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STUDY ON SYNTHESIS OF NAPHTHOQUINONE DERIVATIVES USING DOMINO REACTION AND BIOLOGICAL ACTIVITY

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Thesis can be found in

- The library of the Graduate University of Science and Technology, Vietnam Academy of Science and Technology.

- National Library of Viet Nam.

PUBLICATIONS RELATED TO THE THESIS

1. Tuyet Anh Dang Thi, Yves Depetter, Karen Mollet, Hoang Thi Phuong, **Doan Vu Ngoc**, Chinh Pham The, Ha Thanh Nguyen, Thu Ha Nguyen Thi, Hung Huy Nguyen, Matthias D'hooghe, Tuyen Van Nguyen., *Expedient stereoselective synthesis of new dihydropyrano and dihydrofuranonaphthoquinons*, Tetrahedron Letters, **56**, 2422–2425 (2015).

2. Tuyet Anh Dang Thi, Lena Decuyper, Hoang Thi Phuong, **Doan Vu Ngoc**, Ha Thanh Nguyen, Tra Thanh Nguyen, Thanh Do Huy, Hung Huy Nguyen, Matthias D'hooghe, Tuyen Van Nguyen., *Synthesis and cytotoxic evaluation of novel dihydrobenzo[h]cinnoline-5,6-diones*, Tetrahedron Letters, **56**, 5855–5858 (2015).

3. Trung Quang Nguyen, Thuy Giang Le Nhat, **Doan Vu Ngoc**, Tuyet Anh Dang Thi, Ha Thanh Nguyen, Phuong Hoang Thi, Hung Huy Nguyen, Hai Thuong Cao, Kourosch Abbaspour Tehrani, Tuyen Van Nguyen., *Synthesis of novel 2-aryl-3-benzoyl-1H-benzo[f]indole-4,9-diones using a domino reaction*, Tetrahedron Letters, **57**, 4352-4355 (2016).

4. Tuyet Anh Dang Thi, Karen Mollet, Phuong Hoang Thi, **Doan Vu Ngoc**, Chinh Pham The, Ha Thanh Nguyen, Thu Ha Nguyen Thi, Hung Huy Nguyen, Matthias D'hooghe, Tuyen Van Nguyen., *Expedient stereoselective synthesis of trifluoromethylated pyrannonaphthoquinons,* Analytica Vietnam Conferense 2015, April, 15, (**2015**).

5. **Vu Ngoc Doan**, Dang Thi Tuyet Anh, Hoang Thi Phuong, Le Nhat Thuy Giang, Nguyen Ha Thanh, Luc Quang Tan, Dinh Thi Cuc, Ngo Hanh Thuong, Pham Thi Tham, Vu Thi Thu Ha, NguyenVan Tuyen., *Sythesis of novel Trifluoromethylated Tetrahydrobenzo[g]chromene*, Vietnam Journal of Chemistry, **54**(6e2), Tr.205-209 (2016).

6. **Vu Ngoc Doan**, Dang Thi Tuyet Anh, Hoang Thi Phuong, Le Nhat Thuy Giang, Nguyen Ha Thanh, Cao Hai Thuong, Nguyen Thanh Tra, Nguyen Quang Trung, Pham The Chinh, Vu Duc Cuong, Nguyen Van Tuyen., *Synthesis and cytotoxic evaluation of novel dihydrobenzo[h]cinnoline-5,6-diones*, Vietnam Journal of Chemistry, **54**(6e2), Tr.6-10 (2016).

7. Le Nhat Thuy Giang, **Vu Ngoc Doan,** Hoang Thi Phuong, Dang Thi Tuyet Anh, Nguyen Van Tuyen., *Synthesis of 2,3-dihydronaphtho[2,3-b]furan-4,9-diones*, Vietnam Journal of Chemistry, **54**(6e2), Tr.200-204 (2016).

A-INTRODUCTION

1. The necessary of the thesis

Cancer is one of dangerous diseases with high mortality rate in the world. There is growing rapidly with abnormalities. In addition, the phenomenon of drug resistance, antibiotics of many types of bacteria, fungus that are global urgent problem today. Investigating useful drug to treat this disease is a major concern for many scientists. They are still working to find out new compounds with bioactivity to against cancer.

Many scientists are working in naphthoquinones and its derivatives with their biological relevance. Its characteristic capable a cytotoxic, can effect enzymes as topoisomerase – a group of enzymes that are important for the replication of DNA process in the cell nucleus.

Heterocyclic naphthoquinones widely occurred in the three domains of life such as bacteria, fungi and plants. A lot of natural product and total synthesized product and, semisynthesis drugs as pyranonapthoquinones, azaanthraquinones, naphtho[2,3-*b*]furan-4,9-diones, benzo[*f*]indole-4,9-diones, benzo[*h*]cinnoline-5,6-diones have good bioactivity, for example: antibacteria (especially Gram (+)), antifungal, antimalarial, and antineoplastic characteristic. Therefore, the study of this substance with novel derivatives and better bioactivities is still necessary.

Thus, we have chosen the thesis named as **"Study on synthesis of naphthoquinone derivatives using domino reaction and biological activity"**.

2. Objectives of the thesis

From the results of study, heterocyclic naphthoquinones compounds had exhibit interesting biological activity. This is one of the potential compounds to synthesized anticancer drugs for pharmaceuticals in the future.

The objectives of the thesis research focuses on synthesis 4 heterocyclic naphthoquinones: pyranonapthoquinones, naphtho[2,3-*b*]furan-4,9-diones, benzo[*f*]indole-4,9-diones, benzo[*h*]cinnoline-5,6-diones. The key of this method used multi-component domino reaction. And

investigating the cytotoxic activity of compounds to help scientist carry out new researches in the future.

3. New contributions of the thesis

1. Successfully synthesized several heterocyclic naphthoquinones as compounds **169, 181, 188, 199** by using novel and modern of methodology to synthesis (multi-component domino reaction).

2. We have successfully designed and synthesized 53 of heterocyclic naphthoquinones derivatives, 48/53 new compounds, including:

- 12 compounds of triflometylat tetrahydrobenzo[*g*]chromene (**169**), with 7 new compounds are compounds: **169f, 169g, 169h, 169i, 169j, 169k, 169l**.
- 12 new compounds of dihydronaphtho[2,3-*b*]furan-4,9-diones (**181**).
- 15 new compounds of benzo[*h*]cinnoline-5,6-diones (**188**).
- 14 new compounds of benzo[*f*]indole-4,9-diones (**199**).

3. The products and the intermediates products of structure were confirmed by modern spectral methods such as IR, ^{1}H-NMR, ^{13}C-NMR, MS, HR-MS (**199f , 199g, 199j, 199k**) and single crystal X-ray (**169b, 181b, 188f, 199k**).

4. We have evidenced reaction of mechanism for compounds triflometylat tetrahydrobenzo[*g*]chromene (**169**), dihydronaphtho[2,3-*b*]furan-4,9-diones (**181**), benzo[*h*]cinnoline-5,6-diones (**188**) and benzo[*f*]indole-4,9-diones (**199**), which have synthesized by using three-component domino reaction.

5. Investigated the cytotoxic activity of the new derivatives (compounds **188**) on two human cancer cell lines such as HepG2, KB. The structure-activity relationship of these derivatives has been preliminarily discussed. 14/15 of dihydrobenzo[*h*]cinnoline-5,6-diones derivatives with bioactivity for treat cancer cell lines in HepG2 and KB.

6. Nine compounds (**188a, 188b, 188d, 188f, 188g, 188h, 188j, 188k, 188m**) considerable cytotoxic activity - with IC_{50} < 5 µM. Especially compound **188j** (1-metyl-3,4-bis(4-nitrophenyl)-1,4-dihydrobenzo[*h*]cinnolin-5,6-dion) is most strongest bioactivity with IC_{50} = 0,56 µM (for KB) và IC_{50} = 0,77 µM (for HepG2). That information is better than Ellipticine anticancer drug with IC_{50} = 1.26 µM (for KB) và IC_{50} = 1.42 µM (for HepG2).

4. The main contents of the thesis

The thesis consists of 120 pages:

Introduction: 2 pages

Chapter 1: Overview (29 pages)

Chapter 2: Experimental (45 page)

Chapter 3: Results and discussion (42 pages)

Conclusions: (2 pages)

150 documents were referenced in the thesis, the documents were updated to 2016.

The appendix includes 78 pages, including spectra of synthesized derivatives (except IR spectra).

5. Methodology

Derivatives were synthesized by known organic synthesis methods and using improvement method for synthesis. The products of reactions were purified by column chromatography and recrystallized. The structures of products were determined by modern spectroscopic methods such as IR, MS, HR-MS, ^{1}H-NMR, ^{13}C-NMR, single crystal X-ray. Compound of bioactivities were investigated human cancer cell lines for KB and HepG2 by using Mossman' method.

