Pergamon

Bioorganic & Medicinal Chemistry Letters 8 (1998) 2881–2884

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

DIASTEREOSELECTIVE SYNTHESIS OF OCTAHYDRO-14H-BENZO[G]QUINOLINO-[2,3-A]QUINOLIDINES. IMPROVED CYTOTOXIC ACTIVITY AGAINST HUMAN BRAIN TUMOR CELL LINES AS A RESULT OF THE INCREASED RIGIDITY OF THE MOLECULAR BACKBONE.

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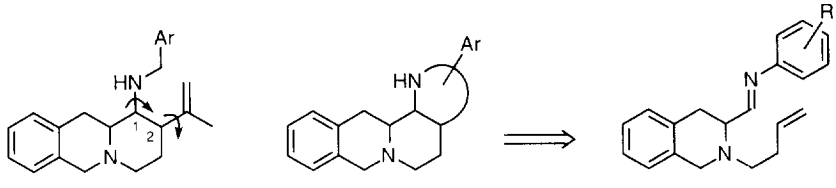
Received 16 June 1998; accepted 4 September 1998

Abstract: *Cis*-Octahydro-14H-benzo[*g*]quinolino[2,3-*a*]quinolidines **6** were obtained in 6 steps from L-phenylalanine. The key step utilizes a diastereoselective intramolecular $EtAlCl_2$-catalyzed hetero-Diels-Alder reaction. Compounds **6a-f** were tested *in vitro* against human medulloblastoma D283 Med and glioblastoma A-172 and T98G cell lines and showed improved cytotoxicity compared to the corresponding, less rigid pyrido[1,2-*b*]isoquinolines **1**.

In contrast to the successful chemotherapy of leukemia, melanoma and other human tumors using taxol.[1] *cis*-platin,[2] and camptothecin,[3,4] treatment of brain tumors is much less promising.[5] We have recently reported that 1-amino-substituted hexahydro-2H-pyrido[1,2-*b*]isoquinolines **1** show interesting *in vitro* cytotoxicity against human medulloblastoma (D283 Med) and glioblastoma (A-172 and T98G) cell lines.[6] However, the activities were still not sufficient. We surmised that a restriction of the rotational freedom of the C1–N and C2–C12 bonds should lead to a derivative **2** with increased lipophilicity and thus enhanced cytotoxicity. In



1 **2** **3**

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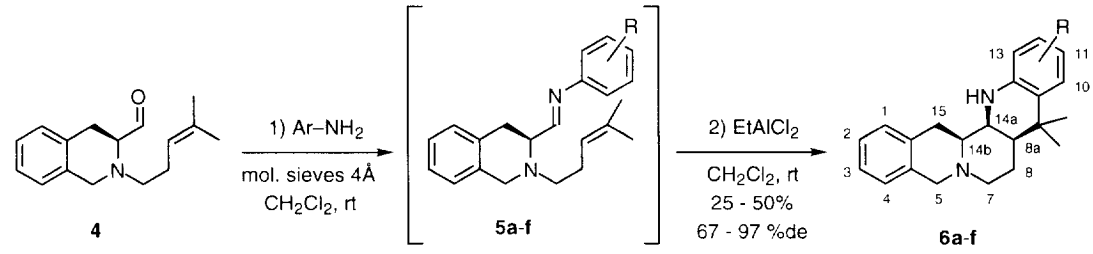
0960-894X/98/$ - see front matter
PII: S0960-894X(98)00506-X

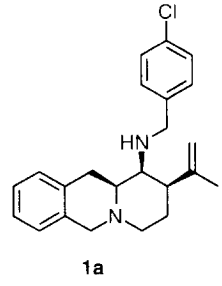
order to achieve this goal we planned to use a hetero-Diels-Alder methodology previously established in our laboratory.[7,8] Following this approach, Lewis acid-catalyzed cyclization of *N*-arylimines **3** should give the pentacyclic products **2**. The results concerning the synthesis and biological activity are reported in this manuscript.

