcarbamate.

In the second step, dropwise addition of 2-aminoethanol (500 mol%) to ethyl (2-ethoxycarbonyl)phenylcarbamate dissolved in chloroform caused initially apparition of white vapor dissipated after a few minutes. Heating the reaction mixture at 150°C for 4 h allowing chloroform to be evaporated from the reaction medium afforded 3-(2-hydroxyethyl)-2,4-(1*H*,3*H*)-quinazolinedione as white precipitates in the reaction medium at RT with a yield of 68%. GC–MS analysis of the product and the presence of fragment with *m/z* of 207, 189, 163, and 146 attributed respectively to the M, M – OH, M – CH_2CH_2OH, and M – NCH_2CH_2OH, and ^{1}H-NMR and ^{13}C-NMR spectra were conformed to the structure of ethyl 3-(2-ethoxyethyl)-2,4-(1*H*,3*H*)-quinazolinedione.

Scheme 2

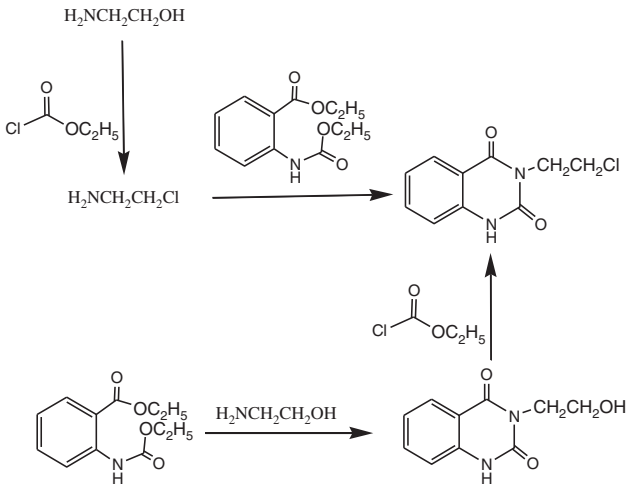


In the last step, ethyl 3-(2-ethoxyethyl)-2,4-(1*H*,3*H*)-quinazolinedione was dissolved in chloroform prior to the dropwise addition of $SOCl_2$ (200 mol%). After addition of $SOCl_2$ and 30 min of heating, a white precipitate appeared and disappeared after a few hours. Finally, after 24 h at reflux temperature, the product appears as a white precipitate at the bottom of the flask with a yield of 78%. GC–MS analysis of the product and the presence of fragment with *m/z* of 188 and 146 attributed respectively to $M - Cl$ and $M - NCH_2CH_2Cl$, and ^{1}H-NMR and ^{13}C-NMR spectra were conformed to the structure of ethyl 3-(2-chloroethyl)-2,4-(1*H*,3*H*)-quinazolinedione (**2**).

In some of our experiment, in the second step, conjoint presence of ethyl 3-(2-ethoxyethyl)-2,4-(1*H*,3*H*)-quinazolinedione and ethyl 3-(2-chloroethyl)-2,4-(1*H*,3*H*)-quinazolinedione (**2**) has been observed. We have expected the presence of minor amount of ethyl chloroformate with the product of the first step that cause chlorination of 2-aminoethanol [before cyclization reaction with ethyl (2-ethoxycarbonyl)phenylcarbamate] or chlorination of the product [after cyclization reaction with ethyl (2-ethoxycarbonyl)phenylcarbamate] in the second step. So, we have tried a one-pot procedure in which ethyl chloroformate was used as the reactant of the first step and chlorinating agent for both 2-aminoethanol and ethyl 3-(2-ethoxyethyl)-2,4-(1*H*,3*H*)-quinazolinedione (Scheme 3).

Thus, dropwise addition of ethyl 2-aminobenzoate to 250 mol% of ethyl chloroformate dissolved in chloroform, stirring the reaction mixture for 0.5 h at 50°C, finally addition of 500 mol% of 2-aminoethanol (as reactant and solvent with bp of 170°C), and continuing the reaction during 4 h at 150°C afforded ethyl 3-(2-chloroethyl)-2,4-(1*H*,3*H*)-quinazolinedione (**2**) with a yield of 87%. The overall yield of the precedent three-step method was 36% (Scheme 4).

