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Original Article

A Green and Efficient NH_4OAc-catalyzed Synthesis of 2-Hydroxy-3-(arylmethyl)(4-hydroxy-2-oxo-2,5-dihydrofuran-3-yl)-1,4-naphthoquinones

Le Nhat Thuy Giang[1,2,*], Dang Thi Tuyet Anh[1,2], Nguyen Ha Thanh[1,2], Hoang Thi Phuong[1], Nguyen Tuan Anh[1], Nguyen Thi Quynh Giang[1], Vu Thi Thu Ha[3], Nguyen Van Tuyen[1,2]

[1]*Institute of Chemistry, Vietnam Academy of Science and Technology, 18 Hoang Quoc Viet, Cau Giay, Hanoi, Vietnam*
[2]*Graduate University of Science and Technology, Vietnam Academy of Science and Technology, 18 Hoang Quoc Viet, Cau Giay, Hanoi, Vietnam*
[3]*Hanoi University of Natural Resources and Environment, 41A Phu Dien, Nam Tu Liem, Hanoi, Vietnam*

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Abstract: The green and efficient approach for synthesis of 2-hydroxy-3-(arylmethyl)(4-hydroxy-2-oxo-2,5-dihydrofuran-3-yl)-1,4-naphthoquinones starting from 2-hydroxy-1,4-naphthoquinone, tetronic acid, and aromatic aldehydes was developed. These reactions were carried out in ethanol under microwave irradiation in the presence of ammonium acetate as catalyst. These multicomponent domino reactions presumably occur via NH_4OAc-catalyzed Mannich reaction - Michael addition - hydration - tautomerism - elimination sequence of reactions.

Keywords: 1,4-Naphthoquinones, furan-fused compounds, ammonium acetate, multicomponent domino reactions.

1. Introduction

1,4-Naphthoquinone compounds are of great importance in medicinal chemistry due to their broad spectrum of pharmacological properties [1, 2], among which anticancer and antibiotics activities are specially highlighted. Several lead 1,4-naphthoquinone compounds are lawsone, α-lapachone and bostrycoidin). The synthesis of bioactive 1,4-naphthoquinone derivatives based on multicomponent domino reactions is currently one of major research strategies of our group [3-7].

Besides that, furan-fused polycylic compounds have been also attracted lots of attention as anti-inflammatory and antimicrobial [8], antiproliferative [9], and antiviral agents [10]. Therefore, the

* Corresponding author.
E-mail address: lenhatthuygiang@yahoo.com

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combination of naphthoquinone scaffold and furan ring into a single molecular could give more interesting biological properties. In our previous study [6], we have successfully synthesized a series of 3-arylate-2-hydroxy-1,4-naphthoquinone derivatives containing γ-butyrolactone at C-3 side chain of naphthoquinone scaffold, which exhibited interesting cytotoxic activities against KB and HepG2 human cancer cell lines. These compounds were obtained in moderate yields by reaction of 2-hydroxy-1,4-naphthoquinone (lawsone), tetronic acid and aldehyde in acetic acid under microwave irradiation (MW).

In recent years, the use of microwave irradiation techniques has allowed to reduce significantly reaction times and chemical agents in several organic syntheses [11]. Furthermore, ammonium acetate has been widely used as an efficient catalyst in the synthesis of heterocyclic compounds [12-14]. With the aim to develop a green and eco-friendly procedure and improve the reaction yields, in this study, the green and efficient approach for synthesis of 2-hydroxy-3-(arylmethyl)(4-hydroxy-2-oxo-2,5-dihydrofuran-3-yl)-1,4-naphthoquinones 4a-g using ethanol and ammonium acetate as green solvent and catalyst was developed.

2. Experimental

General conditions. Reactions were performed in an Anton Paar Microwave Synthetic Reactor Monowave 400. All reagents and solvents were purchased from Aldrich or Merck unless noted otherwise. Solvents for reactions were dried and distilled by standard methods. Solvents for liquid chromatography and extraction were distilled prior to use. Silica gel (60Å, particle size 40-60 μm) was used for column chromatography. Solvent systems were determined via initial TLC analysis on glass-backed silica plates (Merck Kieselgel 60 with F254 indicator, precoated 0.25 mm). High resolution ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance III spectrometer (500 and 125 MHz) using deuterated solvents and tetramethylsilane (TMS) as internal standard. HRMS was recorded on SCIEX X500 QTOF system. Melting points were measured using a Buchi Melting Point B-545 and are uncorrected.

