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[Hmim]HSO_4 Catalyzed Synthesis and Biological Evaluation of Quinoline Derivatives as Potential Anticancer Agents

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Abstract: An efficient methodology was developed using ionic liquid [Hmim]HSO_4 as catalyst to afford quinoline derivatives at reflux condition. A convenient synthesis of quinoline derivatives has been achieved *via* coupling reaction of *o*-nitrobenzaldehyde and substitutated *o*-hydroxy acetophenone using [Hmim] HSO_4 as catalyst in solvent ethanol. All the synthesized derivatives were evaluated for inhibition of cancer cell. The initial assays reveals that some of the newly synthesized compounds displayed significantly good inhibition activities against human breast cancer cell (MCF7), cell lines compared with the control (Adriamysin), which might be developed as novel lead scaffold for potential anticancer agents.

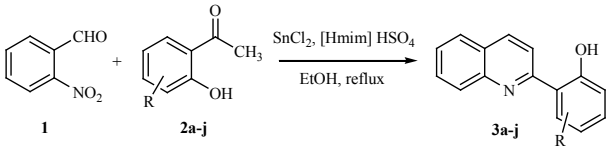
Keywords: Anticancer activity, *o*-Hydroxy acetophenone, *o*-Nitrobenzaldehyde, [Hmim]HSO_4, Quinolines

Introduction

Nitrogen containing heterocycles play an essential role in both drug discovery and medicinal chemistry. For that reason the development in synthetic protocols used for the synthesis of nitrogen containing heterocycles has concerned more awareness to the organic chemist. Quinoline moiety has exhibit considerable applications in pharmaceutical chemistry [1-3] and their wide-ranging occurrences in natural products such as camptothecin [4-5] and luotonin A [6]. Quinolines are noteworthy intermediates in organic synthesis and prove a range of pharmacological activities such as antitubercular [7], anti-inflammatory [8], anti-platelet [9], antibacterial [10-11], anti-asthmatic [12], anticancer [13-14], antihypertensive [15], antimalarials [16], antifungals [17] and anti-proliferative [18].

Furthermore quinolines act as an antifoaming

agent in refineries [19]. They are also employed in a number of nanostructures and meso structures with better electronic and photonic functions [20-21]. Because of such influence in drug discovery, the synthesis of quinolines has become a desirable target for the organic chemists. A number of protocols for the synthesis of quinolines have been described in the literature [22-23]. Now the elimination of unsafe organic solvents in chemical reactions is the striking target in green chemistry. Therefore use of ionic liquid is a useful methodology to accomplish this target. Ionic liquid including elevated thermal stability, low volatility, recyclability, non-flammability and catalytic activity has attracted much awareness as environmentally benign reagents in synthetic organic chemistry. Several protocols have been successfully developed using ionic liquids as catalyst and solvent [24-26]. Herein, we have developed an ionic liquid [Hmim]HSO_4 catalyzed synthesis of quinoline derivatives using the condensation of *o*-nitrobenzaldehyde and substituted *o*-hydroxy acetophenone under reflux condition (**Scheme 1**).



Scheme 1

Experimental

All solvents were utilized as commercial anhydrous grade without further purification. Melting points were determined in open capillary tube and are uncorrected. The column chromatography was performed with silica gel (80-120 mesh). ^{1}H NMR and ^{13}C NMR were recorded on Avance-300 MHz spectrometer in $CDCl_3$ solvent and TMS as an internal standard. Mass spectra were run on Polaris Q Thermoscintific GC-MS.