B-CONTENT

CHAPTER 1. OVERVIEW

1.1. Naphthoquinone, derivatives and biologically active

1.1.1. Naphthoquinone and its derivatives

1.1.2. Biological activity of naphthoquinone

1.1.3. Some pathways synthesis naphthoquinone

1.2. Domino reaction and application for synthesis of naphthoquinone compounds

1.2.1. Multi-component domino reactions

1.2.2. Application of multi-component domino reactions for the synthesis naphthoquinone compounds

1.3. Isolated, synthesis and bioactivitiy of naphthoquinone heterocyclic

1.3.1. Isolated, synthesis and bioactivity of pyranonaphthoquinone

1.3.2. Isolated, synthesis and bioactivity of naphtho[2,3-b]furan-4,9-diones

1.3.3. Isolated, synthesis and biolactivity of benzo[h]cinnoline-5,6-diones

1.3.4. Isolated, synthesis and bioactivity of benzo[f]indole-4,9-diones

Chapter 2. EXPERIMENT

Experimental (45 pages), detailing of the research methodology, synthesis and purification process, physical properties of the products for example: melting point, morphology, color, yield of reactions and data of IR, MS, HR-MS, ^{1}H-NMR, ^{13}C-NMR, single crystal X-ray. Main contents include:

2.1. Research methods, materials and equipment

2.1.1. Research methods

2.1.2. Chemicals and solvents

2.1.3. Determination the structure

2.1.3.1. Nuclear Magnetic Resonance Spectrum (NMR)

2.1.3.2. Mass spectrometry (MS, HR-MS)

2.1.3.3. Single crystal X-ray spectrum

2.1.3.4. Infrared Spectroscopy (IR)

2.1.3. 5. Determination the melting point

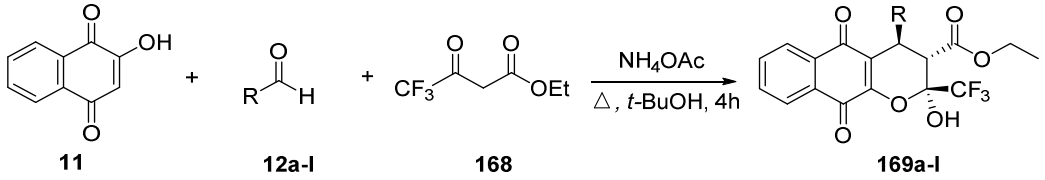
2.2. Synthesis of reaction agents

2.2.1. Synthesis of pyridine salt

2.2.2. Synthesis of 2-amino-1,4-naphthoquinone (135)

2.3. Synthesis of tetrahydrobenzo[*g*]chromen (169)

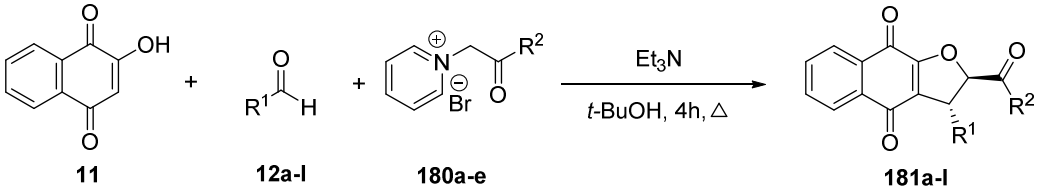
General procedure for the synthesis of tetrahydrobenzo[*g*]chromen **(169a-1)** were performed according to the Scheme 2.2.



Scheme 2.2. Synthesis of compounds **169**

2.4. Synthesis of 2,3-dihydronaptho[2,3-*b*]furan-4,9-diones (181)

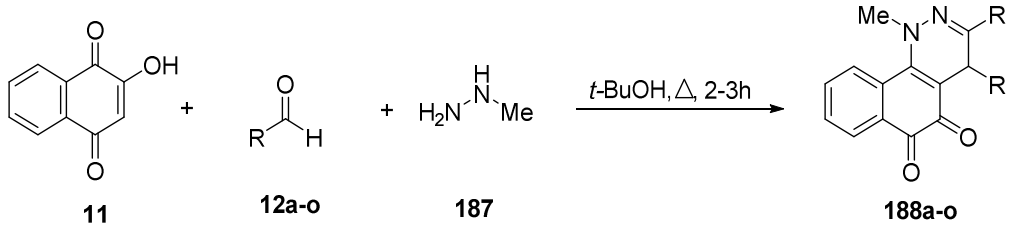
General procedure for the synthesis of 2,3-dihydronaphtho[2,3-*b*]furan-4,9-diones **(181)** were performed according to the Scheme 2.3.



Scheme 2.3. Synthesis of compounds **181**

2.5. Synthesis of dihydrobenzo[*h*]cinnoline-5,6-diones (188)

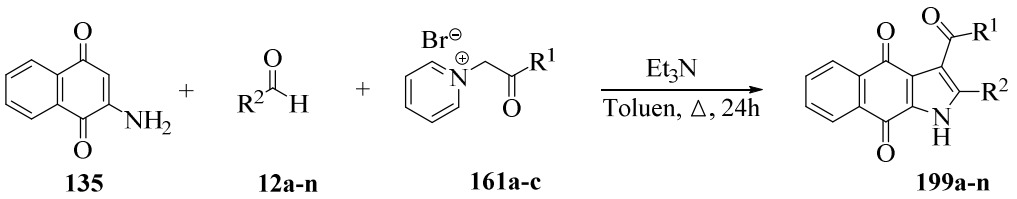
General procedure for the synthesis of dihydrobenzo[*h*]cinnoline-5,6-diones **(188)** were performed according to the Scheme 2.4.



Scheme 2.4. Synthesis of compounds **188**

2.6. Synthesis of benzo[*f*]indole-4,9-diones (199)

General procedure for the synthesis of benzo[*f*]indole-4,9-diones **(199a-n)** were performed according to the Scheme 2.5.



Scheme 2.5. Synthesis of compounds **199**

2.7. Cytotoxic activity evaluation methods

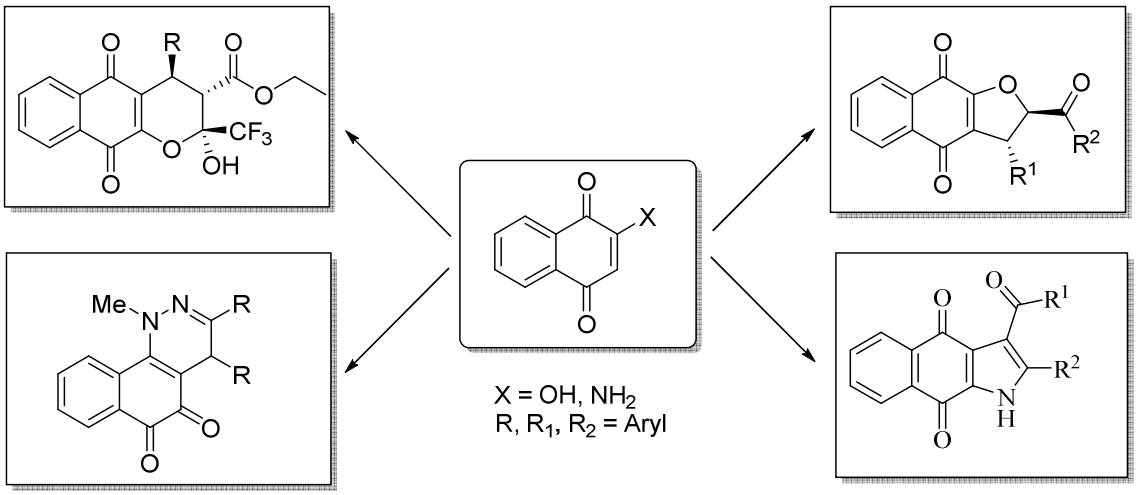
In order to evaluate cytotoxic potential of compounds, 15 compounds benzo[*h*]cinnoline-5,6-diones (**188**) were carried out *in vitro* biological assessment against two human cancer cell lines from Museum standard varieties USA (ATCC), including carcinoma epithelial mouth KB (Human epidermic carcinoma; CCL -17^{TM}), HepG2 liver cancer (Human hepatocellular carcinoma; HB - 8065^{TM}) using MTT method of Mosmann (3-

(4,5-dimetylthiazol-2-yl)-2,5-diphenyltetrazolium) on the model tested for cytotoxicity *in vitro* by the National Cancer Institute, US (NCI) confirmed to be allowed test preparation to cell toxicity screening, detection of substances capable inhibit or destroy the growth of cancer cells *in vitro*.

Chapter 3. RESULTS AND DISCUSSIONS

3.1. Strategy of thesis

3.1.1. The goal of the thesis



Scheme 3.1. Synthesis strategy of the thesis

The objective of the thesis focuses on synthesis 4 heterocyclic naphthoquinone: pyranonapthoquinon, naphtho[2,3-*b*]furan-4,9-diones, benzo[*f*]indole-4,9-diones and benzo[*h*]cinnolin-5,6-diones which based on the available naphthoquinone frame (Scheme 3.1) using multi-component domino reaction. Its evaluation of the cytotoxic activity compounds was provided information for scientist in the next further researches.