Synthesis of compounds 4a-g. A vial containing a mixture of 2-hydroxy-1,4-naphthoquinone 1 (5.3 mg, 0.3 mmol), tetronic acid 2 (30 mg, 0.3 mmol), aromatic aldehyde 3a-g (1.0 mmol), ammonium acetate (3 mg, 0.1 mmol) in ethanol (5 ml) was sealed and placed in a Anton Paar Microwave Synthetic Reactor. The vial was subjected to microwave irradiation, programmed at 98 ^{o}C and 150 W. After a period of 30 second, the temperature reached a plauteau, 98 ^{o}C, and remained constant. After completion of the reaction (15-20 min), the vial was cooled to room temperature. The crude products were purified by column chromatography using a MeOH/CH_2Cl_2/EtOAc (1:4:5 v/v) to yield pure compounds 4a-g.

2-Hydroxy-3-[(4-hydroxy-2-oxo-2,5-dihydrofuran-3-yl)(3-methoxyphenyl) methyl]naphtha lene-1,4-dione (4a). Reaction time 15 min. Yield 110 mg (92%), orange solid, decomp. 227-228V °C (decomp. 226-228 ^{o}C [6]). ^{1}H NMR (MeOD, 500 MHz): δ 8.07 (1H, d, *J* = 7.5 Hz), 7.94 (1H, d, *J* = 8.0 Hz), 7.74 (1H, td, *J* = 1.0 Hz, *J* = 7.5 Hz), 7.62 (1H, td, *J* = 1.5 Hz, *J* = 7.5 Hz), 6.98 (1H, t, *J* = 8.0 Hz), 6.76-6.74 (2H, m), 6.54 (1H, dd, *J* = 2.5 Hz, *J* = 8.5 Hz), 5.81 (1H, s), 4.62 (1H, d, *J* = 16.0 Hz), 4.60 (1H, d, *J* = 15.5 Hz), 3.64 (3H, s). ^{13}C NMR (MeOD, 125 MHz): δ 188.4, 185.3, 180.8, 179.8, 160.9, 144.7, 135.5, 135.4, 132.9, 132.4, 129.7, 127.3, 127.0, 125.4, 120.6, 114.4, 111.4, 101.2, 68.7, 55.5, 33.2. HRMS (ESI+) *m/z* [M-H]$^{-}$ calc. for: $C_{22}H_{15}O_7$: 391.0818, found: 391.0807.

2-Hydroxy-3-[(4-hydroxy-2-oxo-2,5-dihydrofuran-3-yl)(4-methoxyphenyl) methyl]naphthalene-1,4-dione (4b). Reaction time 15 min. Yield 106 mg (90%), orange solid, decomp. 176-178 °C (decomp. 179-182 ^{o}C [6]). ^{1}H NMR (MeOD, 500 MHz): 8.07 (1H, d, *J* = 8.0 Hz), 7.96 (1H, d, *J* = 7.5 Hz), 7.74 (1H, td, *J* = 1.0 Hz, *J* = 7.5 Hz), 7.63 (1H, td, *J* = 1.0 Hz, *J* = 7.5 Hz), 7.10 (2H, d, *J* = 8.0 Hz), 6.89

(2H, d, *J* = 9.0 Hz), 5.80 (1H, s), 4.63 (1H, d, *J* = 15.5 Hz), 4.56 (2H, br.s), 4.49 (1H, d, *J* = 16.0 Hz), 3.67 (3H, s). HRMS (ESI+) *m/z* [M-H]$^-$ calc. for: $C_{22}H_{15}O_7$: 391.0818, found: 391.0837.

