Studies Towards the Synthesis of the Benzodiazepine Alkaloid Auranthine. Synthesis of an Acetylated Derivative

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Different approaches towards the synthesis of auranthine have been investigated. A completed synthesis of 3-[2-(4-oxo-3,4-dihydro-quinazolin-2-yl)-ethyl]-3,4-dihydro-1*H*-benzo[*e*][1,4]-diazepine-2,5-dione, an auranthine precursor, which after dehydration with 50% propylphosphonic acid anhydride solution in ethyl acetate and DMA gave a *C*-acetyl derivative of auranthine. Additionally studies towards the synthesis of fused quinazolinones yielded the *C*-acetylated pyrido[2,1-*b*]quinazolinones or butyric acid derivatives.

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Introduction.

One of the earliest fungal benzodiazepines to be characterised was cyclopenin (**1**), produced by *Penicillium cyclopium*, and biosynthesised from anthranilate and phenylalanine [1]. Although **1** shows some structural similarities with the antidepressant drug diazepam (**2**), it does not appear to be biologically active. The knowledge of the structural diversity of fungal benzodiazepines has been broadened with the discovery of asperlicin (**3**), produced by *Aspergillus alliaceus*, which is a potent cholecystokinin antagonist [2]. During the isolation and characterisation of nephrotoxins [3] and other metabolites from *Penicillium aurantiogriseum* a new fungal benzodiazepine was reported, auranthine (**4**) (Figure 1) [4], the structure of which was deduced not only with spectroscopic methods but also by biosynthetic studies [5a]. Recently, this alkaloid was found by UV-guided screening of benzodiazepine producing species in *Penicillium* [5b]. Several syntheses of cyclopenin (**1**) [6], diazepam (**2**) [7] and asperlicin (**3**) [8] are available, but no synthesis of auranthine (**4**) has yet been published. Here, we discuss attempts to synthesise auranthine (**4**), as well as a completed synthesis of an acetylated derivative, namely **15a,b**.

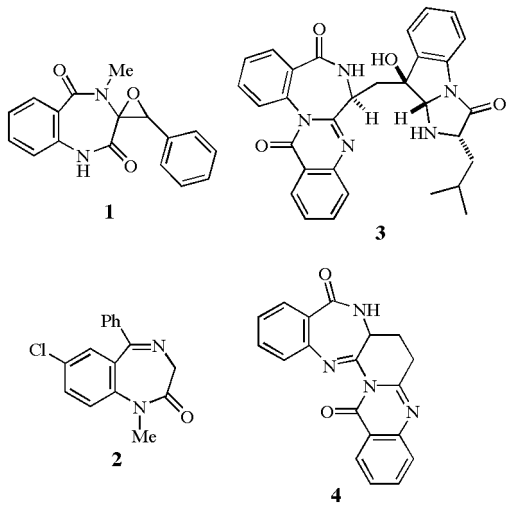


Figure 1

Results and Discussion.

A retrosynthetic analysis of auranthine (**4**) reveals at least three possible synthetic routes towards compound (**4**) (Figure 2). One conceivable synthesis towards compounds **5** and **7** involves the aza-Wittig methodology [9], which is a powerful tool in the synthesis of heterocycles containing a C=N double bond. Dehydration of a quinazoline ring in natural products [10] is very useful and dehydration of the precursor **6** thus should represent an alternative route.

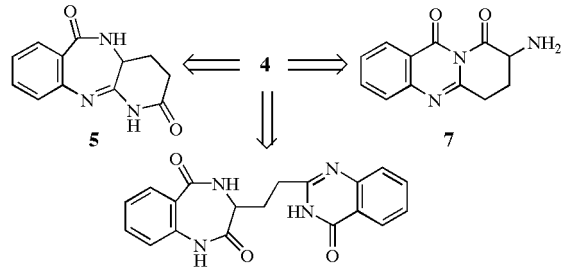
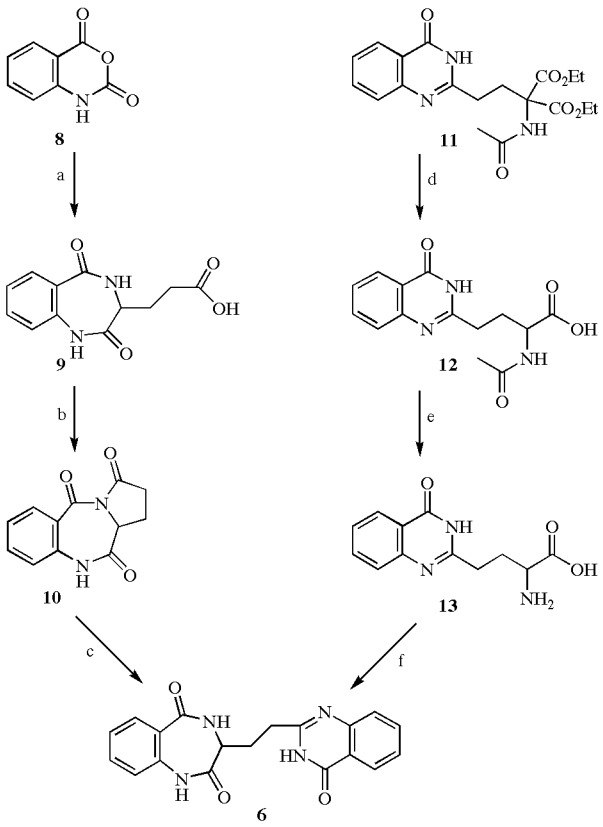


Figure 2

The benzodiazepine **9** [11] was easily prepared from the inexpensive starting material isatoic anhydride (**8**) and glutamic acid (Glu) according to Gates [7b] in 45% yield (Scheme 1). Cyclisation to the pyrrolobenzodiazepine **10** was achieved by heating compound **9** in acetic anhydride (Ac_2O) for a few minutes or in *N*,*N*-dimethylacetamide (DMA) overnight (Scheme 1). Compound **10** was isolated in 57% or 25–40% yield, respectively. Compound **10** crystallised readily from Ac_2O, and a second crop could be isolated containing the *N*-acetylated compound **14a** [12] in various amounts depending on the reaction time. When a longer reaction time was used the amount of compound **14a**

