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Synthesis of the antitumoural agent batracylin and related isoindolo[1,2-*b*]quinazolin-12(10*H*)-ones

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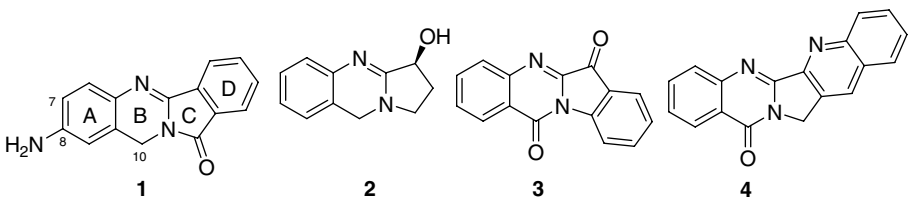
Abstract—The synthesis of batracylin and related isoindolo[1,2-*b*]quinazolin-12-ones from easily accessible *o*-acylanilines is reported. The preparation of these tetracyclic compounds through a Mitsunobu reaction followed by spontaneous cyclodehydration shows the ability of this methodology to afford good yields of a wide variety of diversely 7, 8, 9, 10-substituted isoindoloquinazolinones in two steps.

Batracylin[1] (8-aminoisoindolo[1,2-*b*]quinazolin-12(10*H*)-one) displays antitumour activity in vivo against murine leukaemia P-388 and colon adenocarcinoma 38 cell lines that are resistant to adriamycin, cisplatin and methotrexate. It acts as a topoisomerase II inhibitor and induces unscheduled DNA synthesis. Nevertheless, the low water solubility of batracylin, which limited its oral administration, and its high toxicity, which reduced the maximal dose possible to use in vivo, are the causes that it has never been approved for further clinical trials in human beings. Structurally, it is a quinazoline fused with an isoindolone. Similar structures are present in many natural products of great pharmacological interest,[2] including vasicine and tryptanthrin, which have anti-inflammatory activity, and luotonin A, which has antitumoural activity (Scheme 1). This structure is also present in synthetic products with activity against asthma and Alzheimer's disease.[3]

All current methods for the synthesis of batracylin (**1**) involve the establishment of a phthalimidylmethyl group on a 1,4-dinitrogenated benzene ring,[1] followed by an intramolecular cyclodehydration reaction between what is now the 2-amino unit and a phthalimide carbonyl group.[4] Kabbe,[5] for example, proposed the condensation of 2,5-diaminobenzylamine with phthalic anhydride (Scheme 2), which involved heating the substrates in dioxane for 4 h under mild conditions and gave a yield of 56%. However, 2,5-diaminobenzylamine is not commercially available, is difficult to prepare, and is very unstable. LaVoie's group[6] subjected 5-nitro-2-aminobenzylamine to the same conditions, reducing the resulting 8-nitroisoindolo[1,2-*b*]quinazolin-12-one with hydrogen in the presence of the catalytic amounts of Pd in glacial acetic acid. A third approach, initially proposed by Rosevear and Wilshire[7] and recently improved by Dzierzbicka's group,[1a] uses the Czerniak–Einhorn



1 **2** **3** **4**

Scheme 1. Batracylin (**1**) and related natural products: (−)-vasicine (**2**), tryptanthrin (**3**) and luotonin A (**4**).

