http://dx.doi.org/10.21577/0103-5053.20160207

*J. Braz. Chem. Soc.*, Vol. 28, No. 4, 681-688, 2017.
Printed in Brazil - ©2017 Sociedade Brasileira de Química
0103 - 5053 $6.00+0.00

*Short Report*

# New Strategies for Molecular Diversification of 2-[Aminoalkyl-(1*H*-1,2,3-triazol-1-yl)]-1,4-naphthoquinones Using Click Chemistry

***Ronaldo N. de Oliveira,*,[a] Mauro G. da Silva,[a,b] Moara Targino da Silva,[a] Valentina N. Melo,[a,b] Wagner O. Valença,[a] Josinete Angela da Paz[a] and Celso A. Camara[a]***

[a]*Laboratório de Síntese de Compostos Bioativos, Universidade Federal Rural de Pernambuco, 52171-900 Recife-PE, Brazil*

[b]*Departamento de Química Fundamental, Universidade Federal de Pernambuco, 50740-540 Recife-PE, Brazil*

Click chemistry-based strategies for the synthesis of 2-amino-alkyl-1,2,3-triazole-1,4-naphthoquinone derivatives make it possible to obtain desired products from 1,4-naphthoquinone (1,4-NQ), and bio-based lawsone, *nor*-lapachol and lapachol. The first route (Strategy A) starting from 1,4-NQ and amino alcohols, then 2-amino-alkyl-1,4-NQ alcohols, were tosylated. The azide ion displaced the tosylate group to afford 2-azide-alkyl-1,4-NQ, which was submitted to a copper-catalyzed azide alkyne cycloaddition (CuAAC) condition. The triazole-naphthoquinones were obtained in an overall yield of roughly 47%. Another pathway (Strategy B) substituted bromo-alkyl-phthalimides using $NaN_3$ as the nucleophile, sequential CuAAC and deprotection of phthalimide group with hydrazine producing amino-triazoles. The subsequent reaction with 1,4-NQ produced 2-amino-alkyl-1,2,3-triazole-1,4-NQ derivatives in an overall yield of 45-76% in four steps. After we developed these two strategies, linear synthesis (Strategy A) was chosen to prepare 2-[(2-(1*H*-1,2,3-triazol-1-yl)ethylamino)]-3-(3-methylpropenyl)-1,4-naphthoquinones from lawsone with an overall yield of approximately 27% in six steps. On the other hand, convergent synthesis (Strategy B) was employed for the synthesis of 2-[(4-phenyl-1*H*-1,2,3-triazol-1-yl)alkyl-amino)]-3-(3-methylbut-2-en-1-yl)-1,4-naphthoquinones from the reaction between 2-methoxy-lapachol with amino-triazoles with a global yield of about 21%. These synthetic strategies might lead us to new opportunities to build small-molecule libraries for future biological exploration.

**Keywords:** click chemistry, amino-naphthoquinone, lapachol, *nor*-lapachol, 1,2,3-triazole

## Introduction

The synthesis of New Chemical Entities (NCE) remains unaffected by changes in the focus of chemical science.[1] A number of synthetic strategies have been developed recently to allow organic chemists to create a great variety of molecules. In order to access novel and diverse chemical libraries of compounds with potential biological activity the use of catalytic methods is prominent.

From a synthetic point of view, the Huisgen 1,3-dipolar cycloaddition reaction between organic azides and terminal alkynes has been a straightforward method to assemble a large number of molecules, especially since Sharpless and co-workers[2] and Meldal and co-workers[3] proposed the copper-catalyzed azide-alkyne cycloaddition (CuAAC). This protocol has permitted easy access to molecular diversity of 1,2,3-triazoles and encouraged synthetic chemists to design projects based on this scaffold.[4-11] This reaction has provided the opportunity to synthesize molecules having new properties or biological activities,[12,13] including anti-tuberculosis,[14] antiviral,[15] antitumoral,[16-18] antifungal,[19] antibiotic (e.g., tazobactam, see Figure 1a),[20] among others, as can be found in the literature.[21] Moreover, naphthoquinones moieties such as potent trypanocidal and leishmanicidal activities have been synthesized (Figure 1a).[22-24]

Since molecular hybridization between 1,4-naphthoquinone (1,4-NQ) and 1,2,3-triazole nucleus appeared as an important pharmacophore,[25-29] this type of derivatives has become attractive as bioactive compounds. Various approaches have been focused on the connection between these derivatives. As a consequence,

*e-mail: ronaldo.noliveira@ufrpe.br

triazole-naphthoquinone hybrids have recently stood out in research on medicinal chemistry because of their structural diversity and biological properties. For instance, we recently synthesized triazole-naphthoquinone compounds,[29] which after biological assays showed interesting activities against anti-*T. cruzi*,[22] tumor cells[17,30] and *Leishmania* sp.[31] Furthermore, we published a study on the synthesis of a new class of compounds combining ultrasound and click chemistry, named amino-naphthoquinone-triazole-phthalimide (ANT-Phthalimide); and ever since, we have been using this procedure in our laboratoty.[32] To continue in this direction, our research group reported new building blocks with expressive medicinal properties; for example, 2-aminomethyl-naphthoquinone alkynes also reacted with azide-sugar to afford new ANT-sugars, which increased antitumor activity (Figure 1b).[17] Another interesting example indicated amine substituted 1,4-naphthoquinones as potent GTPase inhibitors.[33]

