Radical reactions with 3H-quinazolin-4-ones: synthesis of deoxyvasicinone, mackinazolinone, luotonin A, rutaecarpine and tryptanthrin†

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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 3H-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 2,1 mackinazolinone 3,3 tryptanthrin 4,4 luotonin A 5, B 6 and E 7† and rutaecarpine 8.5 3H-Quinazolin-4-one alkaloids have been recently reviewed.6 All the 3H-quinazolin-4-one natural products have interesting biological activity and have therefore been extensively investigated for useful pharmaceutical activity. The 3H-quinazolin-4-one ring is regarded as a ‘privileged structure’ in combinatorial synthesis.7 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.7

Our study involved the development of protocols involving radical cyclisation for the synthesis of polycyclic 3H-quinazolin-3-ones (Scheme 1). The protocols have also been used for the synthesis of novel polycyclic quinazolinones including the natural 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,8,9 imidazoles,8 pyrazoles,10 indoles,11,12 1,2,3-triazoles,13 pyridinium salts,14 and quinolones;15 b. acyl radicals onto pyrroles,16 quinolines,17 pyridines18 and arenes;19 c. aryl radicals onto indoles,20 pyrroles,9 pyridones,22 and 5-amino- and 5-hydroxyuracils,23 2-quinolones,24 quinolines25 and pyridines.26 All of the above cyclisations are ‘oxidative’ i.e. the intermediate π-radicals are not reduced by triorganometal hydrides [e.g. tributyltin hydride (Bu3SnH)] 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 reviewed27 and the mechanism of Bu3SnH 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 π-radical 10). However, the lower aromaticity could favour reductive cyclisation in which the intermediate π-radical 10 is intercepted by reagents such as Bu3SnH. 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,21,24

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quinoxalines\textsuperscript{22-25} and pyridinones.\textsuperscript{22,29,30} However, the lower aromaticity in the pyrrole ring of indole, facilitates both reductive and oxidative cyclisation depending on the conditions.\textsuperscript{11,12,31} 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\(_3\)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 \( \alpha \)-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 as precursors for cyclisation. The radical leaving group is introduced during our studies, a synthesis of luotonin A analogues 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.\textsuperscript{32} Aryl radicals are very reactive and the most likely to cyclise onto quinoxalines. Therefore, suitable radical precursors for 5- and 6-\( \alpha \)-cyclisation were prepared (Scheme 2).

The 5-membered ring cyclisation with the precursor 16 using Bu\(_3\)SnH gave only the reduced uncyclised product 19 (Scheme 3). Even syringe pump addition of Bu\(_3\)SnH, with either Et\(_3\)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\(_3\)SnD which gave only deuteriation on the aryl 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\(_3\)SnH. Therefore, hexamethylditin \([\text{Me}_3\text{Sn}]_2\) was used so that the intermediate radical (cf. 9 in Scheme 1) was not reduced. The reaction was repeated with (Me\(_3\)Sn), 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\(_3\)Sn), (Scheme 4). The reaction with Bu\(_3\)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 is more favourable.\textsuperscript{8,10,16,32} Therefore, the higher yields of 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 quinoxalines as observed for other heteroarenes.

![Scheme 2](https://example.com/scheme2.png)

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

![Scheme 3](https://example.com/scheme3.png)

**Scheme 3** Reagents and conditions: i, Et\(_3\)B, PhMe, r.t., Bu\(_3\)SnH (fast addition) 96% (19), slow addition, 30% (19); AIBN, Bu\(_3\)SnH (slow addition), PhMe, reflux, 45% (19); Et\(_3\)B, TTMSS, 35% (19); (Me\(_3\)Sn), tert-BuPh, reflux, 18% (20), 65% (19).

