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Design of new anticancer drugs. II. Easy arynic access to benzocyclobutacarbazoles, a new family of antitumor agents

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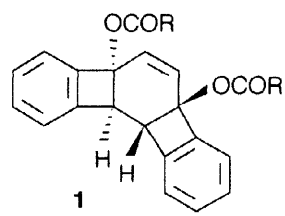
Abstract: Tetrahydrobenzocyclobutacarbazoles with antitumoral properties were obtained either by arynic condensation of aryl halides with 3-carbazolone enolates or arynic cyclisation of halogenated arylimine enolates of 2-biphenylenones in the presence of the complex base $NaNH_2$-*t*BuONa.

As mentioned in the preceding paper of the present journal[1], a program aiming at designing new anticancer families was undertaken in our laboratory. One of the conclusions which may be reached from the literature[2] is that numerous efficient anticancer agents are planar or partially planar π electron containing molecules with a reactive functional group allowing efficient interaction with DNA.

Several years ago one of us[3] found that compounds **1** and **2** synthesized during our studies on arynic reactions[4] strongly interacted with phagic double stranded DNA while they did not interact with single stranded DNA. The corresponding saturated substrates were found inactive.



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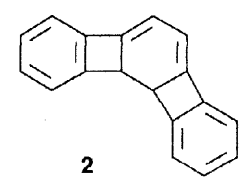

2

These results could be indicative of some intercalant properties and/or DNA interaction with the strained reactive unsaturations of the central ring. Furthermore, **1** and **2** presented no cytotoxicity against human lymphoblasts, a result confirmed during the present work which may be due to a lack of hydrophilicity as well as an incapacity to cross the cellular membrane. To avoid these drawbacks and to obtain new lead compounds we designed, as a first target, compounds **3** which associated tetrahydrocarbazoles, structure parts of

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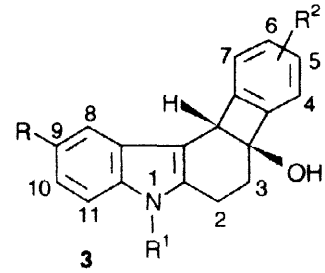
numerous anticancer agents, and reactive benzocyclobutenols.

	3a	3b	3c	3d	3e	3f	3g	3h	3i	3j
R	H	OMe	OH	OMe	OMe	OMe	OH	OMe	OMe	OMe
R^1	Me	Me	Me	Me	H	H	H	H	H	H
R^2	H	H	H	H	4.CHO	H	H	4.OMe	4.OH	6.OH



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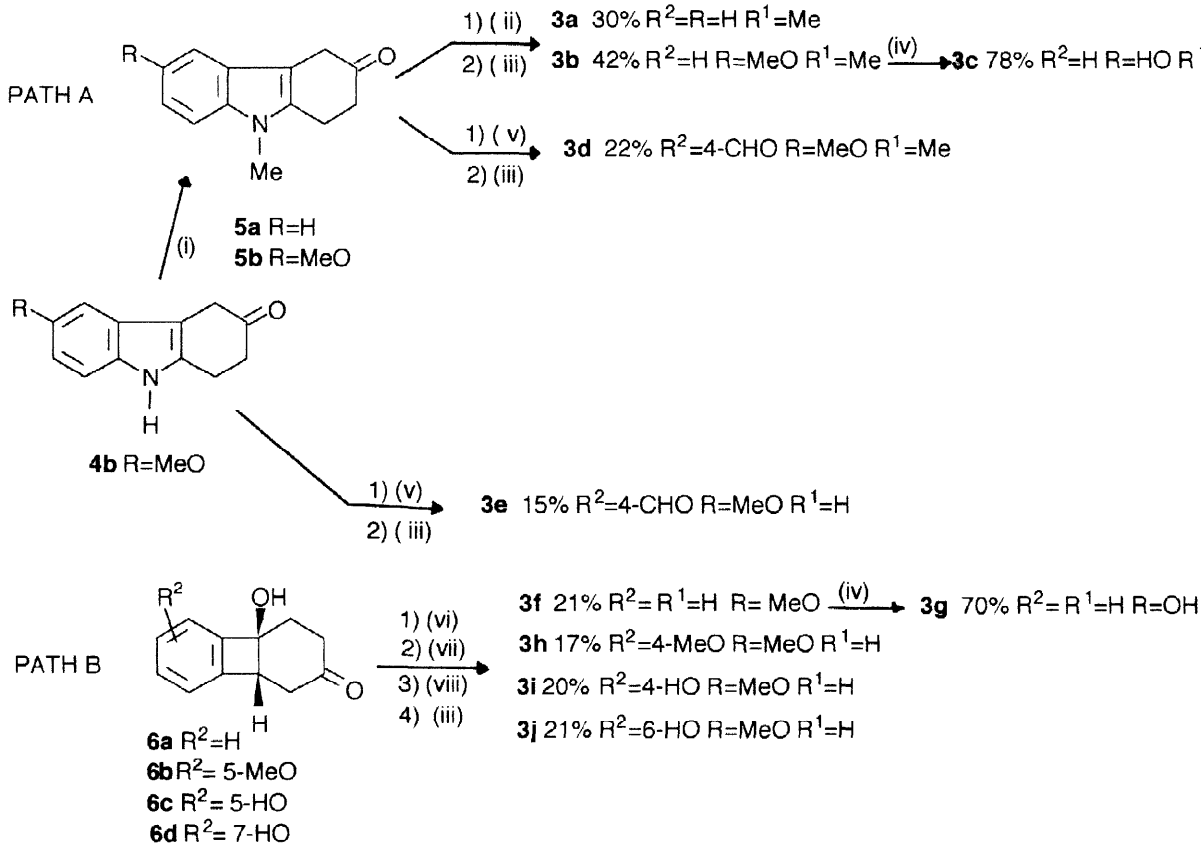
The exploratory experiments presently reported show that compounds **3** may be obtained by appropriate use of synthetic methods previously devised in our laboratory and that a number of them are, as expected, potential anticancer agents. The synthetic pathways used during this work are reported in Scheme 1.[5]