Scheme 3



We first tried to prepare **5** from the reaction of **2** with the free base of **3**. Only the hydrochloride salt of **3** was commercially available, and it had to be transformed into the free base. An aqueous solution of NaOH caused hydrolysis of the hydrochloride salt of **3** and substitution of the fluorine atom by a hydroxyl group. Using a methanolic solution of NaOH and Na_2CO_3 afforded the free base of **3** with a yield of 48% and 82%, respectively. When an aqueous solution of 32% ammoniac was used, the free base of **3** was obtained with a yield of 63%.

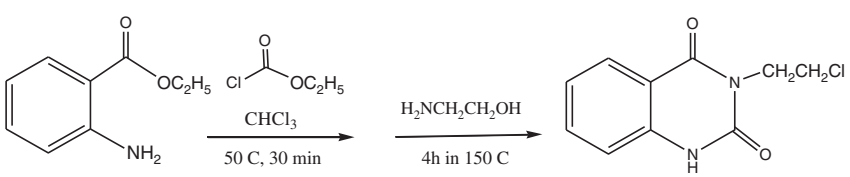
The preparation of **5** was accomplished with a yield of 86% via refluxing the mixture of **2**, the free base of **3**, sodium carbonate, and ethyl methyl ketone for 24 h. The previous reporting yield was 20%.[7]

Another method for the preparation of **5** was to use **1** as reactant. Fusion of the powder mixture of the free base of **3** with **1** at 110°C afforded a yellow solid with a yield of 85% and an mp of 200–205°C. The resulting product was not pure and was recrystallized to obtain pure **5** (mp = 235–240°C).

In another attempt, **5** was synthesized from the solventless reaction by fusion of the powder mixture of **1** (mp = 160–163°C) and the hydrochloride salt of **3** (mp = 222–224°C). Heating at 150°C for 25 min do not affect the powder mixture. Above 160°C, the melting began and was completed after 10 min, forming an orange compound. The mixture was solidified at RT (with an mp of 225–230°C) and dissolved in chloroform. The clear solution of orange solid in chloroform was transformed to a turbid solution after approximately 30 min because of the precipitation of a white precipitate, the amount of which increased over 2 h (Fig. 1). After filtering, washing with chloroform, and drying the precipitate, the hydrochloride salt of **5** was obtained with a purity over 95%. Using different temperatures and reaction times afforded different yields of the hydrochloride salt of **5** (Table 1). Under optimized conditions, the target compound was obtained with a yield of 72% at 180°C with a total reaction time of 30 min.

The advantages of this method compared with those reported previously is the direct use of the hydrochloride

Scheme 4



salt of **3** and obtaining the pure hydrochloride salt of **5** without the need of further recrystallization.

The transformation of the orange solid to the hydrochloride salt of **5** does not take place in DMSO, as it does in chloroform, and after several days at RT, only small amounts of the hydrochloride salt of **5** were observed. The nature of this orange solid is ambiguous, and GC–MS analysis of the solution in chloroform showed two reactants (**1** and **3**) with the same retention time and mass spectroscopic pattern. It can be hypothesized that the orange solid product is due to weak intermolecular binding between **1** and the hydrochloride salt of **3** and is the major cause that afforded the hydrochloride salt of **5** in chloroform by an unknown mechanism.

The ^{13}C-NMR and ^{19}F-NMR characteristics of **3** and **5**, the hydrochloride salts of **3** and **5** (in DMSO-d_6), and the tartaric salt of **5** (in D_2O) are outlined in Table 2.

The chemical shifts of one of the carbons of the piperidine ring in the hydrochloride salt of **3** and **5** and the carbonyl carbon (C_9 or C_7) in the tartaric salt of **5** were not observed. The chemical shift of the fluorine atom was decreased (in absolute value) between **3** and **5** and their hydrochloride salt forms.

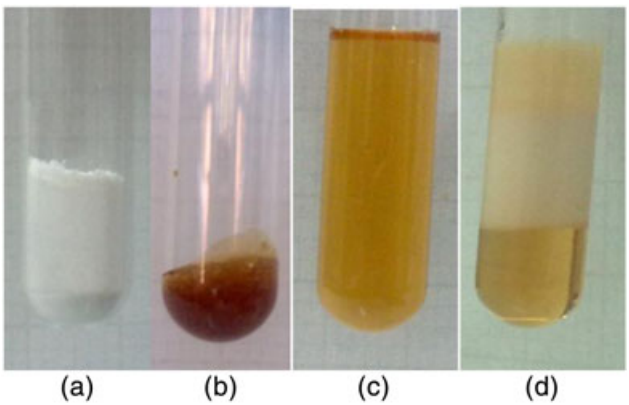


Figure 1. Different steps in the formation of the hydrochloride salt of **5** via fusion of a powder mixture of **1** and the hydrochloride salt of **3**. (a) Before heating, (b) After heating above 160°C, (c) Immediately after dissolution in CH_3Cl at RT, and (d) 2 h after dissolution in CH_3Cl at RT. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