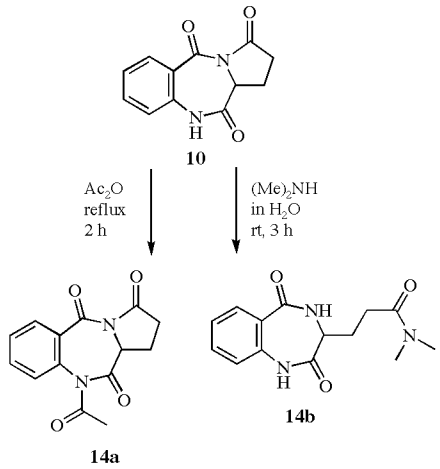
increased. When a simple experiment was performed, by heating compound **10** in a small amount of Ac_2O, the sole product was the *N*-acetylated compound **14a** (Scheme 2). When using DMA at reflux the non-cyclised product **14b** was isolated in 30% yield along with compound **10**. The non-cyclised adduct **14b** could be synthesised in 95% yield, by treating compound **10** with dimethylamine in water (Scheme 2). When the pyrrolobenzodiazepine **10** was heated with anthranilamide in diphenyl ether for 48 h the auranthine precursor **6** was isolated in 94% yield (Scheme 1). When a shorter reaction time was used the yield decreased. Compound **6** could also be independently synthesised from the quinazolinone adduct **11** [13]. As expected, compound **11** was easily decarboxylated to the protected acid **12** (Scheme 1). The *N*-protected aminoacid **12** could be isolated in 96% yield and after removel of the acetyl group in 3 *M* HCl the synthetic amino acid **13** was isolated in 64% yield. This amino acid could be converted to the auranthine precursor **6** according to Gates [7b] in 59% yield. To sum up, the auranthine precursor **6** has been attained in 4 steps and in 24% overall yield from **8** or in 36% overall yield from **11**.

Scheme 1



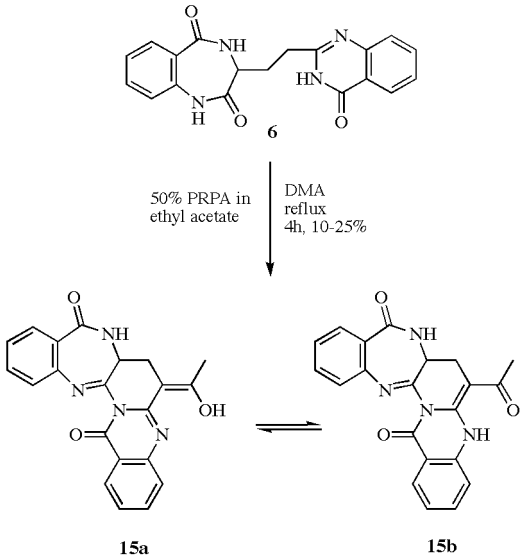
Reagents and conditions: (a) i: Glu, Et_3N, water, rt, 48 h; ii: acetic acid, reflux, 4-5 h, 45%; (b) Ac_2O, reflux, 5 min, 57% or DMA, reflux, 9h, 25-40%; (c) anthranilamide, diphenyl ether, reflux, 48 h, 94%; (d) 20% KOH, 90-100°, 2-3 h, add diluted H_2SO_4, 96%; (e) 3 *M* HCl, reflux, overnight, 64%; (f) i: isatoic anhydride, Et_3N, water, rt, overnight; ii: acetic acid, reflux, 3 h, 59%.

Scheme 2

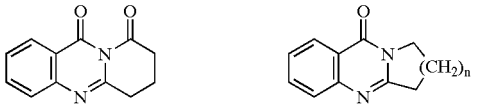


Several attempts, *e.g.* DCC, $POCl_3$ or PCl_3, have been made to cyclise compound **6** to auranthine (**4**) with almost no success except for one type of reaction, which involved peptide coupling, and the reagent selected was propylphosphonic acid anhydride (PRPA). When a mixture of the auranthine precursor **6**, 50% PRPA solution in ethyl acetate and DMA was heated at reflux, a solid product could be collected after 4 h (Scheme 3). This solid was poorly soluble in all organic solvents and on the basis of the spectral data we propose structure **15a** or its tautomer **15b**, *i.e.* a *C*-acetyl derivative of auranthine (**4**). When using *N*,*N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO) or *N*-methylpyrrolidone as solvent no such cyclisation occurred. The structural analysis of **15a,b** indicated the enol-imine structure **15a**, but due to low solubility in DMSO-d_6, trifluoroacetic acid (TFA) was added and the equilibrium might be influenced by this condition.

Scheme 3



In a second approach to auranthine (**4**) the fused quinazolinone **7** or the fused benzodiazepine **5** was investigated using the aza-Wittig methodology [9]. The quinazolinone **16** has been synthesised from the 2-azidobenzoyl derivatives of glutarimide in boiling toluene [14], and also the natural product, deoxyvacisinone **17a**, has been obtained from a 2-azidobenzoyl derivative of 2-pyrrolidinone (Figure 3) [15]. Recently a synthesis of fused quinazolinones, such as compound **17a** and its homologue **17b**, by an azido-reductive cyclisation of the corresponding 2-azidobenzoyl derivatives with TMS-NaI has been reported [16]. Also, compounds **17a,b** are readily available from condensation of isatoic anhydride (**8**) with 2-pyrrolidone and 2-piperidone, respectively [17].