![Scheme 4](https://example.com/scheme4.png)

**Scheme 4** Reagents and conditions: i, (Me\(_3\)Sn), tert-BuPh, reflux, 92% (22), 0% (23); Et\(_3\)B, PhMe, r.t., Bu\(_3\)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 quinoxalines 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 quinoxaline moiety. 3H-4-Oxoquinazolin-2-yl radicals,\textsuperscript{33} generated photolytically from 3-(but-1-en-4-yl)-3H-quinazolin-4-one, have been reported to undergo 5-\( \alpha \)-cyclisation onto the pendant alkene.\textsuperscript{13a} 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.\textsuperscript{13a}

![Scheme 5](https://example.com/scheme5.png)

**Scheme 5** Reagents and conditions: i, Br\(_2\), EtOH, 50% (26); ii, NaH, DMF, BuBr, 46% (27); NaI, PhCH\(_2\)CH\(_2\)Br, 6% (28); iii, 27: Bu\(_3\)SnH, Et\(_3\)B, slow addition, 62% (19); Bu\(_3\)GeH, Et\(_3\)B, slow addition, 41% (19); (Me\(_3\)Sn), tert-BuPh, reflux, 41% (19), 27% (20); 28: (Me\(_3\)Sn), tert-BuPh, reflux, 0% (23), 97% (22).
The plan of our protocol was to alkylate 2-bromo-3H-quinazolin-4-one to provide suitable radical precursors (Scheme 5). 2-Bromo-3H-quinazolin-4-one 26 was prepared by an adapted literature procedure from 2-mercapto-3H-quinazolin-4-one 24. 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. Alklylation with activated propargyl halides has also recently been reported. A maximum yield (6%) of alkylation was obtained with 2-phenylethyl 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-3H-4-oxoquinazoline 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-1H-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-1H-quinazolin-4-one 30 was prepared by ring synthesis using the reaction between 2-(methoxycarbonyl)phenyl isothiocyanate and amines. 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 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-1H-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 unactivated halides (Scheme 5) and 36.

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 Bu3SnH and Bu3GeH and yielded only the reduced uncyclised product 19. Radical abstraction of hydrogen from Bu3GeH is 20 times slower than from Bu3SnH which would favour cyclisation over reduction, but still only reduction was observed from the intermediate 29a. When (Me3Sn)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 neoply 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-bromoquinazolineones is still required. Addition of 3H-4-oxoquinazolin-2-yl radicals onto isonitriles has also recently been reported.

### Alkyl radical cyclisation

Several methods have been used for the synthesis of both deoxyvasicinone 2 and mackinazolinone 3 but none involving radicals. 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 Bu3SnH 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 Bu3SnH to yield the respective reduced uncyclised product 33a. Therefore, (Me3Sn)2 was used to facilitate cyclisation which gave moderate yields of deoxyvasicinone 2 and mackinazolinone 3.

The use of Et3B mediated reactions gave better yields of both 2 and 3 (Scheme 6). We suggest that the ethyl radical generated from the reaction between Et3B 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 π-radical intermediates (cf. 10) is also most likely abstracted by ethyl radicals to facilitate rearomatisation. Unusually, some cyclised reduced material 32a,b was obtained suggesting disproportionation was also taking place. GCMS analysis of the crude product from the Et3B facilitated reaction with 31a indicated traces (ca. 5%) of 2-ethyl-3-propyl-3H-quinazolin-4-one and

![Fig. 1 X-Ray structure of 3-(2-phenylethyl)-2-thioxo-2,3-dihydro-1H-quinazolin-4-one 30 with atom labelling.](Image)
3-pentyl-3H-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 and 2-bromoquinoline 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. Luotonin A has been reported to show activity as an antitumour compound and is an inhibitor for human DNA topoisomerase I. Luotonin A was even obtained with Bu3SnH and Bu3GeH, 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 but further optimisation could improve the yield.

**Rutaecarpine 8.** Rutaecarpine 8 has been synthesised by a wide variety of protocols but none involving radicals. 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-o-alkenes and -arenes and in H-translocation reactions towards the synthesis of mitomycin.

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 and synthesis of 10,11-methylene-14-azaxamptothecin and 14-azacamptothecin using cyclisation of 2-quinolinyl radicals onto 3H-pyrimidin-4-one moieties. These cyclisations also proceeded by ‘oxidative cyclisation’ as observed for the 3H-quinazolin-4-ones.