Anticancer Activity

The anti-cancer activity for these compounds was done in the Anti-cancer drug screening facility (ACDF), Tata memorial centre, advanced centre for treatment, research and education in cancer (ACTREC). The in-vitro anti-cancer activity for the corresponding compounds and ADR (Adriamysin or doxorubicin) taken as a known drug, tested using SRB (sulforhodamine B) assay protocol as exactly described by Skehan P. *et al.* Briefly, SRB is a dye binds to the protein. The human breast cancer cell line MCF7 cultured in 96 well plates treated with different concentrations of given compounds (10, 20, 40 and 80 µg/ml). After treatment the cells were fixed in trichloroacetic acid and stained using sulforhodamine B (0.4% wt/vol) prepared in 1% acetic acid for 30 minutes. Four washes with 1% acetic acid were given to remove unbound dye. 10 mM unbuffered tris base was used to extract protein bound dye and subjected for microtiter plate reader. The absorbance of dye was measured at wavelength 565 nm. The absorbance is correlated with the net protein synthesis rate. 50% inhibition of cell growth (GI50), 50% cell kill or lethal concentration (LC50) and 100% (total) growth inhibition (TGI) was calculated. The GI50 value <10 µg/ml is considered to demonstrate activity in case of pure compound. This experiment was done in triplicate and the average values were plotted against % control growth versus drug concentrations.

General procedure for synthesis of catalyst ionic liquid [Hmim]HSO_4:

3-Methylimidazolium hydrogen sulfate [Hmim] HSO_4 was prepared according to literature procedure [27]. 1-Methylimidazole (0.01mol) was placed in two naked flask with magnetic stirrer and was cooled to 0 °C then 10 ml of acetonitrile was added to the reaction mixture and sulfuric acid (0.01 mol) was added slowly under stirring. The mixture was stirred for 30 minutes and acetonitrile was removed by simple decanting to afford the ionic liquid in

quantitative yields.

General procedure for the synthesis of quinoline derivatives: In 50ml round-bottom flask, a mixture of *o*-nitrobenzaldehyde (1 mmol) and *o*-hydroxy acetophenone (1 mmol) were added in 20 ml ethanol. Further $SnCl_2$ (5 mmol), [Hmim]HSO_4 (10 mol %) and approximately 0.5 g of 4 Å molecular sieves were added to the reaction mixture. This mixture was then refluxed for 4-5 hours (Table 2). After the completion of reaction, the reaction mixture was cooled to room temperature and rendered basic (pH 8) with 50 ml of sodium bicarbonate aqueous solution. The reaction mixture was transferred to a separating funnel and was extracted with 20 ml of ethyl acetate. Organic layer was washed with saturated brine solution, dried over $MgSO_4$ and filtered through celite. The desired corresponding quinoline derivatives were obtained in excellent yield.

2,4-dibromo-6-(quinolin-2-yl)phenol (3a): ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.72 (s, 1H), 7.08-7.21 (t, 2H, *J* = 7.0 Hz), 7.42-7.54 (d, 3H, *J* = 7.2Hz), 7.75 (s, 1H), 7.96 (d, 2H, *J* = 7.6Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 114.8, 116.9, 118.2, 123.8, 126.0, 127.9, 128.2, 128.8, 130.0, 132.7, 135.2, 138.4, 146.8, 152.6, 157.0; GC-MS, m/z: 377 (M^+).

4-Chloro-2-(quinolin-2-yl) phenol (3b): ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.68 (s, 1H), 7.32-7.35 (t, 2H, *J* = 7.6 Hz), 7.39-7.43 (d, 3H, *J* = 7.4Hz), 7.82 (s, 1H), 7.86 (d, 3H, *J* = 7.4Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 114.9, 118.4, 121.2, 124.6, 126.2, 127.9, 129.0, 129.6, 130.0, 133.1, 138.9, 146.2, 152.8, 159.0; GC-MS, m/z: 256 (M^+).

2,4-Diiodo-6-(quinolin-2-yl)phenol (3c): ^{1}H NMR(300MHz, $CDCl_3$): δ 5.56 (s, 1H), 7.30-7.42 (m, 3H), 7.48-7.55 (d, 3H, *J* = 7.2 Hz), 7.68 (s, 1H), 7.80 (d, 1H, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 88.8, 89.4, 119.2, 125.2, 127.1, 127.4, 128.2, 129.1, 130.1, 137.4, 137.0, 143.2, 147.4, 153.5, 163.3; GC-MS, m/z: 472(M^+).