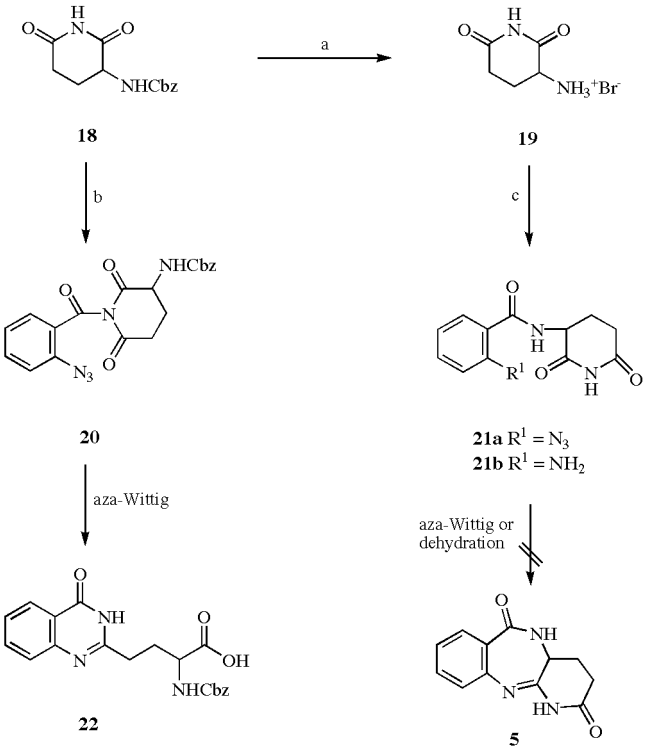


16 **17a** n = 1, **17b** n = 2

Figure 3

Based on these products we prepared the glutarimide **18** [18], by condensation of *N*-Cbz-L-glutamine [19] using *N*-hydroxysuccinimide and DCC in DMF at 0°. The glutarimide **18** was easily deprotected with 45% HBr in acetic acid to the hydrobromide salt **19** in 96% yield (Scheme 4) [20]. *o*-Azidobenzoic acid was converted to the corresponding acid chloride [21], which was allowed to react with the glutarimide **18** in the presence of methyllithium as a base to yield the azide **20** in 52% yield. Alternatively the hydrobromide salt **19** in the presence triethylamine (Et_3N) as a base afforded the azide **21a** in 78% yield. The corresponding amine **21b** was obtained from isatoic anhydride and the hydrobromide salt **19** with Et_3N in acetonitrile in 39% yield. The latter reaction is known between isatoic anhydride and 3-aminopiperidin-2-one, which could be cyclised in acetic acid or phosphorus pentoxide to a pyridobenzodiazepine [22]. In a publication dealing with derivatives of succinimide and glutarimide having a 4(3*H*)-quinazolinone moiety in the α-position [23], the amine **21b** is mentioned as a not-characterised intermediate. Attempts to cyclise compound **20** to a protected analogue of compound **7** using aza-Wittig conditions such as triphenylphosphine or triethylphosphite (TEP) in boiling toluene or xylene yielded a product in low amounts. A solid product was isolated after recrystallisation from toluene/hexane, and on the basis of the spectral data obtained we propose structure **22** (Scheme 4). Compound **22** was also compared with the *N*-acetylated acid **12** and the spectral data agreed well. Attempts were made to cyclise the azide **21a**, using aza-Wittig conditions, or the amine **21b**, using acetic acid, heating or various dehydrating agents such as phosphorus pentoxide, to compound **5** with no success.

Scheme 4

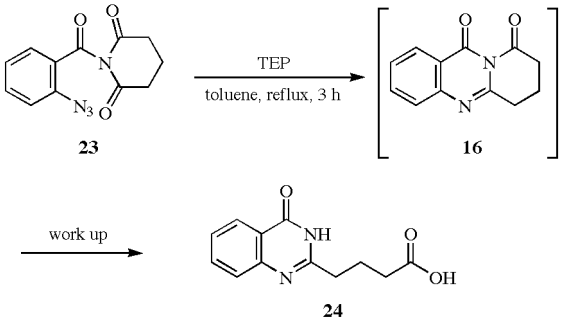


Reagents and conditions: (a) 45% HBr in acetic acid, 50°, 45 min, 96%; (b) MeLi, -78°, 2-azidobenzoyl chloride, THF, overnight, 52%; (c) 21a; 2-azidobenzoyl chloride, Et_3N, 40-50°, dioxane, overnight, 78% and 21b; isatoic anhydride, Et_3N, 60°, 3 h, room temperature, overnight, 39%.

After all the set-backs, using aza-Wittig reactions we decided to investigate the synthesis mentioned in the literature of the quinazolinone **16** [14]. The 2-azidobenzoyl derivatives **23** was synthesised from glutarimide [24] and the acid chloride of *o*-azidobenzoic acid [21] in the presence of methyllithium as a base in 51% yield (Scheme 5). Compound **23** was treated with TEP in boiling toluene. The ^{1}H-nmr spectrum of the crude product pointed towards the quinazolinone **16**, but after work up, such as flash chromatography on silica gel, treatment with water or recrystallisation from toluene/hexane, the sole product was the non-cyclised compound **24**. Thus, the ring-system in compound **16** seems to be very sensitive towards hydrolysis. Compound **24** was independently synthesised from anthranilamide and glutaric anhydride in toluene at reflux [25].

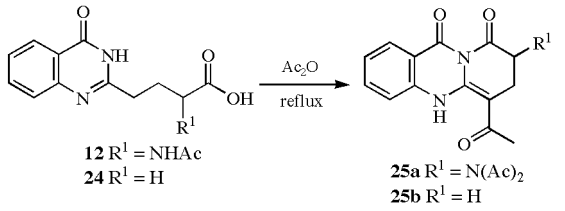
The protected acid **12** and compound **24** can be considered as precursors to the fused quinazolinone **7**, and many attempts were made to cyclise compounds **12** and **24**. Thus, when **12** or **24** were heated with acetic anhydride at reflux the cyclised products **25a,b** could be isolated in 26% and 23% yield, respectively, after flash chromatography on silica gel and recrystallisation from ethanol or methanol (Scheme 6). Spectroscopic analysis, including COSY, HMQC and HMBC experiments, provided

Scheme 5



evidence for the structures **25a,b**. Interestingly, from a structural point of view, compounds **25a,b** show some similarities with the known acetyl derivative **15a,b**. The methylene protons conjugated to the imine in the naturally occurring pyrrolo[2,1-*b*]quinazolinone **17a** and its homologue **17b** react readily with electrophiles [26]. The formylquinazolinone derivatives of compounds **17a,b** have been investigated [27], and three tautomeric forms may exist, namely oxo-imine (**A**), enol-imine (**B**) and oxo-enamine (**C**) forms (Figure 4). In agreement with our results the six-membered formylquinazolinone exists mainly in the oxo-enamine form (**C**) [27].

