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Studies on Quinazolines. VII.[1] Reactions of Anthranilamide with β-Diketones; New Approaches toward the Synthesis of Tetrahydropyrido[2,1-*b*]quinazolin-11-one Derivatives

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Condensation of anthranilamide and its derivatives with various 1,3-cyclohexanediones 5a, b or 2,4-pentanediones under acidic conditions produced a variety of heterocycles, leading to the synthesis of tetrahydropyrido[2,1-*b*]-quinazolin-11-one derivatives. Condensation of anthranilamide with 5a or 5b in the presence of *p*-toluenesulfonic acid at the reflux temperature of tetrahydrofuran (THF) afforded compound 6a (40%) and compound 7a (22%) or compound 6b (47%) and compound 7b (39%), respectively. However, reflux of anthranilamide with 5a or 5b in 6% ethanolic hydrogen chloride provided compounds 6a and 6b in 77% and 73% yields, respectively. Heating 7a with 5a in 6% ethanolic hydrogen chloride furnished 6a in 82.4% yield. Reaction of anthranilamide with 5c under the same conditions resulted in the formation of 11 (57%). Treatment of compounds 6a and 6b with $NaBH_4$ furnished 8a,b (89, 87% yields), which were subsequently subjected to the Mitsunobu reaction to produce 6,7,8,9-tetrahydro-9-methyl-11*H*-pyrido[2,1-*b*]quinazolin-11-one (9a) and 6,7,8,9-tetrahydro-7,7,9-trimethyl-11*H*-pyrido[2,1-*b*]quinazolin-11-one (9b) in 56 and 72% yields, respectively. However, heating 14 with 15a in CH_3CN in the presence of *p*-toluenesulfonic acid furnished 19 in 31% yield. Under similar conditions, treatment of 21 with 15a provided 23a (42.4% yield), a key intermediate for the synthesis of rutaecarpine. Analogous reaction of 21 with 15b, 15c and 5a provided 22b—d in 63—99.3% yield, respectively.

Key words β-diketone; Mitsunobu reaction; ruta alkaloid

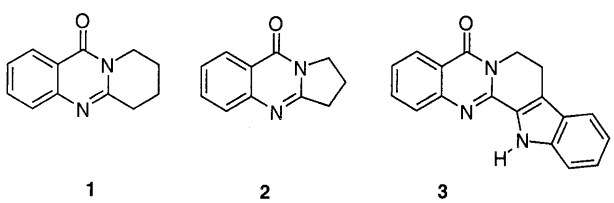
Quinazolinone derivatives constitute a class of biologically active compounds. Several alkaloids with important pharmacological activities are quinazolinone derivatives.[2] In addition, a wide variety of synthetic quinazolinone derivatives possess anticancer,[3] antiinflammatory, antiallergic,[4] anticonvulsant,[5] sedative-hypnotic,[6] and antihypertensive activities.[7] 6,7,8,9-Tetrahydro-11*H*-pyrido-[2,1-*b*]quinazolin-11-one (**1**),[8] isolated from *Mackinlaya subulata*, and 1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazolin-9-one (**2**),[9] isolated from *Peganum harmala*, were found to possess bronchodilator, hypotensive and cardiac depressant activities. Compound **1** is also a key intermediate for the Fischer indole synthesis[10] of ruta alkaloids such as rutaecarpine (**3**). It has recently been reported that dehydroevodiamine, a ruta alkaloid, demonstrated potent antiarrhythmic activity by prolonging refractories, indicating that this alkaloid can be considered as a class III antiarrhythmic agent.[11]

Due to the unique structures associated with the effects of these compounds on the cardiovascular system, the synthesis of analogs, especially ruta alkaloid analogs, may lead to the identification of new biologically active compounds. The 6,7,8,9-tetrahydro-11*H*-pyrido[2,1-*b*]quinazolin-11-one ring system has been synthesized by palladium-catalyzed carbonylation of 2-iodoaniline and α-piperidone[12] or by thermal cyclization of 2-substituted 4(3*H*)-quinazolinones.[13] The former approach gave only 7% yield, whereas the latter afforded a mixture of stereoisomeric products. In addition to the desired product, it led to the formation of 1,2,3,4-tetrahydro-6*H*-pyrido[1,2-*a*]quinazolin-6-one as well. Since our laboratory has a long-term interest in the preparation of quinazoline or fused quinazoline derivatives for pharmacological evaluation,[14] an efficient method to provide various substituted fused quinazoline derivatives was developed.

Results and Discussion

The reaction of β-diketones such as 2,4-pentanedione with a variety of nucleophiles resulted in the formation of various heterocycles.[15] Manhas *et al.*[16] reported that treatment of anthranilamide (**4**) with 2,4-pentanedione under acidic conditions provided a facile synthesis of 2-methylquinazolin-4(*H*)-one in a quantitative yield. We now report the application of this methodology for the synthesis of tetrahydropyrido[2,1-*b*]quinazolin-11-one derivatives. This involved condensation of anthranilamide with cyclic β-diketones, followed by reduction of the resulting 2-substituted quinazolin-4(3*H*)-one and subsequent ring closure by the Mitsunobu reaction.[17]

When **4** was allowed to react with 1,3-cyclohexanedione (**5a**) in tetrahydrofuran (THF) in the presence of a catalytic amount of *p*-toluenesulfonic acid, it afforded not only 1-(3,4-dihydro-4-oxoquinazolin-2-yl)-4-pentanone (**6a**) in 40% yield, but also 1-(1,2,3,4-tetrahydro-2-methyl-4-oxo-2-quinazolinyl)-3-(3,4-dihydro-4-oxo-2-quinazolinyl)-propane (**7a**) in 22% yield. An analogous reaction between anthranilamide and 5,5-dimethyl-1,3-cyclohexanedione (**5b**) afforded 1-(3,4-dihydro-4-oxoquinazolin-2-yl)-2,2-dimethyl-4-pentanone (**6b**, 47%) and 1-(1,2,3,4-tetrahydro-2-methyl-4-oxo-2-quinazolinyl)-3-(3,4-dihydro-4-oxo-