2,4-dichloro-6-(quinolin-2-yl)phenol (3d): ^{1}H NMR(300MHz, $CDCl_3$): δ 5.68 (s, 1H), 7.35-7.48 (m, 3H), 7.56-7.64 (d, 3H, *J* = 7.6 Hz), 7.74 (s, 1H), 7.88 (d, 1H, *J* = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 118.2, 124.5, 126.0, 126.9, 127.2, 127.9, 129.1, 129.7, 130.5, 131.0, 131.7, 136.2, 146.2, 152.8, 155.7; GC-MS, m/z: 290(M^+).

4-iodo-2-(quinolin-2-yl)phenol (3e): ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.75 (s, 1H), 7.38-7.44 (t, 2H, *J* = 7.2 Hz), 7.52-7.60 (d, 3H, *J* = 7.6Hz), 7.78 (s, 1H), 7.90 (d, 3H, *J* = 7.0Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 90.2, 115.8, 118.4, 124.6, 125.2, 127.2, 128.8, 129.6, 130.4, 134.8, 136.0, 137.2, 146.8, 152.5, 155.3; GC-MS, m/z: 347 (M^+).

4-bromo-2-(quinolin-2-yl)phenol (3f): ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.75 (s, 1H), 7.38-7.44 (t, 2H, *J* = 7.2 Hz), 7.52-7.60 (d, 3H, *J* = 7.6Hz), 7.78 (s, 1H), 7.90 (d, 3H, *J* = 7.0Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 114.4, 117.8, 119.0, 124.8, 125.9, 126.8, 128.0, 128.8, 129.7, 131.2, 133.3, 136.8, 145.6, 153.2, 158.0; GC-MS, m/z: 300 (M^+).

4-bromo-2-methoxy-6-(quinolin-2-yl)phenol (3g): ^{1}H NMR(300MHz, $CDCl_3$): δ 3.64 (s, 3H), 5.48 (s, 1H), 7.18-7.30 (m, 3H), 7.42-7.51 (d, 3H, *J* = 6.8 Hz), 7.70 (s, 1H), 7.84 (d, 1H, *J* = 7.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 53.4, 114.7, 116.5, 118.8, 124.6, 125.9, 126.8, 127.4, 128.7, 129.3, 130.0, 137.2, 140.9, 148.2, 152.9, 154.6; GC-MS, m/z: 330(M^+).

2-(quinolin-2-yl)phenol (3h): ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.24 (s, 1H), 7.04-7.18 (t, 2H, *J* = 7.6 Hz), 7.34-7.52 (d, 3H, *J* = 7.0Hz), 7.68 (s, 1H), 7.82-7.92 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 114.2, 118.6, 120.8, 123.0, 125.9, 127.4, 128.5, 129.0, 129.4, 130.1, 130.7,136.2, 146.2, 154.0, 157.2; GC-MS, m/z: 222 (M^+).

2-methoxy-6-(quinolin-2-yl)phenol (3i): ^{1}H NMR(300MHz, $CDCl_3$): δ 3.70 (s, 3H), 5.56 (s, 1H), 7.24-7.35 (m, 4H), 7.48-7.57 (d, 3H, *J* = 7.4 Hz), 7.78 (s, 1H), 7.90 (d, 1H, *J* = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 54.7, 112.5, 118.2, 120.8, 122.0, 123.9, 125.1, 126.8, 128.1, 128.9, 129.7, 135.8, 141.6, 146.2, 151.1, 155.6; GC-MS, m/z: 252(M^+).

4-nitro-2-(quinolin-2-yl)phenol (3j): ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.84 (s, 1H), 7.24-7.38 (t, 2H, *J* = 7.6 Hz), 7.49-7.62 (d, 3H, *J* = 7.2Hz), 7.84 (s, 1H), 7.98 (d, 3H, *J* = 7.4Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 115.2, 118.6, 120.7, 123.0, 124.1, 124.9, 126.7, 127.9, 128.6, 129.4, 135.5, 140.8, 145.4, 154.9, 160.2; GC-MS, m/z: 267(M^+).