The required starting material 34 was prepared by a literature procedure from 2-chloroquinoline-2-carbaldehyde and reacted under several radical conditions. Unusually, the yield from 5-exo cyclisation was significant. The use of (Me3Sn)2, gave a reasonable yield (53%) of luotonin A 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 Bu3SnH and Bu3GeH, 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 but further optimisation could improve the yield.

**Scheme 6** Reagents and conditions: i, NaH, DMF; a. 1-chloro-3-iodopropane, 51%; b. 1-chloro-4-iobutane, 65%; ii, NaI, acetone, reflux, 53% (31a), 67% (31b); iii, (Me3Sn), 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, B (20 equiv.), tert-BuPh, air (yields by 1H NMR analysis): a. 31a gave 40% (2), 10% (32a) and 30% (33a); b. 32b gave 61% (3), 23% (32b) and 0% (33b).

**Scheme 7** Reagents and conditions: i, (Me3Sn), tert-BuPh, reflux, hv. 51% (5), 15% (36); Et, B (20 equiv.), PhMe, r.t., air: Bu3SnH (fast addition), 0% (5), 53% (36) Bu3SnH (slow addition), 14% (5), 32% (36) Bu3GeH (fast addition), 18% (5), 11% (36).

**Scheme 8** Reagents and conditions: i, PBr3, DCM, 56% (38); ii, tert-BuOK, DMF, 3H-quinazolin-4-one, 39% (39); iii, NBS, DCM, 0 °C, 30 min, 38% (40); iv, (Me3Sn), tert-BuPh, reflux, hv. 55% (8), 0% (39); Et, B (20 equiv.), PhMe, r.t., air: Bu3SnH (slow addition), 15% (8), 57% (39).
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.\textsuperscript{46,49,51} We finally used an adapted literature procedure\textsuperscript{46} whereby the 3\textit{H}-quinazolin-4-one moiety was used as the ‘protective group’ for the indole side chain (\textit{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,\textsuperscript{48,49,51,52} 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-(\textit{1H}-Indol-3-yl)ethyl]-4(3\textit{H})-quinazolinone 39 was prepared by alkylation of 4(3\textit{H})-quinazolinone with 3-(2-bromoethyl)-\textit{1H}-indole 38 which was prepared by bromination of tryptophol 37.

Radical cyclisation of the precursor 40 gave the predicted 6-\textit{exo} cyclisation of the intermediate radical 41 to yield rutaecarpine 8. Only cyclisation was obtained when (Me\textsubscript{3}Sn)\textsubscript{2} was used and even reductive conditions with Bu\textsubscript{3}SnH yielded a small amount of cyclisation product. The 6-\textit{exo} cyclisation yields were similar to the equivalent cyclisation with aryl radicals (see Scheme 4). Longer reactions times led to decomposition.

\textbf{Acyl radicals—synthesis of tryptanthrin}

Tryptanthrin has been synthesised by a range of protocols.\textsuperscript{16,31} We prepared an authentic sample of tryptanthrin 4 by a literature procedure in order to obtain full spectroscopic data for comparison.\textsuperscript{51}

Aromatic acyl radical cyclisation has recently been shown to be a useful synthetic technique.\textsuperscript{17,19,54} Although 5-membered ring cyclisation was reported to be unsuccessful,\textsuperscript{19} we have shown that 5-ring cyclisation onto the 3\textit{H}-quinazolin-4-one moiety was possible (\textit{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.\textsuperscript{49,55} 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\textsuperscript{48} and converted to the acyl selenide 43 by standard procedures.\textsuperscript{16} Several conditions were used based on literature reports.\textsuperscript{17,19,54} 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-\textit{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-\textit{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). The acyl radical precursor 47 was prepared by standard procedures. The ester 45 was synthesised by alkylation of 3\textit{H}-quinazolin-4-one with methyl 2-(bromomethyl)-benzoate. Cyclisation using Et\textsubscript{3}B only, AIBN only, UV photolysis only and slow addition of TTMSS with Et\textsubscript{3}B as initiator all gave intractable mixtures. However, reaction with (Me\textsubscript{3}Sn)\textsubscript{2} 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 ‘quinoine’ product caused by oxidation of the benzylic methylene during the reaction.\textsuperscript{17,18} 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 (\textit{e.g.} intermediate acyl or \pi-radical, PhSe\textsuperscript{+}) 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 trimethylsilyl radicals to form a peroxyl radical (Me\textsubscript{3}SnO\textsuperscript{2+}).\textsuperscript{45,57} 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.
**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$_2$ and dichloromethane which was distilled from CaH$_2$. 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-butyllithium in hexane was used. A solution of Et$_3$B in hexane (1.0 M) was recorded on a Bruker DPX-400 instrument, or 1H (250 MHz) internal standard for 1H NMR spectra and deuteriochloroform refers to the bp 40–60 °C.