In summary, a one-pot scalable procedure was proposed for the preparation of 3-(2-chloroethyl)-2,4-(1*H*,3*H*)-quinazolinedione (**2**) via very accessible compound as ethyl 2-aminobenzoate, ethyl chloroform, and ethanol amine with a yield of 87%. The preparation of **5** was accomplished with a yield of 86% via refluxing the mixture of **2**, the free base of **3**, sodium carbonate, and ethyl methyl ketone for 24 h. The fusion reaction of **1** with the hydrochloride salt of **3** afforded a very pure hydrochloride salt of **5** without the need for a further recrystallization procedure; however, at higher temperatures and with 10% lower yield than in previous reports were observed concerning the preparation of free base of **5**. An interesting observation is the initial solubility of the orange solid, formed from the reaction of **1** with the hydrochloride salt of **3**, in chloroform and the subsequent precipitation of the pure hydrochloride salt of **5**.

EXPERIMENTAL

NMR spectra were obtained on a Bruker DPX-250 instrument (235.3 MHz for ^{19}F and 62.5 MHz for ^{13}C), and $CDCl_3$, D_2O, and DMSO-d_6 were used as solvents; chemical shifts are reported in δ (ppm) from TMS for ^{13}C and $CFCl_3$ for ^{19}F. Electronic ionization GC–MS spectra were recorded on a Varian (SATURN 4D) spectrometer with a capillary column (DB-5MS, 0.1 μm, 30 m × 0.250 mm). Only *m/z* values having intensities of more than 10% are given, and retention times are reported using temperature programming (100–250°C, 10°C/min) with an He flow rate of 10 mL/min. HPLC analyses were performed on a Knauer EA 4300F equipped with a UV detector, model 2600, and a C_{18} column (250 × 4.6 mm) with an eluent flow rate of 1 mL/min. Melting points were obtained on a Mettler FP61 apparatus. 2,3-Dihydro-5*H*-oxazole(2,3-*b*)quinazolin-5-one (95%) was purchased from Aldrich company.

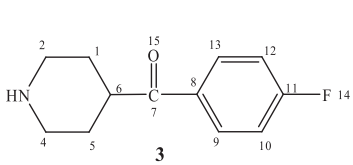
Table 1

Preparation of **5** from the equimolar fusion reaction of **1** and the hydrochloride salt of **3** at 0.01 M scale under different oven temperatures and reaction times.

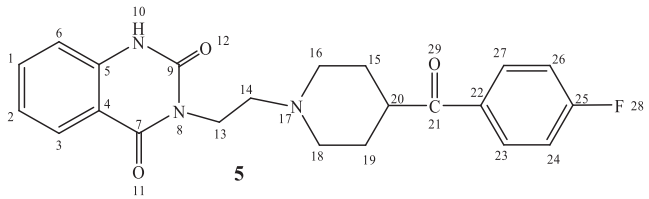
Experiment	Temperature (°C)	Melting time (min)	Reaction time (min)	Yield (%)
1	240	3	6	52
2	240	3	12	59
3	220	4	8	63
4	220	4	15	58
5	200	6	10	39
6	200	6	20	55
7	200	7	10	34
8	200	7	27	53
9	180	10	18	60
10	180	10	20	72
11	160	25	50	62

Table 2

^{13}C-NMR and ^{19}F-NMR characteristics of **3**, **5**, hydrochloride salts of **3** and **5** (in DMSO-d_6) and tartaric salt of **5** (in D_2O).