In the present study, we report on the synthesis of novel 2-amino-alkyl-(1*H*-1,2,3-triazol-1-yl)-1,4-naphthoquinones employing the copper-catalyzed Huisgen reaction between azide-alkyl-amino-1,4-naphthoquinones with terminal alkynes. These new structural diversity was prepared using the tactics of functionality inversion (R–$N_3$ | HC≡C–R' or R–C≡CH | $N_3$–R'), functional variety from alkynes and branched alkyl chains (Figure 1b). In addition, we also report on the combination of bio-based origin scaffolds (lapachol and lawsone) with synthetic triazole-heterocyclic moiety.

## Results and Discussion

Our investigation began with the reaction between naphthoquinone **1** (1,4-NQ) with aminoalcohols to furnish 2-hydroxyalkyl-amino-1,4-NQs **2**-**3** using $CH_3CN$ at room temperature for 3 h in yields of 73 and 67%, respectively (Scheme 1). After that, the alcohol derivatives were tosylated using tosyl chloride and triethylamine in dichloromethane furnishing **4** and **5** in 68 and 81% yields, respectively. Then, the tosylated compounds **4**-**5** were carried out as substrates for the $S_N2$ displacement reaction with $NaN_3$ in DMSO to provide the azide **6** and **7** in almost quantitative yields. With the azide-1,4-NQs **6**-**7** in hands, the click protocol (DMSO/CuI/$Et_3N$) was employed using inert atmosphere at room temperature; thus, obtaining 1,2,3-triazole compounds **8a-d** and **9a-d** in good to excellent yields of 70-96% under copper-catalyzed conditions (Table 1).

In fact, Strategy A (cf. Scheme 1) for the synthesis of 2-amino-alkyl-(1*H*-1,2,3-triazol-1-yl)-1,4-naphtho-

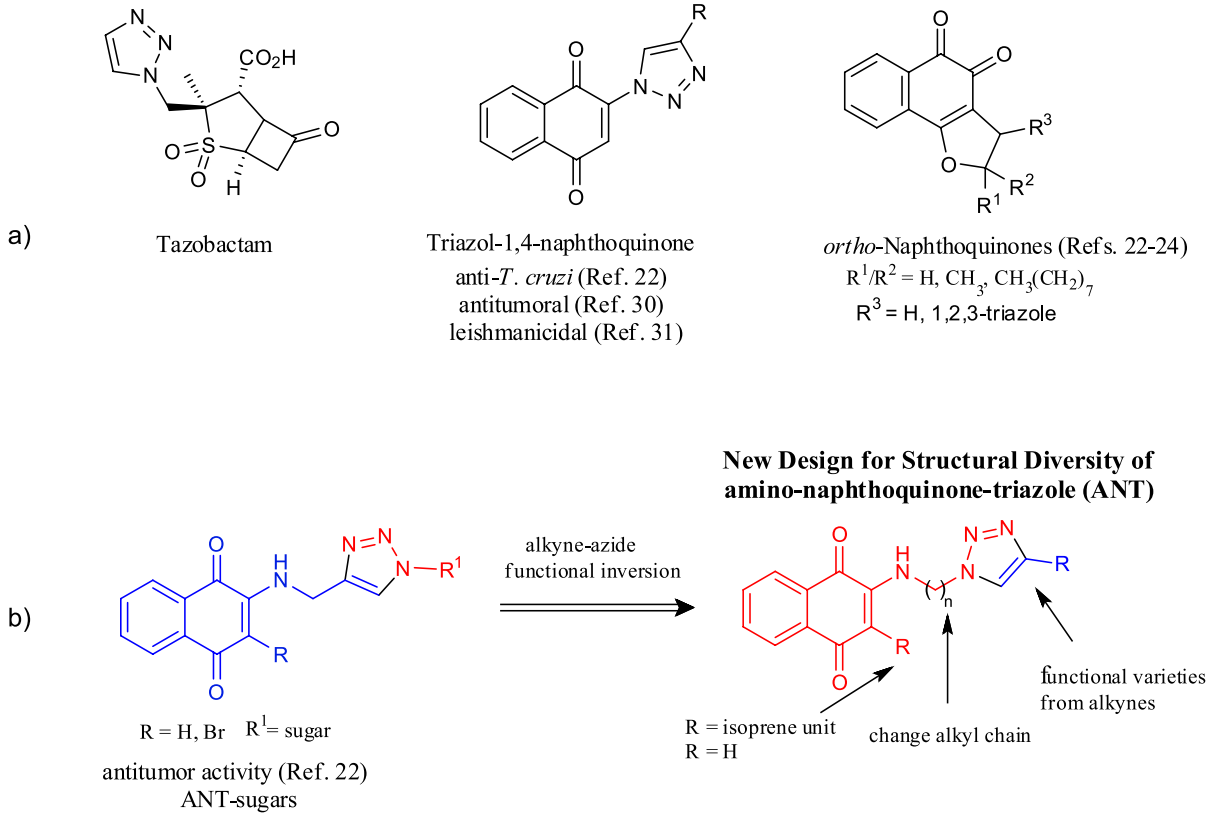
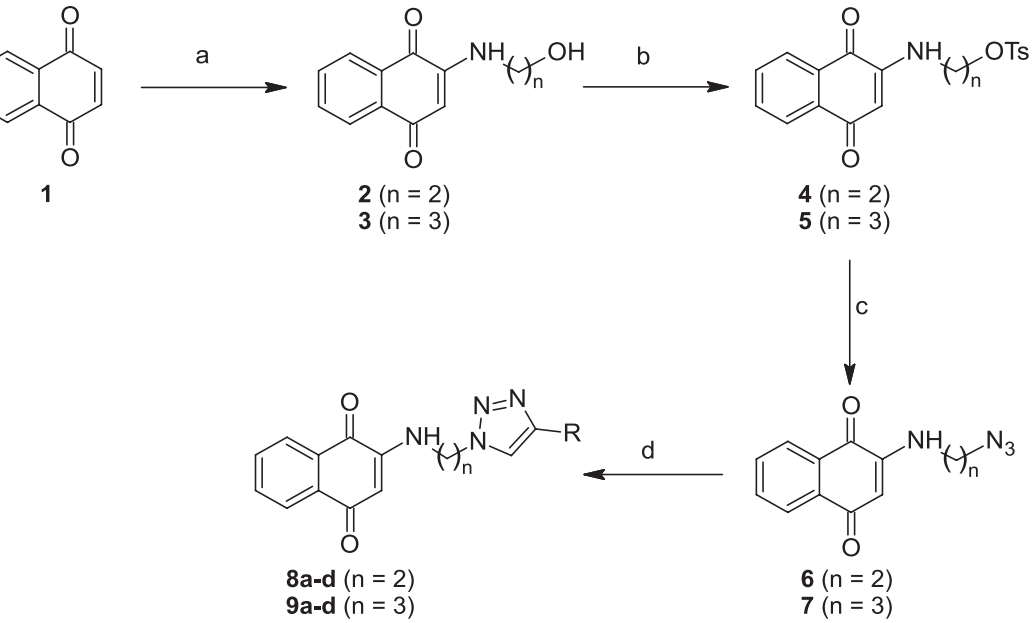
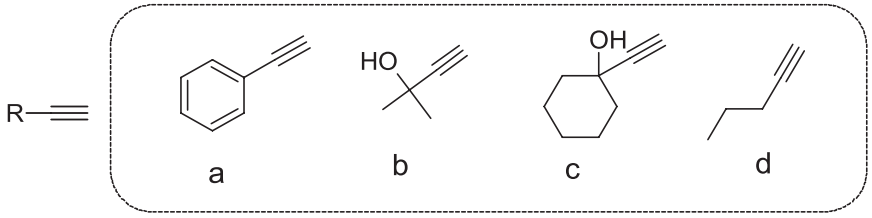