3.1.2. Results and discussions

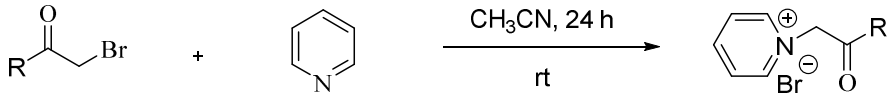
3.1.2.1. The efficient of reaction agents

2-hydroxy-1,4-naphthoquinone (**11**) and 2-ammonium-1,4-naphthoquinone (**135**) can easily participate in reactions to form new bonds C-C, C-N, C-S ... at C-3 position, or possibly both oxygen and nitrogen atoms and formation of new bonds at C-3 in the heterocyclic ... From these problems, we were chosen compound **11** and **135** is one of the important raw

materials for the synthesis of some derivatives of heterocyclic naphthoquinone

3.1.2.2. The synthesis of pyridine salts

Through research, we have successfully synthesized 5 derivates pyridine salts by reactions of α-bromaxetophenone with pyridine in acetonitrile. The reactions were carried out at room temperature for about 24 hours, the yield of reactions were about 90%. The procedure for the synthesis of compounds **161** were performed according to the Scheme 3.2.



159
159a, R= C_6H_5
159b, R= 3-NO_2-C_6H_4
159c, R= 4-NO_2-C_6H_4
159d, R= 4-F-C_6H_4
159e, R= 3-OH-C_6H_4

160

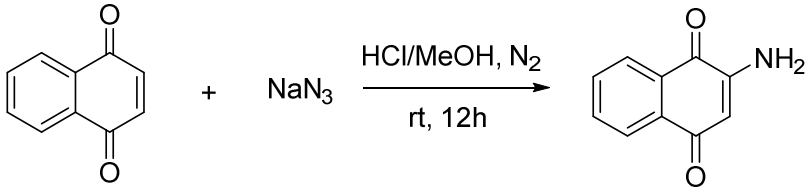
161
161a, R= C_6H_5
161b, R= 3-NO_2-C_6H_4
161c, R= 4-NO_2-C_6H_4
161d, R= 4-F-C_6H_4
161e, R= 3-OH-C_6H_4

Scheme *3.2.* Synthesis of salts pyridine

The reaction product is used immediately for the next step without further purification.

3.1.2.3. Synthesis of 2-amino-1,4-naphthoquinone

Procedure for the synthesis of compound **135** were performed according to the Scheme 3.3.



147

135, 90%

Scheme 3.3. Synthesis of compund **135**

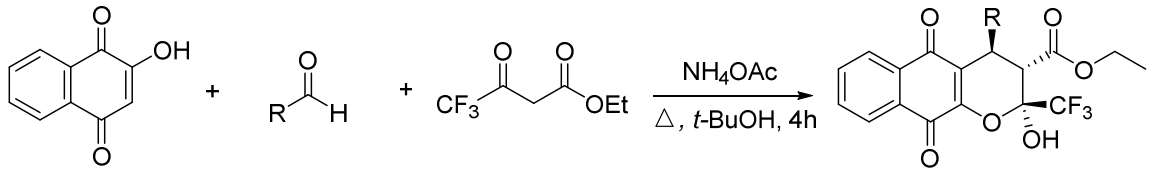
Compound **135** is a solid red-orange, melting point 201-202 ^oC.

^{1}H-NMR (500 MHz; $CDCl_3$), δ (ppm): 8.04-8.08 (2H, m, H-5, H-8); 7.72 (1H, dt, *J* = 7.5 and 1.0 Hz, H-7); 7.63 (1H, dt, *J* = 7.5 and 1.0 Hz, H-6); 6.00 (1H, s, H-3), 5.19 (2H, s, $N\underline{H}_2$).

3.2. The synthesis of triflometylat tetrahydrobenzo[*g*]-chromen (169)

To determine the optimal conditions for synthesis of compound **169**, we were subjiected to different reaction in conditions involving variation of the solvent CH_2Cl_2, toluene, EtOH, *i*-PrOH, *t*-BuOH) and the reaction times (1, 2, 3, 4, 6 and 8 hours). Results from the study showed that the optimal condition for the synthesis of compound **169** as follows: A solution of 2-hydroxy-1,4-naphthoquinone (**11**) (0.5 mmol), benzaldehyde (**12a**) (0.6 mmol), ethyl 4,4,4-triflo-3-oxobutanoat (**168**) (0.6 mmol) and ammonium acetate (1.5 mmol) in *t*-BuOH (15 ml) was heated at reflux for 4 hours. Then, the reaction mixture was extracted three times with EtOAc (3x10 ml) and the combined organic phases were washed with a saturated aqueous solution of $NaHCO_3$, dried (Na_2SO_4) and evaporated in vacuo to afford the crude reaction mixture, which was purified by means of column chromatography on silica gel (n-hexane/EtOAc, 8/2).

Having identified the optimal reaction conditions, we investigated the scope and limitations of this one-pot, three-component reaction. A variety of aromatic aldehydes with substituents of differing electronic properties reacted smoothly and efficiently under the optimized conditions to give the corresponding chromenes **169a-e** in moderate to good yields (Scheme 3.6).



11 **12a-l** **168** **169a-l**

169a, R= C_6H_5, 85%
169b, R= 4-BrC_6H_4, 73%
169c, R= 3-BrC_6H_4, 65%
169d, R= 4-ClC_6H_4, 70%
169e, R= 4-$MeOC_6H_4$, 80%
169f, R= 3-MeO-4-OHC_6H_3, 71%
169g, R= 3-$MeOC_6H_4$, 63%
169h, R= 2-$MeOC_6H_4$, 63%
169i, R= 3,4-$OCH_2OC_6H_3$, 86%
169j, R= Naphth-1-yl, 81%
16k, R= Fur-3-yl, 53%
169l, R= 1-Acetyl-indol-3-yl, 65%

Scheme 3.6. Synthesis of compounds **169**

The structure of the products (**169a-l**) were confirmed by the IR, ^{1}H-NMR, ^{13}C-NMR, MS spectra (compound **169b, 169f, 169e, 169i, 169j, 169g**), single crystal X-ray (compound **169b**).

The IR, ^{1}H-NMR, ^{13}C-NMR, MS spectroscopic data of the representative compound **169b** were given as follow:

IR (KBr) ν_{max}: 3571 (OH); 1733 (CO); 1677 (CO); 1633 (CO); 1590; 1484; 1347; 1200; 1095; 1004; 805; 727 cm^{-1}.

^{1}H-NMR (500 MHz; $CDCl_3$), δ (ppm): 8.12 (1H, dd, *J* = 8.0 và 1.5 Hz, H-6 or H-9); 7.89 (1H, dd, *J* = 8.0 and 1.5 Hz, H-9 or H-6); 7.73-7.67 (2H, m, H-7 and H-8); 7.42 (2H, d, *J* = 8.0 Hz, H-3' and H-5'); 7,05 (2H, d, *J* = 8.0 Hz, H-2' and H-6'); 4.36 (1H, d, *J* = 11.5 Hz, H-3); 4.15-4.08 (2H, m, C$\underline{H}_2$); 3.11 (1H, d, *J* = 11.5 Hz, H-4); 1.09 (3H, t, *J* = 7.0 Hz, C$\underline{H}_3$).

^{13}C-NMR (125 MHz; $CDCl_3$), δ (ppm): 182.2 (C=O); 177.7 (C=O); 171.2 (C=O); 151.0 (C-10a); 138.1; 136.4; 135.0; 134.4; 132.1; 131.7; 130.6; 129.1; 126.5; 126.4; 123.1; 123. 0; 122.3 (q. *J* = 285.0 Hz, $\underline{C}F_3$); 121.5; 94.4 (q. *J* = 34.3 Hz, C-2); 62.8 ($\underline{C}H_2$); 49.0 (C-3); 39.4 (C-4); 13.6 ($\underline{C}H_3$).

ESI-MS (m/z): found 523,0 và 525,0 $[M-H]^-$, calcd: $C_{23}H_{15}BrF_3O_6^-$.

ESI-MS (m/z): found 525,0 và 527,0 $[M+H]^+$, calcd: $C_{23}H_{17}BrF_3O_6^+$.

For example, among the characteristic features of the ^{1}H-NMR spectrum of compound **169b** in $CDCl_3$ were doublets at δ (ppm) = 3.11 (1H, d, *J* = 11.5 Hz, H-4) and 4.36 (1H, d, *J* = 11.5 Hz, H-3), respectively, indicating a trans configuration for the vicinal pair of hydrogen atoms. The stereochemistry of **169** was attributed to the fact that intramolecular cyclization should be an energetically favorable process, affording the more stable *2,3-cis-3,4-trans*-dihydro products **169b**.

In the ^{13}C-NMR spectrum, carbon of trifluoromethyl group appeared as a quartet at δ_C = 122.3 ppm with a coupling constant *J* = 285.0 Hz indicating that this group was bonded to a quaternary carbon atom. Also carbon (C-2) appeared as a quartet at δ_C = 122.3 ppm with a coupling constant *J* = 285.0 Hz.

Crystal of compound **169b** obtained by slow crystallization method in the solvent system EtOAc/Hexane. The structure of compound **169b** was confirmed by single-crystal X-ray analysis; this supported our speculations regarding the structures of the products (Figure 3.10).

