Asian Journal of Chemistry; Vol. 27, No. 11 (2015), 4063-4066

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2015.19087

Synthesis of Naphthoquinone Dendrimer Based Materials as Potential Antimalarial Drugs

T. NDIOR, C.M. NDIAYE*, F.D. FAYE and A. SAMB

Laboratoire de Chimie & Biochimie des Produits Naturels, Département de Chimie, Faculté des Sciences et Techniques, Université Cheikh Anta DIOP de Dakar, Dakar, Sénégal

*Corresponding author: Fax: +221 338246318; Tel: +221 781260035; E-mail: elhcheikhm.ndiaye@ucad.edu.sn

Received: 7 February 2015; *Accepted*: 16 March 2015; *Published online*: 16 July 2015; AJC-17403

The synthesis of two new PPI-G1 dendrimers containing lawsone (2-hydroxy-*p*-naphthoquinone) as pharmacophore is reported. The compounds were synthesized in course of Mannich reaction involving lawsone, the commercial PPI-G1 (polypropyleneimine-G1) dendrimer with functional amino groups on the exterior and acetaldehyde (**1**) or benzaldehyde (**2**) in 4:1:4 molar ratio. Their structures are authenticated *via* FT-IR, ^{1}H and $^{13}C\{^{1}H\}$ NMR and mass spectra.

Keywords: Dendrimer, Polypropyleneimine, Naphthoquinone, Mannich, Antimalarial.

INTRODUCTION

Malaria remains a major cause of morbidity and deaths. It is responsible for 350-500 millions of clinical disease episodes, of which 1.5-2.7 millions of persons die annually[1]. The transmission of the disease occurs in 109 tropical and sub-tropical countries, principally in those located in the sub-Saharan area of the African continent[2]. However 0-4 aged infants[1b,3] and pregnant women[4] are the most vulnerable.

Unfortunately, the malaria epidemiological situation is increasingly worrying by the existence of a multidrug-resistance of *Plamodium falciparum*[5,6], the most deadly parasite. And this is reinforced by the cross resistance among drugs belonging to the same chemical family[7]. That is why, since April 2001, the systematic use of ACTs is required by the WHO for the battle against malaria[8].

But, despite their key role in the fight against drug-resistant malaria, the ACTs are now showing disturbing signs of reduced effectiveness, principally in the nearest two areas of the Thai-Cambodian border[9]. Even in the malarious regions where they still remain useful, their prices are out of reach of the most disadvantaged populations, without an adequate public health policy of subsidizing the medicines[10].

Furthermore, Malarone™, an alternative therapeutic combination composed of atovaquone (**Scheme-I**) and proguanil, but principally used in France for the treatment of the non-complicated form of the *P. falciparum* malaria[11] and for the chemoprophylaxis of the travelers[12] has already faced the chemo-resistance of the malaria parasite[13].

In absence of an operational vaccine to prevent malaria and while waiting to know the accurate potency of drugs currently in development on the battle against disease[14], there is a continuing need for the synthesis of new and safe anti-malarials active against multi-drug resistant *P. falciparum* strains with different mode of action. Hence, the interest that we have focused on preparing polypropyleneimine dendrimers-based naphthoquinone as potential antimalarial drugs.

EXPERIMENTAL

A typical experimental procedure for the synthesis of the compound **1** is representative and was as follow: In a 150 mL Erlenmeyer protected of the light by a sheet of aluminum, a solution of PPI-G1 (polypropyleneimine-generation 1) dendrimer or *Dendr*-$(NH_2)_4$ (204.250 mg; 0.645 mmol; 1 eq.) in 10 mL of absolute ethanol was added in a suspension of lawsone (2-hydroxy-*p*-naphthoquinone) (449.42 mg; 2.581 mmol; 4.00 eq.) in 20 mL of ethanol under vigorous magnetic stirring at room temperature. The progressive vanishing of the suspension was observed along with the formation of a red solution of the tetra(ammonium lawsonate) salt. To ensure that the formation of the tetra(ammonium lawsonate) salt is total, the reaction mixture was left to stir for further 15 min. The acetaldehyde (0.152 mL; 2.681 mmol; 4.16 eq) was then added with a syringe. Therefore, the resulting reaction mixture was stirred overnight (12 h) at room temperature in the dark. Hence, the obtained precipitate was twisted and then washed with ethanol until the washings become colourless (590 mg; 82 %).