**Figure 1.** Target small-molecules containing 1,2,3-triazole moiety.




**Scheme 1.** Reagents and conditions: (a) ethanolamine, MeCN, r.t., 3 h (67-73%); (b) TsCl, $Et_3N$, $CH_2Cl_2$, r.t., 5 h (68-81%); (c) $NaN_3$, DMSO, 50 °C, 10 min; (d) RC≡CH, CuI, $Et_3N$, DMSO, r.t., 2-5 h (70-96%).

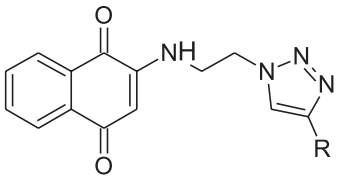
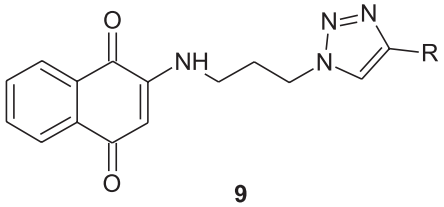
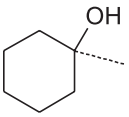
quinones **8a-d** and **9a-d** starting from 1,4-NQ and amino alcohols resulted in an overall yield of roughly 40% after four steps.

The structures of compounds (**8a**-**d**, **9a**-**d**) were assigned on the basis of their $^1$H and $^{13}$C nuclear magnetic resonance (NMR), and electrospray ionization high-resolution mass spectrometry (ESI-HRMS) analysis. The hydrogen H-5' in the triazolic ring appears as a singlet in the $^1$H NMR spectral region between $\delta$ 7.47 and 8.57 ppm. Naphthoquinone hydrogens (Naph-$H_3$) absorb as a singlet at $\delta$ 5.6-5.8 ppm. The methylene hydrogens $(CH_2)_n$ showed the side chain as a more displaced triplet with respect to $CH_2$-triazol. A pseudo quartet for methylene protons in NH-$CH_2$, caused by hydrogens on NH and $CH_2$, is located upfield at $\delta$ 3.6-3.7 ppm (**8a-d**) or $\delta$ 2.8-3.2 ppm (**9a-d**). The NH protons absorbed about $\delta$ 7.5 ppm splitting into a broad triplet ($J_{vic}$ ca. 5.4-6.1 Hz).