On the single-crystal X-ray spectra of the compound **169b** (Figure 3.10) once again confirmed the structure of compound **169b** entirely consistent with the data analyzed. Further, from the X-ray structure shows that two atoms of hydrogen H-3 and H-4 within pyran in position *axial-trans*, dihedral angle of approximately 180°C corresponding with a coupling constant $J_{H\text{-}3}$ = 11.5 Hz, $J_{H\text{-}4}$ = 11.5 Hz, this is consistent with the data according to Karplus graph.

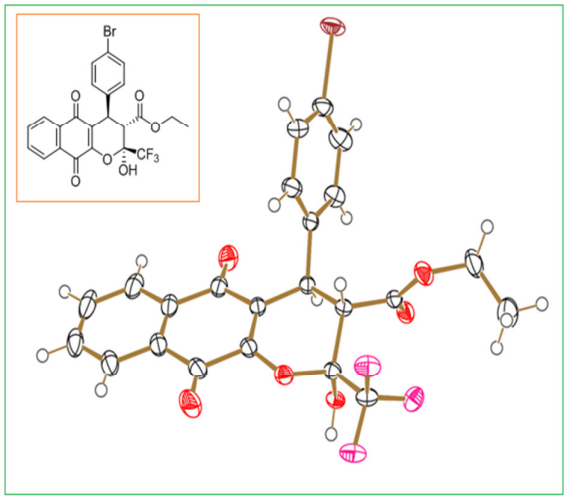
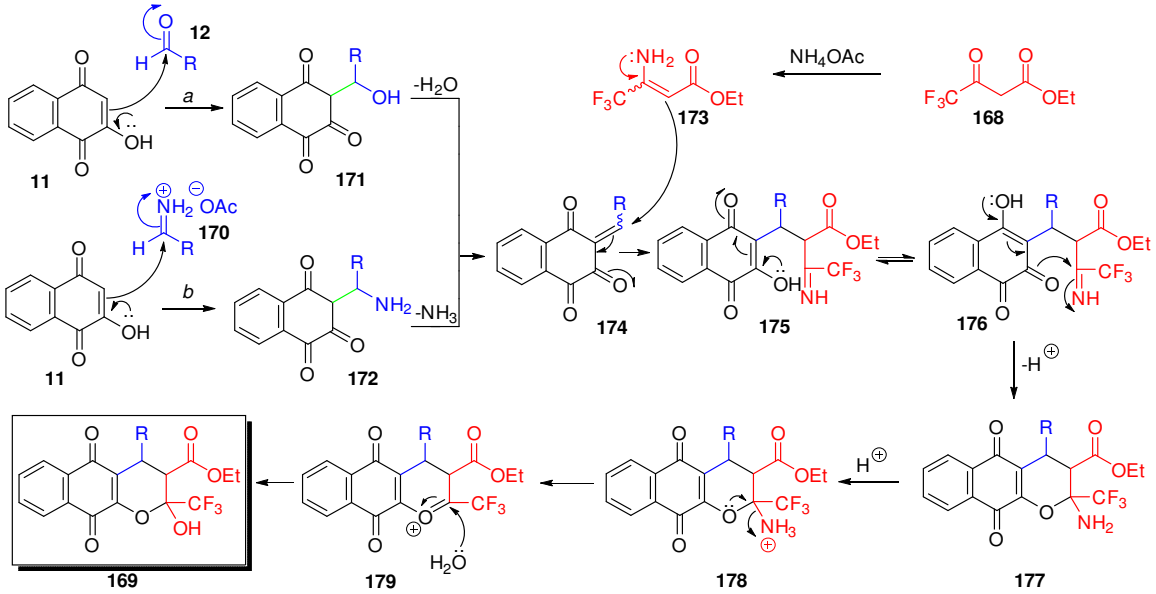


Figure 3.10. Single crystal X-ray structure of compound **169b**

Thus, from results of spectral analysis of nuclear magnetic resonance ^{1}H-NMR, ^{13}C-NMR, MS, single crystal X-ray, the structure of the compound (**169b**) were confirmed.

On the basis of our results, we propose a possible mechanism for the formation of compounds **169** (Scheme 3.7)



Scheme 3.7. Proposed mechanism for the formation of compounds **169**

Products intermediate 1,2,3,4-tetrahydro-1,2,4-naphthalentriones **(174)** *via* (*path a*) direct aldol condensation of 2- hydroxy-1,4-naphthoquinone **(11)** with aldehyde 12 followed by dehydration, or *via* (*path b*) the Mannich reaction of 2-hydroxy-1,4-naphthoquinone (**11**) with iminium ions **170**,

generated from aldehyde **12** through the action of ammonium acetate, followed by elimination of ammonia. A subsequent Michael addition of fluorinated enamine **173**, generated *in situ* by imination of β -keto esters **168** with ammonium acetate, onto intemediates **174** gives raise to the formation of CF_3-containing naphthoquinones **175** and **176**, which undergo a regioselective *6-exo-tig* cyclization towards amino α–lapachones **177**. Finally, deamination and addition of water to oxonium ion **179** furnishes α–lapachones **169.**

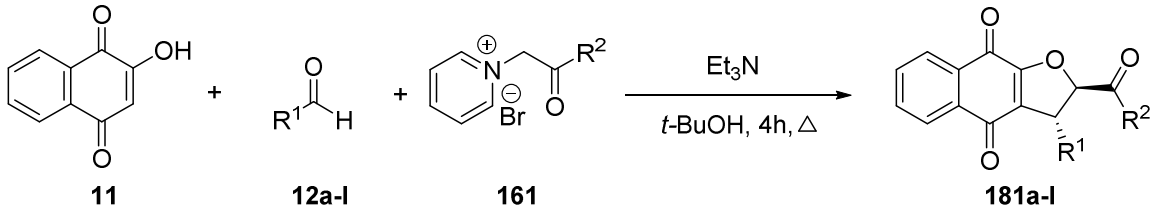
In conclusion, by three-components domino reaction, we were successfully synthesized 12 compounds of triflometylat tetrahydrobenzo[*g*]chromene from 2-hydroxy-1,4-naphthoquinon (**11**), aromatic aldehydes **12** and 4,4,4-triflo etyl-3-oxobutanoat (**168**) in tert - butanol with the presence of ammonium acetate catalyst. 7 novel compounds are compounds: **169f, 169g, 169h, 169i, 169j, 169k, 169l**. Compounds **169a, 169b, 169c, 169d, 169e** was announced by Y. Duan et al. Both electron-donating and electron-withdrawing substituents on the phenyl moieties were selected to assess their influence on the reaction outcome. However, no major effect was observed, leading to comparable yields in all cases. Yield of reactions are about 53-86%.

3.3. The synthesis of 2,3-dihydronaptho[2,3-*b*]furan-4,9-diones (181)

To determine the optimal conditions for synthesis of compound 169, we were subjiected to different reaction in conditions involving variation of the solvent CH_2Cl_2, toluene, EtOH, *i*-PrOH, *t*-BuOH) and the reaction times (1, 2, 3, 4, 6 and 8 hours).

Results from the study showed that the optimal condition for the synthesis of compound **181** as follows: a solution of 2-hydroxy-1,4-naphthoquinone **11** (0.5 mmol), benzaldehyde **(12a)** (0.6 mmol) and pyridinium bromide **161a** (0.6 mmol) in *t*-BuOH was added 0.6 mmol of triethylamine at room temperature. The mixture was heated under reflux for 4 hour, followed by extraction (three times) with EtOAc (3x10 ml). The combined organic phases were washed with a saturated aqueous solution of $NaHCO_3$, dried (Na_2SO_4) and evaporated in vacuo to afford the crude reaction mixture, which was purified by means of column chromatography on silica gel (n-hexane/EtOAc, 4/1).

Having identified the optimal reaction conditions, we investigated the scope and limitations of this one pot, three-component reaction. A variety of aromatic aldehydes and pyridinium bromide with substituents of differing electronic properties reacted smoothly and efficiently under the optimized conditions to give the corresponding chromenes **181a-l** in moderate to good yields (Scheme 3.9).



11 **12a-l** **161** **181a-l**

181a, R_1= C_6H_5, R_2= C_6H_5, 69%
181b, R_1= C_6H_5, R_2= 3-$NO_2C_6H_4$, 67%
181c, R_1= C_6H_5, R_2= 4-$NO_2C_6H_4$, 69%
181d, R_1= C_6H_5, R_2= 4-FC_6H_4, 66%
181e, R_1= 4-BrC_6H_4, R_2= 3-$NO_2C_6H_4$, 62%
181f, R_1= 3-BrC_6H_4, R_2= C_6H_5, 53%
181g, R_1= 3-BrC_6H_4,R_2= 3-$NO_2C_6H_4$, 76%
181h, R_1= 4-ClC_6H_4,R_2= 4-FC_6H_4, 65%
181i, R_1= 4-$MeOC_6H_4$,R_2= C_6H_5, 60%
181j, R_1= 4-$MeOC_6H_4$,R_2= 3-$NO_2C_6H_4$, 70%
181k, R_1= 3-$MeOC_6H_4$,R_2= 4-FC_6H_4, 68%
181l, R_1= Naphth-2-yl,R_2= C_6H_5, 70%

Scheme 3.9. Synthesis of compounds **181a-l**

The structure of the products (**181a-i**) were confirmed by the IR, ^{1}H-NMR, ^{13}C-NMR, MS spectra **(181g)**, single crystal X-Ray **(181b).**

The IR, ^{1}H-NMR, ^{13}C-NMR, spectroscopic data of the representative compound **181b** were given as follow:

IR (KBr), ν_{max}: 3383; 3086; 2908; 1704; 1654; 1626; 1529; 1443; 1351; 1217; 1086; 980; 705 cm^{-1}.