2-((3,4-dimethoxyphenyl)(4-hydroxy-2-oxo-2,5-dihydrofuran-3-yl)methyl)-3-hydroxy-naphthalene-1,4-dione (4c). Reaction time 20 min. Yield 89 mg (82%), orange solid, decomp. 271-272°C. ^{1}H NMR (MeOD, 500 MHz): δ 8.07 (1H, d, *J* = 7.5 Hz), 7.95 (1H, d, *J* = 7.5 Hz), 7.74 (1H, t, *J* = 7.5 Hz), 7.62 (1H, t, *J* = 7.5 Hz), 6.79 (1H, d, *J* = 1.5 Hz), 6.73 (1H, ds, *J* = 8.5 Hz, *J* = 1.0 Hz), 6.66 (1H, d, *J* = 8.5 Hz), 5.79 (1H, s), 4.61 (1H, d, *J* = 16.0 Hz), 4.44 (1H, d, *J* = 16.0 Hz), 3.70 (3H, s), 3.67 (3H, s). ^{13}C NMR (MeOD, 125 MHz): δ 188.3, 185.3, 179.6, 171.9, 150.0, 148.5, 135.9, 135.7, 135.6, 132.9, 132.2, 127.4, 127.1, 125.1, 120.7, 112.8, 112.7, 101.8, 68.5, 56.5, 56.45, 32.9. HRMS (ESI+) *m/z* [M-H]$^-$ calc. for: $C_{23}H_{17}O_8$: 421.0923, found: 421.0930.

2-[(4-Bromophenyl)(4-hydroxy-2-oxo-2,5-dihydrofuran-3-yl)methyl]-3-hydroxy naphthalene-1,4-dione (4d). Reaction time 15 min. Yield 109 mg (83%), orange solid, decomp. 231-233 °C (decomp. 230-232 °C [6]). ^{1}H NMR (MeOD, 500 MHz): δ 8.08 (1H, d, *J* = 7.5 Hz), 7.95 (1H, d, *J* = 7.5 Hz), 7.74 (1H, td, *J* = 1.5 Hz, *J* = 7.5 Hz), 7.63 (1H, td, *J* = 1.0 Hz, *J* = 7.5 Hz), 7.27 (2H, d, *J* = 8.5 Hz), 7.13 (2H, d, *J* = 8.5 Hz), 5.81 (1H, s), 4.65 (1H, d, *J* = 16.0 Hz), 4.51 (1H, d, *J* = 15.5 Hz). ^{13}C NMR (MeOD, 125 MHz): δ 188.2, 185.1, 181.2, 179.7, 142.7, 135.4, 135.3, 132.9, 132.5, 131.8 (2C), 130.3 (2C), 127.3, 126.8, 125.2, 120.0, 100.7, 68.8, 33.0. HRMS (ESI+) *m/z* [M-H]$^-$ calcd. for: $C_{21}H_{12}BrO_6^-$: 438.9817 and 440.9797, found: 438.9806 and 440.9787.

4-((3-Hydroxy-1,4-dioxo-1,4-dihydronaph-thalen-2-yl)(4-hydroxy-2-oxo-2,5-dihydrofuran-3-yl)methyl)benzonitrile (4e). Reaction time 18 min. Yield 101 mg (87%), orange solid, decomp. 266-267 °C. ^{1}H NMR (MeOD, 500 MHz): δ 8.08 (1H, d, *J* = 7.5 Hz), 7.96 (1H, d, *J* = 7.5 Hz), 7.74 (1H, td, *J* = 1.5 Hz, *J* = 7.5 Hz), 7.64 (1H, td, *J* = 0.5 Hz, *J* = 7.5 Hz), 7.53 (2H, d, *J* = 8.0 Hz), 7.40 (2H, d, *J* = 8.0 Hz), 5.91 (1H, s), 4.69 (1H, d, *J* = 16.0 Hz), 4.56 (1H, d, *J* = 16.0 Hz). ^{13}C NMR (MeOD, 125 MHz): δ 187.2, 184.9, 181.7, 179.6, 168.6, 149.9, 135.3, 135.2, 133.0, 132.8 (2C), 132.5, 129.3 (2C), 127.3, 126.8, 124.8, 120.1, 109.9, 100.1, 68.9, 33.8. HRMS (ESI+) *m/z* [M-H]$^-$ calc. for: $C_{22}H_{12}NO_6$: 386.0665, found: 386.0668.