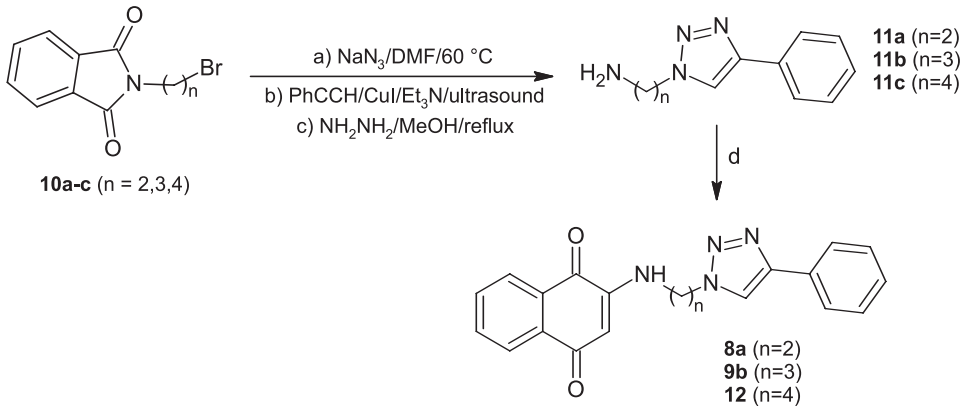
After these initial results, we envisaged the preparation of 2-amino-1,4-NQ derivatives by another synthetic route (Strategy B, cf. Scheme 2). We thought that 2-amino-alkyl-(1*H*-1,2,3-triazol-1-yl)-1,4-naphthoquinones could be synthesized from amine-1,2,3-triazoles; the scope of these reactions is depicted in Scheme 2. To pursue the Strategy B, we started from the reaction of bromo-alkyl phthalimides **10a**-**c** with sodium azide in DMF at 60 °C to obtain azide compounds in isolated yields of 70-93%. Azide substrates were subjected to click protocol with phenyl acetylene to afford the 1,2,3-triazoles under ultrasound irradiation.[32] These crude materials, after ordinary filtration using silica gel, were immediately used for the next step. A mixture of methanol and hydrazine solution (25 wt.% in $H_2O$) was employed to furnish amino-1,2,3-triazoles **11a**-**c** in overall good yields of 49-84% (three steps). The structures of the compounds **11a**-**c** were determined by spectroscopy (see Experimental section). For the compounds **11b** and **11c**, $^1$H NMR spectra show a different chemical shift value for the hydrogen atoms linked to nitrogen from the amine group (Figures S48 and S50). This effect could be explained by a hydrogen bond with nitrogen lone-pair electrons, as already known for 1,2,3-triazole ring.[34] Finally, a facile procedure was introduced for the synthesis of compounds 2-amino-alkyl-1,2,3-triazole-1,4-NQs **8a**, **9a** and **12** with 83-90% of yields (Scheme 2).

The synthesis of **8a** via Strategy A (Scheme 1) showed an overall yield of 47% (four steps). With Strategy B (Scheme 2), all individual steps shown yielded up to 90%

**Table 1.** Synthesis of 1,2,3-triazoles **8a-d** and **9a-d** via Strategy A

| entry | R |  **8** |  **9** |
|---|---|---|---|
| | | Yield[a] / % (reaction time) | |
| 1 | Ph | **a**, 96 (2 h)[b] | **a**, 86 (2 h)[b] |
| 2 |  | **b**, 86 (2 h)[b] | **b**, 81 (2 h) |
| 3 |  | **c**, 74 (2 h) [b] | **c**, 70 (2 h) |
| 4 | $^{n}C_3H_7$ | **d**, 76 (3 h) | **d**, 81 (5 h) |

[a]Yields after column chromatography; [b]yields after crystallization.




**Scheme 2.** Reagents and conditions: (a) $NaN_3$, DMF, 60 °C, 24 h; (b) Ph–C≡CH, CuI, $Et_3N$, ultrasound, 30 min; (c) $NH_2NH_2$, MeOH, reflux, 2 h (49-84% in three steps); (d) 1,4-naphthoquinone, MeCN, r.t., 1.5 h (83-90%).

and, consequently there was an overall yield of 76% (four steps). For compounds **9a** and **12**, the results for global yields are similar as for Strategy A (46%), i.e., the route via Strategy B led to 45% yield after four steps.

Therefore, based on the 1,4-naphthoquinone natural scaffolds, we focused our strategies on preparing new derivatives from *nor*-lapachol **14** and lapachol **15** to exploring their molecular diversification based on nucleophilic displacement of correspondent methoxy-naphthoquinones **16** and **17** with primary amines. This type of analogous has been investigated due to the biological activity of lapachol amine derivatives.[35] To the best of our knowledge, reports on these kinds of hybrids have not been published and represent new opportunities in medicinal chemistry in the design of small molecules libraries for drug discovery.

Using the adapted Kopanski *et al*. method,[36] we prepared **14** from the condensation between lawsone **13** and isobutyraldehyde (92% yield). After this, we converted compounds **14** and **15** into their corresponding methylated products **16** and **17** with yields of 58 and 91%, respectively (Scheme 3).