^{1}H-NMR ($CDCl_3$; 500 MHz), δ (ppm): 8.78 (1H, d, *J* = 1.5 Hz, H-2'); 8.47 (1H, dd, *J* = 1.0 and 7.5 Hz, H-5); 8.31 (1H, d, *J* = 8.0 Hz, H-8); 8.10 (1H, dd, *J* = 1.5 and 7.5 Hz, H-6); 7.96 (1H, dd, *J* = 1.5 và 7.5 Hz, H-7); 7.68-7.74 (3H, m, H-4', H-5' and H-6'); 7.31-7.40 (5H, m, H-2", H-3", H-4", H-5" and H-6"); 6.04 (1H, d, *J* = 5.5 Hz, H-2); 5.13 (1H, d, *J* = 5.5 Hz, H-3).

^{13}C-NMR ($CDCl_3$; 125 MHz), δ (ppm): 190.1 (C=O); 181.0 (C=O); 177.3 (C=O); 158.6 (C-9a); 148.5 (C-3'); 138.7; 134.8 ; 134.7; 134.4; 133.3; 132.8; 131.5; 130.3; 129.4; 128.4 (2xCH); 128.4 (2xCH); 127.6; 126.4; 126.3; 126.0; 124.2; 91.5 (C-2); 48.89 (C-3).

For example, among the characteristic features of the ^{1}H-NMR spectrum of compound **181b** in $CDCl_3$ were doublets at δ_H (ppm) = 6.04 (1H, d, *J* = 5.5 Hz, H-2) and 5.13 (1H, d , *J* = 5.5 Hz, H-3). 9 aromatic

proton signals also resonate at δ_H (ppm) = 8.78 (1H, d, J = 1.5 Hz, H-2'); 7.68-7.74 (3H, m, H-4', H-5' and H-6'); 7.31-7.40 (5H, m, H-2", H-3", H-4", H-5" and H-6").

In the ^{13}C-NMR spectrum, two signals characteristic of carbon atoms C-2 and C-3 in furan ring appeared at δ_C (ppm) = 91.5 (C-2); 48.89 (C-3). Three carbon atoms in the carbonyl group (C = O) appeared at δ_C (ppm) = 190.1 (C = O); 181.0 (C = O); 177.3 (C = O).

The structure of compound **181b** was confirmed by single-crystal X-ray analysis.

Crystal of compound **181b** obtained by slow crystallization method in the solvent system EtOAc/Hexane. The crystal structure of compound **181b** is given in Figure 3.1 6.

On the single-crystal X-ray spectra of the compound **181b** (Figure 3.16) once again confirmed the structure of compound **181b** entirely consistent with the data analyzed. Further, from the X-ray structure shows that two atoms of hydrogen H-2 and H-3 within dihedral angle of approximately

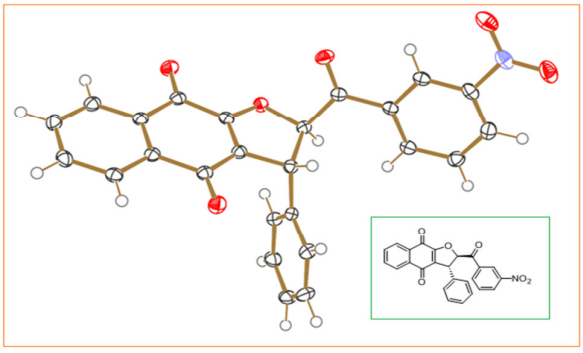
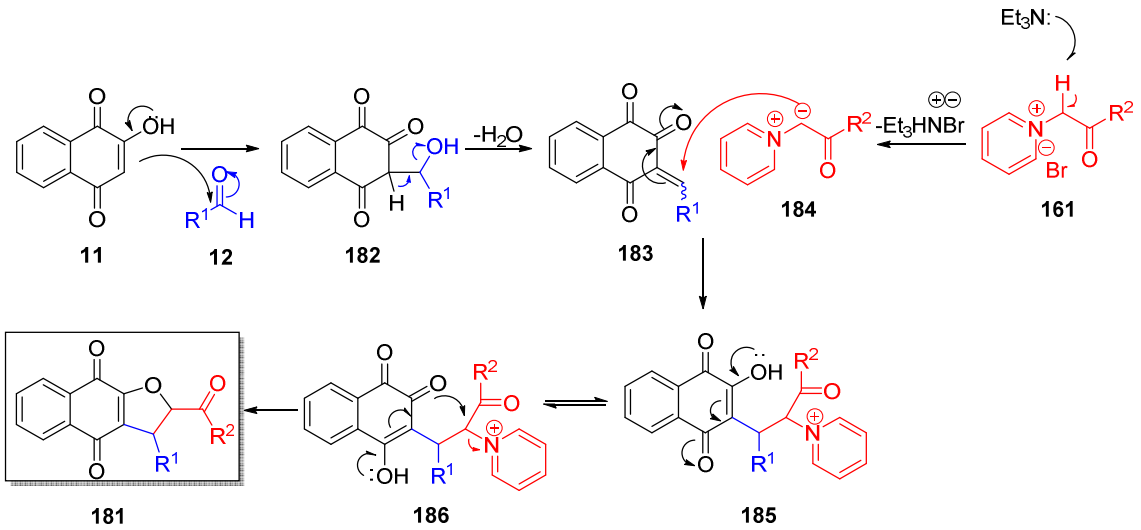


Figure 3.16. Single crystal X-ray structure of compound **181b**

60 °C corresponding with a coupling constant J_{H-2} = 5.5 Hz, J_{H-3} = 5.5 Hz, this is consistent with the data according to Karplus graph.

Thus, from results of spectral analysis of nuclear magnetic resonance ^{1}H-NMR, ^{13}C-NMR, MS, single crystal X-ray, the structure of the compound (**181b**) were confirmed.

On the basis of our results, we propose a possible mechanism for the formation of compounds **181** (Scheme 3.10)



Scheme 3.10. Proposed mechanism for the formation of compounds **181**

A possible mechanistic explanation for this multicomponent reaction starts with a Knoevenagel condensation of 2-hydroxy-1,4-naphthoquinone **11** with aromatic aldehydes **12**, followed by dehydration resulting in the formation of 1,2,3,4-tetrahydro-1,2,4-naphthalenetriones **183**. The next step is a Michael addition of pyridinium ylides **184**, formed in situ by deprotonation of pyridinium bromides **161** by triethylamine, across Michael acceptors **183**. The obtained naphthoquinones **185/186** undergo a cyclization to produce the desired substituted dihydrofuranonaphthoquinone **181**.

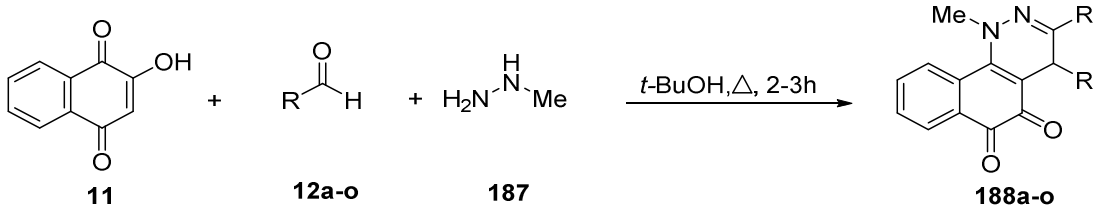
In conclusion, by three-components domino reaction, we were successfully synthesized 12 new compounds of dihydronaphtho[2,3-*b*]furan-4,9-diones from 2-hydroxy-1,4-naphthoquinon (**11**), aromatic aldehydes **12** and pyridinium bromide **161** in tert-butanol with the presence of triethylamine. Both electron-donating and electron-withdrawing substituents on the phenyl moieties were selected to assess their influence on the reaction outcome. However, no major effect was observed, leading to comparable yields in all cases. Yield of reactions are about 53-76%.

3.4. The synthesis of dihydrobenzo[*h*]cinnolin -5,6-diones (188)

To determine the optimal conditions for synthesis of compound **188**, we were subjiected to different reaction in conditions involving variation of the solvent (CH_2Cl_2, toluene, DMF, EtOH, *i*-PrOH, *t*-BuOH) and different times (1, 2, 3, 4 6 and 8 hours).