Keywords: Batracylin; Quinazolines; Mitsunobu reaction; Quinazolinones.
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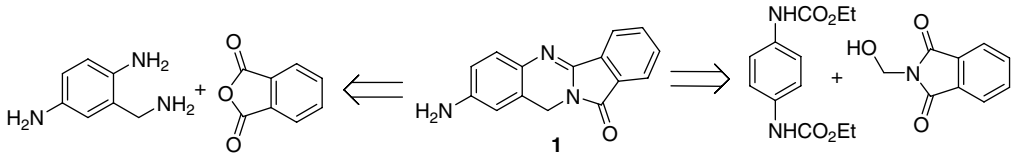
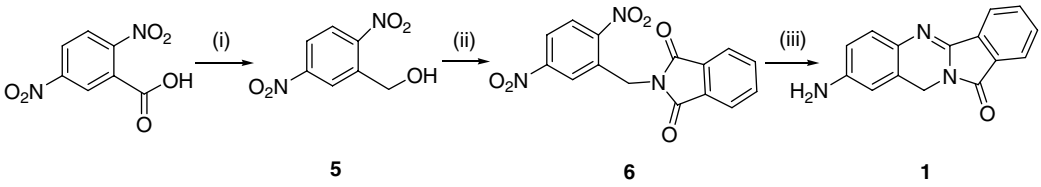
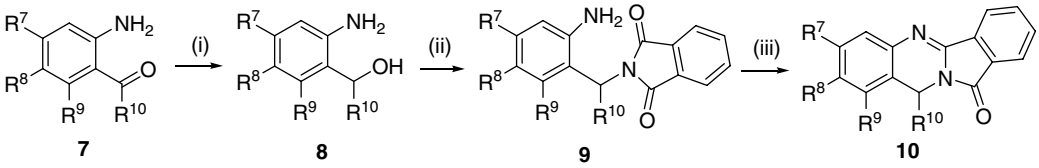


Scheme 2. The Kabbe and Dzierzbicka approaches to batracylin.



Scheme 3. Reagents and conditions: (i) (1) $SOCl_2$, reflux; (2) $NaBH_4$, H_2O, 0 °C, 54%; (ii) Phthalimide, DEAD, PPh_3, THF, rt, 78% and (iii) HCO_2NH_4, Pd/C, EtOH, reflux, 79%.



Scheme 4. Reagents and conditions: (i) $NaBH_4$, EtOH, reflux; (ii) Phthalimide, DEAD or DIAD, PPh_3, THF, rt and (iii) THF, rt.

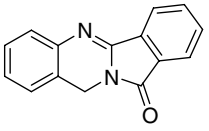
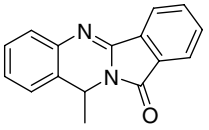
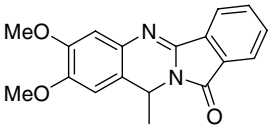
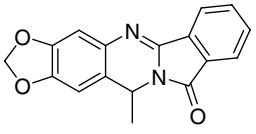
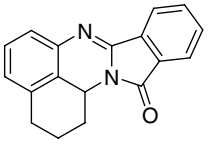
reaction: in the Dzierzbicka version, the reaction of a 1,4-phenylenedicarbamate (or *N*,*N*-diacetyl-1,4-phenylenediamine) with *N*-(hydroxymethyl)phthalimide in the presence of sulfuric acid (Scheme 2), followed by the removal of the protecting groups and treatment with ammonia, affords a 39% yield starting from 1,4-phenylenediamine.

The above methods have allowed the synthesis of batracylin analogues with modifications at rings A and D.[1,7] However, their use for the introduction of diverse substituents on the quinazoline core, especially at position 10, is hampered by the unavailability and difficult preparation of the required starting materials.

In view of the above, and as part of a broader search for new structures with potential pharmacological activity, we have developed a synthetic approach to batracylin that seems capable of providing access to a wide range of analogues with different quinazoline substituents. The new method is simple, rapid and efficient, and requires only readily available starting materials. It is based on the use of a Mitsunobu reaction[8] as the key step in the construction of the 2-phthalimidylmethylaniline required for cyclodehydration.

