# Radical reactions with 3*H*-quinazolin-4-ones: synthesis of deoxyvasicinone, mackinazolinone, luotonin A, rutaecarpine and tryptanthrin<sup>†</sup>

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Alkyl, aryl, heteroaryl and acyl radicals have been cyclised onto the 2-position of 3H-quinazolin-4-one. The side chains containing the radical precursors were attached to the nitrogen atom in the 3-position. The cyclisations take place by aromatic homolytic substitution hence retain the aromaticity of the 3H-quinazolin-4-one ring. The highest yields were obtained using hexamethylditin to facilitate cyclisation rather than reduction without cyclisation. The alkaloids deoxyvasicinone **2**, mackinazolinone **3**, tryptanthrin **4**, luotonin A **5** and rutaecarpine **8** were synthesised by radical cyclisation onto 3H-quinazolin-4-one.

The 3*H*-quinazolin-4-one ring system is important to the biological activity of both naturally occurring alkaloids, biosynthesised from anthranilic acid, and pharmaceuticals. The alkaloids include vasicinone 1 and deoxyvasicinone 2,<sup>1</sup> mackinazolinone 3,<sup>2</sup> tryptanthrin 4,<sup>3</sup> luotonins A 5, B 6 and E 7<sup>4</sup> and rutaecarpine 8.<sup>5</sup> 3*H*-Quinazolin-4-one alkaloids have been recently reviewed.<sup>6</sup> All the 3*H*-quinazolin-4-one natural products have interesting biological activity and have therefore been extensively investigated for useful pharmaceutical activity. The 3*H*-quinazolin-4-one ring is regarded as a 'privileged structure' in combinatorial synthesis.<sup>7</sup> These are structures which represent molecules that are capable of binding at multiple sites with high affinity and facilitate more rapid discovery of useful medicinally active compounds.<sup>7</sup>



Our study involved the development of protocols involving radical cyclisation for the synthesis of polycyclic 3*H*-quinazolin-3-ones (Scheme 1). The protocols have also been used for the synthesis of novel polycyclic quinazolinones including the natural

luotonin E, 7, R = OMe



Scheme 1 General synthetic protocol.

products deoxyvasicinone **2**, mackinazolinone **3**, tryptanthrin **4**, luotonin A **5** and rutaecarpine **8**.

Radical cyclisation onto heteroarenes has been developed in recent years to considerable advantage for the synthesis of novel polycyclic heteroarenes. Examples of these cyclisations include: a. alkyl radicals onto pyrroles,<sup>8,9</sup> imidazoles,<sup>8</sup> pyrazoles,<sup>10</sup> indoles,<sup>9,11,12</sup> 1,2,3-triazoles,<sup>13</sup> pyridinium salts,<sup>14</sup> and quinolones,<sup>15</sup> b. acyl radicals onto pyrroles,<sup>16</sup> quinolines,<sup>17</sup> pyridines<sup>18</sup> and arenes;<sup>19</sup> c. aryl radicals onto indoles,<sup>20,21</sup> pyrroles,<sup>9</sup> pyridones,<sup>22</sup> and 5-amino- and 5-hydroxyuracils,<sup>23</sup> 2-quinolones,<sup>24</sup> quinolines<sup>25</sup>

All of the above cyclisations are 'oxidative' i.e. the intermediate  $\pi$ -radicals are not reduced by triorganometal hydrides [e.g. tributyltin hydyride (Bu<sub>3</sub>SnH)] as normally observed for these reagents. The cyclisations proceed by aromatic homolytic substitution with abstraction of hydrogen in a rearomatisation process. Aromatic homolytic substitution has been recently reviewed<sup>27</sup> and the mechanism of Bu<sub>3</sub>SnH mediated 'oxidative' cyclisation elaborated.28 The pyrimidin-4-one ring of the quinazolin-4-ones has some aromaticity and therefore aromatic homolytic substitution could be predicted, and was observed in our studies, as shown in Scheme 1 (9 to 11 via the  $\pi$ -radical 10). However, the lower aromaticity could favour reductive cyclisation in which the intermediate  $\pi$ -radical 10 is intercepted by reagents such as Bu<sub>3</sub>SnH. Our prediction that radical cyclisation onto the quinazolin-4-one ring would be 'oxidative' was supported by the 'oxidative' radical cyclisation onto related ring systems, e.g. pyrimidine-2,4-diones,<sup>23,24</sup>

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quinolinones<sup>15</sup> and pyridinones.<sup>22,29,30</sup> However, the lower aromaticity in the pyrrole ring of indole, facilitates both reductive and oxidative cyclisation depending on the conditions.<sup>11,12,31</sup> The radical intermediate **10**, whether a  $\pi$ -radical or not, is still a strongly stabilised anilyl radical and therefore the rate of reduction by Bu<sub>3</sub>SnH to yield **12** is probably too low to be competitive with loss of hydrogen to yield the 'oxidised' product. The reactions could also be regarded as *exo*-cyclisations onto imines which are well known.

We used two general methodologies to synthesise the radical precursors. Firstly, heteroarenes containing an NH group facilitate *N*-alkylation and provide a suitable synthetic route to radical precursors for cyclisation. The radical leaving group is introduced as part of the *N*-alkyl substituent. Secondly, there is a wide variety of protocols for the synthesis of 3-substituted quinazolinones using ring synthesis from anthranilic acid derivatives, which were employed as required.

#### Aryl radical cyclisation

Aryl radicals have been successfully cyclised onto pyrroles, indoles and pyrazoles.<sup>32</sup> Aryl radicals are very reactive and the most likely to cyclise onto quinazolinones. Therefore, suitable radical precursors for 5- and 6-*exo* cyclisation were prepared (Scheme 2). The 5-membered ring cyclisation with the precursor **16** using Bu<sub>3</sub>SnH gave only the reduced uncyclised product **19** (Scheme 3). Even syringe pump addition of Bu<sub>3</sub>SnH, with either Et<sub>3</sub>B (r.t.) or AIBN (110 °C) as initiators, gave only **19**. We considered that the lack of cyclisation could be due to 1,5-hydrogen abstraction from the 2-position of the quinazolinone as shown in Scheme 3 (route b: **18** to **21**). This possibility was eliminated by repeating the reaction with Bu<sub>3</sub>SnD which gave only deuteriation on the aryl



Scheme 2 Reagents and conditions: i, tert-BuOK, DMF, 63% (16 from 14), 38% (17 from 15).



Scheme 3 *Reagents and conditions*: i, Et<sub>3</sub>B, PhMe, r.t., Bu<sub>3</sub>SnH (fast addition) 96% (19), slow addition, 30% (19); AIBN, Bu<sub>3</sub>SnH (slow addition), PhMe, reflux, 45% (19); Et<sub>3</sub>B, TTMSS, 35% (19);  $(Me_3Sn)_2$ , *tert*-BuPh, reflux, 18% (20), 65% (19).

radical position, and none on the 2-position of the quinazolinone, and these results indicated that the rate of cyclisation was not favourable compared to reduction with  $Bu_3SnH$ . Therefore, hexamethylditin [( $Me_3Sn$ )<sub>2</sub>] was used so that the intermediate radical (*cf.* **9** in Scheme 1) was not reduced. The reaction was repeated with ( $Me_3Sn$ )<sub>2</sub> which resulted in a small amount of the cyclised product **20** (18%) as well as uncyclised **19** (65%) as the major compound.

The analogous six-membered ring aryl radical cyclisation using precursor 17 gave an excellent yield of the cyclised product 22 (92%) with no reduction using (Me<sub>3</sub>Sn)<sub>2</sub> (Scheme 4). The reaction with Bu<sub>3</sub>SnH again gave largely the uncyclised reduced product 23 (55%) but did also yield a small amount of the cyclised product 22 (8%). We have observed before that 5-ring cyclisation of radicals onto heteroarenes is difficult due to strain whereas 6-ring cyclisation from 17 relative to 16 are expected. The results indicate that the oxidative route is dominant (*i.e.* loss of hydrogen from the  $\pi$ -radical intermediate 10) for cyclisation onto quinazolinones as observed for other heteroarenes.



Scheme 4 *Reagents and conditions*: i, (Me<sub>3</sub>Sn)<sub>2</sub>, *tert*-BuPh, reflux, 92% (22), 0% (23); Et<sub>3</sub>B, PhMe, r.t., Bu<sub>3</sub>SnH (fast addition), 8% (22), 55% (23).

### 3H-4-Oxoquinazolin-2-yl radical cyclisation

As shown in Scheme 5 we envisaged an alternative route to polycyclic quinazolinones by cyclisation of 3H-4-oxoquinazolin-2-yl radicals onto pendant side chains attached to the 3-position instead of cyclisation of side chain radicals onto the quinazolinone moiety. 3H-4-Oxoquinazolin-2-yl radicals,<sup>33</sup> generated photolytically from 3-(but-1-en-4-yl)-3H-quinazolin-4-one, have been reported to undergo 5-*exo* cyclisation onto the pendant alkene.<sup>33a</sup> The procedure however was not suitable for synthetic application. During our studies, a synthesis of luotonin A analogues using 3H-4-oxoquinazolin-2-yl radicals was reported.<sup>33b</sup>



Scheme 5 Reagents and conditions: i,  $Br_2$ , EtOH, 50% (26); ii, NaH, DMF, BnBr, 46% (27); NaI, PhCH<sub>2</sub>CH<sub>2</sub>Br, 6% (28); iii, 27: Bu<sub>3</sub>SnH, Et<sub>3</sub>B, slow addition, 62% (19); Bu<sub>3</sub>GeH, Et<sub>3</sub>B, slow addition, 41% (19); (Me<sub>3</sub>Sn)<sub>2</sub>, *tert*-BuPh, reflux, 41% (19), 27% (20); 28: (Me<sub>3</sub>Sn)<sub>2</sub>, *tert*-BuPh, reflux, 0% (23), 97% (22).