Scheme 6



In conclusion, a *C*-acetyl analogue of auranthine has been achieved in 5 steps and 5% yield from isatoic anhydride (**8**) or 7% yield from compound **11**. Synthetic approaches towards fused quinazolinones, such as **7** or **16**, yielded butyric acid derivatives **22** and **24**.

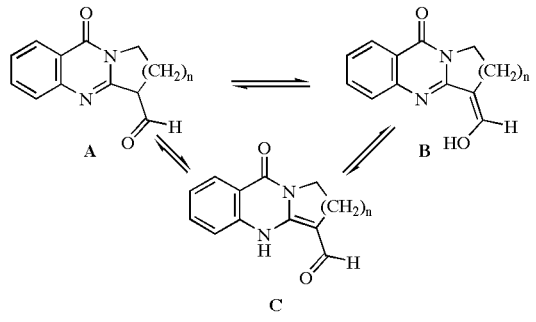


Figure 4.

EXPERIMENTAL

General Aspects. NMR spectra were recorded on a Bruker Avance DPX 300 spectrometer, operating at 300 MHz for ^{1}H-nmr and 75 MHz for ^{13}C-nmr, respectively, or, where indicated, on a JEOL (500 MHz) instrument, δ values are given in ppm. The abbreviation, app t in ^{1}H-nmr stands for apparent triplet. *J*-Values are given in Hz. IR spectra were recorded on a Perkin-Elmer 1600 FT-IR instrument. Elemental analyses were performed by H. Kolbe, Mikroanalytisches Laboratorium, Mülheim an der Ruhr, Germany. HRMS analyses were performed by E. Nilsson, University of Lund, Sweden. Melting points were determined on a Büchi Melting Point B-545 (capillary method) and are uncorrected. All solvents were purified by distillation or were of HPLC grade. Flash chromatography was done on silica gel 60 (230–400 mesh ASTM, Merck), TLC analyses were run on Merck Silica Gel 60 F_{254} plates.

3-(2,5-Dioxo-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin-3-yl)propionic Acid (**9**).

Triethylamine (43.5 g, 0.43 mol) was added to a mixture of isatoic anhydride (31.9 g, 0.20 mol) and glutamic acid (28.8 g, 0.20 mol) in water (400 mL). The mixture was stirred at room temperature for 48 h, whereupon the completely homogeneous solution was concentrated under reduced pressure to a dark oil. The oily residue was then heated at reflux in glacial acetic acid (200 mL) for 4.5 h. The solution was concentrated and poured onto ice/water (~400 mL). Crystalline material was collected and dried to give compound **9** (21.7 g, 45%) as a beige solid, mp 220–222° (Lit. [11] mp 220–222°); ir (KBr): 3161w, 1745, 1684, 1644, 1483, 1411, 1191, 761 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 1.72–1.88 (1H, m, C*H*$_2$), 1.93–2.10 (1H, m, C*H*$_2$), 2.29–2.42 (2H, m, C*H*$_2$), 3.63–3.76 (1H, m, C*H*), 7.10 (1H, d, *J* 7.9, Ar*H*), 7.22 (1H, dd, *J* 7.8, 7.2, Ar*H*), 7.51 (1H, ddd, *J* 8.1, 7.2, 1.4, Ar*H*), 7.74 (1H, dd, *J* 7.8, 1.1, Ar*H*), 8.47 (1H, d, *J* 5.5, N*H*), 10.39 (1H, s, N*H*), 12.08 (1H, br s, COO*H*); ^{13}C-nmr (DMSO-d_6) δ 23.2 (t), 29.9 (t), 51.0 (d), 121.0 (d), 124.0 (d), 126.3 (s), 130.4 (d), 132.2 (d), 136.6 (s), 167.8 (s), 171.4 (s), 174.0 (s).

1*H*-Pyrrolo-[2,1-*c*][1,4]benzodiazepine-1,4,10-trione (**10**).

The acid **9** (6.19 g, 25 mmol) was heated at reflux for 5 minutes in acetic anhydride (100 mL). The solution obtained was allowed to stand overnight, and the white crystals were collected and dried to give compound **10** (3.29 g, 57%), mp 245–247°; ir (KBr): 3279s, 2952, 1763s, 1693, 1478, 1349, 755 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 1.98–2.18 (1H, m, C*H*$_2$), 2.38–2.64 (3H, m, C*H*$_2$), 4.66 (1H, d, *J* 8.2, C*H*), 7.17 (1H, d, *J* 7.8, Ar*H*), 7.28 (1H, dd, *J* 8.0, 7.1, Ar*H*), 7.61 (1H, ddd, *J* 8.1, 7.2, 1.6, Ar*H*), 7.81 (1H, dd, *J* 7.9, 1.4, Ar*H*), 10.71 (1H, s, N*H*); ^{13}C-nmr (DMSO-d_6) δ 17.7 (t), 30.9 (t), 55.9 (d), 121.6 (d), 124.3 (d), 125.7 (s), 131.3 (d), 133.6 (d), 136.6 (s), 164.0 (s), 169.6 (s), 173.2 (s).

Anal. Calcd. for $C_{12}H_{10}N_2O_3$: C, 62.60; H, 4.38; N, 12.17. Found: C, 62.48; H, 4.46; N, 12.08.

5-Acetyl-1*H*-pyrrolo-[2,1-*c*][1,4]benzodiazepine-1,4,10-trione (**14a**).

