SYNTHESIS AND BIOLOGICAL EVALUATION OF NEW NAPHTHOQUINONES DERIVATIVES BY CATALYTIC OXIDATION

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INTRODUCTION

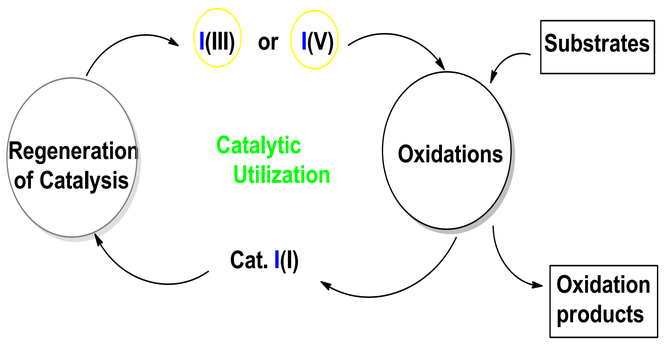


Figure. 2

- Substituted 1,4-naphthoquinones are frequently encountered in many natural products and are associated with a range of diverse pharmacological activities. Among them, anticancer activity was clearly demonstrated for plumbagin [1], isolated from the roots of "*Plumbago zeylania*" [2], lapachol which was obtained from various sources [3-5], shikonin, isolated from the roots of "*Lithosperma erythrohizan*" [6] or smenocerone B isolated from "*Smenospongia ceribriformis*" a sponge from Eastern Sea of Vietnam [7] (Fig. 1).

- Oxidation reactions constitute of a number of important transformations in organic synthesis. They are widely in the productions of a variety of fine chemicals including pharmaceuticals, natural products, and their intermediates [8].

- The catalytic utilization of hypervalent iodine reagents (Fig. 2), largely in consideration of economical and environmental viewpoints, is a most attractive strategy due to their unique features as extremely useful oxidants, with mild, safe, and environmentally friendly characteristics.

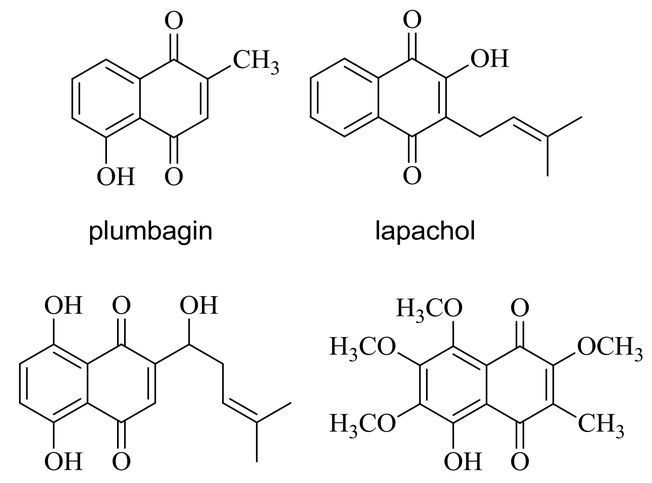
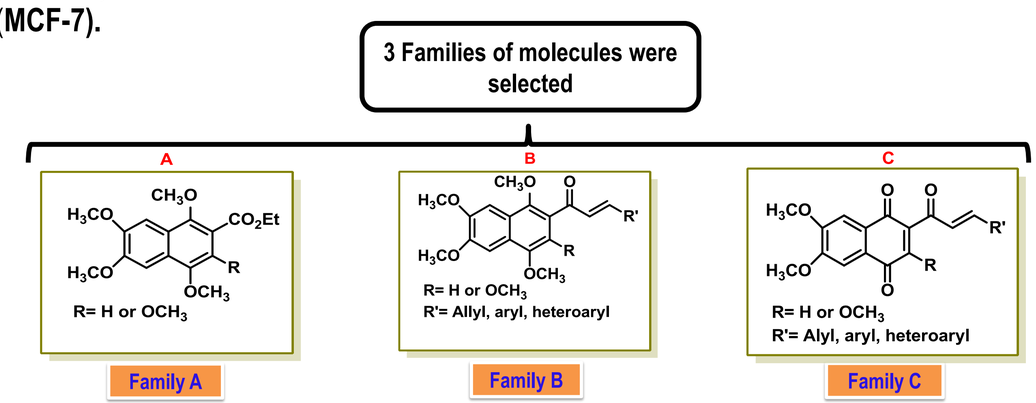


