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SYNTHESIS OF OCTAHYDROQUINAZOLINONE DERIVATIVES AND ITS ANTICANCER ACTIVITY EVALUATION

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ABSTRACT

A convenient method was expanded for the synthesis of octahydroquinazolinones by one-pot reaction of a different salicylaldehyde, dimedone and urea/thiourea using [Hmim]HSO_4 in catalytic amount. The synthesized derivatives were tested for inhibition of cancer cell. The primary analysis showed that number of synthesized molecules exhibited considerably admirable inhibition activities against MCF-7 human breast cancer cell.

KEYWORDS: Anticancer activity, one-pot synthesis, salicylaldehyde, [Hmim]HSO_4, Octahydroquinazolinones.

INTRODUCTION

One-pot synthesis is very considerable for the formation of numerous heterocyclic molecules[1] and this approach has been employed successfully in construction of many bioactive moieties and natural products.[2] The octahydroquinazolinone synthesis has attracted the awareness of chemists due to their highly useful anti-bacterial activity against many kinds of bacteria including *Esherichia coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*.[3] Exceptionally quinazoline derivatives has been employed as an anti-cancer drugs,[4-6] analgesic,[7] anti-inflammatory,[8] anti-bacterial,[9] anti-convulsant,[10] anti-mycobacterial agents[11] and anti-fungal.[12]

A range of protocols have been reported for octahydroquinazolinone synthesis by the reaction of aldehydes with dimedone and urea or thiourea involving the use of catalysts such as thiamine hydrochloride,[13] NH_4VO_3,[14] TMSCl,[15] Nafion-H,[16] conc. H_2SO_4,[17] conc. HCl,[18] heteropolyacid,[19] bakers' yeast[20] and ionic liquids.[21-22] Among these, a number of protocols experiences the few drawbacks such as extended reaction time, reduced product yield and unsafe and costly catalysts with partial reusability.

Here in we describe an useful methodology for the synthesis of octahydroquinazolinones by using ionic liquid [Hmim] HSO_4 catalyst at room temperature (**Scheme 1**). All prepared molecules were evaluated for the inhibition of Breast cancer cell.

MATERIALS AND METHODS

The column chromatography was performed over silica gel (80-120 mesh). Melting points of synthesized derivatives were carried out in open glass capillary tube and were uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker 300 MHz spectrometer in $CDCl_3$ solvent with TMS as an internal standard. Mass spectra were carried out on Polaris-Q Thermo scientific GC-MS spectrometer.

2.1 Typical procedure for the synthesis of octahydroquinazolinones: In 50 ml round bottom flask, A mixture of dimedone (1 mmol), urea/thiourea (1.2 mmol), [Hmim]HSO_4 (10 mol %) and acetonitrile (10 ml) was added. The mixture was stirred at room temperature for half an hour. The substituted salicylaldehyde (1 mmol) was then added and stirring was continued for suitable time (Table 2). After the completion of reaction indicated by TLC, the reaction mixture was diluted with water (15 mL) and extracted with diethylether (3 x 4-5mL). The combined organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. The obtained crude product was purified by column chromatography (silica gel, pet ether-EtOAc) to get analytically pure product.

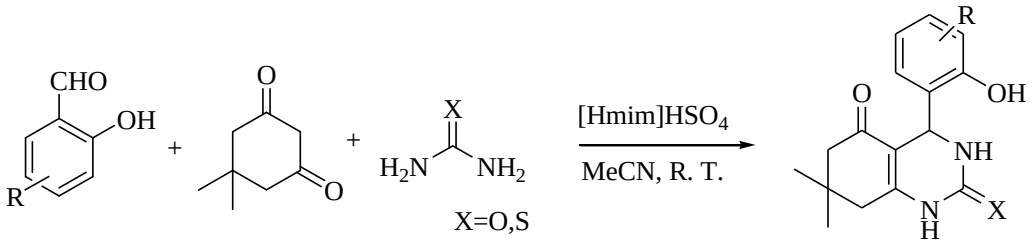
4-(5-Bromo-2-hydroxyphenyl)-3,4,7,8-tetrahydro-7,7-dimethylquinazoline-2,5(1H,6H)-dione(4d): ^1H NMR (300 MHz, $CDCl_3$): δ 9.61 (s, 2H, 2 x NH), 7.10-7.12 (m, 2H), 6.80(d, 1H, *J* = 4.5Hz), 5.82 (s, 1H), 5.28 (s, 1H, OH), 3.21(s, 2H), 3.05(s, 2H, CH_2), 1.92 (s, 6H, 2 x CH_3); ^{13}C NMR (300 MHz, $CDCl_3$): δ 30.2, 33.2, 38.6, 46.5, 58.2, 108.2, 118.0, 121.0, 126.5, 130.8, 134.4, 140.2, 148.6, 170.8, 191.2; GC-MS, m/z: 364 (M^+).

