European Journal of Chemistry 8 (3) (2017) 317-320

European Journal of Chemistry

Journal webpage: www.eurjchem.com

Synthesis of quinazolinones derivatives an antiproliferative agent against human lung carcinoma cells

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COMMUNICATION INFORMATION

DOI: 10.5155/eurjchem.8.3.317-320.1586

Received: 20 May 2017
Received in revised form: 31 July 2017
Accepted: 05 August 2017
Published online: 30 September 2017
Printed: 30 September 2017

KEYWORDS

Ionic liquid
Green chemistry
2-Aminobenzamide
Antiproliferative activity
Lung carcinoma A549 cells
2,3-Dihydroquinazolin-4(1H)-one

ABSTRACT

2,3-Dihydroquinazolin-*4(1H)*-one derivatives (3a-p) were synthesized in excellent yields. These compounds were screened for antiproliferative activity against A549 cells and were found as potent cytotoxicity. Compounds A4, A8, A10 found to be more promising antiproliferative against the lung carcinoma A549 cells. IC_{50} values for compounds A4, A8 and A10 were found to be 8.6, 8.9 and 8.1 µg/L against A549 cells, respectively.

Cite this: *Eur. J. Chem.* **2017**, *8(3)*, 317-320

1. Introduction

Various quinazolinones were found as natural products and attracted a vast attention because of their wide range of biological activities. Previous reports of their derivatives showed significant effects in different pharmaceutical products [1-3]. Quinazolinone derivatives also reported as potential antimicrobial [4], antimalarial [5], antitumor [6,7], antidepressant [8], analgesic [9], CNS stimulant [10], tranquilizing [11] and anticancer agent [12]. Reaction of 2-aminobezamide and aromatic aldehydes were widely used for the synthesis of quinazolinones derivatives. This is an efficient method for the synthesis of potentially active quinazolinone derivatives. Quinazolinone moieties are significant for biological activities in healthcare and medicines. In addition, quinazolinone heterocyclic is also utilized as a backbone skeleton of some drugs such as cloroqualone, afloqualone and quinethazone (Figure 1).

Therefore a simple, mild, and versatile preparation method of quinazolinones in one-pot reaction is still highly desirable. In continuation of our research devoted to the new methods for the preparation of heterocyclic compounds *via* multicomponent reactions, we describe the synthesis of quinazolinone derivatives using 2-anthranilamides and aromatic substituted aldehydes in ethanol under reflux condition.

Several methods has been used for cyclocondensation of 2-anthranilamides with aldehydes in the presence of various promoting agents, such as Lewis acids $CuCl_2.2H_2O$ [13], Cerium (iv) sulphates tertrahydes [14], cyanuric chlorides [15], Amberlyst-15 [16] and $SnCl_2$ [17]. Reaction was also carried out by acids catalyzed one-pot synthesis using PTSA [18], silica-SO_3H [19], acetic acid [20] and also in presence of alum [21] montmorillonite K-10 [22], thiamine hydrochloride (VB1) [23]. Recently, nano-catalyst metal-CNTs [24], Wang-OSO_3H [25], basic ionic liquid [26] and [bmim] HSO_4 [27], ceric ammonium nitrate [28] were also used in this transformation. Eventhough significant improvements and developments using various catalysts have been achieved; this protocol lacks implementation and limitations such as the use of excess of solvent, moisture sensitive, corrosive, expensive catalysts, tedious separation procedures for recovery of catalysts leads to toxic waste generation along with a long reaction time, high temperature and low yield of the desired products.

ISSN 2153-2249 (Print) / ISSN 2153-2257 (Online)
http://dx.doi.org/10.5155/eurjchem.8.3.317-320.1586

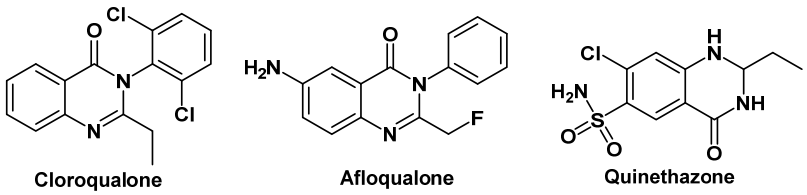
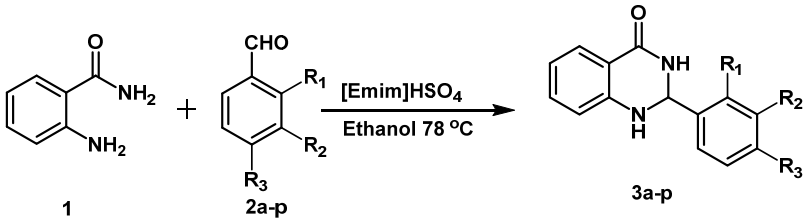


Figure 1. Some example of quinazolinone active heterocyclic compounds.



Scheme 1

Herein, we report a mild and efficient protocol for the synthesis of, 2,3-dihydroquinazolin-4(1*H*)-one derivatives in presence ionic liquid under mild condition (Scheme 1).

2. Experimental

2.1. Instrumentations

^{1}H NMR spectra were recorded in solvent DMSO using Varian spectrometer instrument ^{1}H (400 MHz) at 25 °C temperature. Chemical shifts were reported in δ ppm with tetramethylsilane as an internal standard (TMS, δ = 0.0). Infrared spectra were recorded on a FT-IR spectrometer (Shimadzu FT-IR 8300 spectrophotometer) in a range of 400-4000 cm^{-1}. Mass spectra were recorded on VG-7070H Micromass. Melting points taken are uncorrected.