3



5

Compound	^{13}C δ (ppm)	^{19}F δ (ppm)
3	28.9, 42.3, 115.7 (C_8—F), 116.0 (C_8—F), 131.3 ($C_{9,13}$—F), 131.4 ($C_{9,13}$—F), 131.6 ($C_{10,12}$—F), 131.7 ($C_{10,12}$—F), 163.1 (C_{11}—F), 167.1 (C_{11}—F), 199.9	−105.6
3.HCl	28.4, 39.9, 42.6, 115.6 (C_8—F), 115.9 (C_8—F), 131.1 ($C_{9,13}$—F), 131.2 ($C_{9,13}$—F), 132.1 ($C_{10,12}$—F), 132.2 ($C_{10,12}$—F), 162.9 (C_{11}—F), 166.9 (C_{11}—F), 200.9 (C_7)	−104.7
5	28.4, 37.4, 42.5, 52.6, 55.1, 113.6, 115.0, 115.5 (C_{22}—F), 115.9 (C_{22}—F), 122.4, 127.3, 131.0 ($C_{23,27}$—F), 131.1 ($C_{23,27}$—F), 132.2 ($C_{24,26}$—F), 132.3 ($C_{24,26}$—F), 134.9, 139.3, 150.0, 161.8, 162.8 (C_{25}—F), 166.8 (C_{25}—F), 201.1(C_{21})	−106.5
5.HCl	25.6, 34.8, 51.3, 53.8, 113.9, 115.1, 115.7 (C_{22}—F), 116.0 (C_{22}—F), 122.5, 127.3, 131.2 ($C_{23,27}$—F), 131.4 ($C_{23,27}$—F), 131.7 ($C_{24,26}$—F), 131.8 ($C_{24,26}$—F), 135.1, 139.5, 150.3, 162.3, 163.1 (C_{25}—F), 167.1 (C_{25}—F), 199.1, 199.5	−104.7
5.$C_4H_4O_6$	25.8, 35.5, 40.4, 52.5, 54.7, 72.6 (Tartarate), 113.3, 115.4, 115.8 (C_{22}—F), 116.1 (C_{22}—F), 123.9, 127.2, 130.0 ($C_{23,27}$—F), 131.1 ($C_{23,27}$—F), 131.3 ($C_{24,26}$—F), 131.5 ($C_{24,26}$—F), 136.1, 138.5, 151.6, 164.0 (C_{25}—F), 164.4, 168.1 (C_{25}—F), 176.0 (Tartarate), 202.9	−104.7

Three-step preparation of 3-(2-chloroethyl)-2,4-(1H,3H)-quinazolinedione. In the first step, ethyl 2-aminobenzoate (0.01 mol, 1.47 mL) was added dropwise to a 25-mL double-necked flask equipped with magnetic stir bar and containing ethyl chloroformate (0.011 mol, 1.05 mL) and chloroform (5 mL). The reaction was very exothermic, and after 15–20 s, white precipitates were formed. After 5 min, the precipitates were filtered and washed with ether to afford 1.6 g (68%) of ethyl 2-(ethoxycarbonyl)phenyl carbamate. mp = 175–178°C. GC–MS: retention time: 4.6 min (T_{col} = 150°C); *m/z* [intensity (%)]:166 (15), 165 (100), 120 (31), 119 (33).

In the second step, the mixture of ethyl 2-(ethoxycarbonyl)phenyl carbamate (0.001 mol, 2.1 g), ethanol amine (0.05 mol, 3.1 mL), and chloroform (5 mL) in a one-necked flask equipped with magnetic stir bar was heated at 150°C for 4 h. White precipitates (form at RT) were filtrated and washed with isopropanol affording 1.4 g (68%) of 3-(2-hydroxyethyl)quinazoline-2,4(1*H*,3*H*)-dione. mp = 261–263°C (lit.[7] 273.6°C). GC–MS: retention time: 5.1 min (T_{col} = 250°C); (*m/z*) (%), 28 (24), 29 (12), 31 (24), 39 (12), 63 (24), 64 (14), 90 (22), 92 (18), 119 (50), 146 (95), 147 (17), 163 (81), 188 (32), 189 (100), 207 (64). ^{13}C-NMR (DMSO-d_6, δ ppm): 42.5, 58.2, 114.2, 115.4, 122.8, 127.7, 135.2, 139.7, 150.7, 162.5. ^{1}H-NMR (DMSO-d_6, δ ppm): 3.5 (CH_2), 3.9 (CH_2), 7.1 (CH), 7.6 (CH), 7.9 (CH), 11.2 (NH).

