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Concise Synthesis of Dictyoquinazol A via a Dimerisation–Cyclocondensation Sequence

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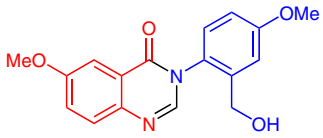

Two-step total synthesis exploiting "hidden symmetry"

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Abstract A two-step total synthesis of the neuroprotective alkaloid, dictyoquinazol A, has been achieved. The brevity of this synthesis was enabled by exploiting the hidden symmetry of the target molecule. Several structural analogues were also prepared using a similar strategy. These results provide a platform for future structure–activity relationship studies in the quest for a novel treatment for stroke.

Key words quinazolinone, natural products, neuroprotective activity, total synthesis, stroke

The quinazolinone moiety (Figure 1) is found within a large number of alkaloids of plant, animal, and microbial origin.[1] A number of drugs containing this motif have also been commercialised for the treatment of a variety of diseases.[1] An interesting subset of the bioactive quinazolinones are those derivatives that have activity towards targets in the central nervous system (CNS). For example, methaqualone (**1**, Figure 1) is a clinical sedative and has also gained notoriety for its abuse as a hypnotic agent.[2] Other examples of CNS-active quinazolinone derivatives include compounds **2** and **3**, which exhibit neuroprotective activity through distinct mechanisms,[3,4] and which therefore have the potential to be developed into new drugs to treat stroke.

The importance of the latter application prompted our interest in another quinazolinone derivative, dictyoquinazol A (**4**, Figure 1).[5] This natural product was isolated in 2002 from the mushroom *Dictyophora indusiata*, which has been employed as a traditional remedy for various ailments including nervous disorders. The purified alkaloid **4** was subsequently shown to have neuroprotective activity against glutamate-induced excitotoxicity, one of the adverse biochemical events caused by stroke.[5] Thus, it appears that compound **4** is a promising candidate for development into a treatment for stroke.

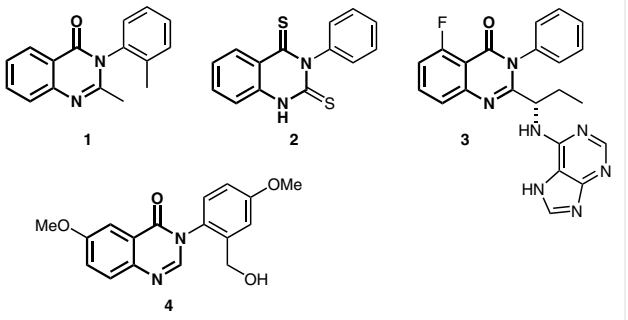
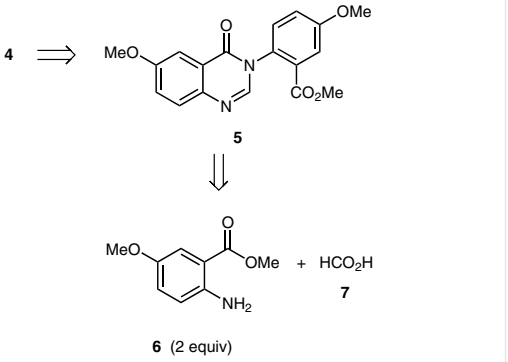


Figure 1 Quinazolinone derivatives that exhibit CNS activity include methaqualone (**1**),[2] the sulfur-containing analogue **2**,[3] idelalisib (**3**),[4] and dictyoquinazol A (**4**)[5]

Many different approaches have been developed over the decades[1] for the synthesis of substituted quinazolinones. Contributing to this body of work, Oh and Song reported in 2007 a total synthesis of **4** requiring six steps and proceeding in 36% overall yield.[6] In 2012, Ma and co-workers reported an alternative (formal) synthesis of **4** in an approach requiring only five steps.[7] Building on this literature precedent, we were motivated to attempt a new total synthesis of **4**, and at the outset we had two goals in mind: first, to identify an even more concise synthetic route; and second, to avoid if possible a radical bromination reaction that featured in the previous synthesis[6] and which required toxic reagents and precise experimental conditions.