Compound **10** (350 mg, 1.5 mmol) was heated at reflux for 2 h in acetic anhydride (5 mL). The white crystals formed were collected and dried to give compound **14a** (160 mg, 39%), mp 204–

205° (Lit. [12] 110–111°); ir (KBr): 1769, 1713, 1335, 1192, 758, 716 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 2.00–2.24 (1H, m, CH_2), 2.38–2.74 (3H, m, CH_2), 2.59 (3H, s, CH_3), 4.77 (1H, d, *J* 8.4, C*H*), 7.39 (1H, d, *J* 8.0, Ar*H*), 7.56 (1H, app t, *J* 7.5, Ar*H*), 7.68 (1H, dd, *J* 8.1, 7.0, Ar*H*), 7.77 (1H, d, *J* 7.6, Ar*H*); ^{13}C-nmr (DMSO-d_6) δ 18.2 (t), 27.3 (q), 31.2 (t), 59.7 (d), 128.3 (d), 129.8 (d), 130.1 (d), 131.1 (s), 132.0 (d), 134.3 (s), 164.1 (s), 170.6 (s), 172.3 (s), 173.2 (s).

3-(2,5-Dioxo-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin-3-yl)-*N*,*N*-dimethylpropionamide (**14b**).

A solution of dimethylamine in water (6 mL, 60%) was added to compound **10** (460 mg, 2.0 mmol), and the reaction mixture was maintained at room temperature for 3 h and then neutralised with 2 *M* HCl. The resulting precipitate was collected and washed with water to give compound **14b** (520 mg, 95%) as a white solid, mp 254–257°; ir (KBr): 3209, 3111, 1677, 1628, 1408, 1156, 754 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 1.73–1.90 (1H, m, CH_2), 1.93–2.08 (1H, m, CH_2), 2.40 (2H, t, *J* 7.2, CH_2), 2.77 (3H, s, CH_3), 2.91 (3H, s, CH_3), 3.66–3.78 (1H, m, C*H*), 7.09 (1H, d, *J* 8.1, Ar*H*), 7.21 (1H, app t, *J* 7.5, Ar*H*), 7.51 (1H, app t, *J* 7.3, Ar*H*), 7.73 (1H, d, *J* 7.6, Ar*H*), 8.45 (1H, d, *J* 5.4, N*H*), 10.37 (1H, s, N*H*); ^{13}C-nmr (DMSO-d_6) δ 23.4 (t), 28.6 (t), 34.8 (q), 36.5 (q), 51.2 (d), 120.9 (d), 123.9 (d), 126.3 (s), 130.4 (d), 132.2 (d), 136.6 (s), 167.8 (s), 171.4 (s), 171.6 (s).

2-Acetylamino-4-(4-oxo-3,4-dihydroquinazolin-2-yl)butyric Acid (**12**).

Compound **11** [13] (10.1 g, 26 mmol) was heated to 90–100° in aqueous 20% KOH (100 mL) for 2 h. Thus the solution was acidified with dilute H_2SO_4 and the resulting precipitate collected and dried to give compound **12** (7.18 g, 96%) as a white solid, mp 262–264° (dec.); ir (KBr): 3229s, 1679, 1610, 1301, 1250, 767 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 1.86 (3H, s, CH_3), 1.92–2.08 (1H, m, CH_2), 2.18–2.34 (1H, m, CH_2), 2.69 (2H, app t, *J* 7.7, CH_2), 4.21–4.33 (1H, m, C*H*), 7.46 (1H, dd, *J* 7.8, 7.2, Ar*H*), 7.59 (1H, d, *J* 8.1, Ar*H*), 7.78 (1H, dd, *J* 8.3, 7.0, Ar*H*), 8.07 (1H, d, *J* 7.9, Ar*H*), 8.21 (1H, d, *J* 7.8, N*H*), 12.19 (1H, s, N*H*), 12.62 (1H, br s, COO*H*); ^{13}C-nmr (DMSO-d_6): δ 22.4 (q), 28.0 (t), 30.7 (t), 51.3 (d), 120.8 (s), 125.7 (d), 126.1 (d), 126.5 (d), 134.4 (d), 148.3 (s), 156.7 (s), 161.6 (s), 169.4 (s), 173.4 (s); HRMS (FAB): $[M+H]^+$ for $C_{14}H_{16}N_3O_4$ requires *M*, 290.1141. Found: *m/z* 290.1162.

2-Amino-4-(4-oxo-3,4-dihydroquinazolin-2-yl)-butyric Acid (**13**).

Compound **12** (5.00 g, 17 mmol) in 3 *M* HCl (100 mL) was heated at reflux overnight. The solution was concentrated under reduced pressure to give **13**-hydrochloride salt, which was dissolved in water and neutralised with 2 *M* NaOH. The precipitate was collected and dried to give the amino acid **13** (2.75 g, 64%) as a white solid, mp 271° (dec.); ir (KBr): 3036, 1662, 1630, 1487, 1328, 774 cm^{-1}; ^{1}H-nmr (DMSO-d_6/TFA(4/1)): δ 2.21–2.48 (2H, m, CH_2), 2.97–3.23 (2H, m, CH_2), 3.92–4.07 (1H, m, C*H*), 7.56 (1H, dd, *J* 7.9, 7.3, Ar*H*), 7.67 (1H, d, *J* 8.1, Ar*H*), 7.84 (1H, ddd, *J* 8.4, 7.2, 1.2, Ar*H*), 8.12 (1H, dd, *J* 7.9, 0.8, Ar*H*), 8.37 (3H, br s); ^{13}C-nmr (DMSO-d_6/TFA(4/1)): δ 29.1 (t), 29.8 (t), 53.0 (d), 121.1 (d), 121.2 (s), 128.3 (d), 130.1 (d), 137.5 (d), 139.9 (s), 161.1 (s), 163.1 (s), 171.8 (s).

3-[2-(4-Oxo-3,4-dihydroquinazolin-2-yl)-ethyl]-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione (**6**).

Method A.