The plan of our protocol was to alkylate 2-bromo-3*H*-quinazolin-4-one to provide suitable radical precursors (Scheme 5). 2-Bromo-3*H*-quinazolin-4-one **26** was prepared by an adapted literature procedure from 2-mercapto-3*H*-quinazolin-4one **24**.<sup>34</sup> Alkylations with activated halides, *e.g.* benzyl bromide, allyl bromide and methyl iodide were successful but alkylations with unactivated halides were very poor or failed. Alkylation with activated propargyl halides has also recently been reported.<sup>33b</sup> A maximum yield (6%) of alkylation was obtained with 2phenylethyl bromide and alkylation with 3-phenylpropyl bromide failed. Alkylation with the corresponding triflates failed to give improved results. We suggest that the anion of 2-bromo-3*H*-4oxoquinazoline is too stabilised and hence not nucleophilic enough to react with unactivated halides.

Various protocols were attempted to circumvent the alkylation problem. For instance, the successful bromination suggested that other 2-thioxo-2,3-dihydro-1*H*-quinazolin-4-ones with the 3-alkyl side chain in place could also be converted to the corresponding 2-bromo compounds. In order to test this hypothesis, 2-(phenylethyl)-2-thioxo-2,3-dihydro-1*H*-quinazolin-4-one **30** was prepared by ring synthesis using the reaction between 2-(methoxycarbonyl)phenyl isothiocyanate and amines.<sup>35</sup> The structure of **30** was confirmed by X-ray crystallography (Fig. 1). However, the bromination procedure yielded only the corresponding disulfide instead of the 2-bromoquinazolinone **28**.

The mechanism of these brominations is unknown. The most likely intermediate is the sulfenyl bromide **25** which can either lose a proton and undergo substitution with bromide, or undergo direct substitution with bromide. The intermediate sulfenyl bromide from 2-(phenylethyl)-2-thioxo-2,3-dihydro-1*H*-quinazolin-4-one cannot lose a proton which is possibly significant in directing the reaction towards disulfide formation. Examples from the literature show bromoimine formation for thioureas with *N*,*N*-substitution (*i.e.* can lose a proton)<sup>36</sup> and disulfides and sulfides from thioamides.<sup>37</sup>

We carried out radical cyclisations with the precursors **27** and **28** (Scheme 5). As observed for the cyclisation of precursor **16**, the 5-membered ring cyclisation from **27** was unfavourable with both Bu<sub>3</sub>SnH and Bu<sub>3</sub>GeH and yielded only the reduced uncyclised product **19**. Radical abstraction of hydrogen from Bu<sub>3</sub>GeH is

20 times slower than from Bu<sub>3</sub>SnH which would favour cyclisation over reduction,<sup>38</sup> but still only reduction was observed from the intermediate **29a**. When  $(Me_3Sn)_2$  was used, a moderate yield of cyclisation product (27%) was obtained but reduction was still the major route (41%). The 6-membered ring cyclisation from precursor **28** via **29b** gave a quantitative yield of cyclisation to **22** with none of the reduced compound **23** formed. This cyclisation could either proceed by 5-exo cyclisation followed by a neophyl rearrangement or directly by 6-endo cyclisation. The results show that radical cyclisation can be used onto, or from, the quinazolinone moiety, but that a useful method of synthesis of the 2-bromoquinazolinones is still required. Addition of 3H-4oxoquinazolin-2-yl radicals onto isonitriles has also recently been reported.<sup>33b</sup>

#### Alkyl radical cyclisation

Several methods have been used for the synthesis of both deoxyvasicinone **2** and mackinazolinone **3** but none involving radicals.<sup>39</sup> Our protocol using cyclisation of an alkyl radical onto 3H-quinazolin-4-one rings was aimed at the synthesis of both natural products (Scheme 6). Routine alkylation yielded the required radical precursors **31a**,**b**. An initial study with Bu<sub>3</sub>SnH using precursor **31a** yielded only reduced uncyclised product **33a** (78%). The rate of cyclisation of the alkyl radical is obviously slow, and it is intercepted by Bu<sub>3</sub>SnH to yield the respective reduced uncyclised product **33a**. Therefore, (Me<sub>3</sub>Sn)<sub>2</sub> was used to facilitate cyclisation which gave moderate yields of deoxyvasicinone **2** and mackinazolinone **3**.

The use of Et<sub>3</sub>B mediated reactions gave better yields of both **2** and **3** (Scheme 6). We suggest that the ethyl radical generated from the reaction between Et<sub>3</sub>B and oxygen is able to abstract iodine from the radical precursors **31a,b** to yield alkyl radicals and ethyl iodide, which is lost from the reaction. The hydrogen in the  $\pi$ -radical intermediates (*cf.* **10**) is also most likely abstracted by ethyl radicals to facilitate rearomatisation.<sup>40</sup> Unusually, some cyclised reduced material **32a,b** was obtained suggesting disproportionation was also taking place. GCMS analysis of the crude product from the Et<sub>3</sub>B facilitated reaction with **31a** indicated traces (*ca.* 5%) of 2-ethyl-3-propyl-3*H*-quinazolin-4-one and



Fig. 1 X-Ray structure of 3-(2-phenylethyl)-2-thioxo-2,3-dihydro-1*H*-quinazolin-4-one **30** with atom labelling.



Scheme 6 *Reagents and conditions*: i, NaH, DMF, a. 1-chloro-3-iodopropane, 51%; b. 1-chloro-4-iodobutane, 65%; ii, NaI, acetone, reflux, 53% (31a), 67% (31b); iii, (Me<sub>3</sub>Sn)<sub>2</sub>, *tert*-BuPh, reflux, hv: a. 31a gave 20% (2), 13% (32a) and 6% (33a); b. 31b gave 30% (3), 23% (32b) and 0% (33b); Et<sub>3</sub>B (20 equiv.), *tert*-BuPh, air (yields by <sup>1</sup>H NMR analysis): a. 31a gave 40% (2), 10% (32a) and 30% (33a); b. 32b gave 61% (3), 23% (32b) and 0% (33b).

3-pentyl-3*H*-quinazolin-4-one indicating addition of ethyl radicals to intermediates. No uncyclised reduced material **33b** was observed for the 6-ring cyclisation of **31b**. Again, this provides evidence that 5-ring cyclisation onto heteroarenes is strained and that 6-ring cyclisation (84% of cyclised products) is more favourable.

#### Heteroaryl radical cyclisation

During our studies, Pd(0) catalysed cyclisations were reported for 2-bromoindole<sup>41</sup> and 2-bromoquinoline<sup>41,42</sup> moieties onto the 2-position of quinazolin-4-one to yield rutaecarpine in poor yield (24% maximum) and luotonin A in good yield (86%) respectively.

**Luotonin A 5.** The luotonins make up a group of pyrroloquinazolino-quinoline alkaloids of which the pentacyclic luotonins A 5, B 6 and E 7 are of most interest. The luotonins are used in traditional Chinese medicine and are reported to exhibit activity against a range of ailments including rheumatism, inflammation, influenza, hepatitis and leukemia.<sup>43</sup> Luotonin A has been reported to show activity as an antitumour compound and is an inhibitor for human DNA topoisomerase I.<sup>43</sup> The compounds were isolated some ten years ago<sup>4</sup> and luotonin A has been a popular synthetic target.<sup>43,44</sup> Two radical syntheses of luotonin A have been reported; a radical domino cyclisation reaction using vinyl radical cyclisation onto nitriles<sup>45</sup> and a bimolecular reaction involving radical addition onto isonitriles.<sup>33b</sup>

The synthesis of luotonin A **5** using 2-quinolinyl radicals was carried out as a further example of cyclisation onto the quinazolinone moiety (Scheme 7). The use of 2-quinolinyl radicals in cyclisation has two literature precedents; synthesis of camptothecin using cyclisation of 2-quinolinyl radicals onto a pyridone moiety<sup>29</sup> and synthesis of 10,11-methylene-14-azaxamptothecin and 14-azacamptothecin using cyclisation of 2-quinolinyl radicals onto 3*H*-pyrimidin-4-one moieties.<sup>30</sup> These cyclisations also proceeded by 'oxidative cyclisation' as observed for the 3*H*-quinazolin-4-ones.

The required starting material **34** was prepared by a literature procedure from 2-chloroquinoline-2-carbaldehyde<sup>46</sup> and reacted



Scheme 7 Reagents and conditions: i,  $(Me_3Sn)_2$ , tert-BuPh, reflux, hv: 51% (5), 15% (36); Et<sub>3</sub>B (20 equiv.), PhMe, r.t., air: Bu<sub>3</sub>SnH (fast addition), 0% (5), 53% (36) Bu<sub>3</sub>SnH (slow addition), 14% (5), 32% (36); Bu<sub>3</sub>GeH (fast addition), 18% (5), 11% (36).

under several radical conditions. Unusually, the yield from 5-*exo* cyclisation was significant. The use of  $(Me_3Sn)_2$  gave a reasonable yield (53%) of luotonin A **5** but also some of the reduced product **36**. The yield was high in comparison to the 5-*exo* cyclisation of the phenyl analogue **16**. Luotonin A was even obtained with Bu<sub>3</sub>SnH and Bu<sub>3</sub>GeH, clearly indicating that the cyclisation is more favourable for 2-quinolinyl radicals as compared to phenyl radicals. The yield was not as high as the Pd(0)-catalysed cyclisation<sup>42</sup> but further optimisation could improve the yield.