The structure of **4** contains an element of pseudosymmetry (Scheme 1). Therefore, a dimerisation strategy might allow a more concise total synthesis to be achieved. If the benzylic alcohol group of **4** is conceptually converted into an ester (**5**, Scheme 1), then compound **5** could in turn be

derived from two molecules of anthranilic ester **6** along with a C_1 source such as formic acid (**7**). In the forward sense, the three fragments **6**, **6** and **7** could potentially be united through a simple, thermodynamically controlled dimerisation–cyclocondensation reaction[8–10] to enable a rapid total synthesis of dictyoquinazol A (**4**).

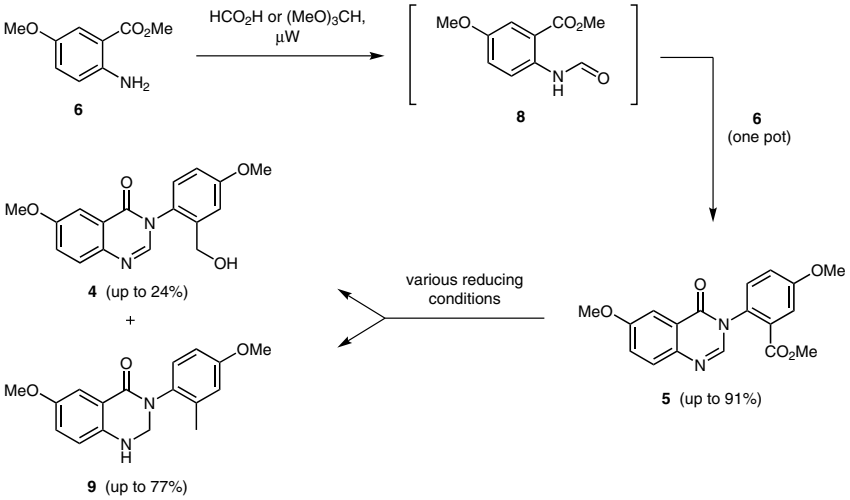


Scheme 1 Potential strategy for a concise synthesis of **4**

To investigate this synthetic plan, the commercially available[11] ester **6** was heated in neat formic acid or trimethyl orthoformate (Scheme 2). When formic acid was used as the C_1 reagent, the desired quinazolinone **5** was obtained in moderate yield, along with a variable quantity of the amide **8** which was presumed to be an intermediate in the dimerisation–cyclocondensation process.[12] When trimethyl orthoformate was used as the C_1 source and strong heating was applied (Scheme 2), the desired quinazolinone **5** was obtained in an excellent yield of 91%.[13]

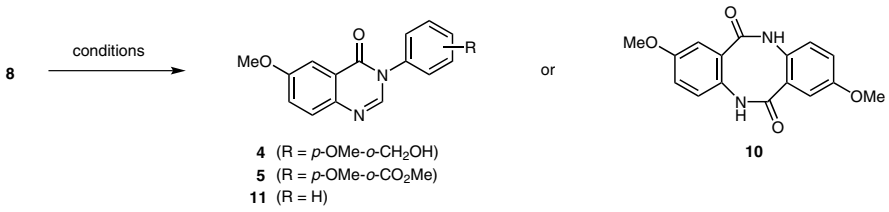
Having secured the quinazolinone **5**, the only task remaining to complete the total synthesis of **4** was to reduce the ester group of **5** (Scheme 2). Unfortunately, this seemingly straightforward transformation proved surprisingly difficult to achieve. When ester **5** was treated with three equivalents of lithium aluminium hydride at 0 °C, the desired product **4** was obtained in low yield alongside 77% of the over-reduced compound **9** (Scheme 2).[14] When the loading of lithium aluminium hydride was reduced, only unreacted **5** and the unwanted compound **9** were obtained. The use of milder reducing agents (e.g., sodium borohydride, diisobutylaluminium hydride, sodium borohydride/zinc chloride) did not improve the yield of **4**, nor did the investigation of a hydrolysis/borane reduction sequence. Finally, the optimal conditions were identified when lithium borohydride in refluxing THF was found to deliver **4** in 24% yield alongside 44% recovered **5**.[15] Overall, despite the low yield in this final reaction (Scheme 2), the synthetic sequence did successfully deliver the natural product **4** in only two steps, with a reasonable overall yield of 22%.