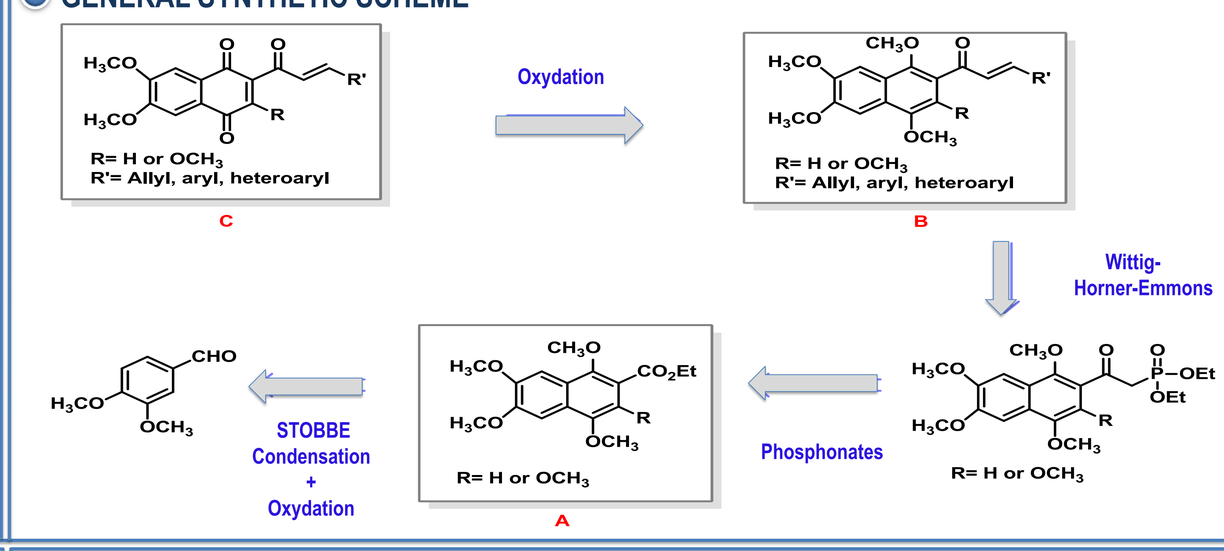
Figure. 1

OBJECTIVE

- This study reports a new synthetic methodology that was optimized to prepare new naphthoquinones derivatives *via* catalytic oxidation.
- The cytotoxicity of these compounds was tested *in vitro* on representative human breast cancer cell lines (**MCF-7).**