**Rutaecarpine 8.** Rutaecarpine **8** has been synthesised by a wide variety of protocols but none involving radicals.<sup>47</sup> Our synthesis of rutaecarpine uses indol-2-yl radical cyclisation onto the quinazolinone motif as a further example of natural product synthesis using the general protocol (Scheme 8). Indol-2-yl radicals have been previously used in radical cyclisation onto pendant 1- $\omega$ -alkenes<sup>48</sup> and -arenes<sup>49</sup> and in H-translocation reactions towards the synthesis of mitomycin.<sup>50</sup>



Scheme 8 Reagents and conditions: i, PBr<sub>3</sub>, DCM, 56% (**38**); ii, tert-BuOK, DMF, 3*H*-quinazolin-4-one, 39% (**39**); iii, NBS, DCM, 0 °C, 30 min, 38% (**40**); iv,  $(Me_3Sn)_2$ , tert-BuPh, reflux, hv: 55% (**8**), 0% (**39**); Et<sub>3</sub>B (20 equiv.), PhMe. r.t., air: Bu<sub>3</sub>SnH (slow addition), 15% (**8**), 57% (**39**).

The preparation of the 2-bromoindole part of the precursor proved troublesome even with protection of the side chain and the NH. The use of NBS has been reported in the literature but the reaction is very sensitive, and can be adversely affected by the NH and side chain groups.<sup>48,49,51</sup> We finally used an adapted literature procedure<sup>41</sup> whereby the 3*H*-quinazolin-4-one moiety was used as the 'protective group' for the indole side chain (*i.e.* **39**). The bromination was rapid and short reaction times and low temperature gave the best yields of the 2-bromoindole precursor **40**. As reported in the literature for 2-bromoindoles,<sup>48,49,51,52</sup> decomposition of the product was a problem until it was purified. The free indole-NH did not interfere and was therefore not protected. A blank reaction between NBS and 3-methylquinazolin-4-one gave no reaction after two days indicating that in the NBS reaction with **39**, bromination of the quinazolinone ring is unlikely to be the cause of the decomposition.

3-[2-(1H-Indol-3-yl)ethyl]-4(3H)-quinazolinone **39** was prepared by alkylation of 4(3H)-quinazolinone with 3-(2-bromoethyl)-1H-indole **38** which was prepared by bromination of tryptophol **37**.

Radical cyclisation of the precursor 40 gave the predicted 6-*exo* cyclisation of the intermediate radical 41 to yield rutaecarpine 8. Only cyclisation was obtained when  $(Me_3Sn)_2$  was used and even reductive conditions with  $Bu_3SnH$  yielded a small amount of cyclisation product. The 6-*exo* cyclisation yields were similar to the equivalent cyclisation with aryl radicals (see Scheme 4). Longer reactions times led to decomposition.

#### Acyl radicals—synthesis of tryptanthrin

Tryptanthrin has been synthesised by a range of protocols. 3,6,53

We prepared an authentic sample of tryptanthrin **4** by a literature procedure in order to obtain full spectroscopic data for comparison.<sup>53</sup>

Aromatic acyl radical cyclisation has recently been shown to be a useful synthetic technique.<sup>17–19,54</sup> Although 5-membered ring cyclisation was reported to be unsuccessful,<sup>19</sup> we have shown that 5-ring cyclisation onto the 3H-quinazolin-4-one moeity was possible (*e.g.* the luotonin synthesis). Therefore, we carried out the syntheses as shown in Scheme 9. The aryl-CO bond in the intermediate acyl radical **44** is strong enough to avoid decarbonylation which is a rapid reaction for alkyl-CO radicals.<sup>55</sup> However, it is possible that we failed to isolate products resulting from CO loss.

The starting material **42** was prepared in one step by a literature procedure<sup>56</sup> and converted to the acyl selenide **43** by standard procedures.<sup>16</sup> Several conditions were used based on literature reports.<sup>17–19,54</sup> The highest yield (15%) was obtained by photolysis at r.t. Although the yield is poor, we believe this is the first example of a 5-*exo* acyl radical cyclisation onto a heterocycle. When AIBN was added to the reaction, an intractable mixture was obtained. Heating under reflux was not required and UV photolysis alone was enough to facilitate the reaction, presumably by homolysis of the carbonyl-SePh bond. In a blank reaction, heating under reflux in benzene yielded only unaltered starting material after 24 h. The mechanism is unclear, other than 5-*exo* acyl radical cyclisation followed by hydrogen abstraction from the resulting  $\pi$ -radical intermediate. Large amounts of diphenyl diselenide were isolated indicating CO–Se bond homolysis.

We also investigated the 6-membered ring cyclisation because these had proved to be more successful than the 5-ring cyclisations



Scheme 9 Reagents and conditions: i, Bu<sub>3</sub>P, PhSeSePh, DCM, 73% (42); ii, LiOH, EtOH, H<sub>2</sub>O; iii, Bu<sub>3</sub>P, PhSeSePh, DCM, 68% (47); iv, (Me<sub>3</sub>Sn)<sub>2</sub>, *tert*-BuPh, reflux, hv, 3% (4); PhH, r.t., hv, 12 h, 15% (4); PhH, reflux, hv, 10 h, 11% (4); AIBN, PhH, reflux, hv, 0% (4); v, (Me<sub>3</sub>Sn)<sub>2</sub>, PhH, reflux, hv, 39% (50).

(Scheme 9). The acyl radical precursor 47 was prepared by standard procedures. The ester 45 was synthesised by alkylation of 3H-quinazolin-4-one with methyl 2-(bromomethyl)-benzoate. Cyclisation using Et<sub>3</sub>B only, AIBN only, UV photolysis only and slow addition of TTMSS with Et<sub>3</sub>B as initiator all gave intractable mixtures. However, reaction with (Me<sub>3</sub>Sn)<sub>2</sub> gave a moderate yield of the unusual product 50 along with an intractable mixture of other products. The structure of the hydroxylated product 50 was confirmed by X-ray crystallography (Fig. 2). The product indicated 6-ring cyclisation as expected but that the product 48 was unstable to the reaction conditions and was readily oxidised introducing an OH group onto the newly formed ring.

Analogous reactions with 2-indolyl acyl radicals have yielded a range of unexpected products which included a 'quinone' product caused by oxidation of the benzylic methylene during the reaction.<sup>17,18</sup> 2-Cyanoprop-2-yl radicals from the breakdown of AIBN were proposed as the abstracting radicals. In our reaction, no AIBN is present so we suggest that any of the intermediate radicals (e.g. intermediate acyl or  $\pi$ -radical, PhSe<sup>•</sup>) can abstract the benzylic hydrogen, which is a favourable process, to form a stable radical intermediate 49. Although air was excluded, traces of oxygen are likely to be present and to react rapidly with trimethylstannyl radicals to form a peroxyl radical (Me<sub>3</sub>SnOO<sup>•</sup>).<sup>45,57</sup> Combination of the peroxyl radical with the benzylic radical 49 would yield a peroxide which could easily break down to yield 50. Alternatively, a standard auto-oxidation mechanism with the traces of oxygen present could explain this unusual product.



Fig. 2 X-Ray structure of 11-hydroxy-11H-isoquinolino[3,2-b]quinazolin-6,13-dione 50 with atom labelling.

### Conclusions

Our results show that radical cyclisation on the quinazolinone moiety can be used for synthesis. The results show that radical cyclisation is also favourable for radicals centred on the 2-position of the quinazolinone moiety but that a better method for the synthesis of 2-bromoquinazolinones is still required.

### Experimental

#### General

Commercial dry solvents were used in all reactions except for light petroleum and ethyl acetate which were distilled from CaCl<sub>2</sub> and dichloromethane which was distilled from CaH<sub>2</sub>. Light petroleum refers to the bp 40-60 °C fraction. Sodium hydride was obtained as 60% dispersion in oil. A 2.5 M solution of n-butyl lithium in hexane was used. A solution of Et<sub>3</sub>B in hexane (1.0 M) was used in all cases. Melting points were determined on a Stuart Scientific SMP3 melting point apparatus and are uncorrected. Elemental analyses were determined on a Perkin Elmer 2400 CHN Elemental Analyser. Infrared spectra were recorded on a Perkin-Elmer Paragon 1000 FT-IR spectrophotometer on NaCl plates. <sup>1</sup>H (400 MHz) and <sup>13</sup>C (100 MHz) NMR spectra were recorded on a Bruker DPX-400 instrument, or <sup>1</sup>H (250 MHz) spectra were obtained using a Bruker AC-250 spectrometer. Spectra were obtained from solutions in CDCl<sub>3</sub> with TMS as the internal standard for <sup>1</sup>H NMR spectra and deuteriochloroform as the standard for <sup>13</sup>C NMR spectra unless otherwise specified. Chemical shifts are given in parts per million (ppm) and J values in hertz (Hz). Assignments were made using a combination of COSY and HMQC analysis. Mass spectra were recorded on a Jeol SX102 high resolution mass spectrometer or were run by the EPSRC MS Service at the University of Wales, Swansea. GCMS was carried out on a Fisons 8000 series mass spectrometer using a 15 m  $\times$ 0.25 mm DB-5 GC column. TLC using silica as absorbent was carried out with aluminium backed plates coated with silica gel (Merck Kieselgel 60  $\mathrm{F}_{\mathrm{254}}$ ), and TLC using alumina as absorbent was carried out with aluminium backed plates coated with neutral aluminium oxide (Merck 150 F<sub>254</sub>, TypeT). Silica gel (Merck Kieselgel 60 H silica) was used for column chromatography unless otherwise specified. Column chromatography using alumina was carried out with Aldrich aluminium oxide, activated neutral,

