Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters
Tetrahedron Letters 46 (2005) 3445–3447

Efficient synthesis of novel pentacyclic 6,7-dihydro-5a,7a,13,14-tetraaza-pentaphene-5,8-diones

Maria de Fatima Pereira,[a] Laurent Picot,[a] Jean Guillon,[b] Jean-Michel Léger,[b] Christian Jarry,[b] Valérie Thiéry[a] and Thierry Besson[a,*]

[a]*Laboratoire de Biotechnologies et Chimie Bio-organique, FRE CNRS 2766, UFR Sciences Fondamentales et Sciences pour l'Ingénieur, Bâtiment Marie Curie, Université de La Rochelle, F-17042 La Rochelle Cedex 1, France*
[b]*EA 2962, Pharmacochimie, UFR de Pharmacie, Université Victor Segalen Bordeaux 2, 146, rue Léo Saignat, 33076 Bordeaux Cedex, France*

Received 8 February 2005; revised 16 March 2005; accepted 21 March 2005
Available online 6 April 2005

Abstract—The convenient synthesis of novel tetraaza-pentaphene-5,8-diones (**3**) is described, in two steps, from anthranilic acid derivatives, via a microwave-assisted Niementowski reaction. A short evaluation of the antiproliferative activity of these new pentacyclic heterocycles was realised.
© 2005 Elsevier Ltd. All rights reserved.

The occurrence of the quinazoline skeleton in various natural and synthetic products has generated interest of many groups on account of its useful biological properties.[1] As a part of our ongoing research activity, we launched a research programme dealing with the preparation and pharmacological evaluation of some original quinazoline derivatives structurally related to the terrestrial alkaloids Rutaecarpine[2] (**I**) and Luotonine[3] A (**II**) (Fig. 1), which possess a quinazolin-4-one moiety fused with indolopyrido and pyrroloquinoline ring systems, respectively (Fig. 1).

Thus, exploring the potential synthetic applications of the Niementowski reaction[4] and in association with our work on the application of microwaves in organic chemistry,[5] we planned to prepare novel pentacyclic tetraaza-pentaphene-5,8-diones (**III**, Fig. 1), from anthranilic acids, by fusing quinazolinones and the piperazine ring. In this letter we describe the synthetic route and a preliminary evaluation of the biological activity of various novel polyheterocyclic congeners.

To our knowledge, the pentacyclic 6,7-dihydro-5a,7a,13,14-tetraaza-pentaphene-5,8-dione skeleton has never been published yet. We suggested that generation of this novel ring may occur via a Niementowski reaction[4] between anthranilic acid and novel 2,3-condensed (3*H*)-quinazolin-4-ones that we recently obtained from anthranilate derivatives.

The synthesis of the 2,3-condensed (3*H*)-quinazolin-4-ones precursors **2** was performed from methyl

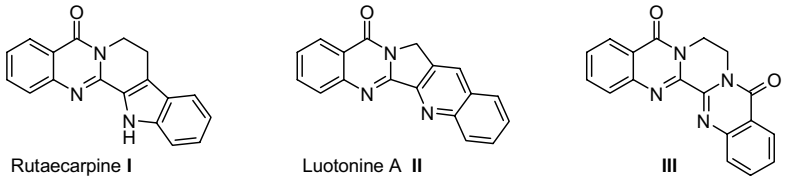
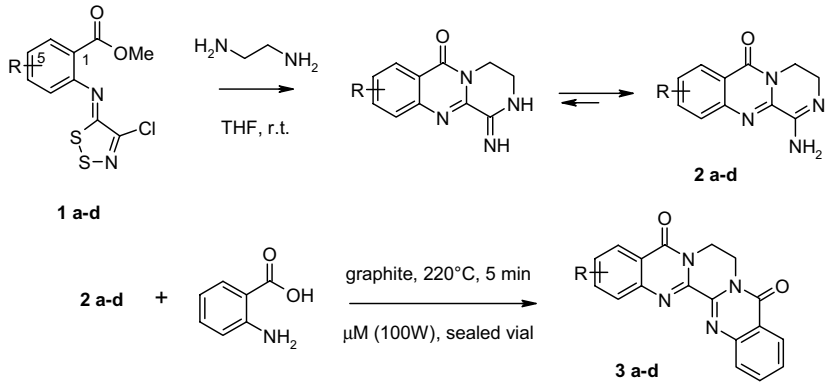


Figure 1.