Results from the study showed that the optimal conditions for the synthesis of compound **188a** as follows: A mixture of 2-hydroxy-1,4-naphthoquinone **11** (0.5 mmol) and benzaldehyde **(12a)** (1.0 mmol) in *t*-BuOH (15 ml) was heated under reflux for 30-60 min, after which methylhydrazine **187** (0.5 mmol) in *t*-BuOH was added. The reaction was heated under reflux for another 2-3 hour, followed by the addition of water and extraction three times with EtOAc (3x10 ml). The combined organic phases were washed with water and dried (Na_2SO_4). Finally, the solvent was removed *in vacuo* to afford the crude product, which was then purified by column chromatography on silica gel (EtOAc/hexane, 3/7).

Having identified the optimal reaction conditions, we investigated the scope and limitations of this one pot, three-component reaction. A variety of aromatic aldehydes with substituents of differing electronic properties reacted smoothly and efficiently under the optimized conditions to give the corresponding chromenes **188a-o** in moderate yields (Scheme 3.12).



188a, R= C_6H_5, 50%
188b, R= 3-BrC_6H_4, 51%
188c, R= 4-$MeOC_6H_4$, 53%
188d, R= 3-$MeOC_6H_4$, 47%
188e, R= Naphth-2-yl, 47%
188f, R= 4-BrC_6H_4, 45%
188g, R= 4-ClC_6H_4, 43%
188h, R= 3,4-OCH_2O-C_6H_3, 53%
188i, R= 2-$MeOC_6H_4$, 60%
188j, R= 4-$NO_2C_6H_4$, 51%
188k, R= 4-($MeSO_2$)C_6H_4, 48%
188l, R= 4-$NMe_2C_6H_4$, 45%
188m, R= 4-HOC_6H_4, 45%
188n, R= 3-MeO-4-OHC_6H_3, 43%
188o, R= 2-NO_2- 5-OHC_6H_3, 47%

Scheme 3.12. Synthesis of compounds **188a-l**

The structure of the products (**188a-l**) were confirmed by the IR, ^{1}H-NMR, ^{13}C-NMR, MS spectra and single crystal X-ray (compound **188f**).

The IR, ^{1}H-NMR, ^{13}C-NMR, spectroscopic data of the representative compound **188f** were given as follow:

IR (KBr), ν_{max}: 3443; 3048; 2928; 1687; 1624; 1529; 1480; 1372; 1254; 1067; 1007; 939; 818; 773 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 500 MHz), δ (ppm): 8.09 (1H, dd, *J* = 1.0 and 7.5 Hz, H-7); 7.80 (1H, d, *J* = 7.5 Hz, H-10); 7.72 (2H, d, *J* = 8.5 Hz, H-2”

and H-6”); 7.63 (1H, dt, *J* = 1.5 and 8.0 Hz, H-8); 7.51 (1H, t, *J* = 8.0 Hz, H-9); 7.49 (2H, d, *J* = 8.5 Hz, H-2’ and H-6’); 7.36 (2H, d, *J* = 8.5 Hz, H-3” and H-5”); 7.17 (2H, d, *J* = 8.5 Hz, H-3’ and H-5’); 5.62 (1H, s, H-4); 4.10 (3H, s, C$\underline{H}_3$).

^{13}C-NMR ($CDCl_3$, 125 MHz), δ (ppm): 179.9 (C=O); 176.6 (C=O); 149.4 (C-3); 147.1 (C-1a); 139.3; 133.7; 132.8; 132.2 (2xCH); 131.9 (2xCH); 131.5; 130.6; 130.4; 130.2; 129.1 (2xCH); 128.6 (2xCH); 126.8; 125.4; 121.4; 109.2 (C-4a); 46.4 (N-$\underline{C}H_3$); 34.8 (C-4).

For example, in the ^{1}H-NMR spectrum of compound **188f** appears fully signals characterizing of protons are present in the molecule. A signal characteristic of protons H-4 was singlet at δ_H (ppm): 5.62 (1H, s, H-4), singlet at δ = 4.10 ppm characterizes of the 3 protons of the metyl group (CH_3 -N).

In the ^{13}C-NMR spectrum, two carbon atoms in the carbonyl group (C = O) appeared at δ_C (ppm) = 179.9 (C = O) and 176.6 (C = O). Carbon atoms C-4 appeared at δ_C (ppm) = 34.8, carbon of methyl group appeared at δc (ppm) = 46.4 (N-$\underline{C}H_3$).

Crystal of compound **188f** obtained by slow crystallization method in solvent DCM/MeOH. The crystal structure of compound **188k** was given in Figure 3. 22.

Results analysis of single crystals X-ray of compound **188f** (Figure 3.22) once again confirmed the structure of compound **188f** fully consistent with the results analyzed, proves.

Thus, from results of spectral analysis of nuclear magnetic resonance ^{1}H-NMR, ^{13}C-NMR, single crystal X-ray, the structure of the compound (**188f**) were confirmed**.**

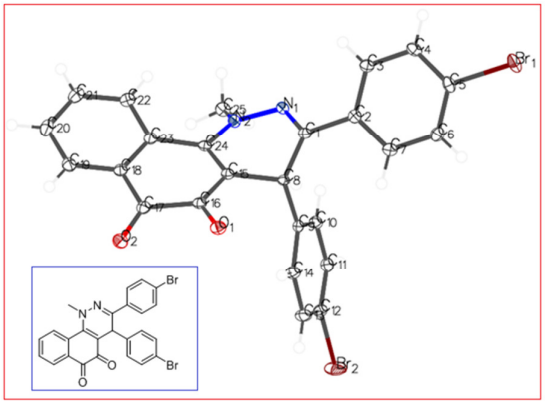
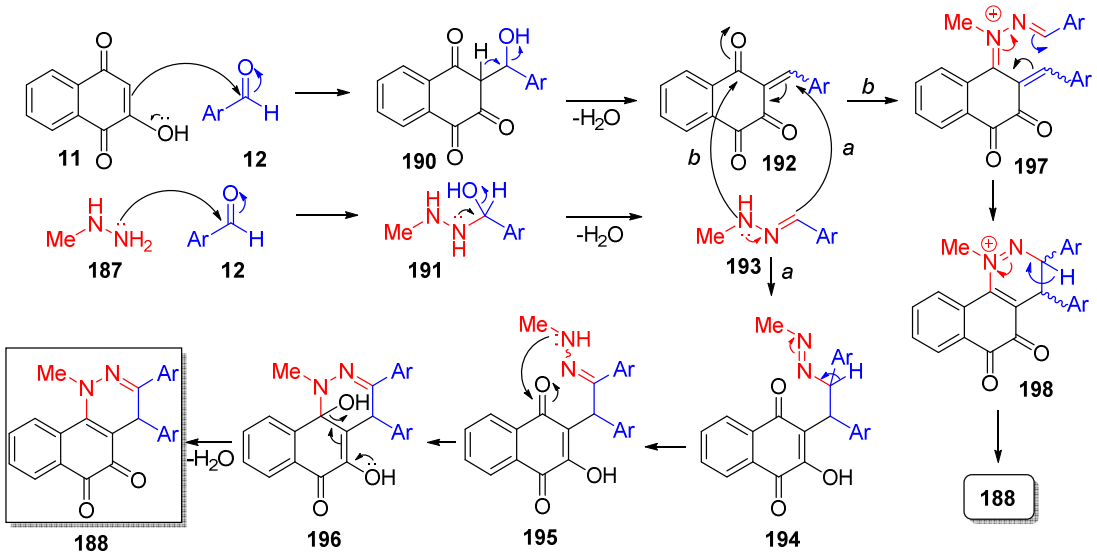


Figure 3.22. Single crystal X-ray structure of compound **188f**

On the basis of our results, we propose a possible mechanism for the formation of compounds **188** (Scheme 3.13)



Scheme 3.13. Proposed mechanism for the formation of compounds **188**

A possible mechanistic interpretation of this multicomponent reaction begins with the formation of 1,2,4-naphtalenetriones **192** by Knoevenagel condensation of 2-hydroxy-1,4-naphthoquinone **11** with the aromatic aldehydes **12**, followed by dehydration. Besides, the nucleophilic addition of methylhydrazine **187** to a second equivalent of aromatic aldehydes **12** results in the formation of 1-arylmethylidene-2-methylhydrazines **193**, after elimination of water. Compounds **192** behave as Michael acceptors for the addition of the *in situ* prepared hydrazones **193** (*route a*). The adducts undergo tautomerization and intramolecular cyclization affording the fused naphthoquinone derivatives **196**. Keto-enol tautomerization and elimination of water finally lead to the title compounds **188** (*Scheme* 3.13). However, other mechanistic proposals, such as for example condensation of hydrazone **193** with trione **192** at C4 (*route b*) to furnish an intermediate **197** prone to undergo electrocyclic cyclization toward tricycle **198**, followed by proton abstraction, should not be ruled out. The mechanism could be further investigated by prestirring methylhydrazine **187** with an aromatic aldehyde (e.g. benzaldehyde **12a**) and 2-hydroxy-1,4-naphthoquinone **11** with a different aldehyde (e.g. 4-methoxybenzaldehyde **12c**) in order to explore the possibility of having two different Ar-groups in the final product and the fidelity of their incorporation, which could be an indication of reversibility.