Brockmann 1, STD Grade, 150 mesh size. Prep-TLC was carried out using aluminium oxide (Merck 60  $PF_{254}$ , Type E). Bu<sub>3</sub>GeH was prepared from GeCl<sub>4</sub> by a known procedure.<sup>38</sup>

General procedure for alkylation of 3H-quinazolin-4-ones. 3-(2-Iodobenzyl)-3H-quinazolin-4-one 16. Potassium tert-butoxide (1.35 g, 12 mmol) was added to 3*H*-quinazolin-4-one **13** (1.17 g, 8 mmol) in dry DMF (50 cm<sup>3</sup>) and the mixture stirred for 1 h under an atmosphere of nitrogen. 2-Iodobenzyl bromide 14 (2.84 g, 9.6 mmol) was added and the reaction mixture stirred for a further 16 h. The mixture was diluted with DCM and washed with H<sub>2</sub>O and brine. The organic layer was dried and evaporated under reduced pressure. The crude product was purified by column chromatography using silica gel as absorbent and light petroleum-EtOAc (2:1) as eluent yielding 3-(2-iodobenzyl)-3H-quinazolin-4-one 16 as pale yellow crystals (1.82 g, 5.0 mmol, 63%), mp 94-95 °C; Found: M<sup>+</sup>, 362.9987. C<sub>15</sub>H<sub>11</sub>IN<sub>2</sub>O requires 362.9989;  $v_{\rm max}$ (thin film)/cm<sup>-1</sup> 3055, 1689, 1469, 1230, 962 and 734;  $\delta_{\rm H}$  5.71 (2 H, s, CH<sub>2</sub>), 6.93 (1 H, ddd, J 7.9, 7.4, 1.7, BnH-4), 7.09 (1 H, dd, J 7.9, 1.8, BnH-3), 7.22 (1 H, ddd, J 8.0, 7.4, 1.2, BnH-5), 7.45 (1 H, ddd, J 8.0, 5.5, 1.7, 6-H), 7.75-7.64 (2 H, m, 7,8-H), 7.81 (1 H, dd, J 8.0, 1.2, BnH-6), 8.11 (1 H, s, 2-H) and 8.26 (1 H, dd, J 8.0, 1.6, 5-H);  $\delta_{\rm C}$  54.90 (CH<sub>2</sub>), 98.6 (C), 122.1 (4a-C), 126.9 (5-C), 127.5 (6-C), 127.6 (8-C), 128.9 (CH), 129.1 (CH), 129.9 (CH), 134.5 (7-C), 137.7 (8a-C), 139.9 (CH), 146.4 (2-C), 148.0 (C) and 161.1 (4-C); m/z (EI) 252 (M<sup>+</sup>, 98%), 129 (43), 107 (41), 90 (100), 89 (77), 76 (51), 63 (58), 50 (42) and 40 (85).

**3-[2-(Bromophenyl)ethyl]-3***H***-quinazolin-4-one 17.** The general procedure for alkylation with 2-(2-bromophenyl)ethyl methanesulfonate **15** (4.90 g, 18.6 mmol) for 48 h was used to yield 3-[2-(bromophenyl)ethyl]-3*H*-quinazolin-4-one **17** as colourless crystals (1.93 g, 5.9 mmol, 38%), mp 119–120 °C; Found: M<sup>+</sup>, 328.0206.  $C_{16}H_{13}^{79}$ BrN<sub>2</sub>O requires 328.0206;  $v_{max}$ (thin film)/cm<sup>-1</sup> 3423, 1972, 1609, 1470, 1069, 1027 and 773;  $\delta_{\rm H}$  3.25 (2 H, t, *J* 7.2, CH<sub>2</sub>), 4.25 (2 H, t, *J* 6.9, NCH<sub>2</sub>), 7.22–7.07 (3 H, m, ArH), 7.58–7.48, (2 H, m, ArH), 7.78–7.64 (3 H, m, ArH) and 8.34 (1 H, ddd, *J* 8.1 1.5 0.5, 5-H);  $\delta_{\rm C}$  35.3 (CH<sub>2</sub>), 46.7 (NCH<sub>2</sub>), 122.0 (C), 124.4 (C), 126.6 (CH), 127.2 (CH), 127.5 (CH), 127.9 (CH), 128.9 (CH), 131.4 (CH), 133.1 (CH), 134.2 (CH), 136.7 (C), 146.4 (CH), 148.1 (C) and 161.1 (C); *m/z* (EI) 330/328 (M<sup>+</sup>, 52/51%), 251 (49), 249 (56) and 52 (14).

# Cyclisation reactions of 3-(2-iodobenzyl)-3*H*-quinazolin-4-one 16.

General procedure for  $Bu_3SnH$  reactions using  $Et_3B$  as initiator. A solution of Bu<sub>3</sub>SnH (0.76 g, 2.6 mmol) and 3-(2-iodobenzyl)-3H-quinazolin-4-one (0.44 g, 1.2 mmol) in dry toluene (40 cm<sup>3</sup>) was deoxygenated under an atmosphere of nitrogen and stirred for 1 h. Triethylborane (3.6 cm<sup>3</sup>, 3.6 mmol) was added via a needle through a septum; the needle was then left open to allow air (oxygen) to enter the reaction and the mixture stirred for 1 h. More triethylborane (3.6 cm<sup>3</sup>, 3.6 mmol) was added and the reaction mixture stirred for a further 10 h. Dilute hydrochloric acid was added to extract the protonated quinazolone products into the aqueous layer. The aqueous layer was washed with light petroleum to remove tributyltin residues. The aqueous layer was basified with sodium hydroxide to pH 14 and extracted with DCM. The combined organic layers were dried and evaporated under reduced pressure yielding the reduced product 3-benzyl-3H-quinazolin-4one 19 as colourless crystals (0.27 g, 1.2 mmol, 96%), mp 116-117 °C (lit.,<sup>58</sup> 117–118 °C); v<sub>max</sub>(thin film)/cm<sup>-1</sup> 3419, 1675, 1609, 1559, 1473, 1369, 1332, 1161, 1026, 773, 709, 694 and 645;  $\delta_{\rm H}$  5.08 (2 H, s, CH<sub>2</sub>), 7.24–7.23 (5 H, m), 7.48 (1 H, ddd, J 8.2 6.3 1.8, 6-H), 7.74–7.68 (2 H, m, 7,8-H), 8.11 (1 H, s, 2-H) and 8.32 (1 H, dd, J 8.2 2.0, 5-H); δ<sub>C</sub> 49.6 (CH<sub>2</sub>), 122.2 (4a-C), 126.9 (5-H), 127.4 (6-H), 127.5 (8-H), 128.0 (CH), 128.3 (CH), 129.0 (CH), 134.3 (7-H), 135.8 (C), 146.4 (2-H), 148.0 (8a-C) and 161.1 (4-C). The data were identical to that in the literature.58 The procedure was repeated using TTMSS in place of Bu<sub>3</sub>SnH to yield 3-benzyl-3Hquinazolin-4-one **19** (35%).

General procedure for slow addition of Bu<sub>3</sub>SnH reactions using Et<sub>3</sub>B as initiator. The general procedure for Bu<sub>3</sub>SnH reactions using Et<sub>3</sub>B as initiator was repeated except that Bu<sub>3</sub>SnH was added by a syringe pump over 6 h to give 3-benzyl-3*H*-quinazolin-4-one **19** (30%).

General procedure for slow addition of Bu<sub>3</sub>SnH reactions using AIBN as initiator. The general procedure for Bu<sub>3</sub>SnH reactions using Et<sub>3</sub>B as initiator was repeated except that AIBN (0.25 molar equiv.) was used as initiator and the reaction was heated under reflux for 6 h to yield 3-benzyl-3*H*-quinazolin-4-one **19** (45%).