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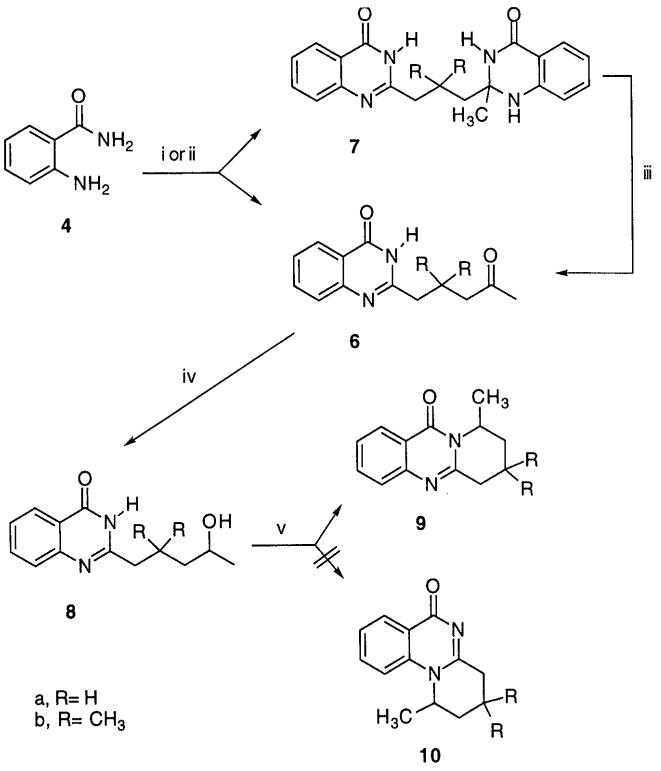
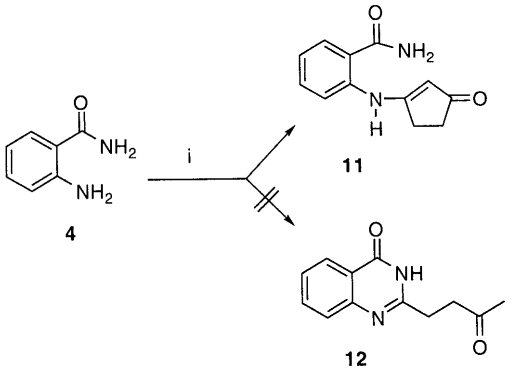


i, *p*-toluenesulfonic acid, CH_3CN or THF with 1,3-cyclohexanedione (**5a**), reflux, **6a** (40%), **7a** (22 %); with 5,5-dimethyl-1,3-cyclohexandione (**5b**), **6b** (47 %), **7b** (39%).
ii, 6% ethanolic hydrogen chloride, with **5a**, reflux, 24 h, **6a** (77%); with **5b**, **6b** (73%).
iii, 6% ethanolic hydrogen chloride with **5a**, reflux 3 h, **6a** (82.4%)
iv, $NaBH_4$, H_2O, r.t., 1 h, **8a** (89%), **8b** (87%).
v, DEAD, Ph_3P, toluene, r.t., 6 h, **9a** (56%), **9b** (72%).

Chart 1

2-quinazolinyl)-2,2-dimethylpropane (**7b**, 39%) (Chart 1). The structures of the compounds **6a, b** and **7a, b** were assigned on the basis of ^{1}H-, ^{13}C-NMR and mass spectra as well as by elemental analyses. The ^{13}C-NMR spectra of **6a** and **6b** exhibited carbonyl group absorptions at δ 207.8 and 208.88, respectively. The ^{1}H-NMR spectrum of **7a** displayed three D_2O-exchangeable peaks at δ 7.11, 7.91 and 12.14; those of **7b** appeared at δ 6.85, 8.22 and 12.15. However, when compound **4** was refluxed with 6% ethanolic hydrogen chloride, compounds **6a** and **6b** were obtained in 77% and 73% yields without production of **7a** and **7b**. We reasoned that compounds **7a** and **7b** had been readily converted to **6a** and **6b** in 6% ethanolic hydrogen chloride. In fact, after heating in 6% ethanolic hydrogen chloride, **7a** was totally converted into **4** and **6a** within minutes. However, after the mixture was cooled to room temperature, **7a** could again be isolated. This was probably due to condensation of **4** and **6a** to give **7a** during the work-up. To avoid this reversible reaction, one equivalent of **5a** was added to the reaction mixture of **7a** in 6% ethanolic hydrogen chloride to trap compound **4**. After reflux for 3 h, **6a** was isolated in 82.4% yield. These results support the above explanation of why **7a** and **7b** were not observed in 6% ethanolic hydrogen chloride. Compounds **6a** and **6b** were subsequently treated with $NaBH_4$ to furnish 1-(3,4-dihydro-4-oxo-2-quinazolinyl)-pentan-4-ol (**8a**) and 1-(3,4-dihydro-4-oxo-2-quinazolinyl)-2,2-dimethylpentan-4-ol (**8b**) in 89% and 87% yields.

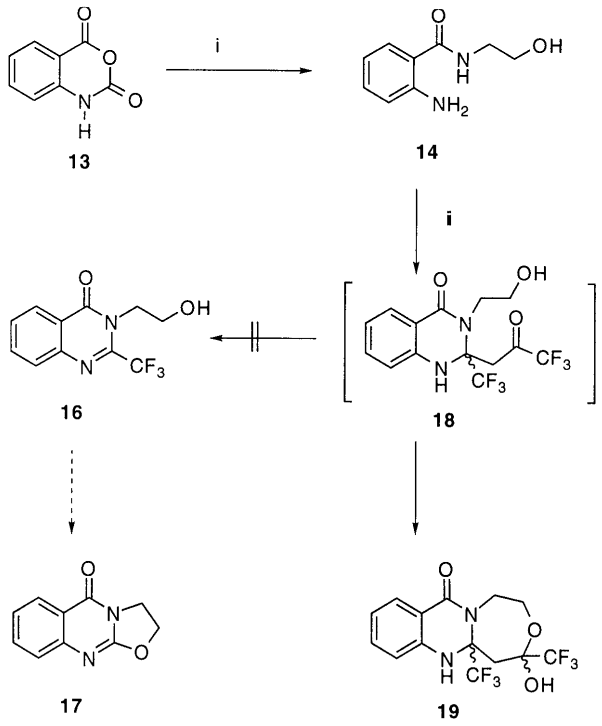


i, 1,3-cyclopentanedione (**5c**), *p*-toluenesulfonic acid, THF, r.t., 1 h, 57%.