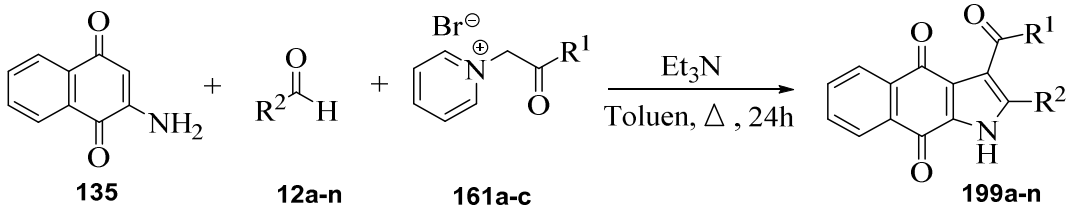
In conclusion, by three-components domino reaction, we were successfully synthesized 15 new compounds of benzo[*h*]cinnoline-5,6-diones from 2-hydroxy-1,4-naphthoquinon (**11**), aromatic aldehydes **12** and metylhydrazin **(187)** in tert-butanol. Both electron-donating and electron-withdrawing substituents on the phenyl moieties were selected to assess their influence on the reaction outcome. However, no major effect was observed, leading to comparable yields in all cases. Yield of reactions are about 43-60%.

3.5. The synthesis of compounds benzo[*f*]indole-4,9-diones (199)

To determine the optimal conditions for synthesis of compound **199**, we were subjiected to different reaction in conditions involving variation of the solvent (CH_2Cl_2, THF, toluene, EtOH, *i*-PrOH, *t*-BuOH) and different times (1, 5, 10, 15, 20, 22, 24, 26 and 30 hours).

Results from the study showed that the optimal conditions for the synthesis of compound **199a** as follows: A solution of 2-amino-1,4-naphthoquinone **135** (0.5 mmol), pyridinium bromide **161a** (0.6 mmol), and Et_3N (2.5 mmol) in toluene (10 ml) was heated at reflux for 30-60 min. Benzaldehyde **12a** (0.6 mmol) was added and the resulting mixture was further heated at reflux for 24 h. The reation mixture was extracted with EtOAc (3x10 ml) and the combined organic phases dried with Na_2SO_4 and evaporated in vacuo. The reaction mixture was purified by column chromatography on silica gel using n-hexane/ethyl acetate (8/2).

Having identified the optimal reaction conditions, we investigated the scope and limitations of this one pot, three-component reaction. A variety of aromatic aldehydes with substituents of differing electronic properties reacted smoothly and efficiently under the optimized conditions to give the corresponding chromenes **199b-n** in moderate yields (Scheme 3.15).



135 12a-n 161a-c 199a-n

199a, R_1=C_6H_5, R_2= C_6H_5, 63%
199b, R_1=C_6H_5, R_2= 3-$MeOC_6H_4$, 59%
199c, R_1=C_6H_5, R_2= 4-$MeOC_6H_4$, 60%
199d, R_1=C_6H_5, R_2= 3-MeO-4-HOC_6H_3, 62%
199e, R_1=C_6H_5, R_2= 3-BrC_6H_4, 48%
199f, R_1=C_6H_5, R_2= 4-BrC_6H_4, 47%
199g, R_1=C_6H_5, R_2= 4-ClC_6H_4, 45%
199h, R_1=C_6H_5, R_2= 4-$Me_2C_6H_4$, 45%
199i, R_1=C_6H_5, R_2= Naphth-2-yl, 48%
199j, R_1=C_6H_5, R_2= 3,4-OCH_2O-C_6H_3, 47%
199k, R_1= 4-FC_6H_4, R_2= C_6H_5, 65%
199l, R_1= 4-FC_6H_4, R_2= Naphth-2-yl, 40%
199m, R_1= 3-HOC_6H_4, R_2= C_6H_5, 47%
199n, R_1= 3-HOC_6H_4, R_2= 4-$MeOC_6H_4$, 45%

Scheme 3.15. Synthesis of compounds **199**

The structure of the compounds were confirmed by the IR, ^{1}H-NMR, ^{13}C-NMR, HRMS **(199f, 199g, 199j, 199k)**, MS **(199a)** spectra and single crystal X-ray **(199k).**

The IR, ^{1}H-NMR, ^{13}C-NMR, HR-MS spectroscopic data of the representative compound **199k** were given as follow:

IR (ATR), ν_{max}: 3219; 1661; 1641; 1594; 1435; 1233; 1146; 967; 904; 766; 708; 685; 615; 510; 441 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 500 MHz), δ (ppm): 10.56 (1H, s, N<u>H</u>), 8.15-8.13 (1H, m, H-5 or H-8); 8.07-8.05 (1H, m, H-8 or H-5); 7.98-7.96 (2H, m, H-6 and H-7); 7.70-7.68 (2H, m, H-2' and H-6'); 7.56-7.54 (2H, m, H-2" and H-6"); 7.39-7.37 (3H, m, H-4", H-3" and H-5"); 7.08 (2H, t, *J* = 7.5 Hz, H-3' and H-5').

^{13}C-NMR ($CDCl_3$, 125 MHz), δ (ppm): 191.52 (C=O); 179.71 (C=O); 176.12 (C=O); 166.06 (d, *J* = 253.7 Hz, <u>C</u>F); 139.47; 134.15; 134.12; 133.93; 133.26; 133.00; 132.21; 132.13; 131.89; 129.63; 129.18; 129.06 (2xCH); 127.72 (2xCH); 127.25; 127.21; 126.48; 120.84; 115.90; 115.72.

HRMS-ESI (m/z): found 394,0875 $[M-H]^-$, calcd: 394,0879; $C_{25}H_{13}FNO_3^-$.

For example, among the characteristic features of the ^{1}H-NMR spectrum of compound **199k** in $CDCl_3$ were singlet at δ (ppm) = 10.56 (1H, s, N<u>H</u>), the characteristic signal for 4 protons of the ring naphthoquinones appeared as δ_H (ppm): 8.15 to 8.13 (1H, m, H-5 or H-8); 8.07 to 8.05 (1H, m, H-8 or H-5); 7.96 - 7.98 (2H, m, H -6 and H-7)

In the ^{13}C-NMR spectrum, carbon of C-F group were doublets at δ = 166.06 ppm with a coupling constant J = 253.7 Hz. Three carbon atoms of carbonyl group (C = O) appeared at δ_C (ppm): 191.52 (C = O); 179.71 (C = O); 176, 12 (C = O).

Crystal of compound **199k** obtained by slow crystallization method in the solvent DCM/MeOH. The structure of compound **199b** was confirmed by single-crystal X-ray (Figure 3.29) and High resolution Mass Spectroscopy (Figure 3.28) analysis this supported our speculations regarding the structures of the products.