Keywords: Fused quinazolinones; Niementowski reaction; Microwave-assisted reactions; Graphite.
* Corresponding author. Tel.: +33 05 46 45 82 55; fax: +33 05 46 45 82 47; e-mail: tbesson@univ-lr.fr

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.03.133



Scheme 1.

N-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-anthranilates **1a**–**d** themselves obtained by condensation of 4,5-dichloro-1,2,3-dithiazolium chloride (Appel's salt) and anthranilic acid esters.[6] We observed that stirring of a solution of these imines (**1**) and ethylenediamine (1 or 3 equiv for **1a**–**c** and **1d**, respectively) at room temperature in tetrahydrofurane, for 1 or 2 h, gave good yields of novel 3,4-dihydro-2,4a,9-triaza-anthracen-10-one derivatives **2a**–**d** (Scheme 1).[6]

Our first goal was to establish unambiguously the 3D structure of compounds **2** in order to evaluate the possibility of condensation of these molecules with anthranilic acids. X-ray crystallography of **2c** confirmed the amidine isomerisation in the solid state: the C(9)–N(8) and C(13)–N(14) bonds in **2c** were found at 1.294(3) and 1.290(3) Å, respectively, as typically observed for the C=N double bonds, while the C(13)–N(17) single bond was noticed at 1.346(3) Å. The quinazoline system was also found quite planar (Fig. 2).[7]

The second step of the route studied involves preparation of the expected molecules **3** via a modified Niementowski condensation. This old reaction[4] usually consists of the fusion between anthranilic acids and various amides and thioamides (in dry media or with solvents)

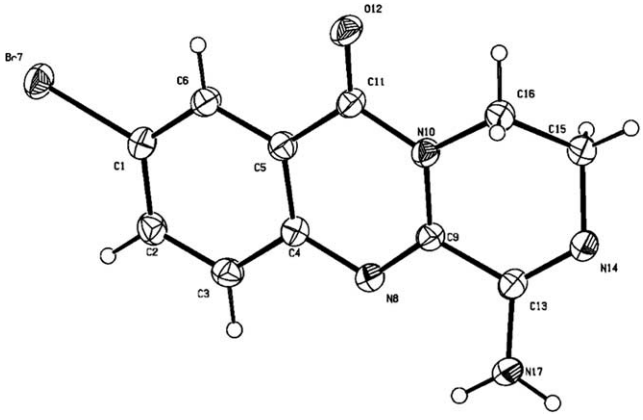


Figure 2. ORTEP view of **2c** with our numbering scheme. Displacement ellipsoids are drawn at the 30% probability level.

Table 1. Synthesis of intermediate quinazolinones **2** and pentacyclic derivatives **3**[10,11]

Starting imine	R	Yield of **2** (%)	Yield of **3** (%)
1a	H	56	52[a,b]
1b	4-Cl	61	68
1c	5-Br	74	65
1d	4,5-di-OMe	68	36

[a] A similar reaction (same quantities in a sealed vial) gave only 11% of the attempted product after 4.5 h of conventional heating (oil bath).
[b] Microwave experiments performed in sealed vial at 220 °C, in the presence of solvents like *N*-methyl pyrrolidinone (NMP), or dimethylformamide (DMF), offered, after 6 min of heating, only 37% of the expected product, besides a large amount of by-products, which were not identified.

to afford substituted quinazolinones, in good yields. To our knowledge, no examples of this reaction are yet reported with amidines (Scheme 1).

Inspired by our previous work on the synthesis of fused quinazolines,[8] we observed that the best procedure for the preparation of the bis-quinazolin-4-ones **3a**–**d** consists of microwave irradiation under pressure at 220 °C of a mixture of the starting amidine **2a**–**d** and an excess of anthranilic acid (4 equiv) in the presence of graphite (10% by weight), one of the solids most efficiently heated by microwaves[9] (for yields see Table 1). The benefits to use microwave irradiation are noticeable and the strong thermal effect due to graphite/microwaves interaction is particularly efficient in such a reaction, which usually needs high temperatures and requires lengthy and tedious conditions. In our case, the use of sealed vials allowed to reach very efficiently the high temperature required, and then, to avoid sublimation of anthranilic acid usually occurring at atmospheric pressure.