Aluminium oxide (Merck 150 F$_{254}$, Type T) was carried out with aluminium backed plates coated with neutral silica gel (Merck Kieselgel 60 F$_{254}$), and TLC using alumina as absorbent was prepared from GeCl$_4$ by a known procedure. Potassium tert-butoxide (1.35 g, 12 mmol) was added to 3H-quinazolin-4-one 13 (1.17 g, 8 mmol) in dry DMF (50 cm$^3$) 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$_2$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$^+$, 362.9987. C$_{16}$H$_{13}$IN$_2$O requires 362.9989; $\nu_{\text{max}}$(thin film)/cm$^{-1}$ 3055, 1649, 1469, 1230, 962 and 734; $\delta_1$ 5.71 (2 H, s, CH$_2$), 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, 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); $\delta_1$ 54.90 (CH$_3$), 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$^+$, 98%), 129 (43), 107 (41), 90 (100), 89 (77), 76 (51), 63 (58), 50 (42) and 40 (85).

**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 3H-quinazolin-4-one 13 (1.17 g, 8 mmol) in dry DMF (50 cm$^3$) 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$_2$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$^+$, 362.9987. C$_{16}$H$_{13}$IN$_2$O requires 362.9989; $\nu_{\text{max}}$(thin film)/cm$^{-1}$ 3055, 1649, 1469, 1230, 962 and 734; $\delta_1$ 5.71 (2 H, s, CH$_2$), 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, 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); $\delta_1$ 54.90 (CH$_3$), 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$^+$, 98%), 129 (43), 107 (41), 90 (100), 89 (77), 76 (51), 63 (58), 50 (42) and 40 (85).

3-[2-(Bromophenyl)ethyl]-3H-quinazolin-4-one 17. The general procedure for alkylation with 2-(2-bromophenyl)ethyl methanesulphonate 15 (4.90 g, 18.6 mmol) for 48 h was used to yield 3-[2-(bromophenyl)ethyl]-3H-quinazolin-4-one 17 as colourless crystals (1.93 g, 5.9 mmol, 38%), mp 119–120 °C; Found: M$^+$, 382.0206. C$_{16}$H$_{13}$BrN$_2$O requires 382.0208; $\nu_{\text{max}}$(thin film)/cm$^{-1}$ 3055, 1649, 1469, 1230, 962 and 773; $\delta_1$ 5.71 (2 H, s, CH$_2$), 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, 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); $\delta_1$ 54.90 (CH$_3$), 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$^+$, 98%), 129 (43), 107 (41), 90 (100), 89 (77), 76 (51), 63 (58), 50 (42) and 40 (85).
Cyclisation reactions of 3-(2-iodobenzyl)-3H-quinazolin-4-one 16.