Result and discussion

An effective approach was developed for the synthesis of quinoline derivatives using ionic liquid [Hmim]HSO_4 as catalyst under reflux condition. Initially for the optimization study, we screened the various solvent on the model reaction of 5-bromo-*o*-hydroxy acetophenone and *o*-nitrobenzaldehyde using 10 mol % catalytic amount of ionic liquid [Hmim]HSO_4 at reflux condition. The polar protic solvents ethanol and methanol were found to be the good solvent for the reaction mainly ethanol. In the solvent methanol, product **3f** was obtained in 68 % yield within reaction time 7 hours (Table1, Entry 1). The reaction performance improved when the reaction was carried out in solvent ethanol which offered excellent 91% yield within the reaction time 4.5 hours (Table 1, Entry 2). In the solvents dichloromethane and toluene, the corresponding product **3f** was obtained in lower yield with extended reaction time (Table 1, Entries 3 and 4 respectively). Moreover the reaction in the acetonitrile and water solvents afforded 64% and 32 % yields with longer reaction time (Table 1, Entries 5 and 6 respectively). Afterward, we investigated the impact of catalytic loading on the model reaction with ethanol as solvent. At the catalytic loading of 5 mol % catalyst [Hmim]HSO_4, the reaction offered 66% yield of the corresponding product **3f** (Table 1, Entry 7).

In our investigation, the best outcome of the reaction was found at the catalytic loading of 10 mol % of the catalyst [Hmim]HSO_4 in solvent ethanol. The reaction was accomplished within 4.5 hours and afforded the product in excellent yield of 91% (Table 1, Entry 2). More raise in the catalytic loading up to 15 mol % did not present considerable progress in the yield even with extended reaction time (Table 1, Entry 8). To ensure the necessity of the catalyst [Hmim] HSO_4 in the reaction, the model reaction was carried out without catalyst in solvent ethanol. The reaction was accomplished with extended reaction time 18 hours and poor yield of desired product (Table 1, Entry 9).

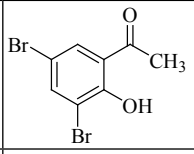
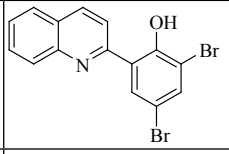
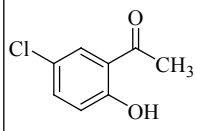
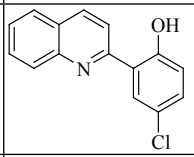
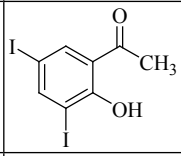
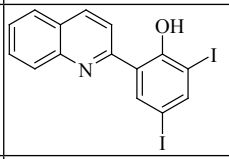
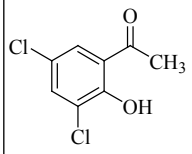
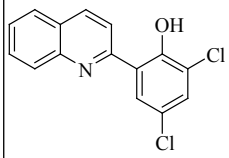
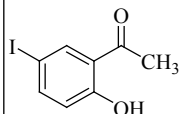
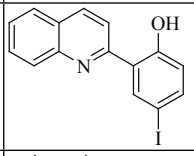
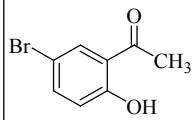
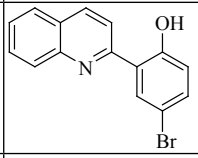
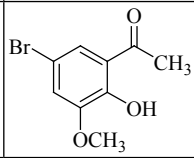
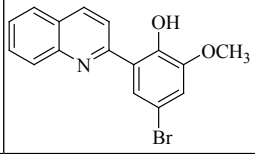
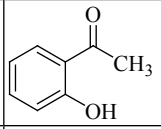
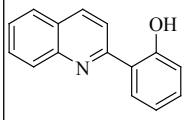
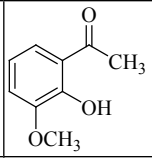
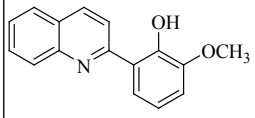
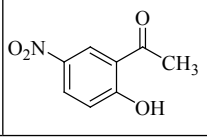
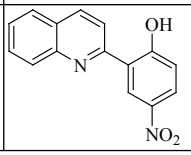
Table 1. The screening of solvent and catalytic loading on the synthesis of quinoline derivatives[a]