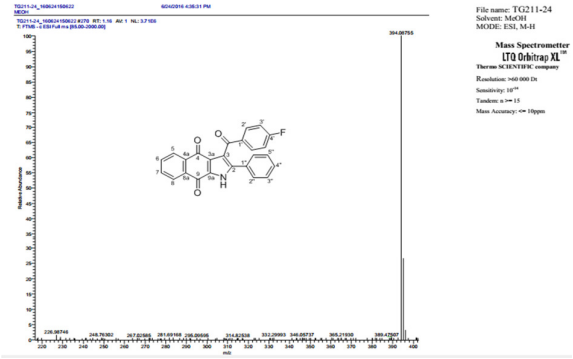


Figure 3.28. HR-MS spectrum of compound **199k**

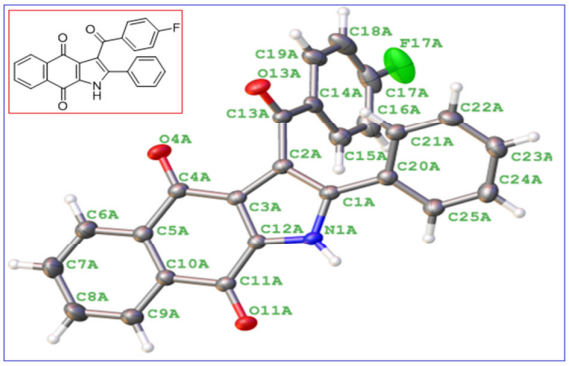
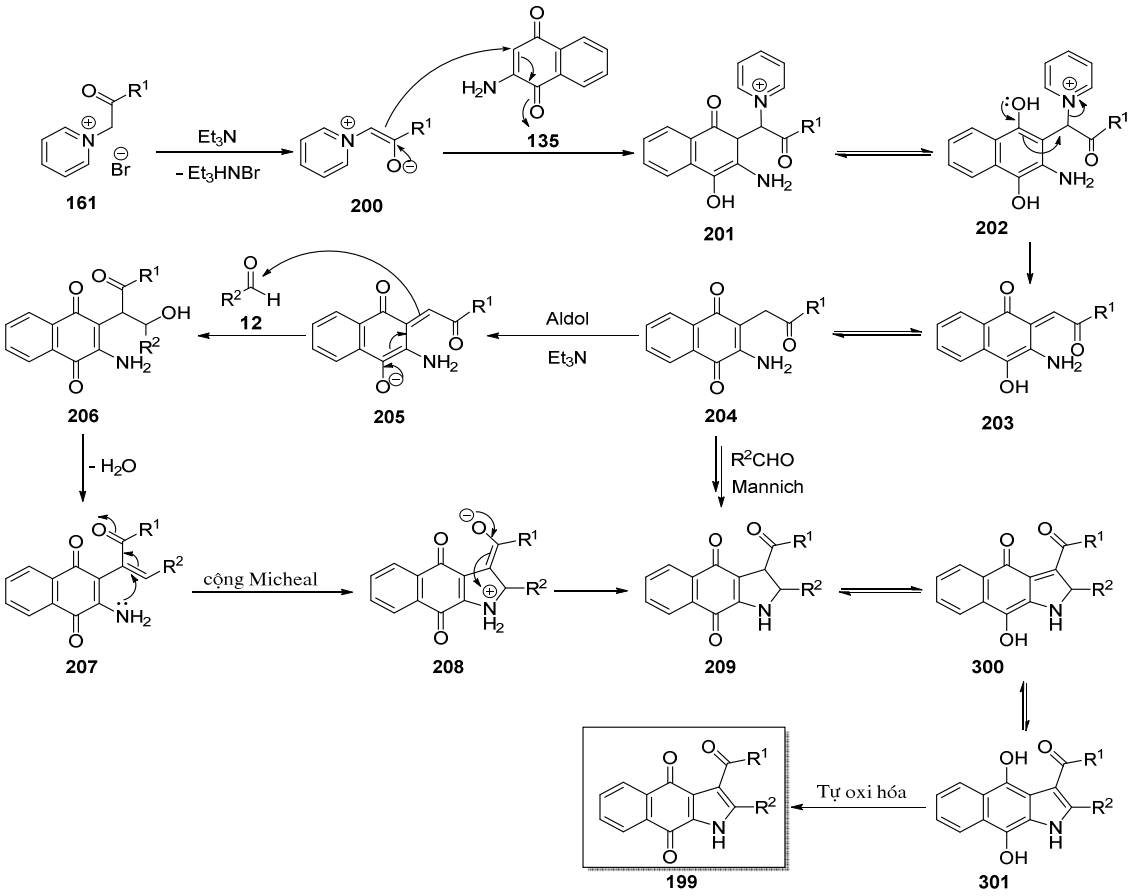


Figure 3.29. Single crystal X-ray structure of compound **199k**

Thus, from results of spectral analysis of nuclear magnetic resonance ^{1}H-NMR, ^{13}C-NMR, MS, HR-MS, single crystal X-ray, the structure of the compound (**199k**) were confirmed.

On the basis of our results, we propose a possible mechanism for the formation of compounds **199** (Scheme 3.16)



Scheme 3.16. Proposed mechanism for the formation of compounds **199**

A possible mechanistic interpretation of this MDR begins with the Michael addition of 2-amino-1,4-naphthoquinone **135** with *N*-acylmethylpyridinium ylides **200**, formed in situ by the deprotonation of pyridinium bromides **161** by Et_3N. After the elimination of pyridine from intermediates **201**, compounds **203** engage in a base promoted Knoevenagel condensation with aromatic aldehydes **12**, resulting in the formation of naphthoquinones **207**. The latter undergo intramolecular nucleophilic attack of the vinyligous amide nitrogen atom to produce compounds **209**, which undergo keto-enol tautomerization and auto-oxidation to furnish the desired substituted 1*H*-benzo[*f*]indole-4,9-diones **199** (Scheme 3.16).

The reaction could also proceed via a Mannich type reaction, in which the condensation of compound **204** with aromatic aldehydes leads to Schiff base which after a subsequent cyclization sequence provides compound **209**. which undergo keto-enol tautomerization and auto-oxidation to furnish the desired substituted 1*H*-benzo[*f*]indole-4,9-diones **199.**

In conclusion, by three-components domino reaction, we were successfully synthesized 14 new compounds of benzo[*f*]indole-4,9-diones from 2-amino-1,4-naphthoquinon (**135**), aromatic aldehydes **12** and salt of pyridine **(161)** in toluene with the presence of triethylamine . Both electron-donating and electron-withdrawing substituents on the phenyl moieties were selected to assess their influence on the reaction outcome. However, no major effect was observed, leading to comparable yields in all cases. Yield of reactions are about 40-65%.

3.6. The bioactivity of naphthoquinone

To evaluate their cytotoxic potential, the newly synthesized 1,2-naphthoquinone derivatives **188a-o** were subjected to *in vitro* biological assessment against two human cancer cell lines, KB and Hep-G2. The results of the cytotoxicity evaluation, as compared to the anticancer reference compound ellipticine, are summarized in Table 3.9. As evidenced by these results, the majority of the derivatives exhibit at least moderate cytotoxic activity against the KB and Hep-G2 cell lines

Table 3.9. Cytotoxic activity of the compounds benzo[*h*]cinnoline-5,6-diones **188a-o**

TT	Compounds	IC_{50} (μM) KB	IC_{50}(μM) HepG2
1	**188a**	3.70	3,63
2	**188b**	3,43	3,22
3	**188c**	23,86	20,69
4	**188d**	4,58	3,56
5	**188e**	7,42	15,40
6	**188f**	2.29	2.93
7	**188g**	3,60	2.14
8	**188h**	2.87	3,64
9	**188i**	> 292	> 292
10	**188j**	**0.56**	**0.77**
11	**188k**	1.33	2,71

12	**188l**	5.81	16.85
13	**188m**	2.02	4,46
14	**188n**	12.61	10,93
15	**188o**	135.73	145,90
16	**Ellipticine**	1.26	1,42

The results from table (3.9) show that, 14/15 derivatives exhibit toxic activity on cancer cell lines HepG2 and KB. Nine of the new dihydrobenzo[*h*]cinnoline-5,6-diones (compounds **188a, 188b, 188d, 188f, 188g, 188h, 188j, 188k, 188m**) even display a considerable activity profile with IC_{50}-values below 5 µM against both cell lines, being only slightly higher than those of the anticancer drug ellipticine. In particular, nitro compound **188j** can be identified as the most promising agent with IC_{50}-values of 0.56 and 0.77 µM against the KB and HepG2 cell lines, respectively. These results clearly suggest the relevance of this interesting new class of dihydrobenzo[*h*]cinnoline-5,6-diones in the framework of cancer therapy research and medicinal chemistry. Further optimization of the core structures toward potent cytotoxic agents should definitely be considered in future research.

CONCLUSIONS

The synthesis of naphthoquinone derivatives by domino and evaluate their bioactivity. The thesis has obtained this results:

1. Using three-component domino reaction, we were successfully designed and synthesized 53 target derivatives of naphthoquinon heterocyclic, 48/53 new compounds, including:

- 12 compounds of triflometylat tetrahydrobenzo[*g*]chromene from 2-hydroxy-1,4-naphthoquinon (**11**), aromatic aldehydes (**12**) and 4,4,4-triflo etyl-3-oxobutanoat (**168**) in *tert*-butanol with the presence of ammonium acetate catalyst. 7 novel compounds: **169f, 169g, 169h, 169i, 169j, 169K, 169l**. The yield of reactions are about 53-86%.

- 12 new compounds of dihydronaphtho[2,3-*b*]furan-4,9-diones from 2-hydroxy-1,4-naphthoquinon (**11**), aromatic aldehydes (**12**) and pyridinium

bromide (**161**) in tert-butanol with the presence of triethylamine. The yield of reactions are about 53-76%.

- 15 new compounds of benzo[*h*]cinnoline-5,6-diones from 2-hydroxy-1,4-naphthoquinon (**11**), aromatic aldehydes (**12**) and metylhydrazin **(187)** in tert-butanol. The yield of reactions are about 43-60%.

- 14 new compounds of benzo[*f*]indole-4,9-diones from 2-amino-1,4-naphthoquinon (**135**), aromatic aldehydes (**12**) and salt of pyridine **(161)** in toluene with the presence of triethylamine. The yield of reactions are about 40-65%.

2. The structures of target products and their intermediates were confirmed by modern spectral methods such as IR, ^{1}H-NMR, ^{13}C-NMR, MS, HR-MS (**199f , 199g, 199j, 199k**) and single crystal X-ray (**169b, 181b, 188f, 199k**).

3. Proposed mechanism for the formation of compounds triflometylat tetrahydrobenzo[*g*]chromene (**169**), 2,3-dihydronaphtho[2,3-*b*]furan-4,9-diones (**181**), benzo[*h*]cinnoline-5,6-diones (**188**) and benzo[*f*]indole-4,9-diones (**199**) synthesiszed from three-component domino reaction.

4. 15 naphthoquinone (compounds **188a-o**) were investigated bioactivity. 14/15 derivatives have toxic activity on cancer cell lines HepG2 and KB. Nine of the new dihydrobenzo[*h*]cinnoline-5,6-diones (**188a, 188b, 188d, 188f, 188g, 188h, 188j, 188k, 188m**) have high toxicity for cancer cell with IC_{50} value below 0,5 µM. In particular, the compound **188j** with IC_{50} = 0,56 µM (KB) và IC_{50} = 0,77 µM (HepG2) anticancer higher than Ellipticine with IC_{50} = 1,26 µM (KB) và IC_{50} = 1,42 µM (HepG2).