General procedure for Bu₃SnH reactions using Et₃B as initiator. A solution of Bu₃SnH (0.76 g, 2.6 mmol) and 3-(2-iodobenzyl)-3H-quinazolin-4-one (0.44 g, 1.2 mmol) in dry toluene (40 cm³) was deoxygenated under an atmosphere of nitrogen and stirred for 1 h. Triethylborane (3.6 cm³, 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 cm³, 3.6 mmol) was added and the reaction mixture stirred for a further 10 h. Dilute hydrochloric acid was added to extract the protonated quinazoline products into the aqueous layer. The aqueous layer was basified to remove tributyltin residues. The aqueous layer was washed with light petroleum added to extract the protonated quinazoline products into the aqueous layer. The aqueous layer was washed with light petroleum reduced pressure to a small volume. The residue was purified using column chromatography with light petroleum as eluent to remove polymeric dimethyltin. A precipitate of polymeric dimethyltin was identified in the mixture and therefore not fully characterised. δH 5.19 (2 H, s, CH₂), 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, J 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); δc 49.6 (CH₃), 120.6 (C), 123.4 (CH), 123.5 (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. GC-MS analysis showed the ratio of the two products to be in the ratio 4 : 1 of the reduced produced and cyclised product: 12H-isoidolo-[1,2-b]-quinazolin-10-one; Rf 22.8 min, m/z 234 (M⁺, 95%), 205 (24), 179 (15), 151 (16), 130 (25), 102 (28), 91 (100) and 77 (20) and 3-benzyl-3H-quinazolin-4-one; Rf 24.5 min, m/z 236 (M⁺, 51%), 130, (37), 91 (100) and 65 (27).

3-(Deutero)benzyl-3H-quinazolin-4-one. The general procedure for reductive reactions with Et₃B with Bu₃SnD as reductant were used with 3-(2-iodobenzyl)-3H-quinazolin-4-one 16 to yield 3-(deutero)benzyl-3H-quinazolin-4-one as colourless crystals (41%); mp 100–101 °C. Found: M⁺, 2381084. CI₂DH₂N₂O requires 2381085; νmax(thin film)/cm⁻¹ 3421, 2359, 1670, 1610, 1471, 1396 and 773; δc 5.21 (2 H, s, CH₂), 7.38–7.29 (4 H, m, PhH); 5.02 (1 H, d, J 8.1 1.4, 6-H), 7.79–7.69 (2 H, m, 7-H, 8-H); 8.12 (1 H, s, 2-H) and 8.34 (1 H, ddd, J 8.1 2.0 0.6, 5-H); δc 49.7 (CH₃), 104.1 (CD), 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. The procedure was repeated using TTMSS in place of Bu₃SnH to yield 3-benzyl-3H-quinazolin-4-one 19 (35%).

General procedure for slow addition of Bu₃SnH reactions using Et₃B as initiator. The general procedure for Bu₃SnH reactions using Et₃B as initiator was repeated except that Bu₃SnH was added by a syringe pump over 6 h to give 3-benzyl-3H-quinazolin-4-one 19 (30%).

General procedure for slow addition of Bu₃SnH reactions using AIBN as initiator. The general procedure for Bu₃SnH reactions using Et₃B 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-3H-quinazolin-4-one 19 (45%).

General procedure for reactions using photocatalysis and hexamethylditin. A solution of 3-(2-iodobenzyl)-3H-quinazolin-4-one 16 (0.36 g, 1.0 mmol) and hexamethylditin (0.99 g, 3.0 mmol) in tert-butylnitrobenzene (20 cm³) in a two-necked pyrex flask (5 × 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 dimethylditin was produced. The product was eluted with ethyl acetate and further worked-up as for the general procedure for Bu₃SnH reactions using Et₃B as initiator. 3-Benzyl-3H-quinazolin-4-one 19 and cyclised 12H-isoidolo-[1,2-b]quinazolin-10-one 20 were obtained as an inseparable white solid. Analysis using ¹H NMR spectroscopy showed 19 (65%) and 20 (18%). 12H-Isoidolo-[1,2-b]quinazolin-10-one 20 was identified in the mixture and therefore not fully characterised.
photolysis and hexamethylditin yielded an inseparable mixture of
(1 H, m, ArH), 7.76–7.62 (2 H, m, ArH) and 8.28 (1 H, dd, 7.9 1.6, ArH); 7.8 1.6, ArH)
\[\text{Et}_3\text{B} \text{ only.} \]