2-(Benzo[*d*][1,3]dioxol-5-yl(4-hydroxy-2-oxo-2,5-dihydrofuran-3-yl)methyl)-3-hydroxy-naphthalene-1,4-dione (4f). Reaction time 20 min. Yield 98 mg (81%), orange solid, decomp. 264-265 °C. ^{1}H NMR (MeOD, 500 MHz): δ 8.06 (1H, d, *J* = 7.5 Hz), 7.95 (1H, d, *J* = 7.5 Hz), 7.73 (1H, td, *J* = 1.0 Hz, *J* = 7.5 Hz), 7.62 (1H, t, *J* = 7.5 Hz), 6.63 (1H, br. s), 6.61 (1H, d, *J* = 8.5 Hz), 6.44 (1H, d, *J* = 8.0 Hz), 5.73 (2H, s, OCH_2O), 5.72 (1H, s), 4.61 (1H, d, *J* = 16.0 Hz), 4.45 (1H, d, *J* = 16.0 Hz). ^{13}C NMR (MeOD, 125 MHz): δ 189.8, 185.8, 180.7, 180.0, 170.9, 148.8, 146.7, 135.4, 132.9, 132.4, 127.3, 126.9, 125.1, 121.0, 108.9, 108.4, 101.9, 101.2, 68.7, 33.0. HRMS (ESI+) *m/z* [M-H]$^-$ calc. for: $C_{22}H_{13}O_8$: 405.0610, found: 405.0620.

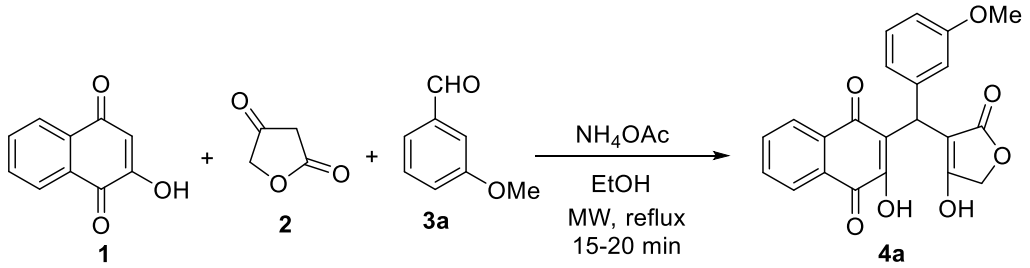
2-Hydroxy-3-((4-hydroxy-2-oxo-2,5-dihydrofuran-3-yl)(pyridin-3-yl)methyl) naphthalene-1,4-dione (4 g). Reaction time 20 min. Yield 89 mg (82%), orange solid, decomp. 251-252 °C. ^{1}H NMR (DMSO-*d6*, 500 MHz): δ 8.32 (1H, d, *J* = 2.0 Hz), 8.23 (1H, d, *J* = 4.0 Hz), 7.95 (1H, d, *J* = 7.5 Hz), 7.82 (1H, d, *J* = 7.0 Hz), 7.72 (1H, td, *J* = 7.5 Hz, *J* = 1.0 Hz), 7.61 (1H, td, *J* = 7.5 Hz, *J* = 1.0 Hz), 7.52 (1H, d, *J* = 8.0 Hz), 7.15 (1H, dd, *J* = 7.5 Hz, *J* = 4.5 Hz), 5.63 (1H, s), 4.40 (1H, d, *J* = 12.0 Hz), 4.30 (1H, *J* = 14.5 Hz). ^{13}C NMR (DMSO-*d6*, 125 MHz): δ 188.8, 185.8, 181.4, 179.7, 167.5, 150.7, 148.7, 145.8, 139.1, 137.9, 134.7, 134.1, 133.7, 131.3, 131.0, 125.7, 125.0, 122.7, 67.5, 30.3. HRMS (ESI+) *m/z* [M-H]$^-$ calc. for: $C_{20}H_{12}NO_6$: 362.0665, found: 362.0664.