General procedure for reactions using photolysis and hexamethylditin. A solution of 3-(2-iodobenzyl)-3H-quinazolin-4one 16 (0.36 g, 1.0 mmol) and hexamethylditin (0.99 g, 3.0 mmol) in *tert*-butylbenzene (20 cm<sup>3</sup>) in a two-necked pyrex flask (5  $\times$  1 cm and 25 cm high, wall thickness = 1 mm), was purged with nitrogen for 30 min. The mixture was irradiated with a combined 300 W sunlamp at 150 °C for 10 h. The reaction mixture was cooled to room temperature, diluted with MeOH and evaporated under reduced pressure to a small volume. The residue was purified using column chromatography with light petroleum as eluent to remove the *tert*-butylbenzene. A precipitate of polymeric dimethyltin was produced. The product was eluted with ethyl acetate and further worked-up as for the general procedure for Bu<sub>3</sub>SnH reactions using Et<sub>3</sub>B as initiator. 3-Benzyl-3H-quinazolin-4-one 19 and cyclised 12H-isoindolo[1,2-b]quinazolin-10-one 20 were obtained as an inseparable white solid. Analysis using <sup>1</sup>H NMR spectroscopy showed 19 (65%) and 20 (18%). 12H-Isoindolo[1,2-b]quinazolin-10-one 20 was identified in the mixture and therefore not fully

characterised.  $\delta_{\rm H}$  5.19 (2 H, s, CH<sub>2</sub>), 7.28–7.35 (3 H, m), 7.51 (1 H, ddd, J 8.0, 8.0, 1.6, 7-H), 7.81 (1 H, ddd, J 8.0, 8.0, 1.6, 8-H), 7.85 (1 H, dd, 8.0, 1.6, 6-H), 8.21 (1 H, d, J 7.2, 4-H) and 8.41 (1 H, dd, J, 8.0, 1.6, 9-H);  $\delta_{\rm C}$  49.6 (CH<sub>2</sub>), 120.6 (C), 123.4 (CH), 123.5 (CH), 126.4 (CH), 126.4 (CH), 127.3 (CH), 128.8 (CH), 132.3 (CH), 132.6 (C), 134.2 (CH), 139.6 (C), 149.4 (C), 154.9 (C) and 160.5 (C). The data were the same as that in the literature.<sup>59</sup> GC-MS analysis showed the ratio of the two products to be in the ratio 4 : 1 of the reduced produced and cyclised product: 12*H*-isoindolo-[1,2-*b*]-quinazolin-10-one;  $R_{\rm T}$  22.8 min, *m*/*z* 234 (M<sup>+</sup>, 95%), 205 (24), 179 (15), 151 (16), 130 (25), 102 (28), 91 (100) and 77 (20) and 3-benzyl-3*H*-quinazolin-4-one;  $R_{\rm T}$  24.5 min, *m*/*z* 236 (M<sup>+</sup>, 51%), 130, (37), 91 (100) and 65 (27).

**3-(2-Deuterio)benzyl-3***H***-quinazolin-4-one.** The general procedure for reductive reactions with Et<sub>3</sub>B with Bu<sub>3</sub>SnD as reductant were used with 3-(2-iodobenzyl)-3*H*-quinazolin-4-one **16** to yield 3-(2-deuterio)benzyl-3*H*-quinazolin-4-one as colourless crystals (41%); mp 100–101 °C (Found: M<sup>+</sup>, 238.1084. C<sub>15</sub>DH<sub>11</sub>N<sub>2</sub>O requires 238.1085);  $v_{max}$ (thin film)/cm<sup>-1</sup> 3421, 2359, 1670, 1610, 1471, 1396, 1153 and 773;  $\delta_{\rm H}$  5.21 (2 H, s, CH<sub>2</sub>), 7.38–7.29 (4 H, m, PhH), 7.52 (1 H, dd, *J* 8.1 1.4, 6-H), 7.79–7.69 (2 H, m, 7,8-H), 8.12 (1 H, s, 2-H) and 8.34 (1 H, ddd, *J* 8.1 2.1 0.6, 5-H);  $\delta_{\rm C}$  49.7 (CH<sub>2</sub>), 104.1 (CD), 122.2 (4a-C), 126.9 (5-C), 127.4 (6-C), 127.6 (CH), 128.0 (CH), 128.3 (CH), 128.9 (CH), 129.1 (CH), 134.3 (CH), 135.7 (C), 146.3 (5-C), 148.1 (8a-C) and 161.1 (4a-C); *m/z* (EI) 237 (M<sup>+</sup>, 48%), 235 (21), 130 (33), 92 (100), 91 (75), 65 (21) and 51 (23).

# Cyclisation reactions of 3-[2-(bromophenyl)ethyl]-3*H*-quina-zolin-4-one 17.

*Hexamethylditin.* The general procedure for reactions using photolysis and hexamethylditin yielded 5,6-dihydroisoquino[1,2-*b*]quinazolin-8-one **22** as colourless crystals (92%), mp 195–197 °C (lit.,<sup>60</sup> 196 °C); Found: M<sup>+</sup>, 249.1025. C<sub>16</sub>H<sub>12</sub>N<sub>2</sub>O requires 249.1022;  $v_{max}$ (thin film)/cm<sup>-1</sup> 3421, 1682, 1590, 1556, 1471, 1150, 762 and 692;  $\delta_{\rm H}$  3.06 (2 H, t, *J* 6.4, CH<sub>2</sub>), 4.35 (2 H, t, *J* 6.4, NCH<sub>2</sub>), 7.22–7.13 (1 H, m, ArH), 7.43–7.37 (3 H, m, ArH), 7.71–7.69 (2 H, m, ArH), 8.25 (1 H, d, *J* 7.6, ArH) and 8.43–8.40 (1 H, m, ArH);  $\delta_{\rm C}$  27.4 (CH<sub>2</sub>), 39.5 (NCH<sub>2</sub>), 120.7 (C), 126.5 (CH), 126.8 (CH), 127.5 (CH), 127.6 (CH), 127.9 (CH), 129.5 (C), 131.7 (CH), 134.2 (CH), 137.0 (C), 147.7 (C), 149.3 (C) and 161.6 (CO); *m/z* (EI) 249 (M<sup>+</sup>, 17%), 247 (100), 128 (20), 116 (46), 104 (30), 90 (34), 89 (62), 77 (85), 76 (97), 63 (53) and 39 (54). One CH signal was coincident or could not be detected.

 $Bu_3SnH$  and  $Et_3B$ . The general procedure for  $Bu_3SnH$  reactions using  $Et_3B$  as initiator yielded an inseparable mixture of 3-[2-(phenylethyl)]-3*H*-quinazolin-4-one **23** (55%) and 5,6-dihydroisoquino[1,2-*b*]quinazolin-8-one **22** (8%). The yields were estimated using <sup>1</sup>H NMR spectroscopic analysis.

**3-Benzyl-2-bromo-3***H***-quinazolin-4-one 27.** The general procedure for alkylation of 3*H*-quinazolin-4-ones (3 h) yielded 3-benzyl-2-bromo-3*H*-quinazolin-4-one **27** as colourless crystals (46%), mp 109–111 °C; Found: M<sup>+</sup>, 315.0128. C<sub>13</sub>H<sub>11</sub>BrN<sub>2</sub>O requires 315.0128;  $\nu_{max}$ (thin film)/cm<sup>-1</sup> 3457, 3064, 1653, 1558, 1494, 1430, 1339, 1234, 1134, 1074, 1023, 901 and 819;  $\delta_{\rm H}$  5.56 (2 H, s CH<sub>2</sub>), 7.29–7.37 (5 H, m, PhH), 7.52 (1 H, ddd, *J* 8.2, 8.1, 2.0, 7-H), 7.66 (1 H, dd, *J* 8.2, 1.2, 8-H), 7.79 (1 H, ddd, *J* 8.1, 8.0, 1.2, 6-H) and 8.27 (1 H, dd, *J* 8.0, 2.0, 5-ArH);  $\delta_{\rm C}$  51.8 (CH<sub>2</sub>), 120.5 (4a-C),

126.9 (6/8-CH), 127.5 (CH), 127.6 (6/8-CH), 127.7 (5-CH), 127.8 (CH), 127.9 (7-CH), 135.1 (CH), 135.4 (C), 136.2 (8a-C), 147.2 (2-C) and 161.6 (4-C); *m/z* (EI) 318 (M<sup>+</sup>, 15%), 317 (100), 315 (100), 237 (75), 235 (39) and 52 (79).

**2-Bromo-3-(phenylethyl)-3***H***-quinazolin-4-one 28.** The general procedure for alkylation of 3*H*-quinazolin-4-ones (12 h) yielded 2-bromo-3-(phenylethyl)-3*H*-quinazolin-4-one as colourless crystals (6%), mp 109–110 °C; Found: M<sup>+</sup>, 328.0206. C<sub>16</sub>H<sub>13</sub><sup>79</sup>BrN<sub>2</sub>O requires 328.0206; mp 195–197 °C;  $\nu_{max}$ (thin film)/cm<sup>-1</sup> 3060, 2930, 2359, 1866, 1714, 1655, 1621, 1604, 1493, 1452, 1405, 1072, 1028, 938 and 908;  $\delta_{\rm H}$  2.99 (2 H, t, *J* 7.6, CH<sub>2</sub>), 4.37 (2 H, t, *J* 7.6, NCH<sub>2</sub>), 7.26–7.15 (5 H, m, PhH), 7.34–7.30 (1 H, m, 6-H), 7.49 (1 H, d, *J* 7.6, 8-H), 7.67–7.63 (1 H, m, 7-H) and 8.20 (1 H, d, *J* 7.6, 5-H);  $\delta_{\rm C}$  34.0 (CH<sub>2</sub>), 42.2 (NCH<sub>2</sub>), 114.5 (4a-C), 114.9 (CH), 123.1 (8-C), 126.4 (6-C), 128.3 (5-C), 128.4 (CH), 128.9 (CH), 134.8 (7-C), 138.5 (C), 138.7 (C), 151.2 (2-C) and 162.3 (4-C); *m/z* (EI) 266 (M<sup>+</sup>, 16%), 264 (15), 249 (20), 185 (100), 129 (52), 102 (23), 90 (35) and 40 (53).