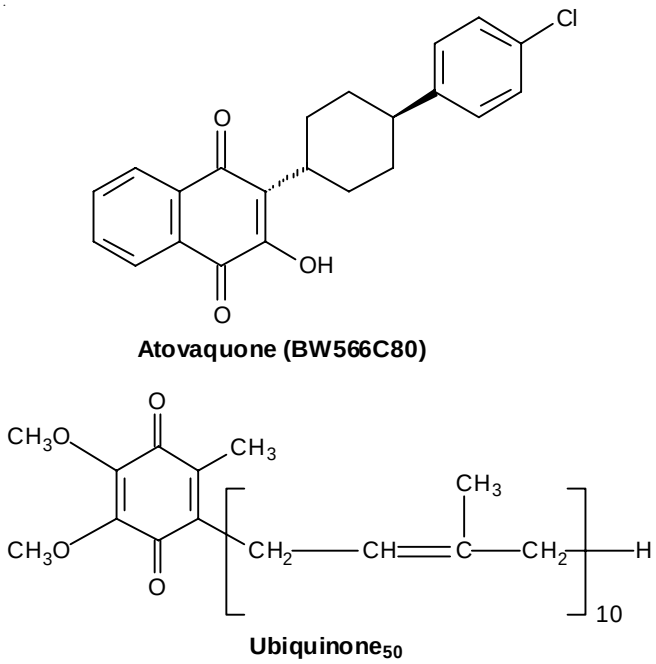
Spectral data for the compound **1** ($C_{64}H_{72}N_6O_{12}$): red solid; m.w.: 1116.4594 g/mol; yield: 82 %. IR (KBr, ν_{max}, cm^{-1}): 3426 ν(O-H); 3066 ν(C-H); 2954 ν(C-H); 2818 (C-H); 1680 ν(C=O); 1590 ν(C=C); 1536 δ(N-H); 1278 ν(C-O). ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 16.80 (br. s, OH); 8.95 (s, NH); 7.90 (d, $^3J_{HH}$ = 6.8 Hz, H^{11}, 4H); 7.83 (d, $^3J_{HH}$ = 6.4 Hz, H^{14}, 4H); 7.68 (t, $^3J_{HH}$ = 7.6 Hz, H^{12}, 4H); 7.56 (t, $^3J_{HH}$ = 7.2 Hz, H^{13}, 4H); 4.56 (q, $^3J_{HH}$ = 4.4 Hz, H^6, 4H); 2.81 (s, H^5, 8H); 2.40-1.95 (unresolv. d [2.23 ppm (H^3, 8H) + 2.14 ppm (H^2, 4H)], 12H); 1.61 (s, H^4, 8H); 1.43 (d, *J* = 4,4 Hz, CH_3, 12H); 1.22 (s, H^1, 4H). ^{13}C{^{1}H} NMR (DMSO-d_6, 75.5 MHz): δ (ppm) 184.7 (s, C=O); 178.9 (s, C=O); 170.2 (s, C-OH); 134.6 (d, C^{IV}-*Napht*); 133.7 (CH-*Napht*); 131.3 (C^{IV}-*Napht*); 130.8 (CH-*Napht*); 125.3 (CH-*Napht*); 125.1 (CH-*Napht*); 111.6 (C^{IV}, C^7); 52.5 (s, C^2); 51.3 (s, C^6); 50.7 (s, C^3); 43.6 (d, C^5); 23.6 (C^1); 23.0 (C^4); 17.42 (s, CH_3). Mass (ESI/ CH_3OH-CH_3Cl-95:5) *m/z* calculated (found (error)) $[M-4H+3Na]^-$ ($C_{64}H_{68}N_6O_{12}Na_3$) 1181.45938 (1181.4594 (0 ppm)) (the numbering of the atoms is based on **Scheme-II**).