3. Results and Discussion

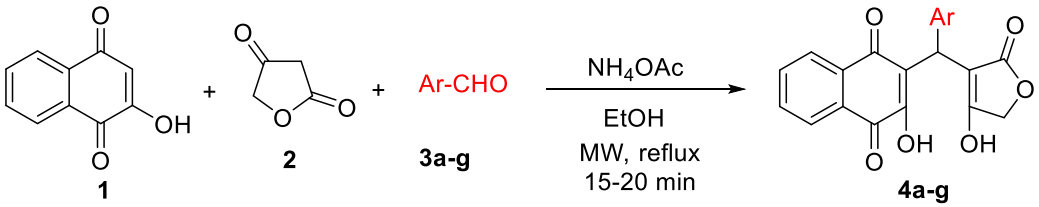
The synthesis of compound 4a was chosen for the screening of optimal reaction conditions.

Thus, the reaction of 2-hydroxy-1,4-naphthoquinone 1 (1 mmol), tetronic acid 2 (1 mmol), 3-methoxybenzaldehyde 3a (1 mmol) and ammonium acetate was carried out in the methanol, ethanol or *i*-propanol at reflux under microwave irradiation (Table 1, entries 1-7). As shown in Table 1 (entries 1-3), ethanol was appropriate solvent for this reaction. The results showed that the reaction in ethanol with 30 mol% NH_4OAc gave the target product 4a with highest yield (92%, entry 5). The use of lower amount of NH_4OAc (10 mol%) required a longer reaction time to give a comparable yield of compound 4a (entry 4). Besides that, the yield was not further improved when an excess amount of catalyst (40 mol%) was loaded (entry 6). Furthermore, we also examined the reaction in the absence of NH4OAc and compound 4a was obtained in 47% yield (entry 7). According to these results, NH_4OAc (30 mol%) in ethanol at reflux under MW came out as the optimized conditions for the synthesis of compound 4[a] (Table 1).

Based on the optimized reaction conditions, different benzaldehyde 3a-g were applied to this reaction to obtain a series of compounds 4a-g (Scheme 1). After purification by means of column chromatography, compounds 4a-g were obtained in high yields (81-92%). The chemical structures of compounds 4a-g were determined by IR, ^{1}H NMR, ^{13}C NMR, and mass spectrometry (Scheme 1, Scheme 2).