Scheme 1



As described earlier (*S*)-*N*-(4-methyl-3-pentenyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxaldehyde **4** was prepared in 4 steps from (*L*)-phenylalanine (Scheme 1).[9] Treatment of **4** with various arylamines in the presence of molecular sieves (4Å) gave the corresponding *N*-arylimines **5a-f**, which were immediately cyclized in the presence of $EtAlCl_2$ to the octahydro-14H-benzo[*g*]quinolino[2,3-*a*]quinolidines **6a-f**. The formal hetero-Diels-Alder reaction of **5a-f** proceeded with high diastereoselectivity in favor of the *all-cis* configurated product (Table 1)[10,11] although the yields were only moderate because of loss of the product during column chromatography.[12,13] The *all-cis* configuration of the major product **6** was established by an X-ray crystal structure determination of compound **6e** (Figure 1).[14]

Scheme 2



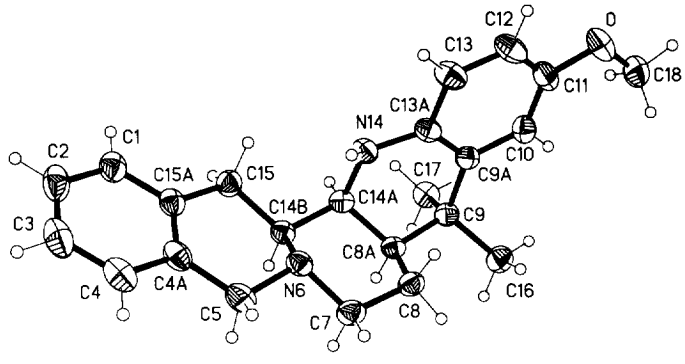


Figure 1 X-ray crystal structure of compound **6e**. Bond lengths [Å] and angles [°] of the intramolecular hydrogen bond: N(14)–H 0.89(3), N(14)H–N(6) 2.45(3), N(14)–H–N(6) 107(2)

In vitro cytotoxicity studies of compounds **6a-f** against D283 Med, A-172 and T98G cell lines[15] revealed an overall increase of the activity as compared to the hexahydro-2H-pyrido[1,2-*b*]isoquinolines (e.g. **1a**).[6] Surprisingly the substitution pattern of the aryl moiety had only a minor influence on the activity, although the 11-chloro-substituted derivative **6b** displayed the lowest LC_{50} values within the series. A similar tendency was found previously for the pyrido[1,2-*b*]isoquinolines **1**.

In conclusion, incorporation of the amino-substituent at C-1 of pyrido[1,2-*b*]isoquinolines **1** into a rigid pentacyclic system like **6** resulted in an increased cytotoxic activity against human brain tumor cell lines.

Table 1 Yields, diastereoselectivities and LC_{50} values [μmol l^{-1}] of octahydro-14H-benzo[*g*]quinolino-[2,3-*a*]quinolidines **6a-f** against three human brain tumor cell lines[a,b,c]

compound	R	yield [%]	%de	LC_{50} values [μmol l^{-1}]		
				D283 Med	A-172	T98G
6a	H	25	93.2	22	45	14
6b	11-Cl	34	87.4	8	22	12
6c	11-CF_3	27	89.6	17	20	13
6d	11-Me	45	97.0	20	25	20
6e	11-MeO	50	67.4	25	42	35
6f	13-Me	47	91.0	20	31	21
1a	*p*-Cl	---	---	29	55	42

[a] LC_{50} values refer to concentrations where 50 % of the tumor cells survived. For details see ref. [15, 16].

[b] Hexahydro-2H-pyrido[1,2-*b*]isoquinoline **1a** was used for comparison. See also ref. [6].

[c] Diastereomeric excesses (%de) were determined by capillary GC of the crude products.

Acknowledgement

Generous financial support by the Deutsche Forschungsgemeinschaft (Gerhard-Hess-Preis for S.L.) and the Fonds der Chemischen Industrie is gratefully acknowledged.