# Cyclisation reactions of 3-benzyl-2-bromo-3*H*-quinazolin-4-one 27.

 $Bu_3SnH$  and  $Et_3B$ . The general procedure for  $Bu_3SnH$  reactions using  $Et_3B$  as initiator were used with  $Bu_3SnH$  added by syringe pump over 6 h and the reaction stirred for a further 5 h. Workup yielded 3-benzyl-3*H*-quinazolin-4-one **19** as colourless crystals (0.15 g, 0.62 mmol, 62%). The data were identical to authentic material. A repeat experiment using  $Bu_3GeH$  in place of  $Bu_3SnH$ gave 3-benzyl-3*H*-quinazolin-4-one **19** in reduced yield (47%).

*Hexamethylditin*. The general procedure for reactions using photolysis and hexamethylditin yielded an inseparable mixture of 12*H*-isoindolo-[1,2-*b*]quinazolin-10-one **20** (27%) and 3-benzyl-3*H*-quinazolin-4-one **19** (41%). The yields were estimated using <sup>1</sup>H NMR spectroscopic analysis.

# Cyclisation reactions of 2-bromo-3-(phenylethyl)-3*H*-quinazolin-4-one 28.

*Hexamethylditin.* The general procedure for reactions using photolysis and hexamethylditin (24 h) yielded 5,6-dihydroiso-quino[1,2-b]quinazolin-8-one **22** as colourless crystals (97%). The data were identical to authentic material.

### Cyclisation reactions of 3-(3-iodopropyl)-3*H*-quinazolin-4-one 31a.

Hexamethylditin. The general procedure for reactions using photolysis and hexamethylditin with 3-(3-iodopropyl)-3Hquinazolin-4-one 31a (24 h) yielded: 2,3-dihydro-1H-pyrrolo[2,1*b*]quinazolin-9-one **2** as colourless crystals (20%), mp 190–192 °C (lit.,<sup>61</sup> 196–198 °C);  $v_{max}$ (thin film)/cm<sup>-1</sup> 3418, 2355, 1651, 1621, 1470, 1385, 1285, 775, 695 and 667;  $\delta_{\rm H}$  2.35–2.23 (2 H, m, CH<sub>2</sub>), 3.18 (2 H, t, J 12.6, CH<sub>2</sub>), 4.21 (2 H, t, J 11.5, NCH<sub>2</sub>), 7.47–7.62 (1 H, m, ArH), 7.76–7.62 (2 H, m, ArH) and 8.28 (1 H, dd, J 12.6, 2.4, ArH;  $\delta_{C}$  19.5 (CH<sub>2</sub>), 32.5 (CH<sub>2</sub>), 46.5 (NCH<sub>2</sub>), 120.4 (C), 126.2 (CH), 126.4 (CH), 126.8 (CH), 134.2 (CH), 149.1 (C), 159.5 (C) and 161.0 (C). 2,3,3a,4-Tetrahydro-1H-pyrrolo[2,1-b]quinazolin-9-one 32a as colourless crystals (12%), mp 187–188 °C (lit., 62 184– 185 °C); v<sub>max</sub>(thin film)/cm<sup>-1</sup> 3421, 1633, 1503, 1470, 1434, 1337, 1151, 752 and 695;  $\delta_{\rm H}$  2.32–2.29 (2 H, m, 2-CH<sub>2</sub>), 3.19 (1 H, t, J 8.0, 1-H), 3.75–3.67 (2 H, m, CHCH<sub>2</sub>), 4.21 (1 H, dd, J 8.0, 7.2, 1-H), 4.5 (1 H, bs, NH), 5.03 (1 H, dd, J 7.2, 5.6, 3a-H), 6.69

(1 H, d, *J* 12.9, ArH), 6.92–6.88 (1 H, m, ArH), 7.27–7.24 (1 H, m, ArH) and 7.91–7.87 (1 H, dd, *J* 12.3, 9.9, ArH);  $\delta_{\rm C}$  21.7 (CH<sub>2</sub>), 33.2 (CH*C*H<sub>2</sub>), 44.3 (NCH<sub>2</sub>), 69.9 (CH), 114.9 (CH), 118.4 (CH), 119.9 (C), 126.8 (CH), 132.9 (CH), 149.1 (C) and 162.2 (C). 3-Propyl-3*H*-quinazolin-4-one **33a** as colourless crystals (6%). The data were identical with those from an independently prepared authentic sample.

 $Bu_3SnH$  and  $Et_3B$ . 3-Propyl-3*H*-quinazolin-4-one **33a** (78%) was the only product.

 $Et_3B$  only. The general procedure for Bu<sub>3</sub>SnH and Et<sub>3</sub>B reactions were used except that the Bu<sub>3</sub>SnH was not added. <sup>1</sup>H NMR spectral analysis showed 2,3-dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one **2** (40%), 2,3,3*a*,4-tetrahydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one **32a** (10%) and 3-propyl-3*H*-quinazolin-4-one **33a** (30%).

## Cyclisation reactions of 3-(3-iodobutyl)-3*H*-quinazolin-4-one 31b.

 $(Me_3Sn)_2$  and photolysis. The general procedure for reactions using photolysis and hexamethylditin (24 h) yielded: 6,7,8,9tetrahydropyrido[2,1-b]quinzolin-11-one 3 as colourless crystals (30%), mp 94-95 °C (lit.,63 96-97 °C); Found: MH+, 201.1020.  $C_{12}H_{13}N_2O$  requires 201.1022;  $v_{max}$ (thin film)/cm<sup>-1</sup> 3423, 2948, 2110, 1655, 1614, 1565, 1477, 1173, 1102, 990, 870, 771 and 583;  $\delta_{\rm H}$  2.18–1.91 (4 H, m, CH<sub>2</sub>CH<sub>2</sub>), 3.00 (2 H, t, J 6.6, NCCH<sub>2</sub>), 4.09 (2 H, t, J 6.3, NCH<sub>2</sub>), 7.44–7.40 (1 H, m, ArH), 7.59 (1 H, dd, J 8.3, 0.5, ArH), 7.73-7.69 (1 H, m, ArH) and 8.26 (1 H, dd, J 8.0 1.5, ArH);  $\delta_{\rm C}$  19.3 (CH<sub>2</sub>), 22.1 (CH<sub>2</sub>), 31.9 (CH<sub>2</sub>), 42.3 (CH<sub>2</sub>), 120.4 (C), 126.1 (CH), 126.4 (CH), 126.6 (CH), 134.1 (CH), 147.4 (C), 154.9 (C) and 162.2 (C); m/z (EI) 200  $(M^+, 50\%)$ , 199 (40), 90 (33), 76 (34), 63 (33), 50 (34) and 41 (90). 5,5a,6,7,8,9-Hexahydropyrido[2,1-b]quinazolin-11-one 32b as colourless crystals (23%), mp 128–130 °C (lit.,<sup>2</sup> 132–133 °C); Found: MH<sup>+</sup>, 203.1180. C<sub>12</sub>H<sub>15</sub>N<sub>2</sub>O requires 203.1179; v<sub>max</sub>(thin film)/cm<sup>-1</sup> 3398, 3058, 2938, 2224, 1632, 1518, 1416, 1218, 1153, 1026, 754 and 692;  $\delta_{\rm H}$  1.52–1.49 (2 H, m), 1.91–1.75 (4 H, m), 2.66-2.59 (1 H, m, 9-H), 4.25 (1 H, m, NH), 4.64-4.59 (1 H, m, 9-H), 4.78 (1 H, dd, J 13.5, 3.1, 5a-H), 6.57 (1 H, d, J 7.1, ArH), 6.79 (1 H, ddd, J 7.8, 2.9, 1.0, ArH), 7.27–7.22 (1 H, m, ArH) and 7.90 (1 H, dd, J 7.8 1.6, ArH); δ<sub>c</sub> 22.3 (CH<sub>2</sub>), 24.2 (CH<sub>2</sub>), 33.4 (CH<sub>2</sub>), 42.0 (CH<sub>2</sub>), 68.5 (CH), 113.7 (CH), 115.2 (C), 118.8 (CH), 128.7 (CH), 133.4 (CH), 145.9 (C) and 164.3 (C); m/z (EI) 202 (M<sup>+</sup>, 30%), 146 (42), 119 (48), 92 (42), 55 (79) and 41 (100).

 $Et_3B$  only. The general procedure for Bu<sub>3</sub>SnH and Et<sub>3</sub>B reactions were used except that the Bu<sub>3</sub>SnH was not added. <sup>1</sup>H NMR spectral analysis showed 6,7,8,9-tetrahydro-pyrido[2,1-*b*]quinzolin-11-one **3**(61%) and 5,5*a*,6,7,8,9-hexahydropyrido[2,1-*b*]quinzolin-11-one **32b** (23%).

### Cyclisation of 3-[(2-bromoquinolin-3-yl)methyl]-4(3*H*)-quinazolinone 34.

 $(Me_3Sn)_2$  and photolysis. The general procedure for reactions using photolysis and hexamethylditin (24 h) yielded: luotonin A **5** (51%). All data were the same as reported.<sup>45</sup> 3-[(Quinolin-3yl)methyl]-3*H*-quinazolin-4-one **36**, colourless crystals, mp 252– 253 °C; Found: MH<sup>+</sup>, 288.1130. C<sub>18</sub>H<sub>13</sub>N<sub>3</sub>O requires 288.1131;  $v_{max}$ (thin film)/cm<sup>-1</sup> 3420, 2357, 2107, 1646, 1558, 1450, 1361, 1332, 510 and 454;  $\delta_{\rm H}$  5.39 (2 H, s, CH<sub>2</sub>), 7.58–7.53 (2 H, m, ArH), 7.81–7.70 (4 H, m, ArH), 8.10 (1 H, dd, *J* 8.9, 0.4, ArH), 8.17 (1 H, d, J 1.8, ArH), 8.35–8.32 (1 H, m, ArH) and 8.99 (1 H, d, J 1.8, ArH);  $\delta_{\rm C}$  47.7 (CH<sub>2</sub>), 122.1 (CH), 126.9 (CH), 127.3 (CH), 127.7 (2 × CH), 127.9 (CH), 128.6 (2 × C), 129.3 (CH), 130.0 (CH), 134.6 (CH), 135.4 (CH), 145.9 (CH), 147.9 (C), 148.0 (C), 150.1 (CH) and 161.1 (C); *m/z* (EI) 287 (M<sup>+</sup>, 45%), 270 (42), 132 (100), 115 (70), 89 (20), and 63 (21).