For *nor*-lapachol **14,** Strategy A (linear synthesis) was chosen to prepare the 2-amino-1,4-NQ-1,2,3-triazoles. This choice was because of the better reactivity of *nor*-lapachol with amines,[35] which then permitted it to be used for a linear strategy. After installation of the isoprenyl group and methylation, compound **18** was prepared from the reaction between amino ethanol and compound **16** in yields of 88%. The tosylated intermediate **19** was prepared and purified (without characterization) and used immediately in the next step. Then, the tosylated compound **19** was treated with $NaN_3$/DMSO to furnish **20** in 65% (two steps). The azide

compound **20** underwent click protocol to obtain **21a-d** in yields of 80-96%, and an overall yield of approximately 27% from lawsone in six steps.

On the other hand, Strategy B (convergent synthesis) was employed to synthesize the 2-amino-1,4-NQs from a reaction between methylated lapachol **17** with amino-triazoles **11a-c**. This strategy led to the amino-lapachol derivatives **22a-c** in moderate to low yields, from 30 to 46%; in all cases the starting materials remained unreacted. Probably a steric hindrance effect of the phenyl in C-3 position determined this behavior. In an attempt to increase the yields, the reactions were carried out under microwave irradiation; however they failed. Using this strategy, we found the global yield to be about 21% (Scheme 3 and Table 2).

The structures of the compounds **8a-d, 9a-d** and **21a-d** were assigned on the basis of their $^{1}H$ and $^{13}C$ NMR spectra, elemental analyses and ESI-HRMS. A complete spectral investigation of compounds **22a-c** through 1D and 2D NMR (correlation spectroscopy (COSY) and heteronuclear multiple-quantum correlation spectroscopy (HMQC)) techniques allowed us to assign its structure as 2-[(4-phenyl-1*H*-1,2,3-triazol-1-yl)alkyl-amino)]-3-(3-methylbut-2-en-1-yl)-1,4-naphthoquinones **22a-c** (see Figures in Supplementary Information). The relations between NH, vinylic hydrogens (*H*C=C) and methylene protons and the methyl groups were assigned using correlated spectral data. For instance, vinylic hydrogens ($\delta$ ca. 5 ppm) show a strong correlation in the COSY spectrum to methylene hydrogens at C-3, which appear at $\delta$ 47-51 ppm according to the HMQC, as expected for lapachol derivatives.[35,37]

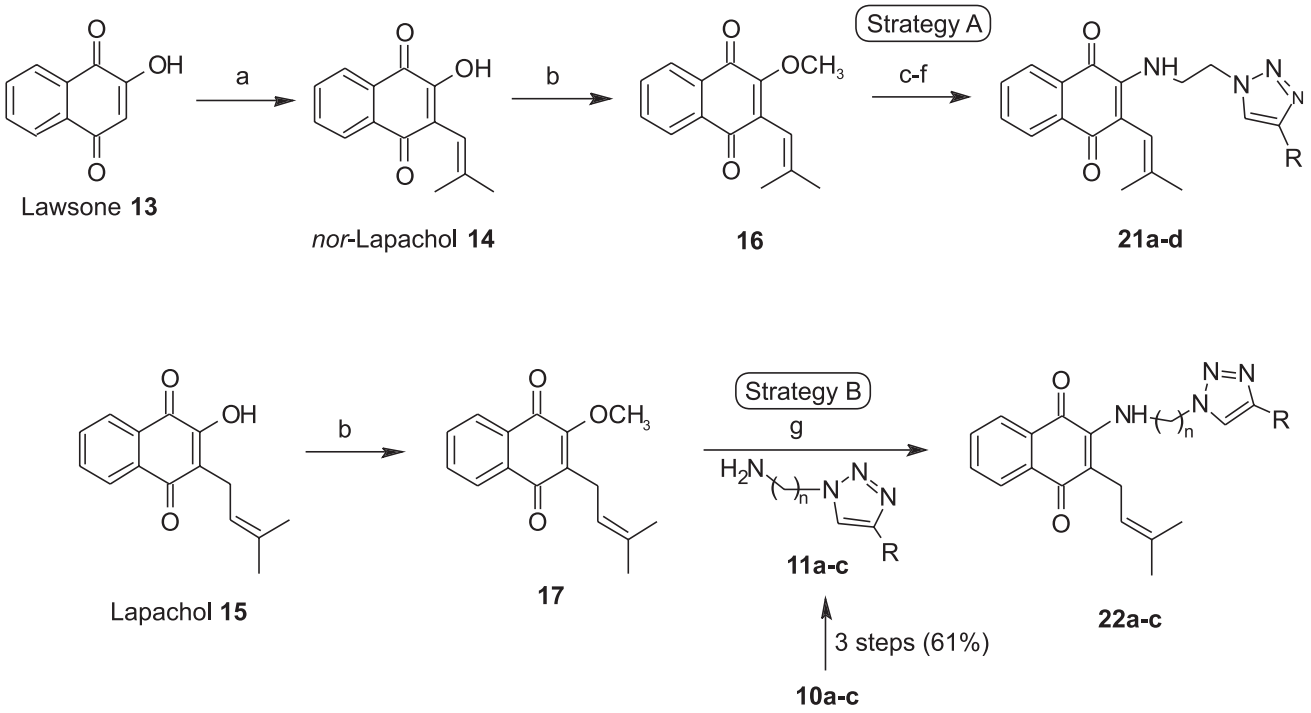
The amino-alkyl-1,2,3-triazole-1,4-naphthoquinones obtained from methylated *nor*-lapachol and lapachol, agreed with those currently proposed mechanisms for nucleophilic substitution reactions (Scheme 4).[37] The first step involved a Michael addition reaction between 1,4-naphthoquinones and the amino compounds; a subsequent proton transfer and solvent-mediated elimination of methanol led to desired products.