To obtain batracylin itself, one can start from commercial 2,5-dinitrobenzoic acid (Scheme 3). One-pot reduction of this substrate by conversion to the acid chloride, followed by a treatment with sodium borohydride in water, gave 54% yield of alcohol **5**; treatment of **5** with phthalimide, DEAD and triphenylphosphine gave the phthalimido derivative **6** in a

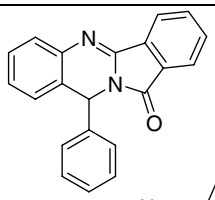
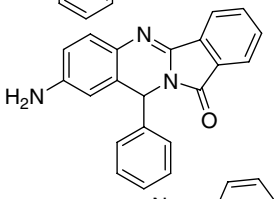
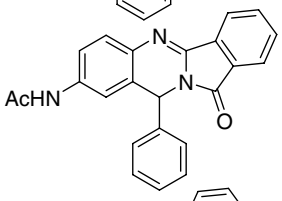
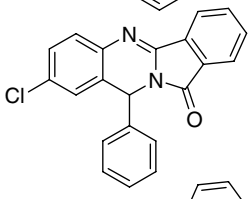
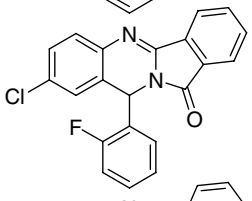
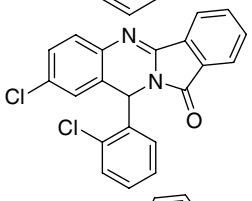
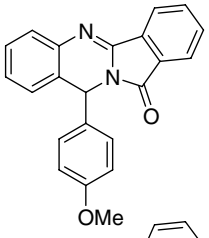
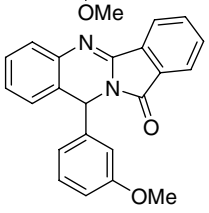
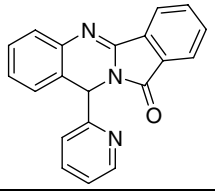
Table 1. 10-Alkylisoindoloquinazolinones **10a–e,** prepared by the Mitsunobu coupling of phthalimide with 2-aminobenzyl alcohols **8a–e**

Entry	Quinazolinone		Yield[a] (%)
1		**10a**	40[b]
2		**10b**	52
3		**10c**	58
4		**10d**	53
5		**10e**	19

[a] After chromatographic purification.

[b] From commercially available 2-aminobenzyl alcohol: (1) Phthalimide, DEAD, PPh_3, THF, rt; (2) $BF_3{\cdot}OEt_2$, THF, reflux.

Table 2. 10-Arylisoindoloquinazolinones **10f–n**, prepared by the Mitsunobu coupling of phthalimide with 2-aminobenzyl alcohols **8f–n**

Entry	Quinazolinone		Yield[a] (%)
1		**10f**	86
2		**10g**	27
3		**10h**	48[b]
4		**10i**	64
5		**10j**	47
6		**10k**	51
7		**10l**	37
8		**10m**	88
9		**10n**	44

[a] After chromatographic purification.
[b] After acetylation of the crude cycloaddition product **10g**: AcCl, DMAP, CH_2Cl_2, rt.

78% yield; and the reduction of **6** with ammonium formate and catalytic amounts of Pd/C gave a diamine that underwent spontaneous cyclodehydration, affording batracylin in a 79% yield (33% for the three steps).

For batracylin analogues with substituent-modified quinazoline moieties, it is more convenient for benzyl alcohol **8** required for the Mitsunobu reaction to be obtained from readily available 2-acyl aniline **7** (Scheme 4). Of the 10-alkyl analogues listed in Table 1, which were obtained in this way via alcohols **8**, only **10a** has been synthesized previously.[6] Compound **10a** was also the only analogue for which the cyclodehydration step did not occur spontaneously, but required heating of phthalimido intermediate **9a** following the treatment with $BF_3{\cdot}OEt_2$. The low yield of pentacyclic compound **10e**, obtained starting from 8-aminotetralone,[9] is attributable to the instability of aminotetralol **8e** under the Mitsunobu conditions.