Chart 2

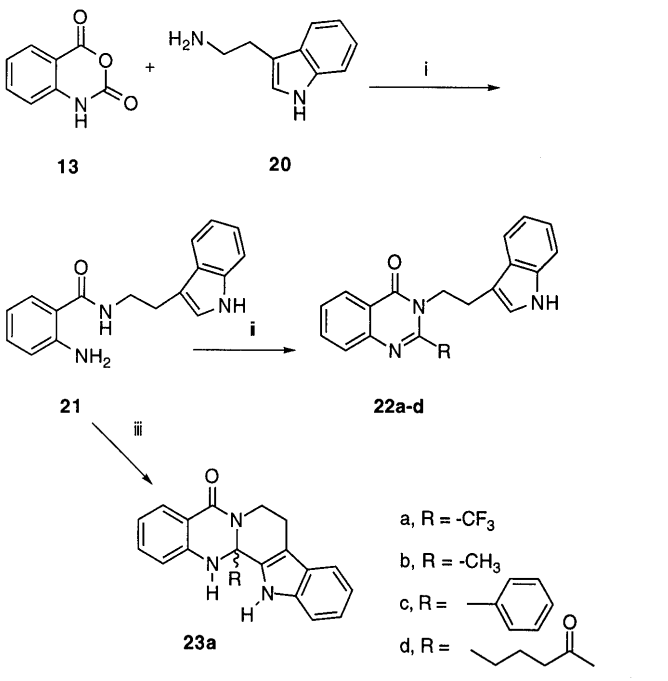
Since a hydroxy group can be replaced with a wide range of nucleophiles by means of the Mitsunobu reaction,[17,18] we reasoned that the ring closure of compounds **8a, b** could be achieved under Mitsunobu's conditions. When these two compounds were treated with DEAD and triphenylphosphine in toluene at room temperature for 6 h, 6,7,8,9-tetrahydro-9-methyl-11*H*-pyrido[2,1-*b*]quinazolin-11-one (**9a**) and 6,7,8,9-tetrahydro-7,7,9-trimethyl-11*H*-pyrido[2,1-*b*]quinazolin-11-one (**9b**) were obtained in 56% and 72% yields, respectively. These reactions provided only the linear tricycles **9** without the angular tricycle 1,2,3,4-tetrahydro-6*H*-pyrido[1,2-*a*]quinazolin-6-ones (**10**). The infrared spectra of these two compounds exhibited an amidic carbonyl stretching band at 1710 and 1715 cm^{-1}, respectively, indicative of linear rather than angular tricycles. The structural assignment of these compounds was based upon the report by Fantin *et al.*[13] who found that the carbonyl group of angular tricycles displays a band at 1635 cm^{-1} due to the conjugated C, N double bond. Furthermore, the ^{13}C-NMR spectra of these compounds displayed the C-11 carbonyl peaks at δ 159.49 and 159.65, respectively, in agreement with the reported values for linear tricycles.[13] However, treatment of compound **4** with 1,3-cyclopentanedione (**5c**) under the same conditions, produced only 2-[(3-oxo-1-cyclopentenyl)-amino]benzamide (**11**) in 57% yield, instead of 1-(3,4-dihydro-4-oxo-2-quinazolinyl)-3-butanone (**12**) (Chart 2). The structural assignment of **11** was based upon the ^{1}H-NMR spectrum which revealed two D_2O-exchangeable proton peaks at δ 7.73 and 8.23 belonging to the carboxamide moiety, indicative of the benzamide form of the product. In addition, an absorption peak at δ 5.54 and another D_2O exchangeable proton peak at δ 10.72 corresponded to an unsaturated proton on the cyclopentene ring and NH proton, respectively. Attempts to close the ring of **11** were unsuccessful and led to a complex mixture of products.

On the basis of Manhas's approach, we assumed that treatment of an anthranilamide derivative possessing a nucleophile side chain at a certain distance, such as 2-amino-*N*-(2-hydroxyethyl)benzamide (**14**), with 1,1,1,5,5,5-hexafluoro-2,4-pentanedione (**15a**) under acidic conditions, would produce 3-(2-hydroxyethyl)-2-trifluoromethyl-4(3*H*)-quinazolinone (**16**). Subsequent ring closure



i, 2-aminoethanol, CH_3CN, r.t., 1 h, 58%.
ii, 1,1,1,5,5,5-hexafluoro-2,4-pentanedione (**15a**), CH_3CN, *p*-toluenesulfonic acid, reflux, **19** (31%).

Chart 3



i . CH_3CN, r.t., 3 h, 82.7%.
ii. CH_3CN, *p*-toluenesulfonic acid, reflux; with 2,4-pentanedione (**15b**), **22b** (99.3 %); with dibenzoylmethane (**15c**), **22c** (63%), with 1,3-cyclohexanedione (**5a**), **22d** (76.4%).
iii. CH_3CN, *p*-toluenesulfonic acid, 1,1,1,5,5,5,-hexafluoro-2,4-pentanedione (**15a**), reflux, **23a** (42.4%).

Chart 4

through nucleophilic addition of the side chain to the 2-position and elimination of the trifluoromethyl group should then provide fused quinazoline derivatives **17** in a one-pot reaction. Interestingly, when compound **14**, obtained in 58% yield by the reaction of isatoic anhydride (**13**) with 2-aminoethanol, was subsequently treated with **15a** in the presence of *p*-toluenesulfonic acid,1,2,4,5,5a,6-hexahydro-4,5a-bistrifluoromethyl-11*H*-4-hydroxyquinazolino[3,2-*d*][1,4]oxazepin-11-one (**19**) rather than **17** was obtained in 31% yield (Chart 3). The ^{13}C-NMR spectrum of **19** revealed that there are two sets of quartets centered at δ 73.10 with $J=29.2$ Hz and at δ 95.80 with $J=31.1$ Hz, which were assigned to the two trifluoromethyl groups. The mass spectrum also contained a molecular ion peak (M^+) at *m/z* 370 which was in agreement with the formula of **19**. This reaction obviously involved the condensation of **14** and **15a**, to form the intermediate **18**, followed by the addition of a hydroxyl group to the electron deficient trifluoromethyl carbonyl group rather than by the formation of **16** through the elimination of trifluoroacetone from **18**.