Entry	Solvent	[Hmim]HSO_4 (mol %)	Reaction Time (h)	Yield (%)
1	Methanol	10	7	68
2	**Ethanol**	**10**	**4.5**	**91**
3	Dichloromethane	10	12	41
4	Toluene	10	10	36
5	Acetonitrile	10	7	64
6	Water	10	14	32
7	Ethanol	5	5	66
8	Ethanol	15	4	87
9	Ethanol	-	18	24

[a]Conditions: 5-Bromo-*o*-hydroxy acetophenone (1 mmol), *o*-nitrobenzaldehyde (1 mmol), solvent (10 mL) at reflux condition.

Optimistic by these noteworthy results, we screened a variety of substituted *o*-hydroxy acetophenone having electron donating and electron withdrawing substituent for the synthesis of corresponding quinoline derivatives. We found that all products are obtained with good to excellent yields (Table 2, Entries 1-10).

Table 2: An efficient synthesis of quinoline derivatives catalyzed by [Hmim]HSO_4[a]

Entry	Ketones	Products (3a-j)	Reaction Time (h)	Mp. (°c)	Yield[b] (%)
1		 3a	4.30	268	89
2		 3b	5.00	184	86
3		 3c	4.30	252	88
4		 3d	4.20	196	90
5		 3e	4.45	168	87
6		 3f	4.50	182	91
7		 3g	4.55	224	89
8		 3h	5.00	160	84
9		 3i	4.40	214	90
10		 3j	5.05	252	82

[a]Conditions: Substituted *o*-hydroxyacetophenone (1mmol), *o*-nitrobenzaaldehyde (1 mmol), [Hmim]HSO_4 (10 mol %), EtOH (10 mL) at reflux condition. [b]Isolated Yield

Biological Evaluation

Based on the precedence of known anticancer activity of quinoline derivatives we were interested to test anticancer properties in vitro. We evaluated our compounds for their anti-proliferative properties in vitro against cancer cell lines for human breast cancer cell line MCF7. The test compounds were examined at various concentrations in a MTT (3-(4, 5-dimethyl thiazol-2-yl)-2,5-diphenyl tetrazolium bromide) assay and the LC50, TGI and GI50 values obtained for each compounds are summarized in Table 3. ADR (Adriamysin or Doxorubicin known drug) compounds showed cytotoxicity against LC50, TGI and GI50 was used as a reference compound. While most of these compounds showed MCF7 activity shown by LC50, TGI and GI50 values.

The good results however were obtained using compounds 3i, 3g, 3h, 3b (Table 3). Interestingly, all compounds were found to be active against Breast cancer cells and showed good activities against breast cancer cells. In order to understand the mechanism of action some of the compounds were tested for their inhibitory potential against sirtuins. Being considered as important targets for cancer therapeutics sirtuins (class III NAD-dependent deacetylases) are shown to unregulated in various types of cancer. Inhibition of sirtuins allows re-expression of silenced tumor suppressor genes, leading to reduced growth of cancer cells. The activity of test compounds was determined using Sirt1 fluorescence activity assay using suramin, a known inhibitor of Sirt1 as a reference compound. At the concentration of 10 mg/ml compounds 3i, 3g showed 30.9, 33.0 where as for concentration 80 mg/ml for 3i and 3g showed 1.2 and 2.1 inhibition, respectively. In compared to Adriamysin 2.8 and -32.7 inhibition indicating that the anticancer properties of these molecules are possibly due to their sirtuin inhibiting properties. The compound 3b shows good inhibition activities against human breast cancer cell (MCF7) in **Figure 1**.