Spectral data for the compound **2** ($C_{84}H_{80}N_6O_{12}$): red solid; m.w.: 1364.5758 g/mol; yield: 76 %. IR (KBr, ν_{max}, cm^{-1}): 3424 ν(O-H); ν(C-H); 2950 ν(C-H); ν(C-H); 1679 ν(C=O); 1591 ν(C=C); 1522 δ(N-H); 1276 ν(C-O). ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 16.50 (s, OH); 9.60 (s, NH); 7.88 (d, $^3J_{HH}$ = 8 Hz, H^{11}, 4H); 7,81 (d, $^3J_{HH}$ = 7.6 Hz, H^{14}, 4H); 7.66 (t, $^3J_{HH}$ = 7,2 Hz, H^{12}, 4H); 7.50-7.60 (m, H^{13} + H-*Ph*, 12H); 7.21-7.33 (m, H-*Ph*, 12H); 5.55 (s, H^6, 4H); 2.91 (s, H^5, 8H) ; 2.40-2.00 (unresolv. d [2.28 ppm (H^3, 8H) + 2.11 ppm (H^2, 4H)], 12H); 1.69 (s, H^4, 8H); 1.22 (s, H^1, 4H). ^{13}C NMR (DMSO-d_6, 400 MHz): δ (ppm) 184.5 (s, C=O); 178,9 (s, C=O); 170.0 (s, C-OH); 138.4 (C^{IV}-Ph); 134.3 (d, C^{IV}-*Napht*); 133.6 (CH-*Napht*); 131.3 (C^{IV}-*Napht*); 130.9 (CH-*Napht*); 128.2 (CH-*Ph*); 127.7 (CH-*Ph*); 127.6 (CH-*Ph*); 125.3 (CH-*Napht*); 125.0 (CH-*Napht*); 111.2 (C^{IV}, C^7); 58.7 (s, C^6); 52,2 (s, C^2); 50.5 (s, C^3); 44.7 (d, C^5); 23,5 (s, C^1); 22.4 (s, C^4). Mass (ESI/CH_3OH-CH_3Cl-95:5). *m/z* caculated [found (error)] $[M-H]^-$ ($C_{84}H_{79}N_6O_{12}$) 1363.57615 [1363.5758 (0 ppm)]; $[M-2H+Na]^-$ ($C_{84}H_{78}N_6O_{12}Na$) 1385.55809 [1385.5564 (1 ppm)]; $[M-3H+2Na]^-$ ($C_{84}H_{77}N_6O_{12}Na_2$) 1407.54004 [1407.5389 (1 ppm)]); $[M-4H+3Na]^-$ ($C_{84}H_{76}N_6O_{12}Na_3$) 1429.52198 [1429.5200 (1 ppm)].

RESULTS AND DISCUSSION

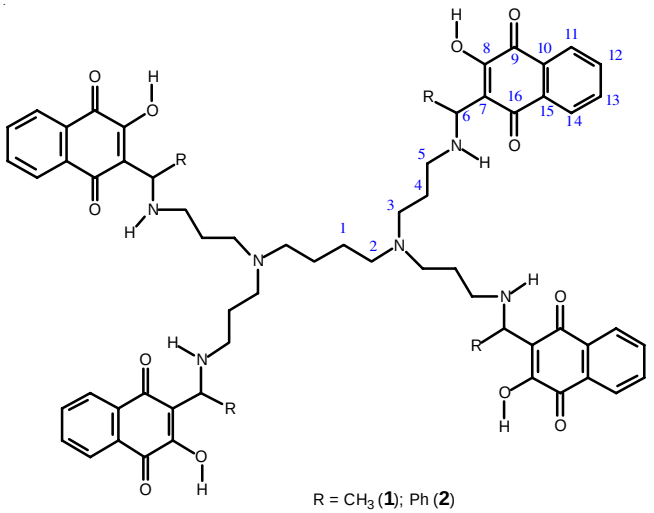
Since a decade or more, the synthesis of dendrimers is an active area of research. Because of their biocompatibility and safety[15], dendrimers are attractive materials for pharmacochemists. They have a large spectrum of applications in both medical and biomedical sciences in areas such as: medical diagnostic[16], cancer therapy[17], gene transfection[18], medical imagine as contrast agents[19], treatment and prevention of viral, like HIV and HSV-2[20] and bacterial infections[21], *etc*. But to our best of knowledge, the only experiments carried out on dendrimers as potential antimalarial materials are those undertaken by Bhadra *et al.* about the encapsulation of chlorquine diphosphate[22], primaquine[23] and artemisinine[24].

On the other hand, it is generally known that the naphthoquinone and quinone derivatives in general exhibit antimalarial *in vitro* activities[25]. Additionally, the ubquinone$_{50}$ (**Scheme-I**), a co-enzyme hydrogen transporter, is known to be the major