In the third step, the mixture of 3-(2-hydroxyethyl)quinazoline-2,4(1*H*,3*H*)-dione (0.02 mol, 4.1 g), chloroform (50 mL), and $SOCl_2$ (0.04 mol, 2.9 mL) was refluxed for 4 h. White precipitates (at RT) were filtered and washed with chloroform to afford 3.2 g (78%) of 3-(2-chloroethyl)quinazoline-2,4(1*H*,3*H*)-dione (**2**) (lit.[7] 86%). mp = 196–198°C (lit.[7] 215.3°C). GC–MS: retention time: 4.1 min (T_{col} = 250°C); (*m/z*) (%), 146 (59), 188 (100), 189 (22). ^{13}C-NMR (DMSO-d_6, δ ppm): 41.1, 41,5, 113.9, 115.6, 123.1, 127.8, 135.6, 139.7, 150.4, 162.4. ^{1}H-NMR (DMSO-d_6, δ ppm): 3.7 (CH_2), 3.9 (CH_2), 7.1 (CH), 7.6 (CH), 7.9 (CH), 11.5 (NH).

One-pot preparation of 3-(2-chloroethyl)-2,4-(1H,3H)-quinazolinedione. Ethyl 2-aminobenzoate (0.01 mol, 1.47 mL) was added dropwise to a 25-mL double-necked flask equipped with magnetic stir bar and containing ethyl chloroformate (0.025 mol, 2.4 mL) and chloroform (5 mL). The reaction was very exothermic, and after 15–20 s, white precipitates were formed. The reaction mixture was stirred at 50°C for 30 min after which ethanol amine (0.05 mol, 3.1 mL) was added dropwise, and the reaction mixture was stirred at 150°C for 4 h. White precipitates (form at RT) were filtrated and washed with isopropanol affording 1.95 g (87%) of 3-(2-chloroethyl)quinazoline-2,4(1*H*,3*H*)-dione. mp = 205–207°C (lit.[7] 215.3°C).

Preparation of ketanserin (5). 3-(2-Chloroethyl)-2,4-(1*H*,3*H*)-quinazolinedione (**2**) (0.002 mol, 0.45 g) and 4-(parafluorobenzoyl) piperidine (**3**) (0.002 mol, 0.49 g), Na_2CO_3 (1.3 mol, 0.8 g), and methyl ethyl ketone (8 mL) were placed into a 50-mL one-necked flask equipped with a magnetic stir bar. The mixture was stirred and refluxed for 24 h after which the precipitates were appeared. Water (50 mL) was added to the mixture, and the precipitates were filtrated, washed with water, and dried to afford 0.68 g (86%) of ketanserin (lit.[7] 27%). mp = 231–234°C (lit.[7,11] 227–235°C). ^{13}C-NMR ($CDCl_3$, δ ppm): 28.9, 37.9, 43.5, 53.1, 55.6, 114.1, 115.7, 116.1, 116.4, 122.7, 127.7, 131.5, 131.6, 132.7, 135.3, 140.1, 150.6, 162.3, 167, 201.6. ^{1}H-NMR (DMSO-d_6, δ ppm): 1.5 (CH_2), 2.1 (CH_2), 2.5 (CH_2), 3 (CH), 3.3 (CH_2), 3.7 (CH), 7.2 (CH), 7.3 (CH), 7.6 (CH), 7.9 (CH), 8 (CH).

Preparation of ketanserin hydrochloride (5.HCl). Powders of 2,3-dihydro-5*H*-oxazole(2,3-*b*)quinazolin-5-one (**1**) (0.02 mol, 3.72 g) and hydrochloride salt of 4-(parafluorobenzoyl) piperidine (**3.HCl**) (0.02 mol, 4.88 g) were mixed together and

were placed into a 250-mL one-necked flask equipped with a 3-cm magnetic stir bar. Fusion of the mixture started after stirring at 180°C for 10 min. The mixture was kept at 180°C and stirred for another 20 min. The initial white powders were transformed into an orange liquid that solidified at RT as a glassy orange solid (mp = 225–230°C), dissolution of which in chloroform (50 mL) was accompanied by the appearance of white precipitates started after 30 min and continued for 2 h. The precipitates were filtrated and washed with $CHCl_3$ to afford 6.5 g of white powder (72%) mp = 305–307°C, HPLC: retention time = 3.3 min (H_2O/MeOH (75:25); 1 mL/min; detection at 220 nm).