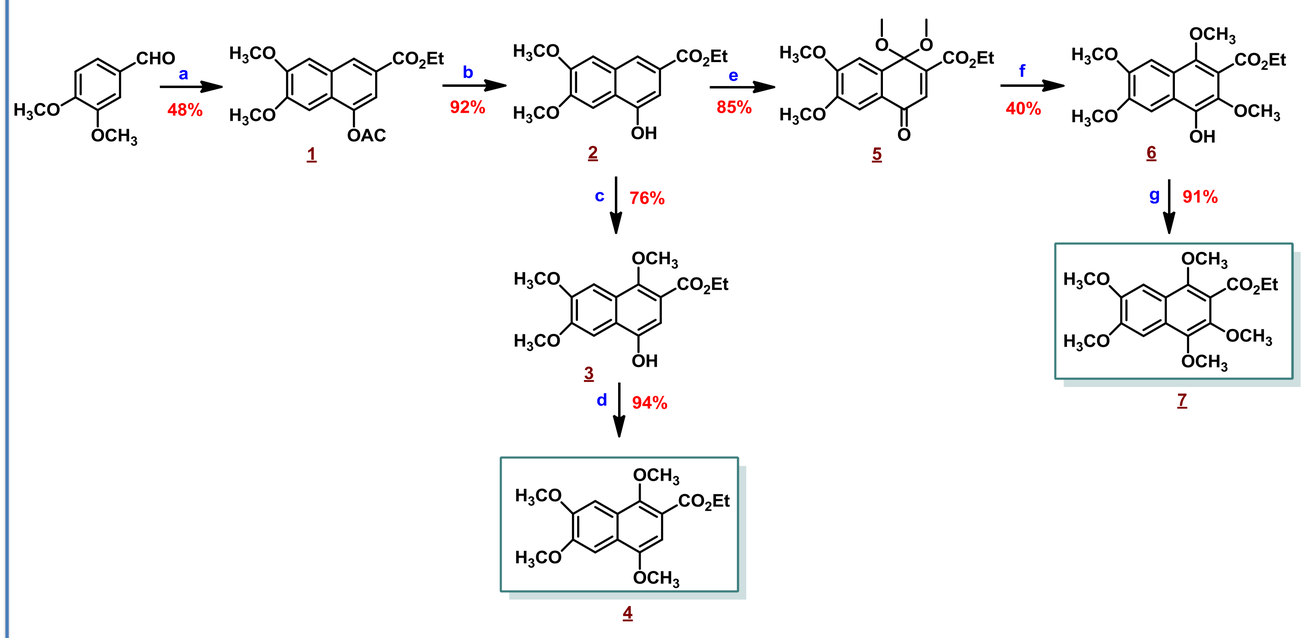


GENERAL SYNTHETIC SCHEME



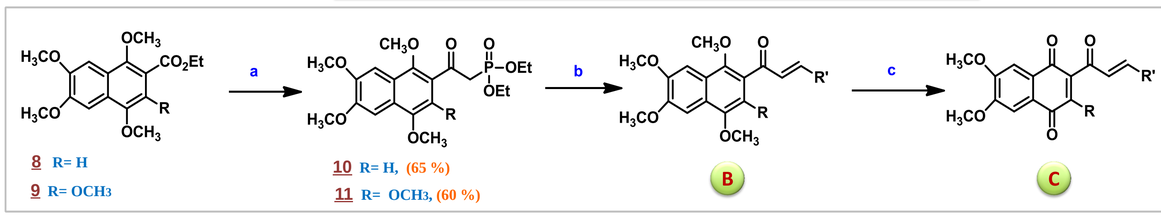
RESULTS

Synthesis of compounds of family A



a) (1) Diethyl succinate, NaOEt, THF, 2h, reflux, (2) NaOAc, Ac_2O, 3h, reflux, 48 % Over two steps; b) 1% KOH/EtOH, 30min, reflux; C) PIDA, MeCN:MeOH (1:1), 2h, r.t.; d) K_2CO_3, $(CH_3)_2SO_4$, Acetone, 10h, reflux; e) PIFA, MeOH, 1h, r.t; f) NaOMe, MeOH, 2h, r.t.; g) K_2CO_3, $(CH_3)_2SO_4$, Acetone, 10h, reflux.

Synthesis of compounds of family B and C



a) $(EtO)_2P(O)Me$, *n*-BuLi, THF, -78°, 2h; 60-65 %; b) R_3-CHO, $Ba(OH)_2$: H_2O, THF:H_2O (40:1), r.t., 2h, 60-79 %; c) CAN, MeCN:H2O (4:1), 0 °C, 25 min, 60-67 %.

Family	Compounds	R	R'	Yield %
B	12	H		79
	13	H	$(CH_2)_2CH_3$	63
	14	OCH_3		67
	15	OCH_3	$(CH_2)_2CH_3$	60
C	16	H		67
	17	H	$(CH_2)_2CH_3$	60
	18	OCH_3		62
	19	OCH_3	$(CH_2)_2CH_3$	63

Table 1. Optimization studies for the synthesis of 16 -19.

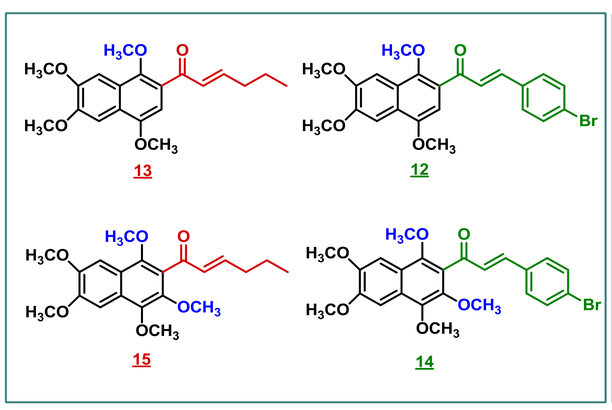
Entry	Conditions	Yield % [a]
1	CAN (3eq), AcOEt, 0 C°, 8 min	0
2	CAN (3eq), MeCN:H_2O (1:1), rt, 1h	0
3	PIDA (2.5eq), MeCN:H_2O (1:1), 0 C°, 5 min	0 [b]
4	PIDA (2.5eq), MeCN:H_2O (1:1), rt, 2h	0
5	CAN (3eq), MeCN:H_2O (4:1), 0 C°, 25 min	16 (67) 17 (60)
6	CAN (1.5eq), MeCN:H_2O (1:1), 0 C°, 25 min	18 (62) 19 (63)