## Conclusions

In this work, two strategies based on click-chemistry for the synthesis of new 2-amino-alkyl-1,2,3-triazole-1,4-naphthoquinones derivatives were defined. These strategies permitted us to obtain the desired products in an overall good yields from 1,4-NQ, lawsone and lapachol. These synthetic strategies may lead us to new opportunities to build small-molecule libraries for future biological exploration.

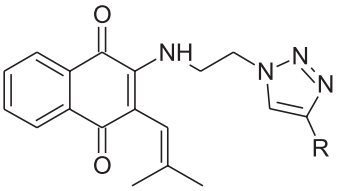
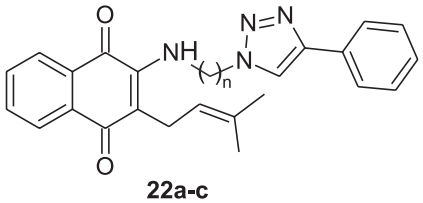
## Experimental

Air- and moisture-sensitive reactions were carried out under argon atmosphere. Reagents were purchased

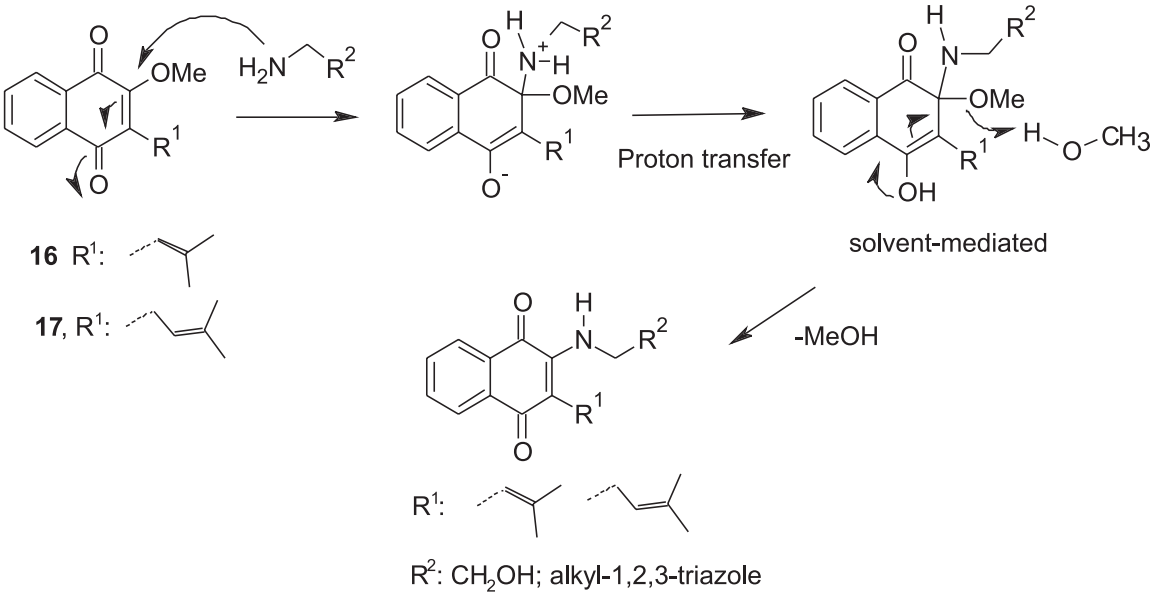



**Scheme 3.** Reagents and conditions: (a) isobutyl aldehyde, β-alanine, AcOH, toluene, 120 °C, **14** (92%); (b) $Me_2SO_4$, $K_2CO_3$, acetone, r.t., 3 h, **16** (58%), **17** (91%); (c) ethanolamine, MeOH, r.t., 24 h, **18** (88%); (d) TsCl, $Et_3N$, $CH_2Cl_2$, r.t., 3 h, **19**; (e) $NaN_3$, DMSO, r.t., 8 h, **20** (65%, two steps); (f) RC≡CH, CuI, $Et_3N$, DMSO, r.t., 2 h, **21a-d** (80-96%); (g) amino-triazole, MeOH, r.t., 24 h, **22a-c** (30-46%).

**Table 2.** Synthesis of compounds **21a-d** and **22a-c**

| Product | Strategy and yield | |
|---|---|---|
|  | Strategy A | Yield[a] / % |
| | **21a**, R = Ph | 83 |
| | **21b**, R = 4-MeOPh | 80 |
| | **21c**, R = 4-MePh | 96 |
| **21a-d** | **21d**, R = $(CH_3)_2COH$ | 90 |
|  | Strategy B | Yield[a] / % |
| | **22a**, n = 2 | 30 |
| | **22b**, n = 3 | 46 (31)[b] |
| **22a-c** | **22c**, n = 4 | 38 (30)[b] |

[a]Yields after column chromatography; [b]yields in brackets are where microwave irradiation was applied.




