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# Synthesis of unsymmetrical 3,3′-biquinazoline-2,2′-diones by condensation of 3-aminoquinazolinones with benzoxazinones; fortuitous discovery, and further syntheses of 4-*H*-3-oxo-1,9a,10-triazaanthracen-9-ones

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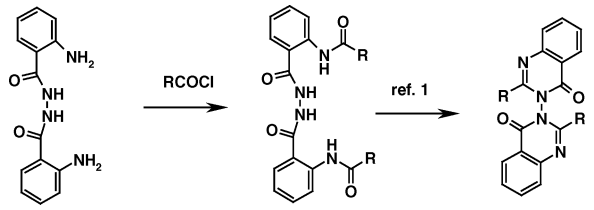
Condensation of 2-alkyl- or 2-aryl-3-aminoquinazolin-4-ones with benz[1,3]oxazin-4-ones gives the unsymmetrical 2,2′disubstituted 3,3′biquinazoline-4,4′-diones. The reaction is tolerant to a range of heteroatom and unsaturated functionality in the quinazolinone 2-position. However, treatment of 3-amino-2-hydroxymethyl-3*H*-quinazolin-4-ones with benz[1,3]oxazinone at high temperatures gave 4*H*-3-oxo-1,9a,10-triazaanthracen-9-ones, an unreported fused heterocyclic system, a more direct synthesis of which, replacing benzoxazinones with orthoesters is presented.

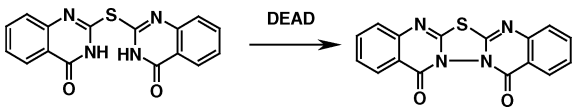
## Introduction

This group is interested in the preparation, and application as ligands and in asymmetric synthesis, of 3,3′-biquinazoline-4,4′-diones,[1] a family of axially chiral bis-heterocycles which have high barriers to rotation around an N–N bond and thus form stable atropisomers. Our previous reports have demonstrated that the syntheses of $C_2$ symmetrical 3,3′-biquinazolinone are readily achieved from bisanthranoyl hydrazine, (Scheme 1) however this route seems unpromising for the synthesis of unsymmetrical 2,2′ disubstituted 3,3′-biquinazolinones, and thus other routes were explored which would allow the synthesis of each quinazolinone unit separately followed by the coupling of the two halves.



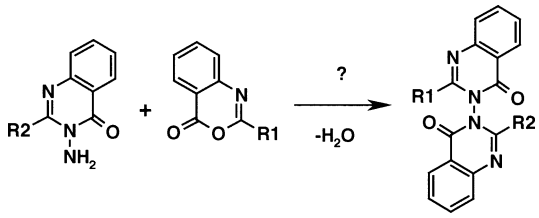

**Scheme 1**

Although an intramolecular oxidative coupling of quinazolinone fragments has been reported[2] (Scheme 2) this reaction, if applied to the intermolecular coupling of unsymmetrically substituted quinazolinones, would be expected to give statistical mixtures of products of homo- and hetero-coupling. Therefore a heterocoupling route seemed indicated, in which the two halves of a non-symmetrical biquinazolinone could be independently prepared and reliably coupled in a controlled manner to give the unsymmetrical product.




**Scheme 2**

One promising avenue seemed to be the condensation of 3-aminoquinazolinones with benz[1,3]oxazin-4-ones, which would allow the synthesis of both symmetrical and unsymmetrical 3,3′-biquinazoline-4,4′-diones, and seemed a feasible† route by analogy with the reliable route to 3-aminoquinazolinones *via* the treatment of benz[1,3]oxazin-4-ones with hydrazines.[3] As a large range of 2-substitution patterns are known and readily available both for 3-aminoquinazolin-4-ones and for benz[1,3]oxazin-4-ones, thus, at least in theory, a wide range of 3,3′-biquinazoline-4,4′-diones should be available from this specific heterocoupling reaction (Scheme 3).




**Scheme 3**

## Results and discussion

### Synthesis of 3,3′-biquinazoline-4,4′-diones *via* reaction of 3-aminoquinazolin-4-ones and benz[1,3]oxazin-4-ones

To investigate the viability of this synthesis a range of 3-aminoquinazolinones (**1–5**)[4–7] were prepared, both known compounds by literature methods or adaptations, with a range of substituents of various steric bulks, and reactivity profiles, including heteroatoms, unsaturation and free hydroxyl groups. Three examples of the other partner in the coupling were prepared, the parent 2-protio-[8], 2-methyl[9] and 2-ethylbenz[1,3]oxazin-4-one[10] in order to test the effect on the reaction of increased steric demands in this partner. The initial attempts at condensation were run under conditions which mimicked those used in the synthesis of 3-aminoquinazolin-4-ones from the reaction of benz[1,3]oxazinones with hydrazine,[3] that is reflux in alcoholic solvents, but it soon became clear that, especially in the case of the unsubstituted benz[1,3]oxazin-4-one, alcoholysis of the oxazine ring dominates the reaction. Presumably, this is a reflection of the much diminished nucleopilicity of 3-aminoquinazolin-4-ones when compared with hydrazine itself, again reflecting the electron-withdrawing nature of the

† We thank a referee to drawing our attention to other precedent[16] for this approach of which we were unaware.

