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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 4707–4710

Synthesis of aza analogues of the anticancer agent batracylin

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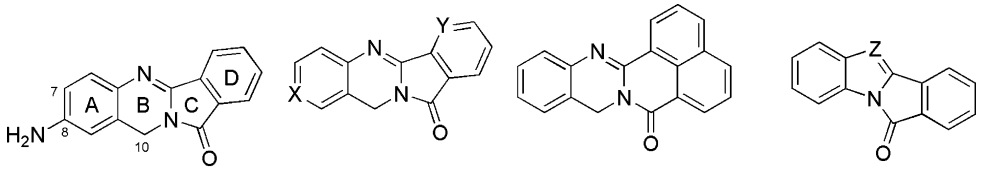
Received 22 March 2007; revised 18 April 2007; accepted 2 May 2007
Available online 10 May 2007

Dedicated to the memory of Dr. M. V. Laksmikantham (deceased on January 20th, 2006)

Abstract—Three series of pyrido-fused pyrimido[2,1-*a*]isoindol-7-ones were prepared from readily available (aminopyridinyl)(aryl)-methanones by reduction followed by a Mitsunobu reaction with phthalimide and acid-catalysed cyclodehydration. This approach provides a wide variety of aza analogues of the antitumour agent batracylin.

Batracylin (**1**),[1] a topoisomerase II inhibitor,[2] displays antitumoural activity in vivo against murine colon adenocarcinoma 38 and leukaemia P-388 strains that are resistant to adriamycin, cisplatin and methotrexate.[3,4] However, it also induces unscheduled DNA synthesis in nonreplicating cells;[5] its poor solubility in water prevents its oral administration; and its high toxicity limits the dose that can be administered in vivo. Accordingly, numerous studies have sought analogues with more favourable characteristics. Structural modifications effected in the hope of retaining ability to inhibit topoisomerase II while reducing toxicity and increasing water solubility include the introduction of diverse substituents on the isoindoloquinazolinone core (Cl, Br, NO_2, Me, CO_2Me, OMe, acids, dipeptides and sugar moieties);[5,6] the inclusion of a nitrogen atom in ring A[5] or ring D (**2**, **3**);[6c] an increase in the size of the polycyclic system (**4**);[6c] and contraction of the ring B from six to a five-membered to obtain benzimidazole (**5**)[5] or indole (**6**)[7] analogues (Fig. 1).

We recently reported the synthesis of batracylin and 14 related isoindolo[1,2-*b*]quinazolin-12(10*H*)-ones from easily prepared *o*-aminobenzyl alcohols and phthalimide by a cascade Mitsunobu coupling/cyclodehydration process. This approach is suitable for the preparation of analogues with a variety of substituents at positions 7, 8, 9 and, of particular interest, 10, a position that is difficult to functionalize by previous approaches.[8] We now report the extension of this methodology to the synthesis of azabatracylins **7**–**9**, in which aniline ring A has been replaced by a pyrido ring (Fig. 2). The only batracylin derivative of this kind to have been prepared previously, compound **2**, inhibited topoisomerase II (thought less potently than batracylin) without modifying DNA in nonproliferating cells.[5]



1 **2**, X = N, Y = CH; **3**, X = CH, Y = N **4** **5**, Z = N; **6**, Z = CH

Figure 1. Batracylin (**1**) and various reported analogues.

Keywords: Batracylin; Quinazolines; Pyridines; Mitsunobu reaction; Quinazolinones.
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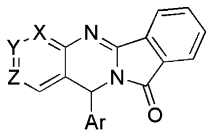
0040-4039/$ - see front matter
doi:10.1016/j.tetlet.2007.05.025

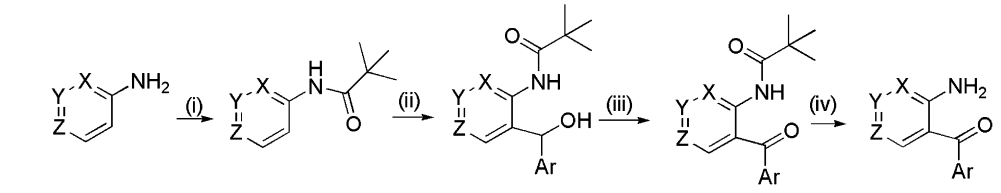


7 (X = N, Y = Z = CH)
8 (Y = N, X = Z = CH)
9 (Z = N, X = Y = CH)

Figure 2. Aza analogues of batracylin synthesized in this work.