Preparation of the free base of 3. Hydrochloride salt of 4-(parafluorobenzoyl)piperidine (**3.HCl**) (0.01 mol, 2.44 g) was dissolved in methanol (50 mL), and then Na_2CO_3 (0.02 mol, 2.10 g) was added to the solution. The mixture was stirred for 4 h at RT. After the evaporation of methanol, extraction with chloroform, and evaporation of solvent, 1.7 g of the free base of **3** (82%) was obtained. The same procedure using NaOH and an aqueous solution of NH_3 (32%) as a base afforded 1 and 1.3 g, respectively, of **3** (48% and 63%, respectively). mp = 109–114°C. GC–MS: retention time: 3.2 min; *m/z* [intensity (%)]:78 (20), 79 (62), 84 (17), 123 (32), 207 (19), 208 (30).

Preparation of ketanserin tartarate (5.$C_4H_4O_6$). Dissolution of **5** (0.001 mol, 0.39 g) and tartaric acid (0.001 mol, 0.15 g) in ethanol (60 mL) and evaporation of the solvent afforded quantitative yield of ketanserin tartarate with an mp of 185–190°C (Sigma-Aldrich 183–184°C). The solubility of this salt in ethanol was 8 g/L.

REFERENCES AND NOTES

[1] Reimann, I. W.; Okonkwo, P. O.; Koltz, U. Eur J Clin Pharmacol 1983, 25, 73.

[2] Barendregt, J. N. M.; Van Peer, A.; Van Der Hoeven, J. G.; Van Oene, J. C.; Tjandra, Y. I. Br. J. Clin. Pharmac. 1990, 29, 715.

[3] Pietzch, H. J.; Scheunemann, M.; Spies, H.; Brust, P.; Johansen B. Forschungszent. Rossendorf, [ber] FZR 1996, (FZR-122), 31; Chem Abstr 1996, 125, 74599y.

[4] Scheunemann, M.; Pietzch, H. J.; Brust, P.; Wober, J.; Spies, H.; Johansen, B. Forschungszent. Rossendorf, [ber] FZR 1996, (FZR-122), 34; Chem Abstr 1996, 125, 58427k.

[5] Scheunemann, M.; Pietzch, H. J.; Spies, H.; Brust, P.; Johansen, B. Forschungszent. Rossendorf, [ber] FZR 1996, (FZR-122), 44; Chem Abstr 1996, 125, 58428m.

[6] Janssen, C. G. M.; Lenoir, H. A. C.; Thijssen, J. B. A.; Knaeps, A. G.; Verluyten, W. L. M.; Heykans, J. J. P. J Labelled Compd Radiopharm 1988, 25(7), 783.

[7] Vandenberk, J.; Kennis, L. E. J.; Van Der Aa, M. J. M. C.; Van Heertum, A. H. M. Theresia Eur Pat Appl EP 13,612; Chem Abstr 1981, 94, 65718a.

[8] Vandenberk, J.; Kennis, L. E. J.; Van Der Aa, M.; Van, Heertum, A. U.S. Patent 4,335,127; Chem Abstr 1982, 97, 216203u.

[9] Berridge, M.; Comar, D.; Crouzel, C.; Baron, J. C. J. Labelled Compd Radiopharm 1983, 20(10), 73.

[10] Kennis, L. E. J.; J. Vandenberk, Boey, J. M.; Martens, J. C.; V. Heertum, Albert H. M.; Janssen, M.; Awouter, F. Drug Dev Res 1986, 8 (1–4), 133.

[11] Signorini, R.; Verga, A. Eur Pat Appl EP 98499; Chem Abstr 1984, 100, 174849g.

[12] Sun, L.; Fang, Y. Chinese Patent CN 1,793,138; Chem Abstr 2006, 145, 167271 p.

[13] Gueyrard, D.; Leoni, O.; Palmieri, S.; Rollin, P. Tetrahedron: asymmetry 2001, 12, 337.

[14] Willis, M.; Snell, R. H.; Fletcher, A. J.; Woodward, R. L. Org Lett, 2006, 8(22), 5089.

[15] Eleftherios, P. P. J Heterocyclic Chem 1980, 17, 1553.

[16] Dou, G.-L.; Wang, M.-M.; Huang, Z.-B.; Shi, D. -Q. J Heterocyclic Chem 2009, 46(4), 645.

[17] El-Baih, F. E. M.; Bakari, S. B. A.; Hijaz, A. A. JKAU: Sci 2004, 16, 41.

[18] Dou, G.-L.; Wang, M.-M.; Huang, Z.-B.; Shi, D.-Q. Tetrahedron 2007, 63, 9764.

[19] Qin Li, X. Chin Chem Lett 2009, 20, 1201.