It became of interest to probe the mechanism of the cyclocondensation reaction (i.e., **6** → **5**, Scheme 2), and more specifically to ascertain whether the amide **8** was a true intermediate in this process or simply a shunt product.[12] If the amide **8** was an intermediate and could be carried forward to a quinazolinone derivative, then this might broaden the variety of structural analogues of **4** that could be created, because the substitution pattern on the quinazolinone moiety could be different from that on the pendant aryl ring. Accordingly, the purified amide **8** was re-subjected to the cyclocondensation reaction conditions (Table 1, entry 1). Under these conditions a small quantity of the quinazolinone **5** was obtained, but it was not possible to ascertain whether this product was derived from **8** or from two molecules of **6**. The reaction was repeated with less or no formic acid (Table 1, entries 2 and 3), but this necessitated the use of acetonitrile as the solvent and none of the quinazolinone **5** was formed in these instances.



Scheme 2 Two-step total synthesis of dictyoquinazol A (**4**)

Table 1 Probing the Mechanism of the Cyclocondensation Reaction



4 (R = *p*-OMe-*o*-CH_2OH)
5 (R = *p*-OMe-*o*-CO_2Me)
11 (R = H)

10

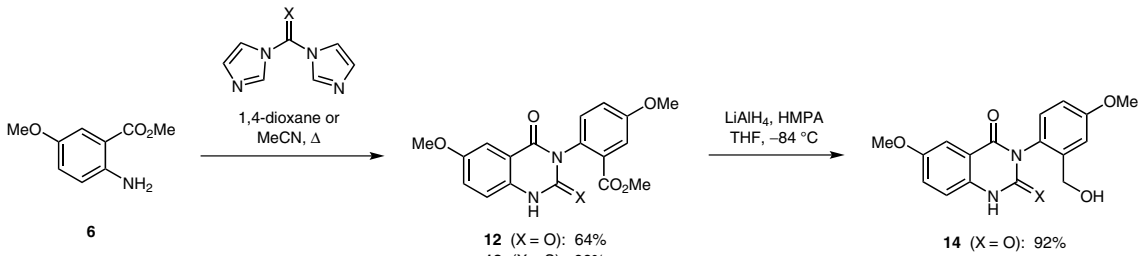
Entry	Conditions	Product, yield (%)
1	**6** (1 equiv), HCO_2H (excess), MW, 4 h	**5** 5
2	**6** (1 equiv), HCO_2H (1 equiv), MeCN, MW, 4 h	**8** 100
3	**6** (1 equiv), MeCN, MW, 4 h	NR[a]
4	**6** (1 equiv), KO*t*-Bu (2 equiv), THF, air, 3 h	**10** 87
5	2-amino-5-methoxybenzyl alcohol (1 equiv), KO*t*-Bu (2 equiv), THF, air	**4** 17
6	aniline (1 equiv), KOt-Bu (2 equiv), THF, air	**11** 17

[a] NR = no reaction.

Since it was not possible to directly demonstrate that **8** was an intermediate in the dimerisation–cyclocondensation reaction (**6** → **5**, Scheme 2), an alternative method was investigated for elaborating **8** into quinazolinone derivatives. Ester **8** was treated with a variety of aniline derivatives under conditions that selectively convert esters into amides (Table 1, entries 4–6).[16] When the aniline **6** was employed in this process (Table 1, entry 4), it unexpectedly dimerised to give **10** instead of reacting with **8**. However, when other anilines were employed (Table 1, entries 5 and 6), the expected quinazolinones **4** and **11** were successfully obtained, presumably *via* bisamide intermediates which were not isolated or observed.[12] Incidentally, this constitutes an alternative two-step synthesis of the natural product **4**, but more importantly it also confirms that 'nonsymmetrically' substituted analogues (e.g., **11**) can be created through this approach, albeit in low yields.