1,2,3,4,7,8-Hexahydro-4-(2-hydroxy-5-iodophenyl)-7,7-dimethyl-2-thioxoquinazolin-5(6H)-one (4i): ^1H NMR (300 MHz, $CDCl_3$): δ 10.24 (s, 2H, 2 x NH), 7.22-7.26

(m, 2H), 6.92(d, 1H, J = 4.8Hz), 5.88 (s, 1H, CH), 5.37 (s, 1H, OH), 3.18(s, 2H), 2.98(s, 2H, CH_2), 1.86 (s, 6H, 2 x CH_3); ^{13}C NMR (300 MHz, $CDCl_3$): δ 30.5, 33.8, 46.7, 50.2, 58.0, 95.2, 108.0, 115.6, 122.8, 132.0, 135.7, 148.4, 154.1, 168.6, 189.0; GC-MS, m/z: 428 (M^+).

RESULTS AND DISCUSSION

Here in we describe an useful protocol for the synthesis of octahydroquinazolinones using ionic liquid [Hmim]HSO_4 as catalyst under ambient temperature condition.



1 2 3 4a-l

Scheme 1

For initial optimization study, we studied the solvent effect on model reaction of 5-bromo salicylaldehyde (1 mmol), dimedone (1 mmol) and urea (1.2 mmol) using catalyst [Hmim]HSO_4 (10 mol %) at room temperature. The polar protic solvents ethanol and methanol were found to be the good solvent for the reaction. In the solvent methanol, product 4d was obtained in 65% yield within 3 h (Table 1, entry 1) and in solvent ethanol reaction afforded 72% yield (Table 1, entry 2). The reaction performance enhanced when reaction carried out in solvent acetonitrile. The reaction afforded excellent 93% yield within reaction time 1.3 hours (Table 1, entry 3). In the solvents dichloromethane and chloroform, the preferred product 4d was obtained in lower yield with elongated reaction time (Table 1, entries 4 and 5 respectively).

Table 1: The screening of the solvent and catalyst amount for the synthesis of octahydroquinazolinone[a]

Entry	Solvent	[Hmim]HSO_4	Time(h)	Yield[b](%)
1	Methanol	10	3	65
2	Ethanol	10	3.2	72
3	**Acetonitrile**	**10**	**1.3**	**93**
4	Dichloromethane	10	6	41
5	Chloroform	10	6	36
6	Water	10	5	48
7	Acetonitrile	5	3	69
8	Acetonitrile	15	1.5	85
9	Acetonitrile	20	1.5	86
10	Acetonitrile	-	8	32

[a]Conditions: 5-Bromosalicylaldehyde (1 mmol), dimedone (1 mmol) and urea (1.2 mmol), solvent (10ml), catalyst (mol %) and ionic liquid [Hmim]HSO_4 at r.t.
[b]Isolated yield.

Furthermore the reaction in the solvent water offered 48% yields with longer reaction time (Table 1, entries 6). Subsequently, we examined the influence of catalyst amount on model reaction with acetonitrile as solvent. At first, with 5 mol % catalyst [Hmim]HSO_4, the reaction afforded 69% yield of the product 4d (Table 1, entry 7).