To obtain the target derivatives, three series of (aminopyridinyl)(aryl)methanones were prepared from 2-, 3- and 4-aminopyridines (**10**–**12**) by a method described by Quéguiner. The key step, the regioselective metallation of the corresponding pivalamides, is followed by reaction with commercially available aromatic aldehydes (Scheme 1).[9]

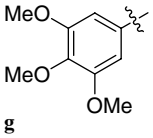
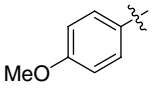
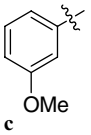
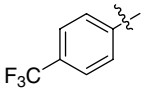
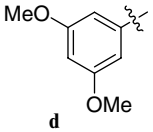
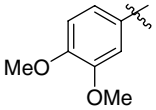
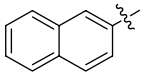
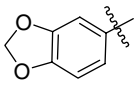
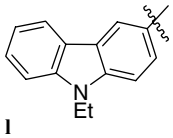
Pivalamides **13**–**15** were prepared by acylation of the corresponding aminopyridines **10**–**12** with pivaloyl chlo-



10 (X = N, Y = Z = CH) **13** **16** **19** **22**
11 (Y = N, X = Z = CH) **14** **17** **20** **23**
12 (Z = N, X = Y = CH) **15** **18** **21** **24**

Scheme 1. Reagents and conditions: (i) Me_3CCOCl, Et_3N, THF/Et_2O, 0 °C; (ii) (1) *n*-BuLi, TMEDA, Et_2O, −70 °C to −20 °C; (2) ArCHO (**a-l**), THF, −70 °C to rt; (iii) MnO_2, CH_2Cl_2, rt; (iv) HCl 3 M, 95 °C.

Table 1. (Aminopyridinyl)(aryl)methanones **22**–**24**, prepared in four steps from 2-, 3- and 4-aminopyridines (**10**–**12**) and ArCHO (**a-l**),[10] as shown in Scheme 1

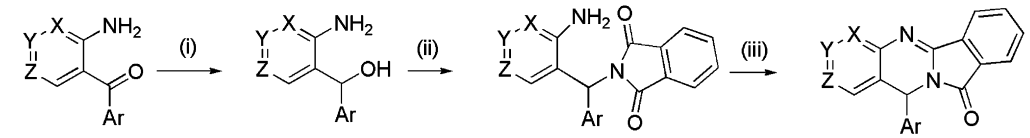
Entry	Ar	**22** (%)	**23** (%)	**24** (%)	Entry	Ar	**22** (%)	**23** (%)	**24** (%)
1	 **a**	60[a]	35	54	7	 **g**	42	—[b]	56
2	 **b**	57	45	56	8	 **h**	44	28	28
3	 **c**	43	63	23	9	 **i**	49	29	39
4	 **d**	48	55	36	10	 **j**	58	8	31
5	 **e**	51	—[b]	41	11	 **k**	50	33	49
6	 **f**	42	44	48	12	 **l**	55	13	48

[a] (i) Me_3CCOCl, Et_3N, THF/Et_2O, 0 °C; (ii) (1) *n*-BuLi, TMEDA, Et_2O, −70 °C to −20 °C; (2) PhCN, THF, −70 °C to rt; (iii) HCl 3 M, 95 °C.
[b] Not prepared.

ride. Following regioselective metallation with *n*-BuLi and TMEDA, reaction with aromatic aldehydes **a-l** afforded alcohols **16**–**18**.[10] Since these compounds were unstable under acidic deprotection conditions and were very insoluble and difficult to purify, they were oxidized to ketones **19**–**21** with activated manganese dioxide at room temperature. Finally, removal of the pivaloyl protecting group by hydrolysis with aqueous HCl afforded (aminopyridinyl)(aryl)methanones **22**–**24**, mostly in overall yields of 40–60% (Table 1). The aryls borne by these compounds include phenyl, phenyls with electron-donating substituents (alkoxyl, alkyl), phenyl with an electron-withdrawing substituent (trifluoromethyl), heteroaryls (furyl, 9-ethyl-3-carbazolyl) and bicyclic aryls (2-naphthyl).