\[\text{Bu}_3\text{SnH and Et}_3\text{B.} \text{ 3-Propyl-3H-quinazolin-4-one 33a (78\%)} \text{ was the only product.} \]

\[\text{3-iodobutyl-3H-quinazolin-4-one 31b.} \]

\[\text{Me}_3\text{Sn}, \text{ and photolysis.} \text{ The general procedure for reactions using photolysis and hexamethylditin (24 h) yielded: 6,7,8,9-tetrahydropyrido[2,1-b]quinolin-11-one 3 as colourless crystals (30\%), mp 94–95 °C (lit.,}^{27} 96–97 °C \text{; Found: MH}^{+}, 201.1020. \]

\[\text{C}_{12}\text{H}_{13}\text{N}_{2}\text{O requires 201.1022; } \nu_{\text{max}}(\text{thin film})/\text{cm}^{-1} 3423, 2948, 2110, 1655, 1614, 1477, 1173, 1102, 990, 870, 771 and 583; \]

\[\text{Bu}_3\text{SnH and Et}_3\text{B reactions were used except that the Bu}_3\text{SnH was not added.} \]

\[\text{3-iodobutyl-3H-quinazolin-4-one 33a (10\%) and 3-propyl-3H-quinazolin-4-one 33a (30\%).} \]

\[\text{Cyclisation reactions of 3-(3-iodobuty1)-3H-quinazolin-4-one 31b.} \]

\[\text{Me}_3\text{Sn}, \text{ and photolysis.} \text{ The general procedure for reactions using photolysis and hexamethylditin (24 h) yielded: 6,7,8,9-tetrahydropyrido[2,1-b]quinolin-11-one 3 as colourless crystals (30\%), mp 94–95 °C (lit.,}^{27} 96–97 °C \text{; Found: MH}^{+}, 201.1020. \]

\[\text{C}_{12}\text{H}_{13}\text{N}_{2}\text{O requires 201.1022; } \nu_{\text{max}}(\text{thin film})/\text{cm}^{-1} 3423, 2948, 2110, 1655, 1614, 1477, 1173, 1102, 990, 870, 771 and 583; \]

\[\text{Bu}_3\text{SnH and Et}_3\text{B reactions were used except that the Bu}_3\text{SnH was not added.} \]

\[\text{3-iodobutyl-3H-quinazolin-4-one 33a (10\%) and 3-propyl-3H-quinazolin-4-one 33a (30\%).} \]

\[\text{Cyclisation reactions of 3-(3-iodobuty1)-3H-quinazolin-4-one 31b.} \]

\[\text{Me}_3\text{Sn}, \text{ and photolysis.} \text{ The general procedure for reactions using photolysis and hexamethylditin (24 h) yielded: 6,7,8,9-tetrahydropyrido[2,1-b]quinolin-11-one 3 as colourless crystals (30\%), mp 94–95 °C (lit.,}^{27} 96–97 °C \text{; Found: MH}^{+}, 201.1020. \]

\[\text{C}_{12}\text{H}_{13}\text{N}_{2}\text{O requires 201.1022; } \nu_{\text{max}}(\text{thin film})/\text{cm}^{-1} 3423, 2948, 2110, 1655, 1614, 1477, 1173, 1102, 990, 870, 771 and 583; \]

\[\text{Bu}_3\text{SnH and Et}_3\text{B reactions were used except that the Bu}_3\text{SnH was not added.} \]

\[\text{3-iodobutyl-3H-quinazolin-4-one 33a (10\%) and 3-propyl-3H-quinazolin-4-one 33a (30\%).} \]

\[\text{Cyclisation reactions of 3-(3-iodobuty1)-3H-quinazolin-4-one 31b.} \]

\[\text{Me}_3\text{Sn}, \text{ and photolysis.} \text{ The general procedure for reactions using photolysis and hexamethylditin (24 h) yielded: 6,7,8,9-tetrahydropyrido[2,1-b]quinolin-11-one 3 as colourless crystals (30\%), mp 94–95 °C (lit.,}^{27} 96–97 °C \text{; Found: MH}^{+}, 201.1020. \]