Table 2 lists the results of using the new method to prepare 10-arylisoindoloquinazolinones (**10f–n**).[10] Yields ranged from 27% for **10g** to 88% for **10m**. The low yield of **10g** is attributable mainly to losses during chromatographic purification; *N*-acetylation of the crude product of the Mitsunobu reaction raised the yield to 48% (entry 3). The halogenated compounds **10i–k** were obtained in the yields of 47–64%, while the yields obtained with electron-rich 10-(methoxyphenyl) substituents[11] depended heavily on the position of the methoxy group (*p*, 37%; *m*, 88%). Entry 9 shows that the new method also accommodates 10-heteroaryl substituents.[12]

To sum up, a representative set of substituted batracylin analogues have been synthesized from commercially available or easily prepared aminoacetophenones and aminobenzophenones by reduction to the corresponding benzylic alcohol followed by cyclocondensation with phthalimide under Mitsunobu conditions.

Acknowledgements

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Supplementary data

IR, ^{1}H NMR and ^{13}C NMR/DEPT, MS (CI and/or EI) and HRMS (CI and/or EI) spectra of compounds **1**, **5**, **6**, **8b–n** and **10a–n**, and the procedures for their preparation. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.11.168.

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10. *Typical procedure for the synthesis of isoindoloquinazolinones*: To a deoxygenated solution of alcohol **8f** (0.091 g, 0.46 mmol), phthalimide (0.083 g, 0.55 mmol) and PPh_3 (0.146 g, 0.55 mmol) in dry THF (15 mL), DEAD (0.250 mL, 0.55 mmol) was added dropwise and the mixture was stirred under argon at room temperature for 2 days. The solvent was evaporated and the residue was purified by flash chromatography on silica gel (8:2, hexanes–EtOAc), providing 10-phenylisoindolo[1,2-*b*]quinazolin-12(10*H*)-one (**10f**) as a white solid (0.123 g, 86%), mp 206–208 °C. IR (KBr): 1732, 1648 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.08 (d, $J = 7.6$ Hz, 1H, ArH), 7.79 (d, $J = 7.4$ Hz, 1H, ArH), 7.69 (t, $J = 7.4$ Hz, 1H, ArH), 7.62 (d, $J = 7.5$ Hz, 1H, ArH), 7.56 (d, $J = 8.0$ Hz, 1H, ArH), 7.37–7.12 (m, 7H, ArH), 7.08 (d, $J = 7.6$ Hz, 1H, ArH), 6.32 (s, 1H, CH). ^{13}C NMR/DEPT ($CDCl_3$, 75 MHz): δ 166.0 (CO), 148.9 (C), 142.2 (C), 139.8 (C), 134.6 (C), 133.1 (CH), 132.1 (CH), 130.4 (C), 128.81 (CH), 128.77 (2 × CH), 128.1 (CH), 128.0 (CH), 127.9 (2 × CH), 127.3 (2 × CH), 126.0 (C), 123.4 (CH), 122.2 (CH), 55.7 (CH). MS (CI), *m*/*z* (%): 339 ($[M+C_2H_5]^+$, 23), 311 $[M+H]^+$, 100), 310 (M^+, 39), 233 ($[M-Ph]^+$, 17). MS (EI), *m*/*z* (%): 310 (M^+, 14), 233 ($[M-Ph]^+$, 100). HR-MS (EI): Calcd for $C_{21}H_{14}N_2O$, 310.1106. Found, 310.1100.
11. For the starting compounds, see: Adger, B. M.; Rees, C. W.; Storr, R. C. *J. Chem. Soc., Perkin Trans. 1* **1975**, 45, [for (2-aminophenyl)(4-methoxyphenyl)methanone]; Hasegawa, H.; Muraoka, M.; Ohmori, M.; Matsui, K.; Kojima, A. *Bioorg. Med. Chem.* **2005**, *13*, 3721, for (2-aminophenyl)(3-methoxyphenyl)methanone.
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