The next objective was to determine whether the original dimerisation–cyclocondensation approach could be modified to produce structural analogues of **4** in which the heterocyclic moiety was varied. Accordingly, the dimerisation reaction of **6** was repeated but using carbonyldiimidazole or thiocarbonyldiimidazole as the C_1 source instead of formic acid (Scheme 3). The dimerisation–cyclocondensation reactions successfully delivered the heterocycles **12** and **13** in good yield (Scheme 3). Gratifyingly, the subsequent reduction reactions (Scheme 3) were also found to be straightforward and efficient in the absence of an easily reduceable heterocyclic moiety, and this provided two new structural analogues of the natural product (**14** and **15**).

Finally, attention was turned to another method for producing structural analogues of **4** in which the substitution patterns on the quinazolinone and phenyl moieties can be different (Scheme 4). Related cyclocondensation approaches have previously been developed by Wang[9] and Khajavi,[10] starting from anthranilic acids instead of anthranilic esters; these methods allow 'nonsymmetrical' targets to be created in high yields and without requiring any intermediates to be isolated. In the current work, the anthranilic acid method was successfully employed to generate several structural analogues of **4** in which the substitution on the pendant aryl ring was varied (**11**, **17**–**20**, Scheme 4). The modest yields were mostly attributable to losses during chromatographic separation from close-running side products. The



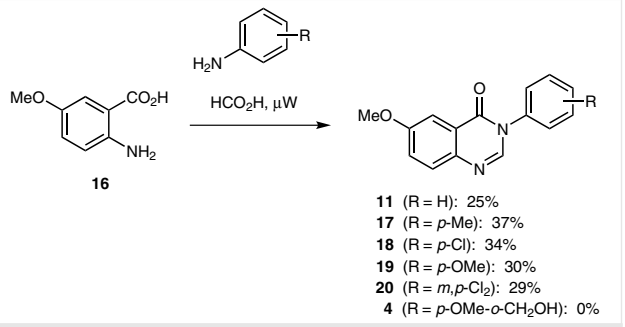
6

12 (X = O): 64%
13 (X = S): 66%

14 (X = O): 92%
15 (X = S): 62%

Scheme 3 Synthesis of structural analogues of **4** in which the heterocycle is modified

anthranilic acid method was also investigated for an attempted one-step synthesis of the natural product (**16** → **4**, Scheme 4), but this was unsuccessful; an intractable mixture of products was formed, and the expected benzylic hydrogen signals were absent from the ^{1}H NMR spectrum of the crude product mixture. This outcome is perhaps unsurprising given the known propensity of *ortho*-aminobenzyl alcohols to undergo iminoquinone methide chemistry,[17] which in this context would be expected to lead to polymerisation or decomposition.



Scheme 4 Synthesis of nonsymmetrically substituted analogues

In conclusion, a two-step total synthesis of the neuroprotective alkaloid dictyoquinazol A (**4**) has been achieved, proceeding in 19% overall yield. The key step was a dimerisation–cyclocondensation reaction, the design of which was guided by the insight that the target molecule possesses hidden symmetry. Related cyclocondensation reactions were also successfully employed in this work for the production of structural analogues of **4**. These results should facilitate the medicinal development of **4** towards a possible future treatment for stroke.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561569.