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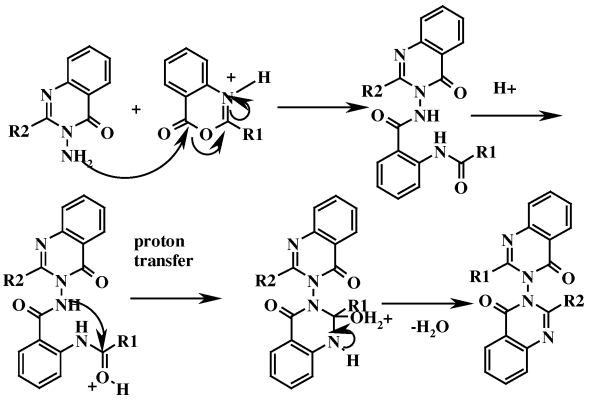
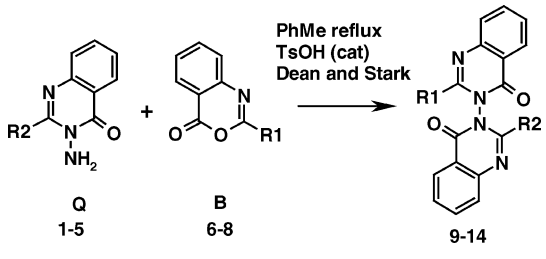
quinazolin-4-one ring. Refluxing toluene or other inert solvents gave condensation, but with poor yields and unacceptably slow rates (reaction times of many days or weeks) however the addition of catalytic *p*-toluene sulfonic acid accelerated the reaction to such an extent that, typically, moderate to good yields could be obtained in a few hours to a day reaction time under Dean–Stark conditions. In most cases the reaction proceeded smoothly to give the 3,3′-biquinazoline-4,4′-dione as the only major product and as a crystalline solid, isolable at analytical purity by simple crystallisation of the crude reaction mixtures without the need for extractions, separations or chromatography. The limitations of this synthesis of unsymmetrical 2,2′-substituted 3,3′-biquinazoline-4,4′-diones initially appeared to be essentially steric with heteroatom and unsaturated substitution tolerated. While 2-*tert*-butyl-3-aminoquinazolin-4-one condenses efficiently with 2-unsubstituted benzoxazinone, it fails to give any 3,3′biquinazoline-4,4′-dione with the methyl or ethyl analogues, only the open amide being observed in the reaction mixture, no matter how forcing the conditions used for the reaction, even when strong dehydrating agents such as acetic anhydride or even thionyl chloride were employed at reflux, eventually giving decomposition of the intermediate without providing the ring-closed product. These open amide products proved to be unstable and, in cases where the cyclisation to the desired product failed, were never isolated as homogeneous substances. It is non-intuitive that the sterically hindered 2-*tert*-butyl-3-aminoquinazolinone should react readily with all the benzoxazinones, and only demonstrate a steric problem at the cyclisation stage, but this can be rationalised in terms of the planarity of the benzoxazinone electrophile. Initial attack at the benzoxazinone carbonyl will suffer from only slight steric clashes with the quinazolinone 2-substituent, and the benzoxazinone side chain will be almost irrelevant, however in the cyclisation step the two substituents are forced into proximity, and thus it is at this stage that the bulk of the *tert*-butyl group becomes too demanding a match for all but the smallest benzoxazinone (Scheme 4).




**Scheme 4**

Other than this steric limitation a number of examples of condensation of each benz[1,3]oxazine with various 3-aminoquinazolin-4-ones were demonstrated (see Scheme 5, Table 1) and the reaction did not seem to be unduly effected by




**Scheme 5**

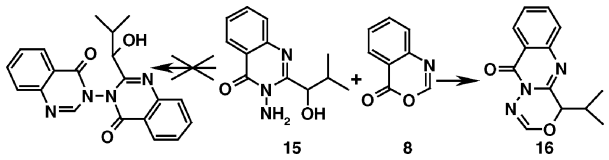
**Table 1**

| Entry | $QNH_2$, R2 | R1 | % cat/h | BiQ | Yield (%) |
|---|---|---|---|---|---|
| 1 | **1** Ph[4] | **6** Et[10] | 5/10 | **9** | 79 |
| 2 | **2** SEt (this paper) | **6** Et | 5/10 | **10** | 44 |
| 3 | **1** Ph[4] | **7** Me[9] | 5/6 | **11** | 62 |
| 4 | **3** $^t$Bu[5] | **8** H[8] | 8/8 | **12** | 40 |
| 5 | **4** $CO_2Et$[6] | **6** Et | 8/24 | **13** | 51 |
| 6 | **5** $CHMeCH_2CH{=}CHPh$[7] | **8** H | 5/24 | **14** | 47 |

the presence of either heteroatoms or unsaturation in the 2-substituent of the quinazolin-4-one which would be important in attempts to apply such products as ligands for metals in asymmetric catalysis, or as chiral auxiliaries in which faces of a double bond could be rendered diastereotopic by the chiral axis.

### Attempted synthesis of chiral, non-racemic biquinazolinones

All of the examples of biquinazolinones synthesised by this coupling reaction above are racemic, only **5** being chiral and itself a racemate, and although we have previously demonstrated deracemisation of a small number of examples of 3,3′-biquinazolinones[1] attempts to apply this protocol to other examples have proved less successful. Thus a synthesis of a biquinazolinone in non-racemic form, or at least bearing a non-racemic chiral centre which would assist with the resolution of the chiral axis was desirable. Incorporation of a chiral centre into the 3-position of a 3-aminoquinazolinone seemed the simplest approach, as such compounds are well known in the literature. It was hoped that a single chiral centre in the 2-alkyl substituent may be sufficient to give good control of the formation of the chiral axis, and it seemed likely that the best control may come from a chiral group containing a hydroxyl substituent which could hydrogen bond to the amide intermediate in the condensation. Thus a sample of 2-(1-hydroxy-2-methyl)propyl)-3-aminoquinazolin-4-one 15 (prepared from L-valine by the procedure of Atkinson[11]) was treated with benz[1,3]oxazinone **8** in toluene at reflux with a catalytic quantity (5 mol%) of toluene-4-sulfonic acid under Dean–Stark conditions. None of the expected biquinazolinone was recovered, instead a highly crystalline compound of molecular weight $m/z = 244$ was recovered in 49% yield after cooling to room temperature and crystallisation of the precipitate from methanol (Scheme 6).




**Scheme 6**

Proton and carbon NMR suggested that the structure was derived from the 3-aminoquinazolinone with the addition of an additional methine which, from the chemical shift data ($\delta$H 7.2, $\delta$C 126) appeared to be heterocyclic, which, along with the loss of all exchangeable protons, suggested the structure **16**. This structure was eventually confirmed by single crystal X-ray diffraction measurements on crystals grown by slow evaporation of a methanol solution (Fig. 1).