\[\text{C}_{12}\text{H}_{13}\text{N}_{2}\text{O requires 201.1022; } \nu_{\text{max}}(\text{thin film})/\text{cm}^{-1} 3423, 2948, 2110, 1655, 1614, 1477, 1173, 1102, 990, 870, 771 and 583; \]

\[\text{Bu}_3\text{SnH and Et}_3\text{B reactions were used except that the Bu}_3\text{SnH was not added.} \]

\[\text{3-iodobutyl-3H-quinazolin-4-one 33a (10\%) and 3-propyl-3H-quinazolin-4-one 33a (30\%).} \]
Tributylphosphine (2.5 cm\(^3\), 10 mmol) was slowly added to ArH); 8 and 161 (1 C); \(m/z\) (EI) 287 (M\(^+\), 45%), 270 (42), 132 (100), 115 (70), 89 (20), and 63 (21).

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

**Bu\(,Ge\)H and Et\(,B\).** Luotonin A (18%) and 3-[(quinolin-3-yl)methyl]-3H-quinazolin-4-one (11%) were obtained.

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

**Bu\(,Sn\)H addition.** The general procedure for Bu\(,Sn\)H reactions using Et\(,B\) as initiator were used with Bu\(,Sn\)H added by syringe pump over 12 h to yield rutaecarpin 4 as yellow crystals (0.24 g, 0.59 mmol) was obtained (53%). The reaction mixture was cooled to 0 \(^\circ\)C and filtered. The filtrate was diluted with DCM, washed with H\(_2\)O (3 × 50 cm\(^3\)) and brine (50 cm\(^3\)) and then dried and evaporated under reduced pressure. The residue was purified by column chromatography using DCM 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]selenobenzoic acid Se-phenyl ester 45. N-Bromosuccinimide (19.0 g, 107.1 mmol, 1.5 equiv.), methyl 2-methylbenzoate (10.0 cm\(^3\), 71.4 mmol) and AIBN (1.16 g, 7.1 mmol) were refluxed in benzene heated under reflux for 4 h. The crude product was purified by column chromatography using silica gel as absorbent and light petroleum-\(\text{EtOAc} (2 : 1)\) yielding tryptanthrin 4 (5 mg, 0.02 mmol, 3%).
2.1 mmol, 34%); Found: M+, 281.0918. C16H12N2O3 requires (CHCl3); Found: (M + H)+, 279.0764. C16H11N2O3 requires C22H17N2O2.

The same procedure as for the seleno-ester 43 was used to convert 2-[4-oxy-4H-quinazolin-3-yl]methyl]benzoic acid Se-phenyl ester 47.

11-Hydroxy-11H-isouquinolino[3,2-b]quinazolin-6,13-dione 50. The reaction between 2-[4-oxy-4H-quinazolin-3-yl]methyl]benzoic acid Se-phenyl ester 47 (0.044 g, 0.1 mmol) and hexamethylthiadi (0.099 g, 0.3 mmol) was carried out in benzene (20 cm³) and was refluxed and irradiated with a UV lamp for 18 h. The mixture was acidified with HCl and extracted with EtOAc. The organic layers were combined and washed with H2O and brine. The organic extract was dried over MgSO4, and evaporated to dryness under reduced pressure yielding 2-[4-oxy-4H-quinazolin-3-yl]methyl]benzoic acid 46 as a colourless oil (0.044 g, 0.1 mmol) and was purified by column chromatography using silica gel as absorbent and light petroleum–EtOAc (4 : 1) as eluent yielding 2-[4-oxy-4H-quinazolin-3-yl]methyl]benzoic acid Se-phenyl ester 47.

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 for 30 and Bruker-Nonius CCD diffractometer with rotating anode source for 50. The structures were solved by direct methods and refined by full-matrix least-squares on F² using the SHELXTL suite of programs. 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 CHCl3 in the asymmetric unit and molecules are linked into chains via strong intermolecular H-bonds O(2)···H(2)···O(2).

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References


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