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(11) Also available in two synthetic steps from 2-nitro-4-methoxybenzoic acid, see Supporting Information.
(12) Various intermediates in related cyclocondensation processes have been proposed: (a) Alexandre, F.-R.; Berecibar, A.; Besson, T. *Tetrahedron Lett.* **2002**, *43*, 3911. (b) Mhaske, S. B.; Argade, N. P. *J. Org. Chem.* **2001**, *66*, 9038. (c) Mhaske, S. B.; Argade, N. P. *Tetrahedron* **2004**, *60*, 3417. (d) Wang, H.; Sim, M. M. *J. Nat. Prod.* **2001**, *64*, 1497.
(13) A microwave reaction vessel was charged with compound **6** (355 mg, 1.96 mmol) then cooled to –20 °C. Trimethyl orthoformate (110 µL, 1.01 mmol) was added, and the mixture was irradiated at 170 W (155 ± 4 °C) for 4 h. The mixture was cooled and concentrated under a stream of nitrogen. The residue was diluted with CH_2Cl_2 (25 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography using EtOAc–CH_2Cl_2 (1:6) as eluent to give compound **5** as a white solid (303 mg, 91%); mp 155–156 °C. IR (neat): ν_{max} = 3081, 2626, 2105, 1938, 1847, 1719, 1668, 1610, 1482 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.92 (s, 1 H, ArH), 7.72 (d, *J* = 9.0 Hz, 1 H, ArH), 7.70 (d, *J* = 3.0 Hz, 1 H, ArH), 7.67 (d, *J* = 2.9 Hz, 1 H, ArH), 7.38 (dd, *J* = 8.9, 3.0 Hz, 1 H, ArH), 7.29 (d, *J* = 8.6 Hz, 1 H, ArH), 7.20 (dd, *J* = 8.7, 2.9 Hz, 1 H, ArH), 3.92 (s, 6 H, OMe), 3.70 (s, 3 H, OMe). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 165.0, 161.4, 160.2, 159.0, 144.4, 142.6, 130.6, 130.2, 129.3, 129.2, 124.7, 123.2, 119.4, 116.8, 106.8, 55.6, 56.0, 52.7. ESI-HRMS (+ve): *m/z* calcd for $C_{18}H_{16}N_2O_5Na^+$ [MNa^+]: 363.0951; found: 363.0948.
(14) For spectral data of similar compounds, see: (a) Yoo, C. L.; Fettinger, J. C.; Kurth, M. J. *J. Org. Chem.* **2006**, *70*, 6941. (b) Khurana, J. M.; Kukreja, G. *J. Heterocycl. Chem.* **2003**, *40*, 677.
(15) A solution of compound **5** (57.7 mg, 0.170 mmol) and $LiBH_4$ (5.0 mg, 0.23 mmol) in anhydrous THF (1 mL) was heated at reflux for 2 h, then quenched by the addition of sat. aq NH_4Cl solution at 0 °C. The mixture was diluted with CH_2Cl_2 (20 mL) then washed with H_2O (2 × 20 mL) and brine (2 × 20 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (1:6 → 1:2 EtOAc–CH_2Cl_2) to give compound **4** as a white solid (12.7 mg, 24%); mp 199–202 °C. IR (neat): ν_{max} = 3163, 3058, 2909, 2837, 2685, 2111, 2081, 1684, 1611, 1493 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 (s, 1 H, ArH), 7.71–7.69 (m, 2 H, ArH), 7.41 (dd, *J* = 8.9, 2.9 Hz, 1 H, ArH), 7.18 (d, *J* = 2.8 Hz, 1 H, ArH), 7.16 (d, *J* = 8.6 Hz, 1 H, ArH), 6.99 (dd, *J* = 8.6, 2.9 Hz, 1 H, ArH), 4.45 (d, *J* = 12.6 Hz, 1 H, C*H*H), 4.39 (d, *J* = 12.6 Hz, 1 H, CH*H*), 3.93 (s, 3 H, OMe), 3.88 (s, 3 H, OMe). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 162.0, 160.8, 159.3, 144.6, 142.8, 139.7, 129.3, 128.9, 128.6, 125.3, 122.9, 115.6, 115.0, 106.7, 61.7, 56.1, 55.8. ESI-HRMS (+ve): *m/z* calcd for $C_{17}H_{16}N_2O_4Na^+$ [MNa^+]: 335.1002; found: 335.0948.
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