Compounds **22**–**24** were reduced with sodium borohydride to obtain alcohols **25**–**27**. These were condensed with phthalimide under Mitsunobu conditions to obtain intermediates **28**–**30**,[11] which then underwent cyclodehydration (most required acid catalysis and heating)[12] (Scheme 2 and Table 2).

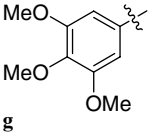
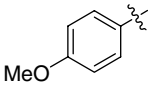
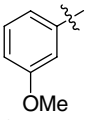
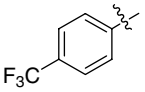
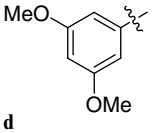
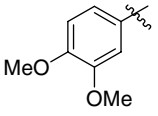
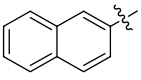
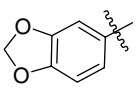
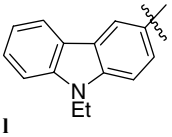
The pyrido[2′,3′:4,5]pyrimido[2,1-*a*]isoindol-7(5*H*)-ones **7a-l** were obtained with overall yields ranging from 42% to 70%, except in the cases of the toluyl and furyl



22 (X = N, Y = Z = CH) **25** **28** **7**
23 (Y = N, X = Z = CH) **26** **29** **8**
24 (Z = N, X = Y = CH) **27** **30** **9**

Scheme 2. Reagents and conditions: (i) $NaBH_4$, EtOH, reflux; (ii) phthalimide, DEAD or DIAD, PPh_3, THF, rt; (iii) PTSA, PhMe, reflux, Dean–Stark.

Table 2. Overall yields (%) of 5-arylpyrido[*x*′,*y*′:4,5]pyrimido[2,1-*a*]isoindol-7(5*H*)-ones **7**–**9**, prepared in three steps from (aminopyridinyl)(aryl)methanones **22**–**24** as shown in Scheme 2

Entry	Ar	**7** (%)	**8** (%)	**9** (%)	Entry	Ar	**7** (%)	**8** (%)	**9** (%)
1	 **a**	70	25	26	7	 **g**	42	—[a]	12
2	 **b**	49	24	34	8	 **h**	27	26	30
3	 **c**	—[a]	29	41	9	 **i**	53	—[c]	27
4	 **d**	57	10	10	10	 **j**	11	14[b]	—[c]
5	 **e**	52	—[a]	14	11	 **k**	42	—[d]	21
6	 **f**	40	35[b]	23	12	 **l**	46	—[d]	27

[a] Not prepared.
[b] Cyclodehydration took place under the Mitsunobu conditions.
[c] Decomposition.
[d] Inseparable mixture with $OPPh_3$.

derivatives (27% and 11%, respectively). The poorer yields of the [3′,4′:4,5] and [4′,3′:4,5] series (**8** and **9**) are attributable mainly to two factors: firstly, the lower reactivity of alcohols **26** and **27** under the Mitsunobu conditions, even when prolonged reaction times and 2 equiv of phthalimide, PPh_3 and DEAD or DIAD were employed; and secondly, the difficulty in purifying intermediates **29** and **30** and the final pyridopyrimidoisoindolones **8** and **9**, which were very hard to separate from $OPPh_3$. Interestingly, when phthalimide was condensed with (3-aminopyridin-4-yl)(benzo[*d*][1,3]dioxol-5-yl)methanol (**26f**) and (3-aminopyridin-4-yl)(furan-2-yl)methanol (**26j**), the cyclized products **8f** and **8j** were obtained directly, without any need for acid catalysis or heating. This is attributable to the amino group of **29** being more nucleophilic than those of **28** and **30**, and also to the nature of the aryl groups of **29f** and **29j**, because the other members of series **29** only cyclised in trace amounts without catalysis and heat.

To sum up, a diverse set of aryl-substituted aza analogues of batracylin have been synthesised from easily prepared (aminopyridinyl)(aryl)methanones by reduction to the corresponding alcohols followed by condensation with phthalimide under Mitsunobu conditions and final acid catalysed cyclodehydration.

Acknowledgements

Support of this work by the Spanish Ministry of Education and Science (Project CTQ2005-02338, in collaboration with ERDF), by the Xunta de Galicia (Project PGIDITO6PXIC209067PN) and by Johnson & Johnson Pharmaceutical Research and Development is gratefully acknowledged. C.M. also thanks the University of Santiago for a pre-doctoral grant. We also thank M. F. Martínez-Esperón for her collaboration in the analytical characterization of compounds.