 $Bu_3SnH$  and  $Et_3B$ . The general procedure for  $Bu_3SnH$  reactions using  $Et_3B$  as initiator were used with  $Bu_3SnH$  added by syringe pump over 5 h and the reaction stirred for a further 5 h to yield luotonin A 5 (14%) and 3-[(quinolin-3-yl)methyl]-3*H*-quinazolin-4-one 36 (32%). When the  $Bu_3SnH$  was added at the beginning of the reaction only 3-[(quinolin-3-yl)methyl]-3*H*-quinazolin-4-one 36 was obtained (53%).

 $Bu_3GeH$  and  $Et_3B$ . Luotonin A (18%) and [(3-quinolin-3-yl)methyl]-3*H*-quinazolin-4-one **36** (11%) were obtained.

### Cyclisation of 3-[2-(2-bromoindol-3-yl)ethyl]-4(3*H*)-quinazolinone 40.

*Bu<sub>3</sub>SnH addition.* The general procedure for Bu<sub>3</sub>SnH reactions using Et<sub>3</sub>B as initiator were used with Bu<sub>3</sub>SnH added by syringe pump over 12 h to yield rutaecarpine **8** (15%), mp 254– 255 °C (lit.,<sup>41</sup> 256–257 °C) and 3-[2-(1*H*-indol-3-yl)ethyl]-4(3*H*)quinazolinone **39** (57%), both as colourless crystals. The data for rutaecarpine were the same as those in the literature.<sup>41</sup> The data for **39** were the same as obtained in the previous synthesis.

 $(Me_3Sn)_2$  and photolysis. The general procedure for reactions using photolysis and hexamethylditin (6 h) yielded rutaecarpine (55%) as the only product.

2-(4-Oxo-4H-quinazolin-3-yl)selenobenzoic acid Se-phenyl ester 43. Tributylphosphine (2.5 cm<sup>3</sup>, 10 mmol) was slowly added to diphenyl diselenide (2.47 g, 7.9 mmol) in anhydrous DCM and the mixture left to stir for 15 min. 2-(4-Oxo-4H-quinazolin-3-yl)benzoic acid 42 (1.40 g, 5.2 mmol) was then added and the reaction stirred for 12 h till no precipitate was visible. The reaction mixture was diluted with DCM and washed with H<sub>2</sub>O  $(3 \times 50 \text{ cm}^3)$  and brine (50 cm<sup>3</sup>). The organic layer was dried over MgSO<sub>4</sub> and evaporated to dryness under reduced pressure. The crude product was purified by column chromatography using silica gel as absorbent and light petroleum/EtOAc (4:1). The resulting yellow solid was recrystallised from hot EtOH yielding 2-(4-oxo-4H-quinazolin-3-yl)selenobenzoic acid Se-phenyl ester 43 as long yellow needles (1.55 g, 3.8 mmol, 73%); (Found: M<sup>+</sup>, 407.0289. C<sub>21</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub>Se requires 407.0293); mp 234–236 °C;  $v_{max}$ (thin film)/cm<sup>-1</sup> 3165, 2831, 2063, 1798, 1519, 1367, 1118, 960 and 915;  $\delta_{\rm H}$  7.36 – 7.30 (3 H, m, ArH), 7.42 (1 H, dd, J 9.2 1.6, ArH), 7.55 - 7.45 (3 H, m, ArH), 7.70-7.66 (1 H, m, ArH), 7.81-7.72 (3 H, m, ArH), 8.02 (1 H, s, 2-H), 8.14 (1 H, dd, J 9.2 1.6, ArH) and 8.34–8.32 (1 H, m, ArH); δ<sub>c</sub> 122.3 (C), 125.9 (C), 127.1 (5-C), 127.6 (6-C), 127.7 (CH), 129.2 (CH), 129.4 (2 × CH), 129.4 (CH), 129.8 (CH), 130.1 (CH), 133.6 (C), 133.7 (CH), 134.6 (CH), 136.0 (2 × CH), 136.9 (C), 145.6 (2-C), 148.0 (C), 160.7 (4-C) and 192.7 (CO); *m*/*z* (EI) 407 (M<sup>+</sup>, 100%), 251 (39), 235 (55) and 223 (46).

# Radical reactions of 2-(4-oxo-4*H*-quinazolin-3-yl)selenobenzoic acid Se-methyl ester 43.

UV and reflux. -(4-Oxo-4*H*-quinazolin-3-yl)selenobenzoic acid Se-phenyl ester **43** (0.24 g, 0.59 mmol) was heated under reflux in benzene (20 cm<sup>3</sup>) for 12 h under UV irradiation. The solvent was removed under vacuum and the crude product was purified by column chromatography using silica gel as absorbent and light petroleum-EtOAc (2:1) yielding tryptanthrin 4 as yellow crystals (0.02 g, 0.07 mmol, 13%), mp 213–214 °C (lit.53 215–217 °C); Found: MH<sup>+</sup>, 249.0659.  $C_{15}H_9N_2O_2$  requires 249.0660;  $\delta_H$  7.43 (1 H, t, J 8.0, ArH), 7.68 (1 H, t, J 8.0, ArH), 7.79 (1 H, t, J 8.0, ArH), 7.86 (1 H, t, J 8.0, ArH), 7.92 (1 H, d, J 8.0, ArH), 8.04 (1 H, d, J 8.0, ArH), 8.44 (1 H, d, J 8.0, ArH) and 8.64 (1 H, d, J 8.0, ArH); δ<sub>C</sub> 118.0 (CH), 122.0 (C), 123.8 (C), 125.4 (CH), 127.2 (CH), 127.6 (CH), 130.2 (CH), 130.7 (CH), 135.1 (CH), 138.3 (CH), 146.4 (C), 146.7 (C), 158.1 (C) and 171.1 (2  $\times$  CH); *m*/*z* (EI) 248 (M<sup>+</sup>, 51%), 220 (22), 130 (28), 102 (54), 90 (100), 76 (81), 63 (55) and 50 (74). The data were identical to the literature data<sup>53</sup> and those of authentic material. Repeating the reaction for 10 h gave a yield of 11% of 4. The procedure was repeated using the same conditions but with the addition of AIBN (2.0 equiv.) for 8 h. An intractable mixture was obtained. A blank reaction with no sunlamp photolysis or added AIBN, in benzene heated under reflux for 24 h gave a quantitative recovery of unaltered starting material 43.

 $(Me_3Sn)_2$ , sunlamp. The reaction between 2-(4-oxo-4*H*-quinazolin-3-yl)selenobenzoic acid Se-phenyl ester **47** (0.29 g, 0.72 mmol) and hexamethylditin (0.70 g, 2.15 mmol) was carried out in *tert*-butylbenzene (20 cm<sup>3</sup>). The mixture was heated under reflux and irradiated with a sunlamp for 4 h. Dilute hydrochloric acid was added to the cooled reaction mixture to extract the protonated quinazolone products into the aqueous layer. The aqueous layer was washed with light petroleum to remove tin residues. The aqueous layer was basified with sodium hydroxide to pH 14 and extracted with DCM. The combined organic layers were dried and evaporated under reduced pressure. The residue was purified by column chromatography using silica gel as absorbent and light petroleum–EtOAc (2 : 1) yielding tryptanthrin **4** (5 mg, 0.02 mmol, 3%).

*Sunlamp.* When the sunlamp irradiation alone was used for 30 min, the highest yield of tryptanthrin (15%) was obtained.