A mixture of anthranilamide (9.15 g, 67 mmol) and compound **10** (9.01 g, 39 mmol) was heated at reflux in diphenyl ether (100 mL) for 48 h. The mixture was cooled and diluted with diethyl ether (100 mL). The brown crystalline material obtained was collected, washed with diethyl ether and dried to give compound **6** (12,8 g, 94%), mp 330° (dec.); ir (KBr): 3171, 3047, 2925, 1688, 1666, 1618, 751 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 1.98–2.15 (1H, m, CH_2), 2.22–2.38 (1H, m, CH_2), 2.63–2.86 (2H, m, CH_2), 3.77–3.91 (1H, m, C*H*), 7.10 (1H, d, *J* 8.1, Ar*H*), 7.22 (1H, app t, *J* 7.5, Ar*H*), 7.39–7.57 (3H, m, Ar*H*), 7.71–7.79 (2H, m, Ar*H*), 8.05 (1H, d, *J* 7.8, Ar*H*), 8.54 (1H, d, *J* 5.5, N*H*), 10.41 (1H, s, N*H*), 12.09 (1H, s, N*H*); ^{13}C-nmr (DMSO-d_6): δ 24.6 (t), 30.5 (t), 51.2 (d), 120.9 (s), 121.0 (d), 124.0 (d), 125.7 (d), 126.0 (d), 126.3 (s), 126.7 (d), 130.4 (d), 132.2 (d), 134.3 (d), 136.7 (s). 148.7 (s), 156.6 (s), 161.7 (s), 167.9 (s), 171.5 (s).

Anal. Calcd. for $C_{19}H_{16}N_4O_3$: C, 65.51; H, 4.63; N, 16.08. Found: C, 65.45; H, 4.57; N, 16.01.

Method B.

Triethylamine (400 mg, 4.0 mmol) was added to a mixture of isatoic anhydride (372 mg, 2.3 mmol) and compound **13** (500 mg, 2.0 mmol) in water (25 mL). The mixture was stirred at room temperature overnight. The solution was concentrated under reduced pressure to a semisolid, which was heated at reflux in glacial acetic acid (15 mL) for 3 h. The white precipitate formed was collected and dried to give compound **6** (250 mg, 35%). The mother liquor was poured onto ice/water to give additional **6** (168 mg, 24%). Total yield 59%, mp 334° (dec.). The spectral data of **6** were identical with those mentioned above.

Acetylated Auranthine (15a,b**).**

50% Propylphosphonic acid anhydride solution in ethyl acetate (4 mL) was added to a mixture of compound **6** (1.18 g, 3.4 mmol) in DMA (25 mL). The mixture was heated to reflux for 4 h. After 2 h a solid precipitate appeared, which was collected and dried to give compound **15a,b** (250 mg, 20%) as a grey solid, mp > 410°; ir (KBr): 3452w, 3246, 1687, 1640, 1399, 1280, 772 cm^{-1}; ^{1}H-nmr (500 MHz, DMSO-d_6/TFA(~1/4)): δ 2.47 (3H, s, CH_3), 3.09–3.17 (1H, m, CH_2), 3.88 (1H, d, *J* 15.1, CH_2), 4.66 (1H, dd, *J* 10.7, 3.0, C*H*), 7.01 (1H, d, *J* 7.8, Ar*H*), 7.11 (1H, app t, *J* 7.8, Ar*H*), 7.37 (1H, ddd, *J* 8.2, 7.3, 1.3, Ar*H*), 7.46 (1H, dd, *J* 8.2, 7.3, Ar*H*), 7.66 (1H, d, *J* 8.0, Ar*H*), 7.69–7.77 (2H, m, Ar*H*), 8.06 (1H, d, *J* 7.9, Ar*H*), 9.62 (1H, s, N*H*); ^{13}C-nmr (125 MHz, DMSO-d_6/TFA(~1/4)): δ 18.4 (q), 30.8 (t), 59.9 (d), 110.3 (s), 121.6 (s), 121.9 (d), 124.2 (d), 127.3 (d), 128.3 (s), 129.6 (d), 131.1 (d), 133.8 (d), 136.0 (d), 138.4 (s), 138.8 (d), 140.7 (s), 156.0 (s), 156.9 (s), 162.1 (s), 167.8 (s), 171.1 (s); HRMS (FAB): $[M+H]^+$ for $C_{21}H_{17}N_4O_3$ requires *M*, 373.1300. Found: *m/z* 373.1303.

Anal. Calcd. for $C_{21}H_{16}N_4O_3$: C, 67.73; H, 4.33; N, 15.05. Found: C, 67.82; H, 4.27; N, 14.96.

[1-(2-Azidobenzoyl)-2,6-dioxo-piperidin-3-yl]carbamic Acid Benzyl Ester (**20**).

Methyllithium (1.6 mL, 1.6 *M* in diethyl ether) was added at –78° to a solution of compound **18** [18] (620 mg, 2.4 mmol) in dry THF (20 mL) under N_2. The solution was stirred for 30 minutes and *o*-azidobenzoyl chloride (530 mg, 2.9 mmol) [21] was added in dry THF (7 mL). The reaction mixture was allowed to

reach room temperature overnight and poured into water and extracted with ethyl acetate (30 mL × 3). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to afford an oily residue, which was purified by flash chromatography (50% ethyl acetate in hexane as eluent) to give the azide **20** (497 mg, 52%) as a light yellow solid; ir (KBr): 3385, 3032, 2952, 2129, 1754, 1712, 1691, 1595, 1481, 1296, 1228, 697 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 1.95–2.32 (2H, m, CH_2), 2.70–2.87 (1H, m, CH_2), 3.03–3.23 (1H, m, CH_2), 4.64–4.79 (1H, m, C*H*), 5.06 (2H, s, CH_2), 7.24–7.44 (6H, m, Ar*H*/N*H*), 7.48 (1H, d, *J* 8.1, Ar*H*), 7.76 (1H, ddd, *J* 8.4, 7.0, 1.4, Ar*H*), 7.84 (1H, d, *J* 8.7, Ar*H*), 7.97 (1H, d, *J* 7.9, Ar*H*); ^{13}C-mnr (DMSO-d_6): δ 23.4 (t), 31.3 (t), 51.2 (d), 65.6 (t), 120.8 (d), 122.7 (s), 125.3 (d), 127.7 (d), 127.8 (d), 128.3 (d), 132.8 (d), 136.0 (d), 136.8 (s), 140.2 (s), 156.1 (s), 167.8 (s), 171.3 (s), 171.8 (s); HRMS (FAB): $[M+H]^+$ for $C_{20}H_{18}N_5O_5$ requires *M*, 408.1308. Found: *m/z* 408.1319.