[a] yield of the pure product after column chromatography
[b] Complex mixture

RESULTS

Biological evaluation: *In vitro* cytotoxic activity against breast cancer cell line (MCF-7)

Methoxynaphthalenes



Naphthoquinones

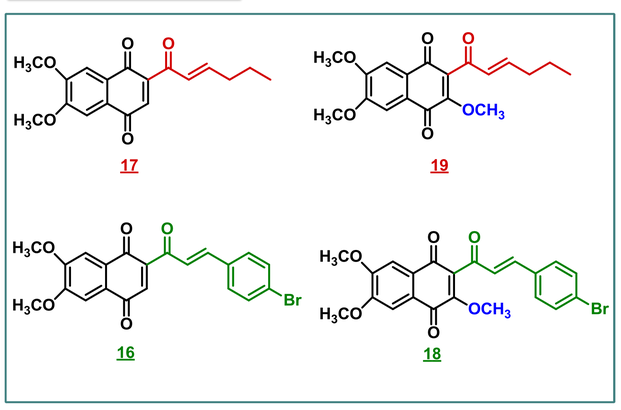


Table 2. Cytotoxicity on MCF-7 cancer cells (3N):

	Methoxynaphthalenes		Naphthoquinones	
	Compounds	CI_{50} (µM)	Compounds	CI_{50} (µM)
Aliphatique Side chain	13 15	4.09 4.52	17 19	18.90 16.11
Bromophenyl Side chain	12 14	23.92 nc	16 18	158.63 82.47
References	5-FU Tamoxifen	4.04 11.91	nc : noncalculable	

- **Methoxynaphthalenes** derivatives exhibited better activities against the MCF-7 tumor cell line than **Naphtoquinones** derivatives;
- A **méthoxy** group in position 3 for naphthoquinones series enhanced the activity 19 and 159 µM for R= H *versus* 16 and 82 µM for R= OCH_3;
- **Aliphatique side chain** exhibited stronger cytotoxic activity toward the breast cancer cell lines (MCF-7) compared to **bromophenyl side chain**.

CONCLUSION

A new synthetic methodology was optimized to prepare new 6,7-methoxy naphthoquinones derivatives 12-19 by catalytic oxidation *via* hypervalent iodine reagents (PIDA and PIFA) . The latter were prepared in 5-6 steps from naphtol 2 in overall yields (11-34%). The primary "*in vitro*" bioassay revealed that all the compounds displayed inhibitory activity against the MCF-7 tumor cell line (IC_{50} 4-159 µM). The results obtained are encouraging and further studies on the influence of the various structural parameters on the cytotoxicity are currently in study and will be reported in due course.

[1] Aziz, M.H.; Dreckschmidt, N.E.; Verma, A.K. *Cancer Res*. **2008,** *68*, 9024-9032; [2] [Sandur, S.K.; Ichikawa, H.; Sethi, G.; Ahn, K.S.; Aggarwal, B.B. *Biol. Chem*. **2006**, *281,* 17023-17033; [3] Hussain, H.; Krohan, K.; Ahmed, V.U.; Miana, G.A.; Green, I.R. *ARKIVOC*. **2007**, (ii), 145-171; [4] Joshi, K.C.; Singh, P.; Parsadani, R.T.; Singh, G. *Planta Med*. **1979,** *37*, 60-63; [5] de Sousa, J.R.; Silva, G.D.F.; Miyakoshi, T.; Chen, C.L. *J. Nat. Prod*. **2006**, *69*, 1225-1227; [6] Andújar, I.; Recio, M.C.; Giner, R.M.; Ríos, J.L. *Curr. Med. Chem*. **2013**, *20*, 2892-2898; [7] Huyen, L.T.; Hang, D.T.T.; Nhiem, N.X.; Yen, P.H.; Anh, H.L.T.; Quang, T.H.; Tai, B.H.; Dau, N.V.; Kiem, P.V. *Chem. Pharm. Bull*. **2017,** *65,* 589-592; [8] Hoelderich , W. F., Kollmer, F. *Pure Appl. Chem*. **2000,** *72,* 1273.