Next, we reasoned that compound **23a**, a reported key intermediate for the synthesis of compound **3**, could be synthesized in a one-pot reaction as described in Chart 4. Although several approaches are available for the synthesis of ruta alkaloids,[19-24] Bergman and Bergman[19] reported that **3** was readily synthesized from **23a** by treating 2-(trifluoromethyl)-4*H*-3,1-benzoxazin-4-one with tryptamine, through **22a**. It was expected that **23a** could be alternatively obtained by the direct condensation of **21** with **15a** under acidic conditions *via* intermediate **22a** in a one-pot reaction. Accordingly, *N*-(2-aminobenzoyl)tryptamine (**21**), obtained in 82.7% yield by the treatment of isatoic anhydride (**13**) with tryptamine (**20**), was then heated with **15a** in the presence of *p*-toluenesulfonic acid at the refluxing temperature of CH_3CN. The isolated product was determined to be 13b-(trifluoromethyl)-13b,14-dihydrorutaecarpine (**23a**, 42.4% yield) on the basis of ^{13}C-NMR, mass spectra and elemental analysis (Chart 5). The ^{13}C-NMR spectrum showed one set of quartet peaks centered at δ 70.15 with $J=31$ Hz, indicating the existence of a trifluoromethyl group. Another set of quartet peaks was centered at δ 125.52 with a coupling constant $J=298$ Hz which was assigned to the carbon adjacent to the trifluoromethyl group. The molecular ion peak (M^+) at 357 was in agreement with the formula of **23a**.

Under similar conditions, treatment of compound **21** with **15b** and **15c** afforded 3-[2-(3-indolyl)ethyl]-2-methyl-4(3*H*)-quinazolinone (**22b**, 99.3%) and 3-[2- (3-indolyl)ethyl]-2-phenyl-4(3*H*)-quinazolinone (**22c**, 63%), respectively. However, compounds **23b** and **23c** could not be obtained by the reaction of **22b** and **22c** under acidic conditions or in the presence of a Lewis acid (Chart 4). Under similar conditions, compound **21** was reacted with **5a** to furnish 3-[2-(3-indolyl)ethyl]-2-(4-oxo-*n*-pentanyl)-4(3*H*)-quinazolinone (**22d**) in 76.4% yield.

In conclusion, the mild and highly efficient methods described here may provide a new and efficient route for the preparation of various quinazolinones and fused quinazolinone derivatives by employing various β-diketones and *ortho*-aminocarboxamides in the initial condensation reaction.

Experimental

General methods: Analytical samples were homogeneous by thin-layer chromatography (TLC) and afforded spectroscopic data which were consistent with the assigned structures. Melting points were obtained on a capillary electrothermal apparatus and are uncorrected. ^{1}H and ^{13}C nuclear magnetic resonance spectra were obtained using a Varian Gemini-300, or a Bruker AMX-400 or AC-200 spectrometer. Chemical shifts are reported in parts per million (δ, ppm) using $CDCl_3$ (δ_H 7.26) or DMSO-d_6 (δ_H 2.49) as the internal standard. EI mass spectra were recorded on a JEOL JMS-D300 mass spectrometer from National Taiwan University, Taipei. Elemental analyses for C, H, and N were carried out on a Perkin-Elmer 240 Elemental Analyzer in the National Taiwan University, Taipei and were within +0.4% of the theoretical values. Analytical thin-layer chromatography (TLC) was performed on precoated plates (Silica gel, 60F-254, Merck) and spots were visualized with UV light and/or phosphomolybdic acid–ethanol. Column chromatography was performed on Kieselgel 60 (70—230 mesh) silica gel (Merck). All nonaqueous reactions were performed in oven-dried glassware under an atmosphere of dry nitrogen or argon. All starting materials were obtained from commercial suppliers (Aldrich, Jannsen, Merck and Fluka) and used without purification. Solvents (HPLC grade) were purchased from Baker Analysed, Lab-scan and Alphs Chem. Co.

1-(3,4-Dihydro-4-oxoquinazolin-2-yl)-4-pentanone (6a) and 1-(1,2,3,4-Tetrahydro-2-methyl-4-oxo-2-quinazolinyl)-3-(3,4-dihydro-4-oxo-2-quinazolinyl)propane (7a) Method A: A mixture of anthranilamide (**4**, 8.0 g, 59 mmol), 1,3-cyclohexanedione (6.6 g, 59 mmol) and *p*-toluenesulfonic acid (0.4 g, 2.1 mmol) in THF (100 ml) was refluxed for 24 h. The solvent was then removed and the residue was subjected to column chromatography [silica gel: 70—230 mesh, 200 g; solvent system: chloroform : ethyl acetate = 97.5 : 2.5]. The *Rf* 0.36 fraction was collected and evaporated to afford **6a** (5.65 g, 40%). An analytical sample was recrystallized from CH_3CN, mp 146—147 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.88 (m, 2H, C$\underline{H}_2$), 2.05 (s, 3H, C$\underline{H}_3$), 2.49 (t, 2H, C$\underline{H}_2$), 2.57 (t, 2H, C$\underline{H}_2$), 7.42—8.07 (m, 4H, Ar-$\underline{H}$), 12.14 (s, 1H, N$\underline{H}$). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 20.60, 29.63, 33.51, 41.73, 120.81, 125.60, 125.58, 126.75, 134.14, 148.80, 156.89, 161.20, 207.8. MS: 230 (M^+). *Anal.* Calcd for $C_{13}H_{14}N_2O_2$ (230.26): C, 67.81; H, 6.13; N, 12.17; Found: C, 67.80; H, 5.86; N, 11.93. The *Rf* 0.11 fraction was collected and the solvent was evaporated to give **7a** (4.75 g, 22%), mp 221—222 °C. ^{1}H-NMR (200 MHz, DMSO-d_6) δ: 1.30 (s, 3H, C$\underline{H}_3$), 1.69—1.75 (m, 4H, (C$\underline{H}_2$)$_2$), 2.46—2.52 (m, 2H, C$\underline{H}_2$), 6.54 (t, 2 H, J = 7.4 Hz, Ar-$\underline{H}$), 7.11 (br s, 1H, N$\underline{H}$, D_2O-exchangeable), 7.15 (t, 1H, J = 7.6 Hz, Ar-$\underline{H}$), 7.41 (t, 1H, J = 7.4 Hz, Ar-$\underline{H}$), 7.53 (t, 2H, J = 6.6 Hz, Ar-$\underline{H}$), 7.72 (t, 1H, J = 7.8 Hz, Ar-$\underline{H}$), 7.91 (s, 1H, N$\underline{H}$, D_2O-exchangeable), 8.07 (d, 1H, J = 7.8 Hz, Ar-$\underline{H}$), 12.14 (s, 1H, N$\underline{H}$, D_2O-exchangeable). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 21.58, 27.79, 34.38, 68.96, 113.52, 114.04, 116.16, 120.80, 125.64, 125.91, 126.79, 127.10, 133.20, 134.22, 147.10, 148.90, 157.23, 161.79, 163.06. MS *m/z*: 348 (M^+). *Anal.* Calcd for $C_{20}H_{20}N_4O_2$ (348.40): C, 68.95; H, 5.79; N, 16.08. Found: C, 68.81; H, 5.83; N, 16.23.