2-Azido-*N*-(2,6-dioxo-piperidin-3-yl)benzamide (**21a**).

2-Azidobenzoic acid (590 mg, 3.6 mmol) and thionyl chloride (3.26 g, 27 mmol) were heated at 80° for 2 h under N_2 [21]. The mixture was cooled to room temperature, and the excess of thionyl chloride was removed under reduced pressure. The residue was dissolved in dioxane (5 mL) and then added to a stirred mixture of the hydrobromide salt **19** (630 mg, 3.0 mmol) and triethylamine (460 mg, 4.5 mmol) in dioxane (20 mL). After stirring at 40–50° overnight, the mixture was filtered through Celite and concentrated under reduced pressure to afford a yellow solid, which was purified by flash chromatography (1% methanol in chloroform) to give the azide **21a** (640 mg, 78%) as a white solid, mp 180–181° (dec.); ir (KBr): 3316, 3202, 3094, 2142, 1711, 1652, 1533, 1202, 752 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 1.95–2.20 (2H, m, CH_2), 2.48–2.65 (1H, m, CH_2), 2.69–2.89 (1H, m, CH_2), 4.68–2.86 (1H, m, C*H*), 7.28 (1H, ddd, *J* 7.6, 7.5, 0.7, Ar*H*), 7.37 (1H, d, *J* 7.8, Ar*H*), 7.56 (1H, ddd, *J* 7.8, 7.6, 1.5, Ar*H*), 7.63 (1H, dd, *J* 7.6, 1.4, Ar*H*), 8.65 (1H, d, *J* 8.1, N*H*), 10.87 (1H, s, N*H*); ^{13}C-nmr (DMSO-d_6): δ 24.1 (t), 30.9 (t), 49.7 (d), 119.9 (d), 124.9 (d), 127.4 (s), 129.9 (d), 131.8 (d), 136.8 (s), 165.2 (s), 171.9 (s), 172.9 (s); HRMS (FAB): $[M+H]^+$ for $C_{12}H_{12}N_5O_3$ requires *M*, 274.0940. Found: *m/z* 274.0935.

2-Amino-*N*-(2,6-dioxo-piperidin-3-yl)benzamide (**21b**).

The hydrobromide salt **19** (0.71 g, 3.4 mmol) and triethylamine (0.69 g, 6.8 mmol) were dissolved in acetonitrile (30 mL) and heated at 60°. Isatoic anhydride (0.66 g, 4.0 mmol) was added and after 3 additional hours at 60° the solution was allowed to stand overnight at ambient temperature. The precipitate obtained was collected and dried to give the amine **21b** (320 mg, 39%) as a solid with a bluish tinge, mp 235° (dec.) (Lit. [23] mp 197–201°); ir (KBr): 3462, 3342, 3191, 3105, 1699, 1634, 1506, 1210, 754 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 1.87–2.22 (2H, m, CH_2), 2.50–2.89 (2H, m, CH_2), 4.66–4.83 (1H, m, C*H*), 6.42 (2H, br s, NH_2), 6.53 (1H, dd, *J* 7.7, 7.1, Ar*H*), 6.71 (1H, d, *J* 7.9, Ar*H*), 7.16 (1H, ddd, *J* 8.2, 7.0, 1.2, Ar*H*), 7.51 (1H, d, *J* 8.0, Ar*H*), 8.46 (1H, d, *J* 8.3, N*H*), 10.83 (1H, s, N*H*); ^{13}C-nmr (DMSO-d_6): δ 24.2 (t), 31.0 (t), 49.1 (d), 114.0 (s), 114.5 (d), 116.4 (d), 128.1 (d), 132.0 (d), 149.8 (s), 168.7 (s), 172.4 (s), 173.0 (s).

1-(2-Azidobenzoyl)piperidine-2,6-dione (**23**).

Compound **23** was prepared similarly to compound **20** using glutarimide [24]. A white solid (720 mg, 28%) was collected and the mother liquor was purified by flash chomatography (60 % ethyl acetate in hexane) to give more **23** (590 mg, 23%) as a light yellow solid: total yield, 51%; mp 153° (dec.); ir (KBr): 2970, 2896, 2134, 1736, 1702, 1679, 1592, 1474, 1348, 1264, 1179, 1145, 938, 776 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 2.00 (2H, quintet, *J* 6.5, CH_2), 2.75 (4H, t, *J* 6.5, CH_2), 7.33 (1H, app t, *J* 7.6, Ar*H*), 7.47 (1H, d, *J* 8.1, Ar*H*), 7.75 (1H, ddd, *J* 8.4, 7.0, 1.4, Ar*H*), 7.95 (1H, dd, *J* 7.9, 1.4, Ar*H*); ^{13}C-nmr (DMSO-d_6): δ 19.7 (t), 31.7 (t), 120.9 (d), 122.9 (s), 125.3 (d), 132.7 (d), 135.9 (d), 140.0 (s), 168.5 (s), 172.6 (s); HRMS (FAB): $[M+H]^+$ for $C_{12}H_{11}N_4O_3$ requires *M*, 259.0831. Found: *m/z* 259.0854.

4-(4-Oxo-3,4-dihydroquinazolin-2-yl)butyric Acid (**24**).