Scheme-I: Molecular structures of atovaquone and ubiquinone$_{50}$

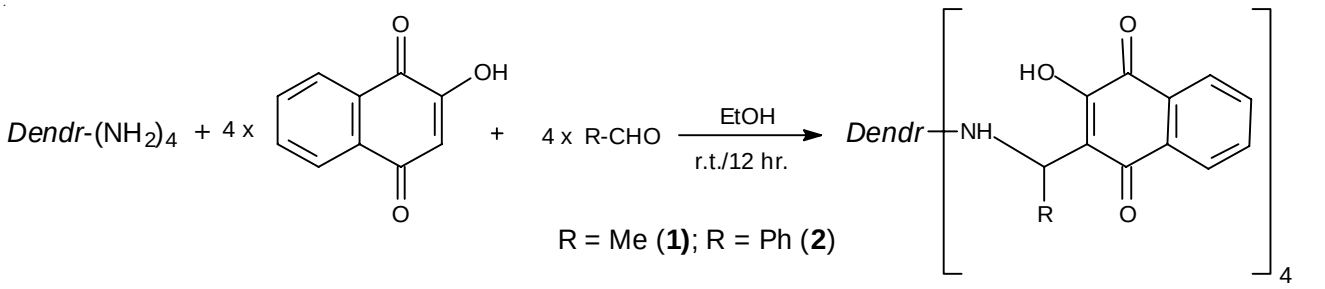
supply of quinones for the malaria parasite[26]. That is why, on the basis of the principle of majority, we hypothesized that the presence of four lawsone systems (**Scheme-II**) on the periphery of PPI-G1 dendrimer, *Dendr*-$(NH_2)_4$[27] could modulate the antimalarial activity of naphthoquinone pharmacophore, in comparison with equimolar amounts of atovaquone or chloroquine.



Scheme-II: Molecular structure of the synthesized compounds

Because the dendritic PPI-G1 reagent exhibits four amine functions on its periphery, we based our synthetic strategy on the Mannich reaction involving the dendrimer, lawsone and aldehyde. The compounds were then prepared in reference to a method developed by Baramee *et al.*[28] and modified by Neves *et al.*[29] (**Scheme-III**).

The reaction took place in ethanol by introducing the reagents in this order: lawsone, dendrimer and acetaldehyde (**1**) or benzaldehyde (**2**) in the molar ratio 4:1:4. So, it is noticeable red colouration attributed to the presence of



Scheme-III: Reaction equation of synthesis of the compounds

tetra(ammoinum lawsonate) salt[29] after adding the dendrimer in the suspension of lawsone. A red precipitate occurs almost instantly when the convenient aldehyde was added. The compounds were then obtained in an air stable red solid form with yields in the order of 80 %. And the expected structures are well established by way of the conventional methods of characterization.

However, a second experiment on the synthesis of compound **1** was launched by reversing the additions of the dendrimer and the acetaldehyde. Therefore, when the latter was added in the ethanolic solution of lawsone, the resultant reaction mixture has become yellow rather than red, along with a temperature rise and a low precipitation of a yellow solid. This vanished when the dendrimer was added, thus allowing the colouration of the solution to move gradually to red in less than 10 min. Therefore, compound **1** was also obtained as a pure red solid with a yield of 75 % for a purification operation identical to that mentioned above.

By comparing the two experiments of synthesis of **1**, it is noticeable that the oxonium lawsonate salt produced by the protonation of the acetaldehyde was responsible for the primary yellow colouration in the second experience. However, in the first experience, the formation of the oxonium lawsonate salt intervened after the transfer of a proton from each ammonium group to a molecule of acetadehyde. Consequently, the reaction mechanism could be explained briefly in a few words, *i.e.* condensation of the amino with the acidified aldehyde to give the imine followed by protonation and addition of the lawsonate anion.

In conclusion, we characterized two PPI-G1 dendrimers containing the *2*-hdroxy-*p*-naphthoquinone (lawsone) in the course of a one pot synthesis based on the Mannich reaction. Investigations toward the functionalization of G2-G5 poly-propyleneimine dendrimers by means of Mannich reaction and the study of the biological activities of the whole compounds are in progress and the results will be reported in due course.

In perspective of future works, we envisioned to extend the chemistry to the corresponding PAMAM dendrimers. Furthermore, some *tris*- and *tetrakis*-quinoline derivatives exhibiting *in vitro* antimalarial activities[30], we imagined that the replacement of the lawsone system by the 7-chloroquinoline core should lead to interesting antimalarial tools.

In a similar manner, menadione[31], thiazolidinone[32] and imidazole[33] groups exhibiting each biological activities, we anticipated that their bio-conjugation on the surface attachment of the two sorts of dendrimers could lead to an increased efficacy of desired compounds, which may or may not incorporate ferrocene group.