The best result for the reaction was obtained at the catalytic loading of 10 mol % of the catalyst [Hmim]HSO_4. The reaction was completed within 1.3 hours and gave the corresponding product in excellent yield of 93% (Table 1, entry 3). Further increase in the catalytic loading up to 15 and 20 mol % did not reveal significant enhancement in product yield even with longer reaction time (Table 1, entry 8 and 9 respectively). To check the necessity of the catalyst [Hmim]HSO_4 in the reaction, the reaction was performed without catalyst. The reaction was accomplished with extensive reaction time 8 hours but the obtained product was very poor in yield (Table 1, entry 10). Further the different substituted salicylaldehydes were allowed to react with dimedone and urea/thiourea. All reactions were carried out nicely with a substituted salicylaldehydes offering excellent product yield (Table 2, entries 1-12).

Table 2: One-pot synthesis of octahydroquinazolinones[a]

Sr. No.	Products (4a-l)	R	Time (h)	Mp. (°C)	Yield[b] (%)
1	**4a**	2-OH	1.3	182-184	90
2	**4b**	2-OH, 3-OCH_3	1.0	172-174	93
3	**4c**	2-OH, 5-I	1.5	220-222	87
4	**4d**	2-OH, 5-Br	2.0	208-211	85
5	**4e**	2-OH, 3, 5-Br	2.2	251-254	83
6	**4f**	2-OH, 3-Br, 5-I	2.4	230-232	80
7	**4g**	2-OH	2.5	190-192	89
8	**4h**	2-OH, 5-Br	1.2	224-226	92
9	**4i**	2-OH, 5-I	1.5	214-217	88
10	**4j**	2-OH, 3,5-Br	2.0	238-240	91
11	**4k**	2-OH, 3-Br, 5-I	2.3	262-265	90
12	**4l**	2-OH, 3-OCH_3	2.5	175-177	86

[a]Conditions: Substituted salicylaldehyde (1 mmol), dimedone (1 mmol) and urea/thiourea (1.2 mmol) in solvent acetonitrile using catalyst 10 mol% $[Hmim]HSO_4$ at r. t. [b]Isolated yield.

Anticancer Activity

We tested the synthesized derivatives for their anti-proliferative activities in vitro against cancer cell lines for MCF7 human breast cancer cell line. The target compounds were observed at different concentrations in MTT (3-(4,5-dimethyl thiazol-2-yl)-2,5-diphenyl tetrazolium bromide) assay (Table 3). The obtained LC-50, GI-50 and TGI values for each compound are listed in Table 4. ADR (Adriamysin known drug) revealed cytotoxicity against LC-50, GI-50 and TGI was utilized as reference compound. Though most of these compounds present MCF7 activity exhibited by LC-50, GI-50 and TGI values.

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

	Experiment 1				Experiment 2				Experiment 3				Average Values			
Drug conc. (mg/ml)	10	20	40	80	10	20	40	80	10	20	40	80	10	20	40	80
Product	% control growth				% control growth				% control growth				% control growth			
4a	84.6	77.5	68.3	40.6	90.5	81.6	75	49	85	82.5	74.9	48.5	86.7	80.5	72.8	46
4b	77.2	72.1	61.2	33.2	83.1	69.3	67.4	41.3	76.2	80.1	71.6	42.1	78.8	73.8	66.7	38.8
4c	88.2	82.1	73.6	46.7	87.8	87.1	81.4	55.7	91.3	88.1	80.3	55.2	89.1	85.7	78.4	52.5
4d	87.2	80.3	72.2	44.3	86.7	85.6	79.3	54.1	89.1	86.4	78.1	53.2	87.6	84.1	76.5	50.5
4e	93.2	88.4	79.2	52.3	92.4	93.2	87.3	61.2	97.2	94.3	86.4	61.2	94.2	91.9	84.3	58.2
4f	91.2	86.2	77.3	50.2	90.3	91.4	85.4	59.4	95.1	92.2	84.3	59.2	92.2	89.3	82.3	56.2
4g	85.2	78.4	70.2	42.1	85.3	83.2	77.4	52.3	87.4	84.3	76.4	51.3	85.9	81.9	74.6	48.5
4h	89.4	84.2	75.3	48.2	88.7	89.7	83.1	57.1	93.1	90.2	82.3	57.2	90.4	88.0	80.2	54.1
4i	80.3	74.6	63.6	35.6	85.6	72.3	71.3	44.8	78.3	81.6	73.8	45.8	81.4	76.2	69.6	44.1
4j	90.2	85.3	77.4	50.5	88.4	91.2	85.3	59.3	95.3	92.1	84.3	58.8	91.3	89.5	82.3	56.2
4k	91.3	86.4	78.3	51.4	89.3	92.4	86.3	61.2	96.4	93.3	85.4	60.2	92.3	90.7	83.3	57.6
4l	75.3	70.2	58.3	31.2	81.2	67.3	64.8	39.2	74.3	78.4	68.5	40.5	76.9	71.9	63.8	36.9
ADR	5.7	4.1	-0.8	-30	1.4	5.0	-2.2	-32	1.2	6.2	2.5	-36.	2.8	5.1	-0.2	-32.7