**Scheme 4.** Mechanism for amino-1,4-NQs from methylated lapachol and *nor*-lapachol.

from Acros or Sigma-Aldrich and used without further purification. Reactions were monitored by TLC analysis on precoated silica gel plates (Merck, Kieselgel 60F254) and compounds were visualized with UV light. Column chromatography was performed on silica gel SI 60 (70-230 mesh, Merck). Melting points were measured in open capillary tubes in a PFM II BioSan apparatus and are uncorrected. Elemental analyses were carried out in an EA1110 CHNS-O analyzer. Microwave reactions were conducted in a focused microwave (FMW) power delivery system, using a CEM Discover Synthesis (Model 908005, 0-300 W, 2455 MHz, CEM Corporation). Power applied for the synthesis was 100 W and procedure temperature was 75 °C. The reactions were performed in sealed glass vessels (capacity 10 mL). The infrared spectra were recorded on an IFS66 Bruker spectrophotometer using KBr discs. HRMS analyses were performed on a LC-MS/ESI(−)TOF spectrometer (Model Xevo G2-XS QTof, Waters). NMR ($^1$H at 400 MHz and $^{13}$C at 100 MHz) spectra were recorded on a Varian Unity Plus-400 spectrometer, using $CDCl_3$ or DMSO-$d_6$ as solvents, and calibrated for the solvent signal. Chemical shifts are expressed in parts *per* million (ppm) and coupling constants are given in Hz. Assignments are based on COSY and heteronuclear single quantum coherence (HSQC) experiments.

## Supplementary Information

Supplementary information (spectra for IR, $^{1}H$ and $^{13}C$ NMR and HRMS of the synthesized compounds) is available free of charge at http://jbcs.sbq.org.br as PDF file.

## Acknowledgments

The authors are grateful to CNPq (448082/2014-4), FACEPE-PRONEM (APQ 0741-1.06/14) and CAPES for financial support and fellowships. Our thanks are also extended to Analytical Center DQF-UFPE and CENAPESQ-UFRPE.