Method B: To a solution of anthranilamide (2.0 g, 14.4 mmol) in 6% ethanolic hydrogen chloride (50 ml) was added 1,3-cyclohexanedione (1.66 g, 14.4 mmol). A white precipitate began to form after 3 min. The suspension was then refluxed. The precipitate disappeared but began to reform after 30 min. After refluxing for 24 h, the white solid, collected by filtration, was suspended in chloroform. Triethylamine (2 ml) was added to form a solution. Activated charcoal was added and the solution was filtered. The solvent was then removed *in vacuo* to give a white product (3.15 g, 95% yield), which was recrystallized from acetonitrile to give 2.55 g (77%) of **6a**, mp 146—147 °C.

Method C: To a suspension of **7a** (187 mg, 0.55 mmol) in 6% ethanolic hydrogen chloride (5 ml) was added 1,3-cyclohexanedione (1.1 mmol). The mixture was refluxed in an oil bath for 3 h, then allowed to cool to room temperature. The white precipitate was collected and suspended in chloroform (10 ml). Triethylamine (1 ml) was added and the mixture was then evaporated *in vacuo* to give a white solid, which was recrystallized from CH_3CN to obtain **6a** (204.6 mg, 82.4%), mp 146—147 °C.

1-(3,4-Dihydro-4-oxo-2-quinazolinyl)-2,2-dimethyl-4-pentanone (6b) and 1-(1,2,3,4-Tetrahydro-2-methyl-4-oxo-2-quinazolinyl)-3-(3,4-dihydro-4-oxo-2-quinazolinyl)-2,2-dimethylpropane (7b) Method A: Compounds **6b** and **7b** were prepared in accordance with method A described for **6a** and **7a**. The *Rf* 0.7 portion was collected and evaporated *in vacuo* to give **6b** in 47% yield. An analytical sample was recrystallized from CH_3CN, mp 159—160 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.05 (s, 6H, (C$\underline{H}_3$)$_2$), 2.10 (s, 3H, C$\underline{H}_3$), 2.54 (s, 2H, C$\underline{H}_2$), 2.63 (s, 2H, C$\underline{H}_2$), 7.44 (t, 1H, J = 6.6 Hz, Ar-$\underline{H}$), 7.57 (d, 1, J = 7.8 Hz, Ar-$\underline{H}$), 7.75 (t, 1H, J = 7.1 Hz, Ar-$\underline{H}$), 8.07 (d, 1H, J = 7.8 Hz, Ar-$\underline{H}$), 12.04 (s, 1H, N$\underline{H}$, D_2O-exchangeable). ^{13}C-NMR (50 MHz, DMSO-d_6) δ: 21.49, 30.60, 34.40, 42.61, 121.73, 126.54, 126.80, 127.68, 135.09, 149.72, 157.82, 162.66, 208.88. MS *m/z*: 258 (M^+). *Anal.* Calcd for $C_{15}H_{18}N_2O_2$ (258.32): C, 69.75; H, 7.02; N, 10.84. Found: C, 69.58; H, 6.98; N, 10.82. The *Rf* 0.58 fraction was collected and evaporated *in vacuo* to give **7b** (39%), mp 239—241 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.08 (s, 6H, (C$\underline{H}_3$)$_2$); 1.39 (s, 3H, C$\underline{H}_3$), 1.77 (s, 2H, C$\underline{H}_2$), 2.71 (s, 2H, C$\underline{H}_2$), 5.56—6.64 (m, 2H, Ar-$\underline{H}$), 6.85 (s, 1H, N$\underline{H}$, D_2O-exchangeable), 7.20 (t, 1H, J = 7.5 Hz, Ar-$\underline{H}$), 7.47 (t, 1H, J = 7.2 Hz, Ar-$\underline{H}$), 7.58 (t, 1H, J = 8.6 Hz, Ar-$\underline{H}$), 7.76—7.81 (m, 1H, Ar-$\underline{H}$), 8.09 (d, 2H, J = 8.0 Hz, Ar-$\underline{H}$), 8.22 (s, 1H, N$\underline{H}$, D_2O-exchangeable), 12.15 (s, 1H, N$\underline{H}$, D_2O-exchangeable). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 28.93, 28.98, 31.23, 35.00, 45.64, 48.53, 69.69, 113.20, 113.98, 116.03, 120.60, 125.71, 126.13, 126.55, 127.15, 133.28, 134.41, 146.72, 148.18, 156.03, 161.64, 162.68. MS *m/z*: 376 (M^+). *Anal.* Calcd for $C_{22}H_{24}N_4O_2$ (376.46): C, 70.19; H, 6.42; N, 14.88. Found: C, 70.20; H, 6.41; N, 14.64.

Method B: Compound **6b** was prepared in 73% yield in accordance with method B described for **6a**. An analytical sample was recrystallized from CH_3CN, mp 159—160 °C.