Compound **16** was observed to have crystallised in space group $P2_1/c$ which is not a chiral space group, with the asymmetric unit being repeated through an improper rotation, which is impossible for crystals containing homochiral material. This indicated that the chiral centre of the valine-derived substituent of the quinazolinone had racemised at some point along the reaction scheme (confirmed for the bulk sample by the zero optical rotation). This racemisation was unexpected as such chiral carbons are usually stable to the reaction conditions involved in this cyclisation, and subsequently it emerged that

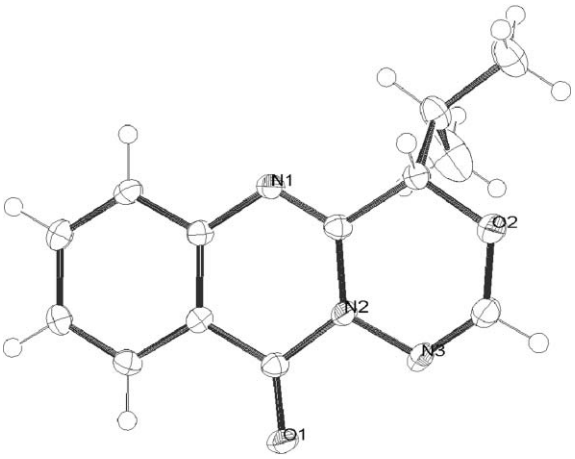


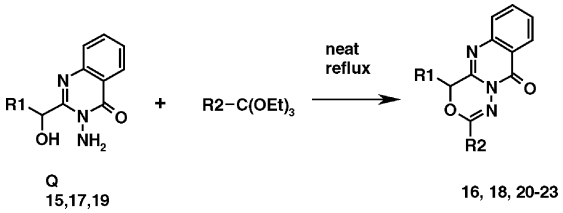

**Fig. 1** ORTEP view of **16** 50% probabilities.

the starting material **15** was itself racemic. As **15** is derived from L-valine it was disturbing that racemisation had occurred, as the diazotization–substituion reaction is a classic double inversion and should proceed with retention of configuration. A reinvestigation of the synthetic pathway to **15** demonstrated that the diazotization step is particularly sensitive to heat and in the absence of efficient cooling to between 0 and 5 °C racemisation will occur as the reaction is also exothermic. It was also noted that cooling to zero lowers the yield due to solidification of the sodium nitrite–acetic acid mixture so a balance is necessary in order to avoid racemisation but maintain high yields.

A simple mechanistic rational suggests that the benz[1,3]-oxazin-4-one is acting as a formate synthon, with loss of anthranilic acid, suggesting that the new heterocyclic system could be accessed *via* the treatment of 2-hydroxymethyl-3-aminoquinazolinones with orthoesters, and indeed it transpired that treatment of 3-aminoquinazolinone **15** with triethyl orthoformate at reflux also gave oxotriazaanthracenone **16** in a better yield of 68%. Initial attack of the quinazolinone nitrogen at the activated carbonyl equivalent obtained from triethyl orthoformate upon protonation–loss of ethanol to give an orthoformamide (no strong acid is required, in fact the reaction occurs without addition of external acid simply upon heating the reactants) followed by another protonation–loss of ethanol sequence gives the activated intermediate for nucleophilic attack by the hydroxymethyl oxygen. The cyclic orthoamide thus formed spontaneously loses ethanol to give the highly conjugated oxatriazaanthracenone.

### Synthesis of 4-*H*-3-oxo-1,9a,10-triazaanthracen-9-ones

Surprisingly, not only was the product unreported, but we could find no reports of this heterocyclic system, or even the bicyclic non-benzanullated analogue, in the literature. As routes to new heterocyclic systems are continuously of interest, an investigation of the synthesis of a small number of analogues was undertaken. Repeating the reaction with a samples of enantiomerically pure quinzolinones (see Scheme 7, Table 2) gave the corresponding enantiomerically pure products with optical rotation unchanged upon recrystallisation demonstrating that the racemisation was solely associated with the synthesis of the 3-



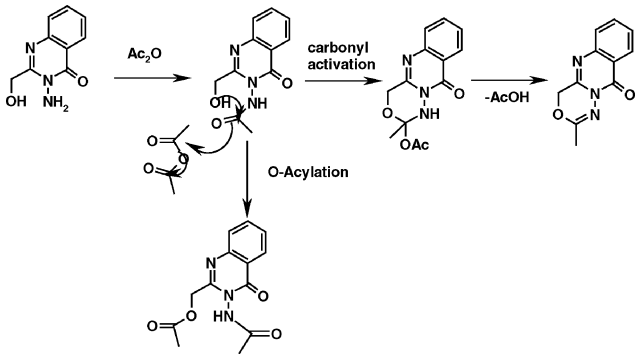

**Scheme 7**

**Table 2**

| Entry | Q, R1 | R2 | Time/h | Product | Yield (%) |
|---|---|---|---|---|---|
| 1 | **15**, $^{i}$Pr | H | 5 | **16** | 68 |
| 2 | **15**, $^{i}$Pr | Me | 24 | **21** | 77 |
| 3 | **15**, $^{i}$Pr | Et | 36 | **22** | 54 |
| 4 | **17**, Ph | H | 24 | **18** | 58 |
| 5 | **19**, H | H | 24 | **20** | 85 |
| 6 | **15**, $^{i}$Pr | Ph | 36 | **23** | 60 |

aminoquinazolinone, and not a function of the new heterocycle synthesis. The mandelic acid-derived 3-aminoquinazolinone **17** also reacted with triethyl orthoformate to give the analogous heterocycle **18** in enantiomerically pure form and with a 60% yield. The simplest 2-hydroxymethyl-3-aminoquinazoline **19**[12] also condensed smoothly with triethyl orthoformate to give the parent oxatriazaanthacenone 20 in 85% yield. All of these compounds were isolated by crystallisation of the reaction mixtures after evaporation of excess orthoformate without the need for chromatography.

Although orthoformates are common starting materials it was felt that other reagents, *e.g* anhydrides or acyl chlorides may be better sources of the products which might be expected from reaction with orthoacetates and higher analogues as these are also electrophilic acyl equivalents, and are more common and more reactive. Unfortunately, while the treatment of 3-amino-2-[(*S*)-1-hydroxy-2-methylpropyl]quinazolin-4-one with either acetic anhydride or acetyl chloride gave some of the desired product, derived from *N*-acylation followed by carbonyl activation, nucleophilic attack of the hydroxyl and loss of carboxylic acid, the major products in each case were the uncyclised *N*-acetyl hydroxyl compound[13] or the *N*,*O*-diacetyl compound, depending upon conditions (Scheme 8). Similar results were obtained using propionyl chloride and benzoyl chloride.




**Scheme 8**

Turning attention back to the reactions of 3-amino-2-hydroxymethylquinazolin-4-ones with orthoesters allowed access to higher analogues of the new heterocycles (Scheme 8, Table 2). Again all of these compounds were isolated in homogeneous form from the crystallisation of the crude residue obtained upon evaporation of the reaction mixture without the need for chromatography.