Table 4: Drug concentrations mg/ml calculated from graph.

MCF7	LC 50	TGI	GI50
4a	>80	>80	74.3
4b	>80	67.6	62.6
4c	>80	>80	84.7
4d	>80	>80	81.5
4e	>80	>80	94.0
4f	>80	>80	90.7
4g	>80	>80	78.3
4h	>80	>80	87.3
4i	>80	76.6	71.2
4j	>80	>80	90.7
4k	>80	>80	93.0

4l	>80	64.1	59.6
ADR	>80	43.7	<10

GI-50	Growth inhibition of 50% (GI-50) 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
LC-50	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.
ADR	Adriamycin (Doxorubicin). Known drug.

The satisfactory results were attained using compounds 4a, 4b, 4i, 4l (Table 4). Delightfully all derivatives were found to be active against Breast cancer cells and exhibited superior activities against the Breast cancer cells. So as to recognize the mechanism action, some of derivatives were analyzed for their inhibitory potential against sirtuins. Being considered as significant targets for cancer therapeutics sirtuins (class III NAD-dependent deacetylases) are revealed to upregulated in several kinds of cancer. The inhibition of sirtuins permits the re-expression of silenced tumor suppressor genes, leading to reduced growth of cancer cells. The activity of 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, the compounds 4a, 4b showed 86.7, 78.8 where as for concentration 80 mg/ml, compounds 4a and 4b showed 46 and 38.8 inhibition respectively.

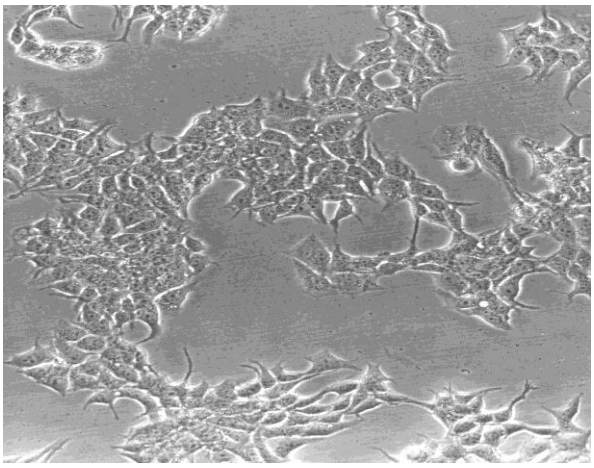


Figure 1: MCF7 of 4l.

As compared to Adriamysin 2.8 and -32.4 inhibitions demonstrating that the anticancer properties of these molecules are possibly due to their sirtuin inhibiting properties. The molecule 4l shows notable inhibition activities against human Breast cancer cell (MCF7) in **figure1**.

CONCLUSION

In conclusion, we have developed a convenient protocol for the synthesis of octahydroquinazolinones by three component reaction of a substituted salicylaldehyde, dimedone and urea/thiourea using catalyst ionic liquid [Hmim]HSO_4. This methodology offers an enhanced performance over the several conventional methods. The notable highlights of this approach are use of environmentally kind catalyst, simple experimental work-up, short reaction time and excellent yields of octahydroquinazolinones. All synthesized derivatives were evaluated for their anti-cancer activity. The initial assays indicated that some of the newly synthesized derivatives showed considerably 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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