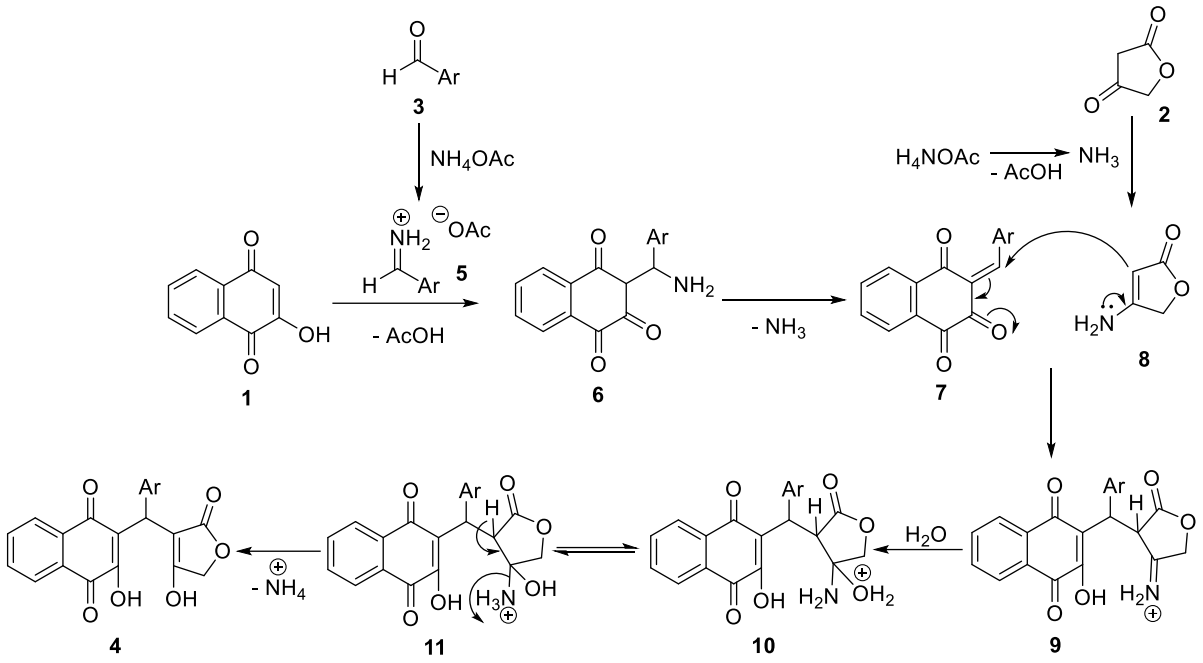


Entry	Solvent	Catalyst	Time	Isolated yield (%)
1	MeOH	NH_4OAc (20 mol%)	15 min	50
2	EtOH	NH_4OAc (20 mol%)	15 min	75
3	*i*-PrOH	NH_4OAc (20 mol%)	15 min	53
4	EtOH	NH_4OAc (10 mol%)	20 min	68
5	EtOH	NH_4OAc (30 mol%)	15 min	92
6	EtOH	NH_4OAc (40 mol%)	15 min	92
7	EtOH	-	15 min	47



Ar = 3-$OMeC_6H_4$ (**a**), 4-$OMeC_6H_4$ (**b**), 3,4-$(OMe)_2$-C_6H_3 (**c**), 4-BrC_6H_4 (**d**), 4-CN-C_6H_4 (**e**), 3,4-OCH_2O-C_6H_3 (**f**), pyridin-3-yl (**g**)

Scheme 1. Synthesis of 2-hydroxy-3-(arylmethyl)(4-hydroxy-2-oxo-2,5-dihydrofuran-3-yl)-1,4-naphthoquinones 4a-g.



Scheme 2. Possible mechanism for the formation of compounds 4.

Compared with results in our previous work [6], the application of ammonium acetate as catalyst and ethanol as solvent significantly enhanced the reaction yields of compounds 4a-c. The yield of compound 4a was 86% in the case of using acetic acid as solvent and catalyst [6], meanwhile its yield increased to 92% when ammonium acetate was employed as catalyst in ethanol. We also examinized the reaction in ethanol in the absense of NH_4OAc and compound 4a was obtained only in 47% yield. This may be explained by the possible mechanism for the formation of products 4 shown in Scheme 2. The Mannich reaction of lawsone (1), aldehydes 3 and ammonium acetate proceeded via the formation of iminium acetates 5, generated in situ from reaction of aldehydes 3 and NH_4OAc, which were then reacted with lawsone (1) to give the 3-(amino(aryl)methyl)naphthalene-1,2,4(3*H*)-triones 6. The elimination of ammonia of intermediates 6 afforded 3-[1-aryl-methylidene]-1,2,3,4-tetrahydro-1,2,4-naphthalenetriones 7. It should be to noted that iminium acetates 5 could be stronger electrophiles than parent aldehydes 3, so this Mannich reaction could prioritized than the Knoevenagel reaction of lawsone (1) and aldehydes 3 to give the intermediates 7 [6]. Ammonium acetate simultaneously reacted with tetronic acid (2) to furnish more electrophilic 4-aminofuran-2(5*H*)-one 8, which was easily subjected to Michael addition with naphthalenetrione 7 to afford iminium ions 9. Finally, oxonium 10, generated by attacking of water in ethanol to iminum ions 9, underwent to tautomerism and elimination of ammonium to afford products 4.

4. Conclusion

For the first time NH_4OAc was applied as an efficient catalyst for the synthesis of 2-hydroxy-3-(arylmethyl)(4-hydroxy-2-oxo-2,5-dihydrofuran-3-yl)-1,4-naphthoquinones 4a-g. The application of ammonium acetate as efficient catalyst and ethanol as eco-friendly solvent significantly improved the reaction yields of products 4.

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References

[1] L. Constantino, D. Barlocco, Curr, Med, Chem., Vol. 13, No. 1, 2006, pp. 65-85, https://doi.org/10.2174/092986706775197999.