Supplementary data

General experimental procedures and characterization data—mp, ^{1}H NMR and ^{13}C NMR/DEPT, MS (CI and/or EI), HRMS (CI and/or EI) and IR—of compounds **7**–**30**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.05.025.

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11. *Typical procedure for the Mitsunobu reaction*: DIAD (0.260 mL, 1.26 mmol) was added dropwise to a deoxygenated solution of alcohol **25a** (0.207 g, 1.04 mmol), phthalimide (0.185 g, 1.23 mmol) and PPh_3 (0.330 g, 1.25 mmol) in dry THF (14 mL), and the mixture was stirred under argon at room temperature for 23 h. The solvent was evaporated and the residue was purified by flash chromatography on silica gel (3:7 hexanes/EtOAc), providing 2-[(2-aminopyridin-3-yl)(phenyl)methyl]isoindoline-1,3-dione (**28a**) as a white amorphous solid (0.254 g, 74%). ^{1}H NMR ($CDCl_3$, 250 MHz): δ 8.04 (dd, $J = 4.9$ and 1.7 Hz, 1H, ArH), 7.88–7.80 (m, 2H, NPht), 7.77–7.68 (m, 2H, NPht), 7.51 (dd, $J = 7.6$ and 1.4 Hz, 1H, ArH), 7.41–7.27 (m, 5H, ArH), 6.66 (dd, $J = 7.6$ and 5.0 Hz, 1H, ArH), 6.62 (s, 1H, CH), 4.81 (br s, 2H, NH_2). ^{13}C NMR/DEPT ($CDCl_3$, 62.5 MHz): δ 168.1 (2 × CO), 156.4 (2 × C), 147.9 (CH), 139.0 (CH), 135.9 (2 × C), 134.3 (2 × CH), 131.4 (CH), 128.5 (2 × CH), 127.83 (CH), 127.79 (2 × CH), 123.5 (CH), 116.5 (C), 113.9 (CH), 53.0 (CH).
12. *Typical procedure for the acid catalysed cyclodehydration reaction*: A suspension of **28a** (0.254 g, 0.77 mmol) and PTSA (0.163 g, 0.84 mmol) in PhMe (10 mL) was refluxed under argon for 25 h using a Dean–Stark trap. The solvent was evaporated, a solution of the residue in CH_2Cl_2 was washed with 1 N NaOH, dried with Na_2SO_4 and filtered, and the solvent was removed under reduced pressure, providing 5-phenylpyrido[2′,3′:4,5]pyrimido[2,1-*a*]isoindol-7(5*H*)-one (**7a**) as a white solid (0.234 g, 98%), mp: 218–220 °C. IR (KBr): 1729, 1641 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.51 (dd, $J = 4.7$ and 1.8 Hz, 1H, ArH), 8.21 (td, $J = 7.3$ and 1.0 Hz, 1H, ArH), 7.82–7.63 (m, 3H, ArH), 7.42 (dd, $J = 7.6$ and 1.8 Hz, 1H, ArH), 7.35–7.21 (m, 5H, ArH), 7.09 (dd, $J = 7.6$ and 4.8 Hz, 1H, ArH), 6.35 (s, 1H, CH). ^{13}C NMR/DEPT ($CDCl_3$, 75 MHz): δ 166.3 (CO), 152.8 (C), 152.3 (C), 149.5 (CH), 141.4 (C), 136.4 (CH), 134.3 (C), 133.5 (CH), 132.8 (CH), 130.0 (C), 128.9 (2 × CH), 128.5 (CH), 127.2 (2 × CH), 123.4 (CH), 123.2 (CH), 122.4 (CH), 121.4 (C), 55.8 (CH). MS (CI), *m*/*z* (%): 340 ($[M+C_2H_5]^+$, 24), 312 ($[M+H]^+$, 100), 311 (M^+, 5), 234 ($[M-Ph]^+$, 9). MS (EI), *m*/*z* (%): 311 (M^+, 62), 234 ($[M-Ph]^+$, 100). HR-MS (EI): calcd. for $C_{20}H_{13}N_3O$: 311.1059; found: 311.1058.