But, the most urgent work in perspective is to isolate and test the five generations of the polypropyleneimine-poly(ammonium lawsonate) salts. In fact, like chloroquine and quinine which are sold as phosphate, sulfate or hydrochloride salts, we assumed that the presence of a great number of the pharmacophore, in an attractive interaction with the ammonium groups of the dendrimers, could lead to more efficient compounds in comparison with equimolar amounts of atovaquone or chloroquine.

ACKNOWLEDGEMENTS

The authors thank Prof. Abdoulaye Samb for his assistance in supervising this work. Also, the authors are indebted to Philippe Jehan and Sourisak Sinbandhit of the CRMPO (Centre Regional de Mesures Physiques de l'Ouest), University of Rennes 1, respectively, for their precious aids with the mass spectra and the NMR spectra experiments.

REFERENCES

1. (a) WHO, World Malaria Report (2008); (b) WHO, World Malaria Report (2005).
2. (a) I.J. Udeinya, J.A. Schmidt, M. Aikawa, L.H. Miller and I. Green, *Science*, **213**, 555 (1981); (b) W.H. Wernsdorfer, in ed.: J.P. Kreier, The Importance of Malaria in the World; In: Malaria, Academic Press, New York, vol. 1, pp. 1-93 (1980).
3. R.W. Snow, M. Craig, U. Deichmann and K. Marsh, *Bull. World Health Organ.*, **77**, 624 (1999).
4. P.I. Trigg and A.V. Kondrachine, The Current Global Malaria Situation, In: Malaria: Parasite Biology, Pathogenesis, and Protection, ASM Press, Washington, pp. 11-22 (1998).
5. B. Pradines, J. Dormoi, S. Briolant, H. Bogreau and C. Rogier, *Revue Francoph. Labo*, 51 (2010).
6. (a) J.-F. Trape, G. Pison, M.-P. Preziosi, C. Enel, A.D. du Lou, V. Delaunay, B. Samb, E. Lagarde, J.-F. Molez and F. Simondon, *C. R. Acad. Sci. III*, **321**, 689 (1998); (b) J.F. Trape, *Am. J. Trop. Med. Hyg.*, **64**, 12 (2001).
7. P. Blolan, Drug Resistance in Malaria, WHO Monograph, WHO/CDS/CSR/4 (2001).
8. T.K. Mutabingwa, *Acta Trop.*, **95**, 305 (2005).
9. *WHO, World Malaria Report* (2009).
10. P.A. Kager, *Trop. Med. Int. Health*, **7**, 1042 (2002).
11. J. Delmont, *Med. Trop.*, **62**, 232 (2002).
12. D. Camus, E. Dutoit, V. Masson, P. Inglebert and L. Delahaes, *Méd. Trop.*, **62**, 225 (2002).
13. (a) J.P. Gil, F. Nogueira, J. Strömberg-Nörklit, J. Lindberg, M. Carrolo, C. Casimiro, D. Lopes, A.P. Arez, P.V. Cravo and V.E. Rosário, *Mol. Cell. Probes*, **17**, 85 (2003); (b) E. Schwartz, S. Bujanover and K.C. Kain, *Clin. Infect. Dis.*, **37**, 450 (2003).
14. C. Biot and B. Pridines, *Biofutur*, **293**, 38 (2008).
15. (a) R. Duncan and L. Izzo, *Adv. Drug Deliv. Rev.*, **57**, 2215 (2005); (b) Y. Cheng, H. Qu, M. Ma, Z. Xu, P. Xu, Y. Fang and T. Xu, *Eur. J. Med. Chem.*, **42**, 1032 (2007); (c) D.G. Mullen, D.Q. McNerny, A. Desai, X. Cheng, S.C. DiMaggio, A. Kotlyar, Y. Zhong, S. Qin, C.V. Kelly, T.P. Thomas, I. Majoros, B.G. Orr Jr., J.R. Baker Jr. and M.M. Banaszak Holl, *Bioconjug. Chem.*, **22**, 679 (2011).