[2] V. K. Tandon, S. Kumar, Expert Opin, Ther, Patents, Vol. 23, No. 9, 2013, pp. 1088-1108. https://doi.org/10.1517/13543776.2013.798303

[3] T. A. Dang Thi, Y. Depetter, K. Mollet, P. Hoang Thi, D. Vu Ngoc, C. Pham The, H. T. Nguyen, T. H. Nguyen Thi, H. H. Nguyen, M. D'hooghe, T. V. Nguyen, Tetrahedron Lett, Vol. 56, No. 19, 2015, pp. 2422-2425, https://doi.org/10.1016/j.tetlet.2015.03.071.

[4] T. A. Dang Thi, Y. Depetter, P. Hoang Thi, D. Vu Ngoc, T. T. Nguyen, T. Do Huy, H. H. Nguyen, M. D'hooghe, T. V. Nguyen, Tetrahedron Lett, Vol. 56, No. 43, 2015, pp. 5855-5858, https://doi.org/10.1016/j.tetlet.2015.08.084.

[5] Q. T. Nguyen, T. G. Le Nhat, D. Vu Ngoc, T. A. Dang Thi, H. T. Nguyen, T. P. Hoang, H. H. Nguyen, H. T. Cao, K. A. Tehrani, V. T. Nguyen, Tetrahedron Lett, Vol. 57, No. 39, 2016, pp. 4352-4355, https://doi.org/ 10.1016/j.tetlet.2016.08.042.

[6] T. A. Dang Thi, G. Le-Nhat-Thuy, Q. G. Nguyen Thi, P. Hoang Thi, A. Nguyen Tuan, H. Hoang Mai, T. Nguyen Ha, T. A. Le, T. V. Nguyen, Chem, Heterocycl, Comp. Vol. 57, No. 2, 2021, pp. 137-142, https://doi.org/10.1007/s10593-021-02884-9.

[7] Q. G. Nguyen Thi, G. Le-Nhat-Thuy, T. A. Dang Thi, P. Hoang Thi, A. Nguyen Tuan, T. H. Nguyen Thi, T. T. Nguyen, T. Nguyen Ha, H. Hoang Mai, V. T. Nguyen, Bioorg, Med, Chem, Lett, Vol. 37, 2021, pp. 127841, https://doi.org/10.1016/j.bmcl.2021.127841.M.

[8] Alizadeh, M. Jalal, K. Hamed, A. Saber, S. Kheirouri, F. P. F. Tabrizi, N. Kamari, J. Inflamm, Res, Vol. 13, 2020, pp. 451-463, https://doi.org/10.2147/JIR.S262132.

[9] Y. Saito, M. Kishimoto, Y. Yoshizawa, S. Kawa, Anticancer Res., Vol. 35, No. 2, 2015, pp. 811-818.

[10] Y. Matsuya, K. Sasaki, M. Nagaoka, H. Kakuda, N. Toyooka, N. Imanishi, H. Ochiai, H. Nemoto, J. Org, Chem, Vol. 69, No. 23, 2004, pp. 7989-7993, https://doi.org/10.1021/jo0486995.

[11] B. Jiang, F. Shi, S. J. Tu, Curr, Org, Chem, Vol. 14, No. 4, 2010, pp. 357-378, http://doi.org/10.2174/138527210790231892.

[12] S. Kanakaraju, B. Prasanna, S. Basavoju, Chandramouli G. V. P. Arabian J. Chem, Vol. 10, No. 2, 2017, pp. S2705-2713, https://doi.org/10.1016/j.arabjc.2013.10.014.

[13] Z. Zhang, X. Gao, Y. Wan, Y. Huang, G. Huang, G. Zhang, ACS Omega, Vol. 2. No. 10, 2017, pp. 6844-6851, https://doi.org/10.1021/acsomega.7b00626.

[14] R. Tayebee, A. Gohari, Eurasian Chem, Comm, Vol. 2, No. 5, 2020, pp. 581-586, https://doi.org/ 10.33945/SAMI/ECC.2020.5.3.