Triethyl phosphite (380 mg, 2.3 mmol) was added to a mixture of compound **23** (520 mg, 2.0 mmol) in toluene (25 mL, distilled from Na) under N_2 and at room temperature. The mixture was heated to 70° for 1 h and then heated at reflux for additional 2 h. The cooled solution was concentrated under reduced pressure to afford a yellow solid, which was treated with a small amount of water to give compound **24** (360 mg, 77%) as a white solid, mp 275–277° (Lit. [25a] >250°); ir (KBr): 3043, 2897, 1713, 1684, 1613, 1474, 1335, 1190, 1010, 906, 776 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 1.96 (2H, quintet, *J* 7.4, CH_2), 2.32 (2H, t, *J* 7.4, CH_2), 2.63 (2H, t, *J* 7.4, CH_2), 7.45 (1H, ddd, *J* 8.0, 6.9, 1.1, Ar*H*), 7.59 (1H, d, *J* 7.8, Ar*H*), 7.76 (1H, ddd, *J* 8.4, 6.9, 1.5, Ar*H*), 8.07 (1H, dd, *J* 7.9, 1.2, Ar*H*), 12.15 (2H, br s, N*H*/COO*H*); ^{13}C-nmr (DMSO-d_6): δ 21.8 (t), 32.8 (t), 33.5 (t), 120.9 (s), 125.7 (d), 126.0 (d), 126.8 (d), 134.2 (d), 148.8 (s), 156.8 (s), 161.8 (s), 174.1 (s).

2-Benzyloxycarbonylamino-4-(4-oxo-3,4-dihydroquinazolin-2-yl)butyric Acid (**22**).

Compound **22** was prepared similarly to compound **24** using compound **20** (170 mg, 0.42 mmol), but the mixture was heated at reflux for 6 h and compound **22** was recrystallised from toluene/hexane in 38% yield as a beige solid; ir (KBr): 3289, 3034, 2920, 1723, 1686, 1610, 1538, 1260, 775 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 1.90–2.14 (2H, m, CH_2), 2.22–2.44 (2H, m, CH_2), 4.46–4.59 (1H, m, C*H*), 5.04 (2H, s, CH_2), 7.23–7.44 (5H, m, Ar*H*/N*H*), 7.50 (1H, app t, *J* 7.5, Ar*H*), 7.63 (1H, d, *J* 8.0, Ar*H*), 7.71 (1H, d, *J* 7.6, Ar*H*), 7.81 (1H, app t, *J* 7.1, Ar*H*), 8.10 (1H, d, *J* 7.3, Ar*H*), 12.22 (2H, br s, N*H*/COO*H*); ^{13}C-nmr (DMSO-d_6): δ 28.1 (t), 30.2 (t), 53.6 (d), 65.5 (t), 121.2 (s), 125.7 (d), 126.4 (d), 127.0 (d), 127.5 (d), 127.7 (d), 128.3 (d),134.4 (d), 136.9 (s), 148.4 (s), 155.8 (s), 157.2 (s), 161.6 (s), 173.6 (s).

N-Acetyl-*N*-(6-acetyl-9,11-dioxo-5,8,9,11-tetrahydro-7*H*-pyrido-[2,1-*b*]quinazolin-8-yl)acetamide (**25a**).

Compound **12** (4.46 g, 15 mmol) was heated at reflux in acetic anhydride (110 mL) for 3 h. The solution was concentrated under reduced pressure to yield a dark oil, and the oily residue was flash chromatographed (ethyl acetate) and recrystallised in ethanol to give compound **25a** (1.40 g, 26%) as yellow needles, mp 194–195°; ir (KBr): 3380w, 1747, 1689, 1637, 1577, 1417, 1275, 1226, 971, 759 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 2.29 (3H, s, CH_3), 2.45 (6H, s, 2×CH_3), 2.95 (1H, dd, *J* 14.2, 6.8, CH_2), 3.09 (1H, dd, *J* 14.2, 12.7, CH_2), 5.10 (1H, dd, *J* 12.7, 6.8, C*H*), 7.45 (1H, ddd, *J* 8.0, 7.0, 1.0, Ar*H*), 7.76 (1H, ddd, *J* 8.6, 7.1, 1.6, Ar*H*), 7.83 (1H, d, *J* 8.0, Ar*H*), 8.00 (1H, dd, *J* 7.8, 1.4, Ar*H*), 13.62 (1H, s, N*H*); ^{13}C-nmr (DMSO-d_6): δ 23.4 (t), 26.3 (q), 28.8 (q), 56.7 (d), 90.9 (s), 118.8 (s), 122.8 (d), 126.0 (d), 126.7 (d), 134.0

(d), 136.4 (s), 145.6 (s), 157.9 (s), 168.0 (s), 172.8 (s), 198.1 (s); HRMS (FAB): $[M+H]^+$ for $C_{18}H_{18}N_3O_5$ requires *M*, 356.1246. Found: *m/z* 356.1260.

Anal. Calcd. for $C_{18}H_{17}N_3O_5$: C, 60.84; H, 4.82; N, 11.83. Found: C, 60.69; H, 4.92; N, 11.67.

6-Acetyl-7,8-dihydro-5*H*-pyrido[2,1-*b*]quinazoline-9,11-dione (**25b**).

Compound **24** (1.19 g, 5.0 mol) was heated at reflux in acetic anhydride (45 mL) for 16 h. The solution was concentrated under reduced pressure to yield a dark oil, and the oily residue was flash chromatographed (75 % ethyl acetate in hexane) and recrystallised in methanol to give compound **25b** (290 mg, 23%) as a light yellow solid, mp 181–183°; ir (KBr): 1725, 1701, 1630, 1579, 1407, 1277, 1122, 963, 757 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 2.27 (3H, s, CH_3), 2.63–2.74 (2H, m, CH_2), 2.74–2.85 (2H, m, CH_2), 7.43 (1H, ddd, *J* 7.9, 7.1, 0.8, Ar*H*), 7.74 (1H, ddd, *J* 8.7, 7.1, 1.7, Ar*H*), 8.00 (1H, dd, *J* 7.8, 1.6, Ar*H*), 8.22 (1H, d, *J* 8.5, Ar*H*), 13.78 (1H, s, N*H*); ^{13}C-nmr (DMSO-d_6): δ 18.6 (t), 28.6 (q), 32.8 (t), 93.3 (s), 118.6 (s), 122.6 (d), 125.7 (d), 126.6 (d), 133.9 (d), 136.7 (s), 146.5 (s), 157.9 (s), 170.4 (s), 197.6 (s).

Anal. Calcd. for $C_{14}H_{12}N_2O_3$: C, 65.62; H, 4.72; N, 10.93. Found: C, 65.60; H, 4.65; N, 10.92.

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