## Conclusions

A route to 2,2′-unsymmetrically substituted 3,3′-biquinazoline-4,4′-diones has been developed coupling 3-aminoquinazolin-4-ones and benz[1,3]oxazinones. After an unexpected product was isolated from one of these attempted coupling reactions a synthesis of a new heterocyclic system the 4-*H*-3-oxo-1,9a,10-triazaanthracen-9-ones was developed.

## Experimental

### General experimental

All starting materials and reagents were purchased from commercial suppliers and used as supplied unless otherwise stated. Benzoxazinones were synthesised by literature routes[8–10] or similar procedures; 3-aminoquinazolinones were synthesised by literature routes[4–7,11] unless described below. NMR spectra were recorded on a Bruker DPX 400 MHz at 400 MHz (proton) and 160 MHz (carbon), or an APX 250 at 250 MHz and 100 MHz respectively. IR spectra were recorded on a Perkin-Elmer 1600 FT IR as thin films or nujol mulls; mass spectra were recorded on a VG Fisons Platform II or at the EPSRC National Mass Spectrometry Service in Swansea (HRMS). Elemental analyses were performed by Warwick Analytical Services (University of Warwick).

**2-Ethylthio-3-aminoquinazolin-4-one 2.** To a stirred solution of 2-mercapto-3-aminoquinazolin-4-one[14] (8.3 g, 0.043 mol) in saturated aqueous sodium hydroxide (100 ml) was added ethanol (25 ml) followed by ethyl iodide (20 ml, 39 g, 0.25 mol). The solution was stirred for a further 1 h then a white solid which had precipitated was collected by filtration. Crystallisation from ethanol gave a white solid (6.6 g, 69%); mp 138–140 °C (ethanol). $\delta_H$ 8.12 (1H, d $J$, = 6.2 Hz, H-5), 7.67 (3H, m), 4.85 (2H, br s, N$H_2$), 3.12 (2H, q, $J$ = 9.0 Hz, SC$H_2$), 1.33 (3H, t, $J$ = 9.0 Hz, $SCH_2CH_3$); $\delta_C$ 161.4, 158.6, 147.6, 134.3, 126.6, 126.4, 125.4, 118.3, 25.6, 13.9; $\nu_{max}$/cm$^{-1}$ 3320, 3220, 1680, 1630; $m/z$(%) (EI) 221 (45)($M^+$) 205(68), 193(47), 174(11), 162(100), 144(69); $C_{10}H_{11}N_3OS$ requires C 54.3; H 5.0; N 19.0%, found C 54.25; H 5.1; N 18.9%.

**2-Ethyl-2′-phenyl-3,3′-bisquinazoline-4,4′-one 9.** A mixture of 2-ethyl-4$H$-3,1-benzoxazin-4-one (3 g, 17.1 mmol), 3-amino-2-phenyl-3$H$-quinazolin-4-one (3 g, 12.6 mmol) and $p$-toluenesulfonic acid (0.147 g, 0.855 mmol) was heated at reflux in toluene for 10 hours. After cooling, the toluene was evaporated *in vacuo* and the solid obtained was triturated with diethyl ether to give a pale yellow solid which was then crystallised from ethanol to give white crystals; mp 94 °C (3.90 g, 78.6%). $\delta_H$ (400 MHz, $CDCl_3$) 8.30 (1H, dd $J$ = 8.0, 1.3 Hz, H5), 8.15 (1H, dd $J$ = 7.9, 1.3 Hz, H5′), 7.83 (2H, m), 7.68 (1H, ddd, $J$ = 8.0, 7.0, 1.3 Hz), 7.54 (m, 5H), 7.38 (ddd, 1H, $J$ = 8.0, 7.1, 0.9 Hz), 7.25 (2H, m), 2.50 (2H, q, $J$ = 7.3 Hz, N=C–C$H_2$CH$_3$), 1.21 (3H, t, $J$ = 7.3 Hz, $CH_2CH_3$); $\delta_H$ (100 MHz, $CDCl_3$) 160.0, 159.5, 156.5, 155.1, 147.0, 136.1, 135,7, 135.3, 132.7, 131.9, 131.2, 129.0, 128.7, 128.4, 128.0, 128.0, 127.8, 127.5, 121.5, 120.9, 26.6, 10.3; $\nu_{max}$/cm$^{-1}$ 1686, 1591, 1464, 1377, 1331, 1274, 1116, 909, 873, 764, 695; $m/z$(APCI)(%) 395.1 (100) [M + H$^+$]; $C_{24}H_{18}N_4O_2$ requires C 73.08; H 4.60; N 14.20%, found C 73.01; H 4.62; N 14.12 (%).

**2-Ethyl-2′-thioethyl-3,3′-bisquinazoline-4,4′-dione 10.** A mixture of 2-ethyl-4$H$-3,1-benzoxazin-4-one (0.63 g, 3.57 mmol), 3-amino-2-thioethyl-3$H$-quinazolin-4-one (0.71 g, 3.58 mmol) and $p$-toluenesulfonic acid (0.030 g, 0.179 mmol) was heated at reflux in toluene for 10 hours. After cooling, the toluene was evaporated *in vacuo* and the solid obtained was triturated with diethyl ether to give a pale yellow solid which was then crystallised from dichloromethane–light petrol to give white crystals mp 173 °C (0.600 g, 44.0%). $\delta_H$ (400 MHz, $CDCl_3$) 8.22 (1H, dd, $J$ = 7.8, 1.3 Hz, H5′), 8.17 (1H, dd, $J$ = 7.9, 1.3 Hz, H5), 7.75 (3H, m), 7.61 (1H, d, $J$ = 7.9 Hz, H8′), 7.44 (2H, m), 3.15 (2H, m), 2.54 (2H, m), 1.28 (6H, m); $\delta_C$ (100 MHz, $CDCl_3$) 158.8, 158.5, 156.6, 156.3, 147.4, 146.82, 135.6, 135.4, 127.8, 127.7, 127.5, 127.1, 126.8, 126.4, 121.0, 119.7, 26.3, 25.8, 13.7, 9.9; $\nu_{max}$/cm$^{-1}$ 1674, 1633, 1609, 1578; $m/z$ (APCI)(%) 379 (100) [M + H$^+$]; $C_{20}H_{18}N_4O_2S$ requires C 63.46; H 4.79; N 14.82, found C 63.16; H 4.73; N 14.58%.