A preliminary evaluation of the potential biological activity of tetraaza-pentaphene-5,8-diones was realised in our group on breast cancer cell lines as previously described.[12] Among the compounds tested, the dimethoxy derivative **3d** was identified as the best antiproliferative compound inducing 10.4%, 9.6% and 8.2% growth inhibition at 10^{-6} M on MCF-7/AZ, MCF-7/6 and MDA-MB-231 cell lines, respectively.

In conclusion, we described the rapid and efficient access to novel pentacyclic heterocycles, which are structurally related to well studied terrestrial alkaloids (e.g., Rutaecarpine and Luotonine A). This work is a further example of the utility of microwave irradiation in organic synthesis where traditional methods failed. Preparation and biological evaluation of various analogues are under development and will be described later.

Acknowledgements

We thank the Comité de Charente & Charente-Maritime de la Ligue Nationale contre le Cancer for financial support and for a Ph.D. grant (F.P.). This work is also supported by the Canceropôle Grand-Ouest programme 'Modulators of apoptosis'. We also thank Biotage for multiform support on microwave experiments.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.03.133.

References and notes

1. (a) Johne, S. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Grisebach, H., Kirby, G. W., Tamm, Ch., Eds.; Springer: Wien, 1984; Vol. 46, pp 159–229; (b) Johne, S. In *The Alkaloids, Chemistry and Pharmacology*; Brossi, A., Ed.; Academic: New York, 1986; Vol. 29, pp 99–140.
2. Yang, L.-M.; Chen, C.-F.; Lee, K.-H. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 465–468, and references cited therein; For a recent synthesis of **I**, see: Mohanta, P. K.; Kim, K. *Tetrahedron Lett.* **2002**, *43*, 3993–3996.
3. Ma, Z.-Z.; Hano, Y.; Nomura, T.; Chen, Y.-J. *Heterocycles* **1997**, *46*, 541–546; For synthesis of **II**, see: Dallavalle, S.; Merlini, L. *Tetrahedron Lett.* **2002**, *43*, 1835–1837.
4. von Niementowski, S. *J. Prakt. Chem.* **1895**, *51*, 564–572.
5. For a recent review in the area, see: (a) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250–6284; (b) For the most cited book on microwaves in chemistry, see: *Microwaves in Organic Synthesis*; Loupy, A., Ed.; Wiley-VCH: Weinhein, 2002.
6. Pereira, M.-F.; Alexandre, F. R.; Thiéry, V.; Besson, T. *Tetrahedron Lett.* **2004**, *45*, 3097–3099.
7. Crystallographic data for the structure **2c** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC-253162 (Supplementary X-ray crystallographic data: Cambridge Crystallographic Data Centre, University Chemical Lab, 12 Union Road, Cambridge, CB2 1EZ, UK; e-mail: deposit@ccdc.cam.ac.uk).
8. Alexandre, F.-R.; Berecibar, A.; Wrigglesworth, R.; Besson, T. *Tetrahedron* **2003**, *59*, 1413–1419.
9. For papers related to the microwave heating of graphite, see: (a) Laporte, C.; Baulès, P.; Laporterie, A.; Desmurs, R.; Dubac, J. *C.R. Acad. Sci. Paris* **1998**, *t.1* (Série IIc), 141–150; (b) Laporte, C.; Marquié, J.; Laporterie, A.; Desmurs, R.; Dubac, J. *C.R. Acad. Sci. Paris* **1998**, *t.2* (Série IIc), 455–465.
10. Pressurized microwave heating was performed in a Smith-Synthetizer™ (Personal Chemistry, AB) single mode cavity. Detailed descriptions of this microwave reactor with integrated robotics was recently published: Schanche, J.-S. *Mol. Diverscity* **2003**, *7*, 293–300.
11. Typical microwave-assisted procedures and selected data for new compounds **3a–d** are available as supporting information.
12. Testard, A.; Picot, L.; Fruitier-Arnaudin, I.; Piot, J. M.; Chabane, H.; Domon, L.; Thiéry, V.; Besson, T. *J. Enz. Inhib. Med. Chem.* **2004**, *18*, 467–473.