2-[(4-Oxo-4H-quinazolin-3-yl)methyl]benzoic methyl ester 45. N-Bromosuccinimide (19.0 g, 107.1 mmol, 1.5 equiv.), methyl 2-methylbenzoate (10.0 cm<sup>3</sup>, 71.4 mmol) and AIBN (1.16 g, 7.1 mmol) were refluxed in cyclohexane in the dark for 5 h. The reaction mixture was cooled to 0 °C and filtered. The filtrate was diluted with DCM, washed with  $H_2O$  (3 × 50 cm<sup>3</sup>) and brine (50 cm<sup>3</sup>) and then dried and evaporated to dryness under reduced pressure. The unpurified methyl 2-bromomethylbenzoate was added to a solution of 3*H*-quinazolin-4-one (7.3 g, 50 mmol) and potassium tert-butoxide (07.3 g, 65 mmol) in DMF (50 cm<sup>3</sup>) that had been stirred for 40 min. The resulting mixture was stirred for 12 h then diluted with DCM, and the solution washed with H<sub>2</sub>O and brine. The organic layer was dried and evaporated under reduced pressure. The crude product was purified by column chromatography using silica gel as absorbent and light petroleum-EtOAc (4:1) as eluent yielding 2-[(4-oxo-4H-quinazolin-3yl)methyl]benzoic methyl ester as a pale oil 45 (4.98 g, 16.6 mmol, 34%); (Found: M<sup>+</sup>, 295.1077. C<sub>17</sub>H<sub>14</sub>N<sub>2</sub>O<sub>3</sub> requires 295.1077);  $v_{\rm max}$ (thin film)/cm<sup>-1</sup> 3541, 3417, 1715, 1681, 1563, 1367, 1322, 1079, 968 and 774;  $\delta_{\rm H}$  3.88 (3 H, s, OMe), 5.62 (2 H, s, CH<sub>2</sub>), 7.31– 7.22 (2 H, m, ArH), 7.70–7.69 (2 H, m, ArH), 7.97 (1 H, dd, J 7.8 1.4, ArH) and 8.28–8.23 (2 H, m, ArH);  $\delta_{\rm C}$  47.9 (CH<sub>2</sub>), 52.4 (Me), 122.2 (4a-C), 126.9 (CH), 127.3 (CH), 127.5 (CH), 128.0 (CH),

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128.6 (C), 129.1 (CH), 131.3 (CH), 133.0 (CH), 134.7 (CH), 147.1 (CH), 148.1 (8a-C), 161.4 (4-C) and 167.4 (CO<sub>2</sub>Me); *m/z* (EI) 262 (M<sup>+</sup>, 53%), 132 (80), 118 (30), 102 (60), 91 (100), 77 (58), 63 (33) and 50 (23).

**2-[(4-Oxo-4***H***-quinazolin-3-yl)methyl]benzoic methyl acid 46.** A solution of 2-[(4-oxo-4*H*-quinazolin-3-yl)methyl]benzoic methyl ester **45** (1.93 g, 6.14 mmol) in ethanolic LiOH (1 M, 200 cm<sup>3</sup>) and water (20 cm<sup>3</sup>) was stirred for 18 h. The mixture was acidified with HCl and extracted with EtOAc. The organic layers were combined and washed with H<sub>2</sub>O and brine. The organic extract was dried over MgSO<sub>4</sub> and evaporated to dryness under reduced pressure yielding 2-[(4-oxo-4*H*-quinazolin-3-yl)methyl]benzoic methyl acid **46** as a colourless oil (0.63 g, 2.1 mmol, 34%); Found: M<sup>+</sup>, 281.0918. C<sub>16</sub>H<sub>12</sub>N<sub>2</sub>O<sub>3</sub> requires 281.0921; *m/z* (EI) 262 (M<sup>+</sup>, 31%), 146 (35), 132 (86), 118 (38), 104 (47), 90 (58), 77 (100), 63 (28), 51 (32) and 43 (53). The carboxylic acid **46** was converted to the acyl selenide without further characterisation.

2-[(4-Oxo-4H-quinazolin-3-yl)methyl]seleno benzoic acid Sephenyl ester 47. The same procedure as for the seleno-ester 43 was used to convert 2-[(4-oxo-4H-quinazolin-3-yl)methyl]benzoic methyl acid 46 to 2-[(4-oxo-4H-quinazolin-3-yl)methyl]seleno benzoic acid Se-phenyl ester 47 as colourless crystals (0.31 g, 0.71 mmol, 68%), mp 314-316 °C; Found: M+H+, 421.0450.  $C_{22}H_{17}N_2O_2^{80}Se$  requires 421.0451;  $v_{max}(thin film)/cm^{-1}$  3361, 1911, 1659, 1589, 1542, 1392, 1336, 1188, 801, 760 and 722;  $\delta_{\rm H}$ 5.43 (2 H, s, CH<sub>2</sub>), 7.37-7.35 (1 H, m, ArH), 7.53-7.45 (6 H, m, ArH), 7.61–7.59 (2 H, ArH), 7.79–7.73 (2 H, m, ArH), 8.04 (1 H, dd, J 7.6 1.3, ArH), 8.13 (1 H, s, 2-H) and 8.33-8.30 (1 H, m, ArH); δ<sub>C</sub> 47.2 (CH<sub>2</sub>), 122.1 (4a-C), 126.3 (C), 126.9 (CH), 127.4 (CH), 127.5 (CH), 128.5 (CH), 129.4 (CH), 129.6 (CH), 129.6 (CH), 129.7 (CH), 133.2 (CH), 133.6 (C), 134.4 (CH), 136.2 (CH), 137.6 (C), 147.0 (CH), 148.0 (8a-C), 161.3 (4-C) and 196.7 (CO); m/z (Electrospray) 421 (M<sup>+</sup>, 7%), 263 (60), 156 (45), 129 (100), 102 (43), 89 (46), 77 (60), 63 (23) and 51 (33).

11-Hydroxy-11*H*-isoquinolino[3,2-*b*]quinazolin-6,13-dione 50. The reaction between 2-[(4-oxo-4H-quinazolin-3-yl)methyl]seleno benzoic acid Se-phenyl ester 47 (0.044 g, 0.1 mmol) and hexamethylditin (0.099 g, 0.3 mmol) was carried out in benzene (20 cm<sup>3</sup>) and was refluxed and irradiated with a UV lamp for 3 h. The benzene was removed under vacuum and the crude product was purified by column chromatography using silica gel as absorbent and light petroleum-EtOAc (4:1) as eluent yielding 11-hydroxy-11H-isoquinolino[3,2-b]quinazolin-6,13-dione 50 as colourless needles (0.011 g, 0.04 mmol, 39%), mp 176-177 °C (CHCl<sub>3</sub>); Found:  $(M + H)^+$ , 279.0768.  $C_{16}H_{11}N_2O_3$  requires 279.0764; v<sub>max</sub>(thin film)/cm<sup>-1</sup> 3421, 2919, 2360, 1699, 1683, 1653, 1559, 1465, 1260, 1100, 963, 910, 728 and 667;  $\delta_{\rm H}$  5.29 (1 H, d, J 4.6, OH), 7.21 (1 H, d, J 4.6, CH), 7.69-7.65 (2 H, m, ArH), 7.80 (1 H, d, J 8.0, ArH), 7.93–7.84 (2 H, m, ArH), 8.10 (1 H, d, J 8.0, ArH), 8.32 (1 H, dd, J 7.6 1.2, ArH) and 8.39 (1 H, dd, J 8.0 1.2, ArH); δ<sub>C</sub> 75.5 (CH), 121.9 (C), 126.7 (CH), 128.0 (CH), 128.7 (CH), 129.2 (C), 129.6 (CH), 130.0 (CH), 130.3 (CH), 135.6 (CH), 135.7 (CH), 137.0 (C), 142.6 (ArC), 146.7 (C), 162.7 (C) and 176.6 (C); m/z (Electrospray) 278 (M<sup>+</sup>, 50%), 262 (43), 249 (40), 221 (26), 135 (38), 119 (36), 105 (100), 91 (45), 84 (60), 77 (68) and 51 (69). The structure was confirmed by X-ray crystallography.

### X-Ray crystallography

Data were collected at 150(2) K on a Bruker SMART 1000 diffractometer with sealed tube source<sup>64</sup> for **30** and Bruker-Nonius CCD diffractometer with rotating anode source<sup>65</sup> for **50**. The structures were solved by direct methods and refined by full-matrix least-squares on  $F^2$  using the SHELXTL suite of programs.<sup>66</sup> All the non-hydrogen atoms were refined with anisotropic atomic displacement parameters and hydrogen atoms were inserted at calculated positions using a riding model except for H(2) for which coordinates were freely refined in both structures. In **30**, molecules form into chains *via* intermolecular H-bonds N(2)–H(2)···O(1'). The structure of **50** additionally contains one molecule of CHCl<sub>3</sub> in the asymmetric unit and molecules are linked into chains *via* strong intermolecular H-bonds O(2)–H(2)···N(2'). Off-set  $\pi$ - $\pi$  stacking is also dominant with separations in the range 3.33–3.5 Å.

Crystal data for **30**: C<sub>16</sub>H<sub>14</sub>N<sub>2</sub>OS, M = 282.35, monoclinic, Cc, a = 4.6405(7), b = 25.329(4), c = 12.1910(17) Å,  $\beta = 97.047(2)^{\circ}$ , U = 1422.1(4) Å<sup>3</sup>, T = 150(2) K, Z = 4,  $\mu$ (Mo–K $\alpha$ ) = 0.224 mm<sup>-1</sup>, 5350 reflections measured, 3005 unique ( $R_{int} = 0.0368$ ) which were used in all calculations, wR = 0.1590 for all data, R1 = 0.0602for 2351 data with  $F^2 \ge 2\sigma(F^2)$ . Absolute structure parameter = 0.13(13)—thus reliably determined.

Crystal data for **50**:  $C_{17}H_{11}Cl_3N_2O_3$ , M = 397.63, triclinic,  $P\overline{1}$ , a = 6.6511(3), b = 8.6274(3), c = 14.5395(7) Å, a = 90.123,  $\beta = 94.525(3)$ ,  $\gamma = 99.594(3)^\circ$ , U = 819.97(6) Å<sup>3</sup>, T = 120(2) K, Z = 2,  $\mu$ (Mo–K $\alpha$ ) = 0.579 mm<sup>-1</sup>, 11250 reflections measured, 3715 unique ( $R_{int} = 0.0370$ ) which were used in all calculations, wR = 0.0939 for all data, R1 = 0.0353 for 2898 data with  $F^2 \ge 2\sigma(F^2)$ .‡

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