## References

1. Hudlický, T.; Reed, J. W.; *The Way of Synthesis. Evolution of Design and Methods for Natural Products*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2007.
2. Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B.; *Angew. Chem., Int. Ed.* **2002**, *41*, 2596.
3. Tornøe, C. W.; Christensen, C.; Meldal, M. P.; *J. Org. Chem.* **2002**, *67*, 3057.
4. Jlaila, I.; Beauvineau, C.; Beauvière, S.; Önen, E.; Aufort, M.; Beauvineau, A.; Khaba, E.; Herscovici, J.; Meganem, F.; Girard, C.; *Molecules* **2010**, *15*, 3087.
5. Goyard, D.; Docsa, T.; Gergely, P.; Praly, J.-P.; Vidal, S.; *Carbohydr. Res.* **2015**, *402*, 245.
6. Yoshida, S.; Nonaka, T.; Morita, T.; Hosoya, T.; *Org. Biomol. Chem.* **2014**, *12*, 7489.
7. Haldón, E.; Álvarez, E.; Nicasio, C.; Pérez, P. J.; *Chem. Commun.* **2014**, *50*, 8978.
8. Kommgalla, Y.; Cornea, S.; Riehle, R.; Torchilin, V.; Degterev, A.; Ramana, C. V.; *Med. Chem. Commun.* **2014**, *5*, 1359.
9. Günther, K. U.; Ziegler, T.; *Synthesis* **2014**, 2362.
10. Dedola, S.; Hughes, D. L.; Nepogodiev, S. A.; Rejzek, M.; Field, R. A.; *Carbohydr. Res.* **2010**, *345*, 1123.
11. Yoshida, S.; Nonaka, T.; Morita, T.; Hosoya, T.; *Org. Biomol. Chem.* **2014**, *12*, 7489.
12. Kolb, H. C.; Sharpless, K. B.; *Drug Discovery Today* **2003**, *8*, 1128.
13. Thirumurugan, P.; Matosiuk, D.; Jozwiak, K.; *Chem. Rev.* **2013**, *113*, 4905.
14. Kumar, K. K.; Seenivasan, S. P.; Kumar, V.; Das, T. M.; *Carbohydr. Res.* **2011**, *346*, 2084.
15. Xia, Y.; Li, W.; Qu, F.; Fan, Z.; Liu, X.; Berro, C.; Rauzy, E.; Peng, L.; *Org. Biomol. Chem.* **2007**, *5*, 1695.
16. Wellington, K. W.; *RSC Adv.* **2015**, *5*, 20309.
17. da Cruz, E. H. G.; Hussene, C. M. B.; Dias, G. G.; Diogo, E. B. T.; de Melo, I. M. M.; Rodrigues, B. L.; da Silva, M. G.; Valença, W. O.; Camara, C. A.; de Oliveira, R. N.; de Paiva, Y. G.; Goulart, M. O. F.; Cavalcanti, B. C.; Pessoa, C.; da Silva Jr., E. N.; *Bioorg. Med. Chem.* **2014**, *22*, 1608.
18. Delarmelina, M.; Daltoé, R. D.; Cerri, M. F.; Madeira, K. P.; Rangel, L. B. A.; Lacerda Jr., V.; Romão, W.; Tarantod, A. G.; Greco, S. J.; *J. Braz. Chem. Soc*. **2015**, *26*, 1804.
19. Sangshetti, J. N.; Nagawade, R. R.; Shinde, D. B.; *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3564.
20. Xu, W. L.; Li, Y. Z.; Zhang, Q. S.; Zhu, H. S.; *Synthesis* **2005**, 442.
21. Agalave, S. G.; Maujan, S. R.; Pore, V. S.; *Chem. - Asian J.* **2011**, *6*, 2696.
22. Diogo, E. B. T.; Dias, G. G.; Rodrigues, B. L.; Guimarães, T. T.; Valença, W. O.; Camara, C. A.; de Oliveira, R. N.; da Silva, M. G.; Ferreira, V. F.; Paiva, Y. G.; Goulard, M. O. F.; Menna-Barreto, R. F. S.; Castro, S. L.; da Silva Jr., E. N.; *Bioorg. Med. Chem.* **2013**, *21*, 6337.
23. Silva, A. O.; Lopes, R. S.; de Lima, R. V.; Tozatti, C. S. S.; Marques, M. R.; Albuquerque, S.; Beatriz, A.; de Lima, D. P.; *Eur. J. Med. Chem.* **2013**, *60,* 51.
24. Naujorks, A. A. S.; da Silva, A. O.; Lopes, R. S.; Albuquerque, S.; Beatriz, A.; Marquesd, M. R.; de Lima, D. P.; *Org. Biomol. Chem.* **2015**, *13*, 428.
25. da Silva Jr., E. N.; Menna-Barreto, R. F. S.; Pinto, M. C. F. R.; Silva, R. S. F.; Teixeira, D. V.; de Souza, M. C. B. V.; de Simone, C. A.; de Castro, S. L.; Ferreira, V. F.; Pinto, A. V.; *Eur. J. Med. Chem.* **2008**, *43*, 1774.
26. Castro, S. L.; Emery, F. S.; da Silva Jr., E. N.; *Eur. J. Med. Chem.* **2013**, *69*, 678.
27. Jardim, G. A. M.; Reis, W. J.; Ribeiro, M. F.; Ottoni, F. M.; Alves, R. J.; Silva, T. L.; Goulart, M. O. F.; Braga, A. L.; Menna-Barreto, R. F. S.; Salomão, K.; Castro, S.L.; da Silva Jr., E. N.; *RSC Adv.* **2015**, *5*, 78047.
28. Lin, L.; Shen, Q.; Chen, G.-R.; Xie, J.; *Bioorg. Med. Chem.* **2008**, *16,* 9757; Bala, B. D.; Muthusaravanan, S.; Choon, T. S.; Ali, M. A.; Perumal, S.; *Eur. J. Med. Chem.* **2014**, *85*, 737.
29. Nascimento, W. S.; Camara, C. A.; de Oliveira, R. N.; Synthesis **2011**, *20,* 3220.
30. Coulidiati, T. H.; Dantas, B. B.; Faheina-Martins, G. V.; Gonçalves, J. C. R.; Nascimento, W. S.; Oliveira, R. N.; Camara, C. A.; Oliveira, E. J.; Lara, A.; Gomes, E. R.; Araújo, D. A. M.; *J. Pharm. Pharmacol.* **2015**, *67*, 1682.
31. Guimarães, T. T.; Pinto, M. C. F. R.; Lanza, J. S.; Melo, M. N.; do Monte-Neto, R. L.; de Melo, I. M. M.; Diogo, E. B. T.; Ferreira, V. F.; Camara, C. A.; Valença, W. O.; de Oliveira, R. N.; Frézard, F.; da Silva Júnior, E. N.; *Eur. J. Med. Chem.* **2013**, *63*, 523.
32. da Silva, M. T.; de Oliveira, R. N.; Valença, W. O.; Barbosa, F. C. G.; da Silva, M. G.; Camara, C. A.; *J. Braz. Chem. Soc.* **2012**, *23*, 1839.
33. MacGregor, K. A.; Abdel-Hamid, M. K.; Odell, L. R.; Chau, N.; Whiting, A.; Robinson, P. J.; McCluskey, A.; *Eur. J. Med. Chem.* **2014**, *85*, 191.

34. Yan, W.; Ye, X.; Akhmedov, N. G.; Petersen, J. L.; Shi, X.; *Org. Lett.* **2012**, *14*, 2358.
35. Barbosa, T. P.; Camara, C. A.; Silva, T. M. S.; Martins, R. M.; Pinto, A. C.; Vargas, M. D.; *Bioorg. Med. Chem.* **2005**, *13,* 6464.
36. Kopanski, L.; Karbach, D.; Selbitschka, G.; Steglich, W.; *Liebigs Ann. Chem.* **1987**, 793.
37. Camara, C. A.; Pinto, A. C.; Rosa, M. A.; Vargas, M. D.; *Tetrahedron* **2001**, *57*, 9569 and cited references.

*Submitted: May 5, 2016*
*Published online: July 13, 2016*