1-(3,4-Dihydro-4-oxo-2-quinazolinyl)pentan-4-ol (8a) A solution of **6a** (5.5 g, 24 mmol) in water (100 ml) was treated with $NaBH_4$ (0.5 g, 0.12 mol). The mixture was stirred at room temperature for 1 h, then filtered, and the filtrate was evaporated *in vacuo* to give **8a** (5.0 g, 89%). mp 174—175 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.03 (d, 3H, J = 6.4 Hz, C$\underline{H}_3$), 1.30—1.42 (m, 2H, C$\underline{H}_2$), 1.66—1.74 (m, 1H, CHaC$\underline{H}$b), 1.75—1.83 (m, 1H, CHaC$\underline{H}$b), 2.58 (t, 2H, J = 6.8 Hz, C$\underline{H}_2$), 3.60 (q, 1H, J = 6.2 Hz, C$\underline{H}$), 4.45 (br, 1H, O$\underline{H}$, D_2O-exchangeable), 7.42—7.46 (m, 1H, Ar-$\underline{H}$), 7.58 (d, 1H, J = 7.8 Hz, Ar-$\underline{H}$), 7.75 (t, 1H, J = 7.6 Hz, Ar-$\underline{H}$), 8.07 (d, 1H, J = 8.0 Hz, Ar-$\underline{H}$). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 23.43, 23.63, 34.58, 38.33, 65.52, 120.77, 125.69, 125.89, 126.78, 134.25, 148.95, 157.60, 161.87. MS *m/z*: 232 (M^+). *Anal.* Calcd for $C_{13}H_{16}N_2O_2$ (232.28): C, 67.22; H, 6.94; N, 12.06. Found: C, 66.89; H, 7.01; N, 12.20.

1-(3,4-Dihydro-4-oxo-2-quinazolinyl)-2,2-dimethylpentan-4-ol (8b) Compound **8b** was prepared in 87% yield in the same manner as described for **8a**, mp 158—159 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 0.95 (s, 3H, C$\underline{H}_3$), 1.04 (s, 3H, C$\underline{H}_3$), 1.10 (d, 3H, J = 5.8 Hz, C$\underline{H}_3$), 1.30 (d, 1H, J = 14.1 Hz, C$\underline{H}$aCHb), 1.44—1.66 (m, 1H, C$\underline{H}$), 2.74 (d, 1H, J = 12.7 Hz, CHaC$\underline{H}$b), 3.92 (s, 1H, OH, D_2O-exchangeable), 5.13 (s, 2H, C$\underline{H}_2$), 7.45 (t, 1H, J = 7.6 Hz, Ar-$\underline{H}$), 7.58 (d, 1H, J = 7.8 Hz, Ar-$\underline{H}$), 7.77 (t, 1H, J = 7.8 Hz, Ar-$\underline{H}$), 8.07 (d, 1H, J = 7.8 Hz, Ar-$\underline{H}$), 12.14 (s, 1H, N$\underline{H}$, D_2O-exchangeable). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 26.07, 27.97, 28.38, 34.10, 45.70, 49.37, 63.34, 120.62, 125.65, 125.98, 126.78, 134.28, 148.67, 155.83, 161.44. MS *m/z*: 260 (M^+). *Anal.* Calcd for $C_{15}H_{20}N_2O_2$ (260.32): C, 69.20; H, 7.74; N, 10.76. Found: C, 69.13; H, 7.44; N, 10.76.

6,7,8,9-Tetahydro-9-methyl-11*H*-pyrido[2,1-*b*]quinazolin-11-one (9a) To a mixture of DEAD (1.26 g, 7.24 mmol) and Ph_3P (1.9 g, 7.24 mmol) in toluene (15 ml) was added **8a** (0.84 g, 3.62 mmol). The mixture was stirred at room temperature for 6 h, then the solvent was removed *in vacuo* and the residue was subjected to column chromatography [silica gel: 70—230 mesh, 50 g; solvent system : chloroform : *n*-hexane = 8.5 : 1.5]. The *Rf* 0.2 fraction was collected and the solvent was then removed *in vacuo* to afford an oil. To this was added a few drops of concentrated hydrochloric acid and then ether (10 ml) to produce a white solid, which was collected by filtration and crystallized from isopropanol to give **9a** (0.4 g, 56%), mp 239—243 °C. IR (KBr) cm^{-1}: 1710 (C=O). ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.35 (d, 3H, J = 6.4 Hz, C$\underline{H}_3$), 1.94—2.07 (m, 4H, C$\underline{H}_2$C$\underline{H}_2$), 3.21 (m, 1H, C$\underline{H}$aHb), 3.37 (m, 1H, CHa$\underline{H}$b), 4.89 (m, 1H, C$\underline{H}$), 7.63 (m, 1H, Ar-$\underline{H}$), 7.98 (m, 2H, Ar-$\underline{H}$), 8.19 (d, 1H, J = 8.3 Hz, Ar-$\underline{H}$). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 20.43, 26.84, 28.89, 30.45, 48.77, 119.64, 121.49, 126.75, 127.65, 135.46, 158.81, 159.49. MS *m/z*: 214 (M^+). *Anal.* Calcd for $C_{13}H_{14}N_2O \cdot HCl$ (250.73): C, 62.28; H, 6.03; N, 11.17. Found: C, 62.02; H, 5.99; N, 11.09.

6,7,8,9-Tetrahydro-7,7,9-trimethyl-11*H*-pyrido[2,1-*b*]quinazolin-11-one (9b) Compound **9b** was prepared in 72% yield in the same manner as described for **9a**. An analytical sample was recrystallized from ethanol, mp 211—213 °C. IR (KBr) cm^{-1}: 1715 (C=O). ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.95 (s, 3H, C$\underline{H}_3$); 1.18 (s, 3H, C$\underline{H}_3$), 1.41 (d, 3H, J = 6.6 Hz, C$\underline{H}_3$), 1.68 (dd, 1H, J = 7.0, 14.0 Hz, C$\underline{H}$aCHb), 2.06 (m, 1H, J = 7.0, 14.0 Hz, CHaC$\underline{H}$b), 2.91 (d, 1H, J = 16.5 Hz, C$\underline{H}$aCHb), 3.08 (d, 1H,

J=16.5 Hz, CHaCHb), 4.85 (m, 1H, CH), 7.61 (t, 1H, J=7.3 Hz, Ar-H), 7.79 (t, 1H, J=5.7 Hz, Ar-H), 7.93 (t, 1H, J=7.7 Hz, Ar-H), 8.17 (d, 1H, J=7.7 Hz, Ar-H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 20.15, 26.80, 28.67, 30.30, 40.61, 41.69, 49.21, 119.36, 120.00, 126.88, 128.05, 135.71, 138.69, 150.05, 159.65. MS m/z: 242 (M^+). *Anal.* Calcd for $C_{15}H_{18}N_2O \cdot HCl$ (278.77): C, 64.62; H, 6.86; N, 10.04. Found: C, 64.44; H, 6.83; N, 9.80.