**2-Methyl-2′-phenyl-3,3′-bisquinazoline-4,4′-one 11.** A mixture of 2-methyl-4$H$-3,1-benzoxazin-4-one (0.628 g, 4.2 mmol), 3-amino-2-phenyl-3$H$-quinazolin-4-one (1 g, 4.26 mmol), and $p$-toluenesulfonic acid (0.047 g, 0.211 mmol) was heated at reflux in toluene for 6 hours. After cooling, the toluene was evaporated *in vacuo* and the solid obtained was crystallised from ethanol to give white crystals mp 162 °C (0.955 g, 61.5%). $\delta_H$ (400 MHz, $CDCl_3$) 8.29 (1H, dd, $J$ = 8.0, 0.9 Hz, H5), 8.14 (1H, dd, $J$ = 8.0, 1.4 Hz, H5′), 7.82 (2H, m), 7.69 (1H, ddd, $J$ = 8.0 7.8 1.2 Hz H7′), 7.52 (M, 5H), 7.39 (1H, ddd, $J$ = 8.0, 7.0, 1.2, H7), 7.28 (2H, m), 2.32 (1H, s, N=C–C$H_3$); $\delta_C$ (100 MHz, $CDCl_3$) 159.8, 159.4, 154.9, 153.6, 147.2, 146.9, 136.2, 135.8, 132.7, 131.3, 129.0, 128.8, 128.4, 128.1, 128.0, 127.8, 127.7, 127.6, 121.4, 120.1, 22.0; $\nu_{max}$/cm$^{-1}$ 1692, 1599, 1566, 1378, 1324, 1268, 776, 698; $m/z$ (APCI) (%) 381 (100) [M + H$^+$]; $C_{23}H_{16}N_4O_2$ requires, C 72.62; H 4.24; N 14.73; found C 72.50; H 4.24; N 14.50%.

**2-*tert*-Butyl-3,3′-bisquinazoline-4,4′-dione 12.** A mixture of 4$H$-3,1-benzoxazin-4-one (1.016 g, 7 mmol), 3-amino-2-*tert*butyl-3$H$-quinazolin-4-one (1 g, 4.6 mmol) and $p$-toluenesulfonic acid (0.066 g, 0.345 mmol) was heated at reflux with a Dean–Stark apparatus in toluene for 8 hours. After cooling, the toluene was evaporated *in vacuo* and the solid obtained was crystallised from ethanol to give pale brown crystals; mp 225 °C (0.64 g, 38%); $\delta_H$ (400 MHz, $CDCl_3$) 8.28 (1H, dd $J$ = 7.9, 1.3 Hz, H4), 8.19 (1H, dd $J$ = 7.7, 1.1 Hz, H4′), 7.80 (1H, s, H2′), 7.75 (4H, m), 7.52 (1H, ddd $J$ = 8.0, 6.7, 1.1 Hz, H6′), 7.44 (1H, ddd, $J$ = 7.2, 6.1, 1.3 Hz, H6), 1.3 (9H, s, C($CH_3$)$_3$); $\delta_C$ (100 MHz, $CDCl_3$), 159.63, 159.06, 158.83, 146.74, 146.09, 145.21, 134.49, 134.40, 127.33, 127.10, 127.09, 126.64, 126.48, 126.20, 121.52, 119.42, 38.71, 28.84; $\nu_{max}$/cm$^{-1}$ 1692, 1594; $m/z$ (APCI)(%) 347 (100) [M + H$^+$]; $C_{20}H_{18}N_4O_2$ requires C 69.35, H 5.24, N 16.17; found C 68.95, H 5.24, N 15.95%.

**2-Ethyl-2′-ethoxycarbonyl-3,3′-bisquinazoline-4,4′-dione 13.** A mixture of 2-ethyl-4$H$-3,1-benzoxazin-4-one (1.35 g, 7.85 mmol), 3-amino-2-ethoxycarbonyl-3$H$-quinazolin-4-one (1.220 g, 5.2 mmol) and $p$-toluenesulfonic acid (0.0746 g, 0.392 mmol) was heated at reflux in toluene for 24 hours. After cooling, the toluene was evaporated *in vacuo* and the solid obtained was triturated with diethyl ether to give a pale yellow solid which was then crystallised from dichloromethane–light petrol to give white crystals mp 175 °C (1.04 g, 50.9%). $\delta_H$ (400 MHz, $CDCl_3$) 8.30 (1H, dd, $J$ = 7.9, 1.0 Hz, H5), 8.15 (1H, dd $J$ = 7.6, 1.1 Hz, H5′), 7.86 (2H, m), 7.74 (2H, m), 7.60 (1H, ddd, $J$ = 7.3, 7.2, 1.0 Hz, H7), 7.42 (1H, ddd, $J$ = 7.3, 7.1, 1.1 Hz, H7′), 4.24 (1H, dq $J$ = 11.2, 7.0 Hz, $\frac{1}{2}$ × $CO_2CH_2$), 4.19 (1H, dq $J$ = 11.2, 7.0 Hz, $\frac{1}{2}$ × $CO_2CH_2$), 2.77 (1H, dq, $J$ = 17.2, 7.2 Hz, $\frac{1}{2}$ × N=C–C$H_2$), 2.58 (1H, dq, $J$ = 17.2, 7.2 Hz, $\frac{1}{2}$ × N=C–C$H_2$), 1.31 (3H, t, $J$ = 7.0 Hz, $CO_2CH_2CH_3$), 1.13 (3H, t, $J$ = 7.2 Hz, N=C–$CH_2CH_3$); $\delta_C$ (100 MHz, $CDCl_3$), 174.1, 158.16, 157.62, 155.90, 145.82, 144.45, 143.43, 134.87, 134.32, 128.47, 128.15, 126.86, 126.73, 126.20, 125.96, 121.42, 119.56, 62.64, 24.95, 12.65, 8.74; $\nu_{max}$/cm$^{-1}$ 1738, 1709, 1686, 1601; $m/z$ (APCI) (%) 391 [M + H$^+$]; $C_{21}H_{18}N_4O_4$ requires C 64.61; H 4.65; N 14.35, found C 64.54; H 4.64; N 14.29%.

**(+)(-)-2-(1-Methyl-4-phenyl)but-3-enyl-3,3′-bisquinazoline-4,4′-one 14.** (Prepared as a 1 : 1 mixture of diastereoisomers and not separated.)