Table 3: In vitro cytotoxicity of the quinoline derivatives against human breast cancer cell line (MCF7)

Human Breast Cancer cell line MCF7																
%control growth																
Drug concentration (mg/ml)																
	Experiment 1				Experiment 2				Experiment 3				Average values			
	10	20	40	80	10	20	40	80	10	20	40	80	10	20	40	80
3a	52.6	41.4	14.8	9.7	53.6	45	20.8	13.4	46.7	46.3	20.5	14.4	51	44.2	18.7	12.5
3b	40.1	33.3	6.4	7.6	39.6	35.4	12.2	6.3	32.2	38.3	11.9	6.3	37.3	35.6	10.1	6.7
3c	54.2	44.3	16.3	11.9	55.4	47.8	23.1	15.7	48.4	49.7	22.6	16.9	52.6	47.2	20.6	14.8
3d	46.2	39.6	12.4	8.6	48.6	43.3	18.3	12.8	41.8	46.3	18.2	12.4	45.5	43.0	16.3	11.2
3e	44.1	37.4	10.3	6.7	45.7	41.4	16.2	10.1	38.7	44.2	16.3	10.2	42.8	43.2	14.2	9.0
3f	42.1	35.3	8/.6	4.2	42.7	38.9	14.1	8.3	35.4	41.9	14.2	8.7	40.0	38.7	12.3	7.0
3g	35.3	29.3	10.6	2.1	35.2	31.1	8.2	2.1	28.7	32.8	7.2	2.1	33.0	31.0	8.6	2.1
3h	38.2	31.2	3.8	5.2	37.4	33.2	10.2	4.1	30.3	35.2	9.3	4.2	35.3	33.2	7.76	4.5
3i	32.1	27.2	-0.23	0.90	34.8	30.2	8.7	1.8	25.9	29.2	5.1	1.1	30.9	28.8	4.5	1.2
3j	57.2	46.3	19.1	13.6	58.2	49.3	25.1	17.2	50.5	51.2	25.1	19.3	55.3	48.7	23.1	16.7
ADR	5.7	4.1	-0.8	-29.9	1.4	5.0	-2.2	-31.8	1.2	6.2	2.5	-36.4	2.8	5.1	-0.2	-32.7

	Drug concentrations mg/ml calculated from graph		
MCF7	**LC 50**	**TGI**	**GI50**
3a	>80	>80	25.8
3b	>80	>80	13.9
3c	>80	>80	30.5
3d	>80	>80	23.1
3e	>80	>80	18.1
3f	>80	>80	14.1
3g	>80	>80	4.3
3h	>80	>80	9.2
3i	>80	>80	2.4
3j	>80	>80	34.4
ADR	>80	43.7	<10

GI50	Growth inhibition of 50 % (GI50) calculated from [(Ti-Tz)/(C-Tz)] x 100 = 50, drug concentration resulting in a 50% reduction in the net protein increase
TGI	Drug concentration resulting in total growth inhibition (TGI) will calculated from Ti = Tz
LC50	Concentration of drug resulting in a 50% reduction in the measured protein at the end of the drug treatment as compared to that at the beginning) indicating a net loss of 50% cells following treatment is calculated from [(Ti-Tz)/Tz] x 100 = -50.

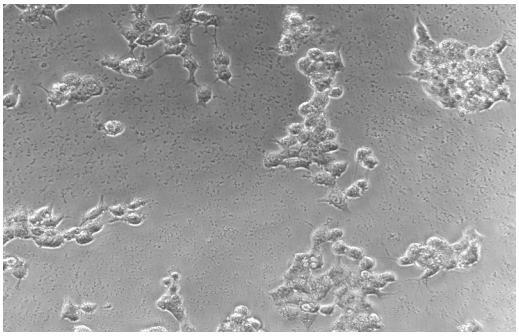


Figure 1: MCF7 of 3b

Conclusion

In conclusion, we have developed an expedient approach for the synthesis of quinoline derivatives by the coupling reaction of substituted o-hydroxy acetophenone and o-nitro benzaldehyde in presence of ionic liquid [Hmim]HSO_4 as catalyst. This modified methodology offers enhanced performance over the many conventional methods. The delightful features of this protocol are easy work up, use of environmentally benign catalyst and excellent yields of the corresponding quinoline derivatives. All the synthesized derivatives were evaluated for their anticancer activities. The initial assays indicated that some of the newly synthesized compounds displayed significantly good inhibition activities against human breast cancer cell (MCF7), cell lines compared with the control (Adriamysin), which might be developed as novel lead scaffold for potential anticancer agents.

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