2-[(3-Oxo-1-cyclopentenyl)amino]benzamide (11) Anthranilamide (4.0 g, 29.4 mmol) was added to a mixture of 1,3-cyclopentanedione (2.97 g, 29.4 mmol) and *p*-toluenesulfonic acid (0.5 g) in THF (20 ml). The mixture was refluxed for 24 h, then the precipitate was collected by filtration and recrystallized from ethanol to give **11** (1.79 g, 57%), mp 209—210 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.25 (t, 2H, J=4.8 Hz, CH_2), 2.75 (m, 2H, CH_2), 5.54 (s, 1H, CH), 7.15 (t, 1H, J=7.8 Hz, Ar-H), 7.45—7.54 (m, 2 H, Ar-H), 7.73 (s, H, NHa, D_2O-exchangeable), 7.76 (d, 1H, J=7.7 Hz, Ar-H), 8.23 (s, 1H, NHb, D_2O-exchangeable), 10.72 (s, 1H, NH, D_2O-exchangeable). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 29.02, 32.80, 102.65, 120.21, 122.25, 122.61, 129.00, 132.28, 140.51, 170.30, 170.62, 204.49. MS m/z: 216 (M^+). *Anal.* Calcd for $C_{12}H_{12}N_2O_2$ (216.24): C, 66.65; H, 5.59; N, 12.95. Found: C, 66.66; H, 5.59; N, 12.90.

2-Amino-*N*-(2-hydroxyethyl)benzamide (14) A mixture of **13** (16.0 g, 0.1 mol) and 2-aminoethanol (6.5 g, 0.1 mol) in CH_3CN (80 ml) was stirred at room temperature for 1 h. The solvent was then removed *in vacuo* to afford an oil, which was recrystallized from chloroform to give **14** (10.35 g, 58%), mp 94—95 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.33 (q, 2H, J=5.9 Hz, CH), 3.54 (t, 2H, J=6.1 Hz, CH), 4.77 (br, 1H, OH, D_2O-exchangeable), 6.39 (br, 2H, NH, D_2O-exchangeable), 6.52 (t, 1H, J=7.6 Hz, Ar-H), 6.71 (d, 1H, J=8.0 Hz, Ar-H), 7.14 (m, 1H, Ar-H), 7.52 (d, 1H, J=8.3 Hz, Ar-H), 8.15 (t, 1H, J=5.4 Hz, NH, D_2O-exchangeable). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 42.66, 60.73, 115.10, 115.78, 117.21, 128.97, 132.46, 150.33, 169.93 (C=O). MS m/z: 180 (M^+), *Anal.* Calcd for $C_9H_{12}N_2O_2$ (180.21): C, 59.99; H, 6.71; N, 15.55. Found: C, 59.88; H, 6.44; N,15.35.

1,2,4,5,5a,6-Hexahydro-4,5a-bistrifluoromethyl-11*H*-4-hydroxyquinazolino[3,2-*d*][1,4]oxazepin-11-one (19) *p*-Toluenesulfonic acid (100 mg) was added to a solution of **14** (3.0 g, 16.7 mmol) and **15a** (3.5 g, 26.4 mmol) in CH_3CN (40 ml). The mixture was refluxed for 2 d, then the solvent was removed *in vacuo* and the residue was recrystallized from chloroform to give **19** (1.9 g, 31%), mp 202—203 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.65 (d, 2H, J=36.4 Hz, CH_2), 3.32 (dd, 1H, J=9.2 Hz, 15.0 Hz, CH), 3.91 (m, 2H, CH_2), 4.69 (d, 1H, J=16.1 Hz, CH), 6.72 (m, 2H, Ar-H), 7.30 (t, 1H, J=6.8 Hz, Ar-H), 7.54 (s, 1H, D_2O-exchangeable), 7.62 (s, 1H, D_2O-exchangable), 7.64 (d, 1H, J=7.8 Hz, Ar-H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 37.07, 43.38, 64.04, 73.10 (q, J=29.2 Hz), 95.80 (q, J=31.1 Hz), 112.03, 113.38, 117.37, 125.28 (q, J=298.1 Hz), 127.52, 133.85, 144.55, 160.99 (C=O). MS m/z: 370 (M^+), 301 (M^+-69). *Anal.* Calcd for $C_{14}H_{12}F_6N_2O_3$ (370.25): C, 45.42; H, 3.27; N, 7.57. Found: C, 45.38; H, 3.10; N, 7.51.

***N*-(2-Aminobenzoyl)tryptamine (21)** A mixture of **13** (2.0 g, 12.3 mmol) and tryptamine (1.9 g, 11.8 mmol) in CH_3CN (80 mmol) was stirred at room temperature for 3 h. The solid was then collected by filtration and recrystallized from ethanol to give **21** (2.72 g, 82.7%), mp 168—169 °C. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 3.09 (s, 2H, CH_2), 3.66 (s, 2H, CH_2), 6.51 (s, 1H, Ar-H), 6.59 (t, 1H, J=7.2 Hz, Ar-H), 6.82 (d, 1H, J=8.0 Hz, Ar-H), 7.06—7.26 (m, 3H, Ar-H), 7.46 (d, 1H, J=7.7 Hz, Ar-H), 7.59 (d, H, J=7.5 Hz, Ar-H), 8.41 (s, 1H, NH, D_2O-exchangeable), 10.86 (s, 1H, NH, D_2O-exchangeable). ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 25.35, 115.50, 112.22, 114.83, 115.33, 116.52, 118.42, 118.49, 121.10, 122.65, 127.47, 128.16, 131.67, 136.42, 149.64, 169.11 (C=O). MS m/z: 280 ($M^+ + 1$). *Anal.* Calcd for $C_{17}H_{17}N_3O$ (279.34): C, 73.10; H, 6.13; N, 15.04. Found: C, 73.38; H, 6.14; N, 15.15.