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10. For details of the mechanism see: ref. [7].
11. Based on ^{1}H NMR spectra of the crude products the minor diastereomer has the *all-trans*-configuration. GC analysis of the reaction mixtures showed complete conversion of **5** to the *cis*-product **6** and the corresponding *trans*-diastereomer.
12. General experimental procedure for the hetero-Diels-Alder reaction: A solution of **4** (3.00 g, 14.0 mmol), arylamine (14.0 mmol) and molecular sieves (4Å; beads, 20 g) in CH_2Cl_2 (25 ml) was stirred for 12 h at rt. After removal of the molecular sieves by filtration via Celite, the filtrate was cooled to -78°C and $EtAlCl_2$ (18.0 ml, 18.0 mmol, 1 M solution in hexane) was added dropwise. The mixture was warmed to rt and stirring was continued for 2 d. Then the mixture was hydrolyzed with 2 M NH_4F (300 ml). The aqueous layer was extracted with CH_2Cl_2 (4 x 100 ml) and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude products were purified by flash chromatography on SiO_2 (hexanes/$CHCl_3$/NEt_3 15 : 3 : 1).
Characteristic spectroscopic data for **6e**: $[\alpha]_D^{22}$ 86.1° (c = 0.82 in CH_2Cl_2); ^{1}H NMR (400 MHz, C_6D_6) δ 7.09-7.01 (m, 3H), 6.98 (d, *J* = 2.5 Hz, 1H), 6.89 (d, *J* = 6.9 Hz, 1 H), 6.64 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.47 (d, *J* = 8.8 Hz, 1H), 3.69 (d, *J* = 15.3 Hz, 1H), 3.64 (s, 1H), 3.44 (s, 3H), 3.35-3.28 (m, 2H), 3.11 (d, *J* = 15.3 Hz, 1H), 2.77 (ddd, *J* = 12.8, 12.8, 3.9 Hz, 1H), 2.39 (dd, *J* = 17.2, 4.9 Hz, 1H), 2.12 (ddd, *J* = 10.8, 4.9, 2.0 Hz, 1H), 1.76 (ddd, *J* = 12.8, 12.8, 3.9 Hz, 1H), 1.40 (ddd, *J* = 12.8, 12.8, 3.9 Hz, 1H), 1.27 (m, 1H), 1.21 (s, 3H), 1.18 (s, 3H), 1.05 (ddd, *J* = 11.8, 3.4, 2.0 Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ 153.5, 136.8, 134.5, 134.3, 131.6, 128.6, 126.5, 126.0, 125.8, 118.3, 112.8, 112.6, 61.2, 58.2, 56.6, 55.3, 50.1, 45.0, 35.7, 33.6, 31.0, 26.2, 22.5; IR (film) 3419, 1647, 801, 744 cm^{-1}; MS (EI), *m/z* 348 (M, 39), 333 (14), 218 (4), 187 (6), 146 (100), 130 (8), 104 (12), 77 (3); HRMS (EI) calcd for $C_{23}H_{28}N_2O$ 348.2202, found 348.2200.
13. All new compounds gave satisfactory analytical and spectroscopic data.
14. X-ray crystal structure analysis of **6e**: colorless prism, 0.55 x 0.50 x 0.45 mm, *T* = 143 K, orthorhombic, space group $P2_12_12_1$, *a* = 7.8252(8), *b* = 10.4712(10), *c* = 23.309(4) Å, *V* = 1909.9(4) Å^3, ρ_{calc} = 1.212 Mg m^{-3}, *Z* = 4, λ = 0.71073 Å, 2519 independent reflections, 242 refined parameters, refinement method: full-matrix least squares on F^2, *R* = 0.0465, wR^2 = 0.0985, max. residual electron density 0.19 e Å^{-3}. Data were collected on a Stoe STADI-4 diffractometer. Programs used: SHELXS-86, SHELXL-93. Full details of the crystal structure (except structure factors) have been deposited at the Cambridge Crystallographic Data Centre, and can be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, England, [Fax: Int.+44 - 1223 - 336033; e-mail: deposit@chemcrys.cam.ac.uk] on quoting the reference number 101871.
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