16. S.-E. Stiriba, H. Frey and R. Haag, *Angew. Chem. Int. Ed.*, **41**, 1329 (2002).
17. C. Kojima, K. Kono, K. Maruyama and T. Takagishi, *Bioconjug. Chem.*, **11**, 910 (2000).
18. (a) M. Guillot-Nieckowski, S. Eisler and F. Diederich, *New J. Chem.*, **31**, 1111 (2007); (b) J.P. Behr, *Med. Sci.*, **12**, 56 (1996).
19. S. Langereis, Q.G. de Lussanet, M.H.P. van Genderen, E.W. Meijer, R.G.H. Beets-Tan, A.W. Griffioen, J.M.A. van Engelshoven and W.H. Backes, *NMR Biomed.*, **19**, 133 (2006).
20. (a) D.I. Bernstein, L.R. Stanberry, S. Sacks, N.K. Ayisi, Y.H. Gong, J. Ireland, R.J. Mumper, G. Holan, B. Matthews, T. McCarthy and N. Bourne, *Antimicrob. Agents Chemother.*, **47**, 3784 (2003); (b) N. Bourne, L.R. Stanberry, E.R. Kern, G. Holan, B. Matthews and D.I. Bernstein, *Antimicrob. Agents Chemother.*, **44**, 2471 (2000); (c) M. Tulu, N.M. Aghatabay, M. Senel, C. Dizman, T. Parali and B. Dulger, *Eur. J. Med. Chem.*, **44**, 1093 (2009).
21. (a) M. Ma, Y. Cheng, Z. Xu, P. Xu, H. Qu, Y. Fang, T. Xu and L. Wen, *Eur. J. Med. Chem.*, **42**, 93 (2007); (b) M.K. Calabretta, A. Kumar, A.M. McDermott and C. Cai, *Biomacromolecules*, **8**, 1807 (2007).
22. D. Bhadra, S. Bhadra and N.K. Jain, Proceedings of the 2004 International Conference on MMEMS, NANO and Smart Systems (ICMENS'04).
23. D. Bhadra, A.K. Yadav, S. Bhadra and N.K. Jain, *Int. J. Pharm.*, **295**, 221 (2005).
24. (a) D. Bhadra, S. Bhadra and N.K. Jain, *J. Pharm. Pharm. Sci.*, **8**, 467 (2005); (b) D. Bhadra, S. Bhadra and N.K. Jain, *J. Drug Del. Sci. Tech.*, **15**, 65 (2005).
25. (a) A.T. Hudson, M. Dickin, C.D. Ginger, W.E. Gutteridge, T. Hodich, D.B. Hutchinson, M. Pudney, A.W. Randall and V.S. Latter, *Drug Expt. Clin. Res.*, **17**, 427 (1991); (b) A.T. Hudson, *Parasitol. Today*, **9**, 66 (1993).; (c) L.F. Fieser and A.P. Richardson, *J. Am. Chem. Soc.*, **70**, 3156 (1948).
26. T. Hudson, in eds.: W. Peter and W.H.G. Richard, Lapinone, Menoctone, Hydroxyquinoline-quinones and Similar Structures, In: Antimalarial Drugs, Current Antimalarial and New Drug Developments, Springer-Verlag, Berlin, Heideburg, New York and Tokyo, p. 343 (1984).
27. http://www.chem.tue.nl/smo.
28. A. Baramee, A. Coppin, M. Mortuaire, L. Pelinski, S. Tomavo and J. Brocard, *Bioorg. Med. Chem.*, **14**, 1294 (2006).
29. A.P. Neves, C.C. Barbosa, S.J. Greco, M.D. Vargas, L.C. Visentin, C.B. Pinheiro, A.S. Mangrich, J.P. Barbosa and G.L. Costa, *J. Braz. Chem. Soc.*, **20**, 712 (2009).
30. S. Girault, P. Grellier, A. Berecibar, L. Maes, P. Lemiere, E. Mouray, E. Davioud-Charvet and C. Sergheraert, *J. Med. Chem.*, **44**, 1658 (2001).
31. (a) N. Chavain, E. Davioud-Charvet, X. Trivelli, L. Mbeki, M. Rottmann, R. Brun and C. Biot, *Bioorg. Med. Chem.*, **17**, 8048 (2009); (b) H. Bauer, K. Fritz-Wolf, A. Winzer, S. Kühner, S. Little, V. Yardley, H. Vezin, B. Palfey, R.H. Schirmer and E. Davioud-Charvet, *J. Am. Chem. Soc.*, **128**, 10784 (2006).
32. (a) S.J. Wadher, N.A. Karande, D.S. Borkar and P.G. Yeole, *Int. J. Chem. Tech. Res.*, **1**, 1303 (2009); (b) T. Srivastava, A. Gaikwad, W. Haq, S. Sinha and S.B. Katti, *ARKIVOC*, 120 (2004).
33. A. Dömling, B. Beck, E. Herdtweck, W. Antuch, C. Oeffner, N. Yehia, A. Gracia-Marques, *ARKIVOC*, 99 (2006).