13b-Trifluoromethyl-13b,14-dihydrorutaecarpine (23a) *p*-Toluenesulfonic acid (100 mg) was added to a mixture of **21** (3 g, 10.7 mmol) and **15a** (5.65 g, 27.2 mmol) in CH_3CN (40 ml). The mixture was refluxed for 5 d, then the solvent was evaporated to dryness and the solid was recrystallized from ethanol to give **23a** (1.62 g, 42.4%), mp 267—268 °C. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.80 (dt, 1H, J=5.8, 8.1 Hz, CH), 2.97 (dd, 1H, J=3.9, 15.6 Hz, CH), 3.28 (dt, 1H, J=3.4, 10.8 Hz, CH), 5.16 (dd, 1H, J=5.3, 13.3 Hz, CH), 6.89 (m, 2H, Ar-H), 7.11 (t, 1H, J=7.3 Hz, Ar-H), 7.25 (t, 1H, J=7.6 Hz, Ar-H), 7.40 (t, 1H, J=7.6 Hz, Ar-H), 7.58 (t, 2H, J=9.0 Hz, Ar-H), 7.78 (s, 1H, NH, D_2O-exchangeable), 7.81 (d, 1H, J=7.8 Hz, Ar-H), 11.00 (s, 1H, NH, D_2O-exchangeable). ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 19.77, 37.14, 70.15 (q, J=31 Hz), 112.14, 112.23, 114.66, 114.82, 118.96, 119.05, 119.46, 123.11, 124.76, 124.91, 125.52 (q, J=298 Hz), 127.70, 133.88, 136.88, 143.88, 161.39 (C=O). MS m/z: 357 (M^+), 288 (M^+-69). *Anal.* Calcd for $C_{19}H_{14}N_3F_3O$ (357.33): C, 63.87; H, 3.95; N, 11.76. Found: C, 63.80; H, 3.93; N, 11.65.

3-[2-(3-Indolyl)ethyl]-2-methyl-4(3*H*)-quinazolinone (22b) A mixture of **13** (2.0 g, 12.27 mmol) and **20** (1.98 g, 12.35 mmol) in CH_3CN (80 ml) was refluxed for 30 min, then **15b** (4 ml) and *p*-toluenesulfonic acid (200 mg) were added. The mixture was refluxed for another 24 h, then the solvent was evaporated *in vacuo* to afford a white solid, which was recrystallized from ethanol : water = 95 : 5 to afford **22b** (3.72 g, 99.3%). mp 190—191 °C. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.81 (s, 3H, CH_3), 3.14 (t, 2H, J=7.7 Hz, CH_2), 4.32 (t, 2H, J=7.8 Hz, CH_2), 6.98 (t, 1H, J=7.3 Hz, Ar-H), 7.09 (t, 1H, J=7.5 Hz, Ar-H), 7.26 (d, 1H, J=2 Hz, Ar-H), 7.37 (d, 1H, J=8.0 Hz, Ar-H), 7.63 (d, 1H, J=7.8 Hz, Ar-H), 7.69 (t, 1H, J=7.2 Hz, Ar-H), 7.96 (m, 2H, Ar-H), 8.25 (d, 1H, J=7.8 Hz, Ar-H), 11.01 (s, 1H, NH, D_2O-exchangeable). ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 19.69, 22.91, 45.65, 109.92, 115.53, 117.97, 118.49, 118.70, 120.74, 121.11, 123.49, 126.88, 126.94, 128.12, 135.75, 136.18, 139.53, 159.25, 159.54. MS m/z: 303 (M^+), 273 (M^+-130). *Anal.* Calcd for $C_{19}H_{17}N_3O$ (303.36): C, 75.21; H, 5.65; N, 13.85. Found: C, 75.31; H, 5.75; N, 13.70.

3-[2-(3-Indolyl)ethyl]-2-phenyl-4(3*H*)-quinazolinone (22c) Compound **22c** was prepared in 63% yield in the same manner described for **22b**. mp 285—286 °C. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.93 (t, 2H, J=7.9 Hz, CH_2), 4.12 (t, 2H, J=8.0 Hz, CH_2), 6.82 (m, 2H, Ar-H), 6.90 (d, 1H, J=2.1 Hz, Ar-H), 7.00 (t, 1H, J=7.3 Hz, Ar-H), 7.28 (d, 1H, J=8.1 Hz, Ar-H), 7.52 (m, 6H, Ar-H), 7.86 (t, 1H, J=7.2 Hz, Ar-H), 8.27 (d, 1H, J=7.2 Hz, Ar-H), 10.77 (t, 1H, Ar-H). ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 23.89, 46.21, 110.13, 111.27, 117.69, 118.14, 120.49, 120.88, 122.7, 126.11, 136.75, 126.89, 127.12, 127.92, 128.72, 129.34, 134.39, 135.37, 136.08, 146.87, 155.98, 161.15. MS m/z: 365 (M^+), 235 (M^+-130), 130. *Anal.* Calcd for $C_{24}H_{19}N_3O$ (365.43): C, 78.88; H, 5.24; N, 11.50. Found: C, 78.81; H, 5.42; N, 11.72.

3-[2-(3-Indolyl)ethyl]-2-(4-oxo-*n*-pentanyl)-4(3*H*)-quinazolinone (22d) Compound **22d** was prepared in 76.4% yield in the same manner described for **22b**, mp 143—144 °C. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 1.84 (t, 2H, J=7.2 Hz, CH_2). 2.05 (s, 3H, CH_3), 2.40 (t, 2H, J=7.1 Hz, CH_2), 2.66 (t, 2H, J=7.4 Hz, CH_2), 3.08 (t, 2H, J=7.5 Hz, CH_2), 4.28 (t, 2H, J=7.5 Hz, CH_2), 6.98 (t, 1H, J=7.4 Hz, Ar-H), 7.08 (t, 2H, J=7.3 Hz, Ar-H), 7.36 (d, 1H, J=8.1 Hz, Ar-H), 7.49 (t, 1H, J=7.4 Hz, Ar-H), 7.60 (t, 2H, J=8.3 Hz, Ar-H), 7.78 (t, 1H, J=7.7 Hz, Ar-H), 8.17 (d, 1H, J=8.0 Hz, Ar-H), 10.87 (s, 1H, NH, D_2O-exchangeable). ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 20.07, 23.80, 29.64, 32.76, 41.64, 44.04, 110.51, 111.40, 118.10, 118.40, 119.99, 121.03, 123.18, 126.05, 126.13, 126.65, 127.06, 134.08, 136.20, 146.81, 156.69, 161.18, 208.03 (C=O). MS m/z: 373 (M^+), 231, 142, 130. *Anal.* Calcd for $C_{23}H_{23}N_3O_2$ (373.45): C, 73.97; H, 6.21; N, 11.25. Found: C, 73.64; H, 6.27; N, 11.34.

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