A mixture of 2$H$-3,1-benzoxazin-4-one (0.76 g, 5.160 mmol), (+)(−) 3-amino-2-(1-methyl-4-phenyl-but-3-enyl)quinazolin-4-one (1.050 g, 3.44 mmol) and $p$-toluenesulfonic acid (0.026 g, 0.13 mmol) was heated at reflux in toluene for 24 hours. After cooling, the toluene was evaporated *in vacuo* and the solid obtained was crystallised from toluene–petroleum ether to give pale yellow crystals; mp 144 °C (0.70 g, 47%); $\delta_H$ (400 MHz, $CDCl_3$, 1 : 1 mixture of isomers referred to as A and B, many signals overlapped assigned as m) 8.28 (1H, d, $J$ = 7.4 Hz, H8$_A$), 8.26 (1H, d, $J$ = 7.4 Hz, H8$_B$), 8.20 (1H, d, $J$ = 7.5 Hz, H8′$_A$),

8.16 (d, 1H, $J$ = 7.5 Hz, H8′$_B$), 7.95 (1H, s, H2′), 7.74 (8H, m), 7.70 (1H, s, H2′), 7.50 (5H, m), 7.14 (9H, m), 6.38 (1H, d, $J$ = 15.8, PhC*H*=C), 6.28 (1H, d, $J$ = 15.8, PhC*H*=C), 6.04 (2H, m, C=C*H*CH$_2$), 2.84 (1H, m), 2.69 (3H, m), 2.48 (2H, m, *H*C(CH$_3$), 1.32 (3H, d, $J$ = 6.4, C*H*$_3$), 1.28 (3H, d, $J$ = 6.4, C*H*$_3$); $\delta_C$ (100 MHz, CDCl$_3$) 159.4, 159.3, 159.2, 159.1, 158.5, 158.4, 147.17, 147.12, 146.6, 146.6 (2 peaks), 145.71, 145.5, 137.1, 136.4, 135.3, 135.3, 132.9, 132.17, 128.7, 128.4, 128.2, 128.1, 128.0, 127.99, 127.94, 127.6, 127.5, 127.37, 127.32, 127.3, 127.1, 127.0, 126.8, 125.9, 125.8, 125.7, 125.0, 122.0, 120.5, 120.4, 40.5, 38.87, 37.03, 35.65, 28.19, 21.73, 20.56, 18.61, 18.49; $\nu_{max}$/cm$^{-1}$ 2920, 1693, 1603, 1568, 1462, 1377, 1266, 768, 741, 692; $m/z$ (EI) (%) 434.5 (38)(M$^+$) 211 (82); HRMS $C_{27}H_{22}N_4O_2$ requires 435.1816, found 435.1815.

**(*S*)-2-(1-Hydroxy-2-methyl)propyl)-3-aminoquinazolin-4-one 15.** This was prepared by the procedure of Atinson[11] from (*S*)-2-acetoxy-3-methylbutanoic acid, prepared by the following adaptation to the original procedure:

To a stirred suspension of L-valine (4 g, 34 mmol) in acetic acid (160 ml) was added portionwise and with stirring over 1 hour sodium nitrite (9.4 g, 136 mmol). During the addition the reaction vessel was cooled in a water bath which was kept between 0 and 5 °C by the intermittant addition of ice, not being allowed to exceed these limits. After the addition was complete the bath was removed and the mixture allowed to attain ambient temperature while it was stirred for a further 1 hour. The acetic acid was then removed under vaccum, the residue disolved in warm water (30 ml), extracted into ether (3 × 30 ml), washed with brine (30 ml), dried (MgSO$_4$) and evaporated to give (*S*)-2-acetoxy-3-methylbutanoic acid (3.79 g, 69.7%) as a pale oil which was used in subsequent steps without further purification.

**4-Isopropyl-3-oxo-1,9a,10-triazaanthracen-9-one 16‡.** A solution of 3-amino-2-[(*S*)-1-hydroxy-2-methylpropyl]-quinazolin-(3*H*)-4-one (0.354 g, 1.5 mmol) in triethyl orthoformate (8 ml) was heated at reflux for five hours. After that period the mixture was allowed to reach room temperature, and then the solvent was removed under reduced pressure. The red residue was crystallised from ethanol to give white crystals; mp 230 °C (0.248 g, 67.5%). $\delta_H$ (400 MHz, CDCl$_3$) 8.30 (1H, dd, $J$ = 8.1, 1.3 Hz, H8), 7.70 (1H, dd, $J$ = 8.1, 7.0 Hz, H7), 7.60 (1H, d, $J$ = 7.7 Hz, H5), 7.50 (1H, dd, $J$ = 7.7, 7.0 Hz, H6), 7.24 (1H, s, H2), 4.95 (1H, d, $J$ = 4.2 Hz), 2.55 (1H, m), 1.05 (3H, d, $J$ = 6.9 Hz, C*H*$_3$), 0.95 (3H, d, $J$ = 6.98 Hz, C*H*$_3$); $\delta_C$ (100 MHz, CDCl$_3$) 155.4, 45.0, 144.9, 143.3, 133.6, 126.8, 126.5, 126.4, 121.2, 77.6, 31.9, 17.5, 15.3; $\nu_{max}$/cm$^{-1}$1699, 1654, 1598, 1463 cm$^{-1}$; $m/z$ (APCI)(%) 244.1 [M + H$^+$]; $C_{13}H_{13}N_3O_2$ HRMS requires MH$^+$ 244.1081, found: MH$^+$244.1084; $C_{13}H_{13}N_3O_2$ requires C 64.12; H 5.39; N 17.27, found C 63.83; H 5.38; N 17.12%.

**4-Isopropyl-3-oxo-1,9a,10-triazaanthracen-9-one 16 (*via* benzoxazinones).** A mixture of 3-amino-2-[(*S*)-1-hydroxy-2-methylpropyl]quinazolin-4-(3*H*)-one (1 g, 4.3 mmol), 4*H*-3,1-benzoxazin-4-one (0.8 g, 5.44 mmol) and *p*-toluenesulfonic acid (0.051 g, 0.272 mmol) was heated at reflux in toluene (30 ml) for 24 hours. After this time the reaction mixture was cooled to room temperature then the pale brown precipitate recrystallised from methanol to give white crystals (0.512 g, 49% yield), properties as above.