Scheme 1



Reagents and conditions: (i) NaH-DMF; Me_2SO_4, 0°C; (ii) C_6H_5Br, $NaNH_2$-*t*BuONa, THF, 0°C, 5 h; (iii) H_3O^+; (iv) $AlCl_3$-$PhCH_2SH$, 0°C, 6 h; (v) 2-BrC_6H_4CH(O)(O), $NaNH_2$-*t*BuONa, THF, 10°C, 2 h; (vi) DHP, H^+, RT; (vii) 3-Cl, 4-MeO-$C_6H_3NH_2$, C_6H_6, reflux, 72 h; (viii) $NaNH_2$-*t*BuONa, THF, 0°C then RT, 40 h.

Compounds **4** and **6** were easily obtained as previously described from inexpensive commercially available starting materials by arynic intramolecular[6a] and intermolecular[6b] cyclisations respectively.

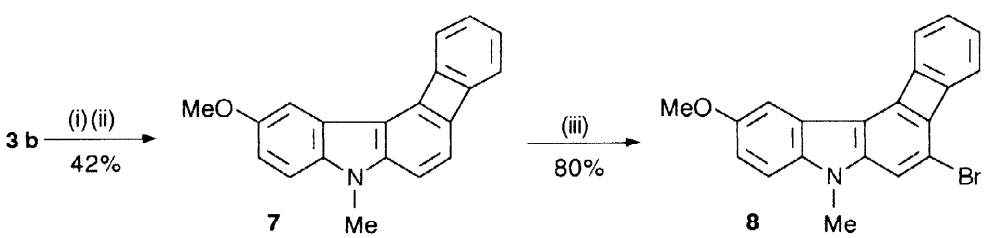
A priori both paths A and B could be used to obtain any product **3**. In fact we found that the two pathways were not equivalent and that yields depended dramatically upon the nature of the aromatic substituents, justifying the synthesis described in Scheme 1.

These results merit brief comments. Arynic cyclisations with **5a** led to **3** as only cyclo-adducts in acceptable yields . Interestingly this reaction also took place easily with **4b** although the indole nitrogen was unsubstituted.

On the other hand free benzocyclobutenols are very sensitive to bases[7] as well as to acids.[8] So protection of the hydroxyl group of **6** was necessary. The THP derivative was found to be sufficient, the reactivity of the keto group was such that the imine with 3-chloroanisidine was formed without an acidic catalyst. Interestingly in the presence of the complex base (CB)[9] $NaNH_2$-*t*BuONa ,the imine intermediates enolized only on the C1 position leading to the expected **3** as the only product.

3c and **3g** were obtained by demethylation with $PhCH_2SH$-$AlCl_3$ as previously described.[10] Compounds **3** thus obtained may be used as the starting material for further transformations. Thus for example with **3b** the saturated six membered ring may be easily aromatized as reported in Scheme 2.

Scheme 2



(i) $CuSO_4$, SiO_2, toluene reflux; (ii) DDQ (1 eq), benzene reflux; (iii) Br_2, CCl_4, 0°C.

The strong unsaturation of the central ring of **7** was confirmed by reaction with Br_2 which led to **8** as the only product.

Finally a number of products **3** were tested against L1210 cells. We found that **3b-d** and **3f-i** had IC_{50} located between 70 and 0.6 μM. Moreover **3f**, **3h**, **3i** acted on the G2 and M cell cycle, an interesting property to develop future drugs.

Extensions of these investigations are currently being actively pursued and will be further published.

Acknowledgments

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References and notes

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2. See for example: Pratt, W.B.; Ruddon, R.W.; Ensminger, W.D.; Maybaum, J. The Anticancer Drugs (second edition), Oxford University Press, 1994. Armand, J.-P. *Jpn Cancer Chemother. (Suppl. I)*, **1997**, *24*, 70-103. Wang, H.-K.; Lee, K.-H. *Bot. Bull. Acad. Sin.* **1997**, *38*, 225-268.
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5. Representative preparation of the tetrahydrobenzocyclobutacarbazoles: a) Procedure path A: To a suspension of $NaNH_2$ (130 mmol) in THF (10 mL) was dropwise added under slow nitrogen flush a solution of *t*BuOH (20 mmol) in THF (1 mL) and the mixture stirred at 45°C for 2 h. To the complex base thus prepared and cooled to room temperature was dropwise added the tetrahydro- carbazolone (10 mmol) in THF (5 mL) and the mixture stirred 2 h at 20°C. After cooling to 0°C aryl bromide (20 mmol) in THF (10 mL) was dropwise added. Progress of the reaction was followed by GCMS. After completion the mixture was poured into ice and extracted with CH_2Cl_2 (3x50 mL). The combined extracts were dried with $MgSO_4$ and the solvent evaporated under vacuum. The residue was flash chromatographed on silica using acetone-hexane (1/3) as eluent. b) Procedure path B: The complex base was prepared from $NaNH_2$ (70 mmol) and *t*BuOH (20 mmol) as described in path A. After cooling to 0°C the imine (10 mmol) in THF (20 mL) was dropwise added and the mixture allowed to gradually warm to room temperature. Progress of the reaction was followed by GCMS. After completion the mixture was hydrolyzed at 0°C. The work up was then identical to that of path A.
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