**3-Amino-2-(phenylhydroxymethyl)quinazolin-4-one 17.** To a solution of methyl anthranilate (20 ml, 23.4 g, 0.15 mol) in diethyl ether (100 ml) under nitrogen was added dropwise a solution of (*S*)-acetoxyphenylacetyl chloride (8.5 g, 0.05 mol)[15] as a solution in diethyl ether (50 ml) over 20 minutes at ice–water temperature then stirred as it attained room temperature over 3 h. After this time the reaction mixture was added to a separating funnel and washed with hydrochloric acid (3 M, 3 × 100 ml), sodium hydrogen carbonate (saturated, aqueous, 2 × 50 ml), brine (100 ml) dried (MgSO$_4$) and evaporated to dryness. Crystallisation of the residue from light petroleum gave 2-(2-acetoxy-2-phenylacetylamino)benzoic acid methyl ester as white crystals; mp 91 °C (11.3 g, 69%). $\delta_H$ (400 MHz, CDCl$_3$) 11.85 (1H, br, NH), 8.63 (1H, d, $J$ = 7.8 Hz, H3), 7.99 (1H, dd, $J$ = 8.0, 1.5 Hz, H6), 7.50 (3H, m, 2 × PhH + H4), 7.30 (3H, m, 3 × PhH), 7.05 (1H, dd, $J$ = 8.0, 7.1 Hz, H5), 6.33 (1H, s, C*H*(*O*)Ph), 3.88 (3H, s, OC*H*$_3$), 2.23 (3H, s, C(O)C*H*$_3$); $\delta_C$ (100 MHz, CDCl$_3$) 169.9, 168.9, 167.9, 141.1, 135.8, 135.0, 131.2, 129.3, 127.8, 126.3, 123.5, 120.8, 115.9, 76.3, 52.7, 21.3; $\nu_{max}$/cm$^{-1}$ 3263, 1751, 1701, 1662 cm$^{-1}$; $m/z$(APCI)(%) 328.3 (100%)(M + H$^+$) 117(58) 107(13); $C_{18}H_{17}NO_5$ requires C 66.05; H 5.23; N 4.28, found C 66.25; H 5.28; N 4.34%. To a solution of 2-(2-acetoxy-2-phenylacetlamino)benzoic acid methyl ester (2.36 g, 7 mmol) in ethanol (20 ml) was added hydrazine monohydrate (2 m1, 2.06 g, 0.04 mol) and heated at reflux for 5 h. The reaction mixture was concentrated under reduced pressure and the residue crystallised from ethanol to give **17** as colourless crystals mp 139 °C (1.19 g, 64%). $\delta_H$ (400 MHz, CDCl$_3$) 8.19 (1H, d, $J$ = 8.0 Hz, H5), 7.78 (2H, m, H6,8), 7.48 (1H, m, H7), 7.37 (5H, m, PhH$_5$), 6.01 (1H, d, $J$ = 5.5 Hz, N=C–C*H*(O)Ph), 5.22 (1H, d, $J$ = 5.5 Hz, O*H*, exchanges D$_2$O), 4.46 (2H, br s, N*H*$_2$); $\delta_C$ (100 MHz, CDCl$_3$) 169.9, 160.7, 156.0, 144.7, 139.0, 133.7, 127.8, 127.4, 126.5, 126.2, 125.7, 119.1, 70.3; $\nu_{max}$/cm$^{-1}$ 3357, 3101, 1673, 1588; $m/z$(APCI)(%) 268.2 (100)(M + H$^+$) 250.0 (77), 233.1 (11), 106.8 (42); $C_{15}H_{13}N_3O_2$ requires C 62.40; H 4.90; N 15.72, found C 61.96; H 4.55; N 15.77%.

**4-Phenyl-3-oxo-1,9a,10-triazaanthracen-9-one 18.** A solution of 3-amino-2-[1-hydroxybenzyl]-quinazolin-(3*H*)-4-one (0.5 g, 1.92 mmol) in triethyl orthoformate (3 ml) was heated at reflux for 24 hours. After that period the mixture was allowed to reach room temperature and then the solvent was removed under reduced pressure. The residue was crystallised from dichloromethane–methanol to give pale orange crystals; mp 228 °C (0.307 g, 58%); $\delta_H$ (250 MHz, CDCl$_3$) 8.35 (1H, dd, $J$ = 8.2, 1.2 Hz H8), 7.70 (1H, ddd, $J$ = 8.2, 7.0 Hz, H7), 7.60 (1H, d, $J$ = 8.2 Hz, H5), 7.48 (1H, ddd, $J$ = 8.2, 7.0, 1.2 Hz, H6), 7.35 (5H, m, 5 × Ph*H*), 7.28 (1H, s, H2), 6.15 (1H, s, C*H*-4); $\delta_C$ (100 MHz, CDCl$_3$) 155.4, 145.1, 144.5, 142.7, 134.3, 133.7, 128.9, 128.2, 126.8, 126.7, 126.6, 125.9, 121.4, 74.2; $\nu_{max}$/cm$^{-1}$ 1708, 1648, 1600, 1463, 1368, 1172; $m/z$ (APCI)(%) 278.0 (100%) [M + H$^+$]; HRMS $C_{16}H_{11}N_3O_2$ requires 278.0924 found MH$^+$ 278.0926; $[a]_D^{25} = -127$ ($c$ = 1.0, CH$_2$Cl$_2$).

**3-Oxo-1,9a,10-triazaanthracen-9-one 20.** A solution of 3-amino-2-(2-hydroxymethyl)-quinazolin-(3*H*)-4-one (0.510 g, 2.66 mmol) in triethyl orthoformate (6 ml) was heated at reflux for 24 hours. After that period the mixture was allowed to reach room temperature and then the solvent was removed under reduced pressure. The residue was crystallised from methanol to give pale yellow crystals; mp 200 °C (0.460 g, 85%). $\delta_H$ (400 MHz, CDCl$_3$) 8.30 (1H, dd, $J$ = 8.3, 1.2 Hz, H8), 7.70 (1H, ddd, $J$ = 8.3, 7.0, 1.2 Hz, H7), 7.60 (1H, d, $J$ = 7.7 Hz H5), 7.46 (1H, ddd, $J$ = 7.7, 7.0, 1.2 Hz H6), 7.24 (1H, s, H2), 5.05 (2H, s, C*H*$_2$-4); $\delta_C$ (100 MHz) 156.6, 146.4, 146.3, 142.1, 135.2, 128.2, 128.0, 127.6, 123.0, 63.4; $\nu_{max}$/cm$^{-1}$ 1703, 1649, 1605,1360; $m/z$ (APCI)(%) 202.1 (100%) [M + H$^+$]; $C_{10}H_7N_3O_2$ requires C, 59.70; H, 3.51; N, 20.89, found C 59.55; H 3.51; N 20.77%.

**4-Isopropyl-2-methyl-3-oxo-1,9a,10-triazaanthracen-9-one 21.** A solution of 3-amino-2-[(*S*)-1-hydroxy-2-methylpropyl]-quinazolin-(3*H*)-4-one (0.200 g, 0.85 mmol) in triethyl orthoacetate (3 ml) was heated at reflux for 24 hours. After that period

‡ Crystallographic data for **16**: $C_{13}H_{13}N_3O_2$, crystal system monoclinic; space group, $P2_1/c$; $a$ = 9.891(5), $b$ = 10.066(5), $c$ = 11.732(c) Å; $\alpha$ = 90, $\beta$ = 96.743(5), $\gamma$ = 90°; $Z$ = 4; $T$ = 150 K; $\mu$ = 0.097 mm$^{-1}$; $l$ = 0.71069 Å (MoK$\alpha$); $F$(000) 512; 3.85 < $\theta$ < 30.02; 8656 reflections, 3323 unique [$R$(int) = 0.0626]; $R1$ = 0.0584, w$R2$ = 0.1410 [$I > 2\sigma(I)$]; $R1$ = 0.0974, w$R2$ = 0.1609 (all data). CCDC reference numbers 259058. See http://www.rsc.org/suppdata/ob/b4/b419108k/ for crystallographic data in .cif or other electronic format.

the mixture was allowed to reach room temperature and then the solvent was removed under reduced pressure. The residue was crystallised from ethyl acetate–petroleum ether to give white crystals mp 147 °C (0.170 g, 77%). $\delta_H$ (250 MHz, $CDCl_3$) 8.30 (1H, dd, $J = 8.1$, 1.2 Hz, H8), 7.68 (1H, ddd, $J = 8.1$, 7.0, 1.0 Hz, H7), 7.60 (1H, dd $J = 8.1$, 1.0 Hz, H5), 7.50 (1H, ddd, $J = 8.1$, 7.0, 1.2 Hz, H6), 4.90 (2H, d, $J = 4.8$ Hz, N=C–C*H*(*O*)$^i$Pr), 2.48 (1H, m, C*H*$Me_2$), 2.2 (1H, s, Me-2), 1.05 (3H, d, $J = 6.9$ Hz, C$H_3$), 0.95 (3H, d, $J = 6.8$ Hz, C$H_3$); $\delta_C$ (100 MHz, $CDCl_3$) 155.5, 145.1, 143.2, 133.4, 126.7, 126.2, 126.1, 125.5, 121.7, 78.0, 31.7, 18.10, 17.6, 15.5; $\nu_{max}$/cm$^{-1}$ 1688, 1654, 1606, 1248, 1028; *m*/*z* (EI)(%) 257.2 (18)($M^+$), 174.1 (80), 119.1 (60); $C_{14}H_{15}N_3O_2$ requires C 65.4; H 5.9; N 16.3, found C 65.1; H 5.9; N 16.1%; $[\alpha]_D^{25} = -51.5$ ($c = 1.0$, $CHCl_3$).

**4-Isopropyl-2-ethyl-3-oxo-1,9a,10-triazaanthracen-9-ones 22.** A solution of 3-amino-2-[(*S*)-1-hydroxy-2-methylpropyl]-quinazolin-(3*H*)-4-one (0.374 g, 1.60 mmol) in triethyl orthopropionate (2 ml) was heated at reflux for 36 hours. The excess of orthoester was then removed by vacuum distillation and the brown residue crystallised from ethyl acetate–petroleum ether to give white crystals; mp 82 °C (0.230 g, yield 54%). $\delta_H$ (400 MHz, $CDCl_3$) 8.30 (1H, dd, $J = 8.4$, 1.0 Hz H8) 7.68 (1H, dd, $J = 8.4$, 7.0 Hz H7) 7.58 (1H, d, $J = 8.1$ H5) 7.42 (ddd, 1H, $J = 8.1$, 7.0, 1.0 H6) 4.90 (1H, d, $J = 4.6$, C*H*-4), 2.51 (2H, q, $J = 7.6$ Hz, 2-C$H_2$), 2.44 (1H, m, C*H*$Me_2$), 1.24 (3H, t, $J = 7.6$ Hz, $CH_2CH_3$), 1.06 (3H, d, $J = 6.9$ Hz, C$H_3$), 0.97 (3H, d, $J = 6.9$ Hz, C$H_3$); $\delta_C$ (62.5 MHz, $CDCl_3$) 159.6, 16.5, 146.1, 144.3, 134.3, 127.6, 127.2, 127.1, 122.2, 88.3, 32.7, 26.6, 18.6, 16.5, 10.4; $\nu_{max}$/cm$^{-1}$ 1692, 1654, 1377, 1328, 1149, 1090, 1062; *m*/*z*(APCI)(%) 272 (100%), [M + $H^+$]; $C_{15}H_{17}N_3O_2$ requires C 66.40; H 6.32; N 15.49, found C 66.21; H 6.32; N 15.40%.

**4-Isopropyl-2-phenyl-3-oxo-1,9a,10-triazaanthracen-9-one 23.** A solution of 3-amino-2-[(*S*)-1-hydroxy-2-methylpropyl]-quinazolin-(3*H*)-4-one (0.400 g, 1.70 mmol) in trimethyl orthobenzoate (3 ml)was heated at reflux for 36 hours. The excess of orthoester was then removed by vacuum distillation and the brown residue was crystallised from diethyl ether to give pale brown crystals mp 240 °C (0.324 g, 60%). $\delta_H$ (250 MHz, $CDCl_3$) 8.38 (1H, dd, $J = 8.0$, 1.2 Hz H8), 8.12 (dd, 2H, $J = 8.0$, 1.6, H7), 7.66 (2H, m), 7.45 (m, 4H), 5.06 (1H, d, $J = 5.2$, C*H*-4), 2.55 (1H, m, C*H*$Me_2$), 1.20 (3H, d, $J = 6.9$ Hz, C$H_3$), 1.05 (3H, d, $J = 6.9$ Hz, C$H_3$); $\delta_C$ (62.5 MHz, $CDCl_3$) 157.0, 154.2, 146.3, 145.2, 134.8, 132.6, 129.6, 128.9, 128.2, 128.0, 127.7, 127.6, 122.6, 79.9, 32.7, 19.3, 17.2; $\nu_{max}$ 1696, 1605, 1465, 1362, 1318, 1176 cm$^{-1}$; *m*/*z* (APCI)(%) 320 (100%) [M + $H^+$]; HRMS $C_{19}H_{17}N_3O_2$ requires 320.1394, found $MH^+$ 320.1389.

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