2.2. Synthesis of the quinazolinones derivatives

In a round bottom flask (10 mL), 2-aminobenzamide (1 mmol) and substituted aldehydes **2a** (1 mmol) were added. To it 1-ethyl-3-methylimidazolium hydrogen sulphate (10 mol %) catalysts was added in ethanol (5 mL). The reaction mixture was heated under reflux for appropriate time. The progress of reactions was monitored by using TLC. After completion of reaction the product obtained was poured onto crushed ice. The solid obtained was filtered and recrystallized in hot ethanol to afford the pure product.

2-(4-Fluorophenyl)-2,3-dihydroquinazolin-4(1H)-one (**3a**): Color: White. M.p.: 203-205 °C. FT-IR (KBr, ν, cm-^{1}): 2915 (C-H), 1625 (C=C). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 5.77 (s, 1H, N-H), 6.69 (d, 2H, Ar-H), 7.19 (s, 1H, Ar-H), 7.27 (t, 1H, C-H), 7.30 (dd, 4H, Ar-H), 7.55 (d, 1H, Ar-H), 8.56 (s, 1H, N-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 66.42, 115.0, 115.51, 115.53, 118.0, 126.99, 130.50, 132.87, 139.25, 149.07, 162.06, 163.00. EI-MS (*m/z*): 243 [M+1]$^+$.

2-(3-Nitrophenyl)-2,3-dihydroquinazolin-4(1H)-one (**3o**): Color: White. M.p.: 205-206 °C. FT-IR (KBr, ν, cm-^{1}): 2914 (C-H), 1610 (C=C), 1456 (C-Cl). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 5.73 (s, 1H, N-H), 6.7 (d, 2H, Ar-H), 7.17 (s, 1H, Ar-H), 7.22 (t, 1H, C-H), 7.4 (dd, 4H, Ar-H), 7.6 (d, 1H, Ar-H), 8.39 (s, 1H, N-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 66.76, 78.11 79.28, 114.37, 118.11, 126.98, 128.14, 132.54, 133.74, 140.34, 146.57, 163.32. EI-MS (*m/z*): 269 [M+1]$^+$.

2.3. Cell culture conditions

A lung carcinoma cell A549 were maintained in RPMI-1640 containing 10 % v/v FBS (Life technologies Inc. USA). The cells sub-cultured and incubated at 37 °C and 5% CO_2 incubator. For all experiments, the cells were freshly grown by diluting the stock solution with D-phosphate-buffered saline (pH = 7.2) (Hi Media, India).

2.4. Determination of cell viability and IC_{50}

The antiproliferative effect of compounds on Lung carcinoma cells was evaluated by Vybrant MTT Cell Proliferation Assay Kit (Life technologies Inc. USA). The procedure was adopted described previously [29]. Briefly, the cells were plated at ~1×10^4 cells in each well of 96 well plate in 100 µL of RPMI-1640 medium. All the compounds (0, 5, 10, 25, 50 µg/mL) were added to each well separately. The standard reference drug Doxorubicin (10 uM) was used. Cell viability was determined after 24 hrs incubation in CO_2 incubator at 37 °C. MTT (5 mg/mL in PBS) was added to each well and incubated for 4 hrs. The absorbance was recorded at 490 nm using a 96 well Multiscan Ascent (Thermo Inc.USA). The IC 50 was calculated by using formula

2.5. Statistical analysis

Dose-response curves were plotted to determine IC_{50} values using the GraphPad Prism. p-*values* < 0.05 were considered significant.

3. Results and discussion

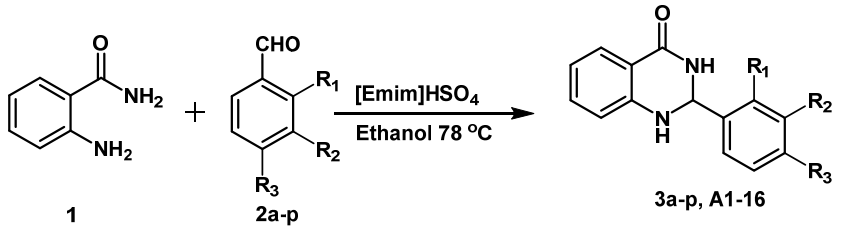
Initially, we tried anthranilamide (1 mmol) and 4-NO_2 benzaldehyde (**2a**) (1 mmol) as the model reaction by using copper silicates catalyst in acetonitrile at room temperature; obtained product formation takes place in very low yield (Table 1, Entry 1). To improve the product yield the reaction condition like sonification and reflux condition of reaction were changed and the yield was increased up to 80-82 % (Table 1, Entry 2-3).

The modified conditions for reactions along with the alteration in the temperature enhance the product yield (Table 1, Entry 4-6).

Table 1. Optimization of reaction conditions using various solvent and catalyst.

Entry	Solvent	Catalyst	Temp. (°C)	Yield (%)
1	Acetonitrile	Copper silicate	RT	60
2	Acetonitrile	Copper silicate	Sonication	80
3	Acetonitrile	Copper silicate	78	82
4	Ethanol	Copper silicate	RT	70
5	Ethanol	Copper silicate	Sonication	84
6	Ethanol	Copper silicate	78	86
7	Acetonitrile	Camphor sulphonic acid	RT	68
8	Acetonitrile	Camphor sulphonic acid	Sonication	72
9	Acetonitrile	Camphor sulphonic acid	78	74
10	Ethanol	Camphor sulphonic acid	RT	70
11	Ethanol	Camphor sulphonic acid	Sonication	74
12	Ethanol	Camphor sulphonic acid	78	77
13	Acetonitrile	1-Ethyl-3-methylimidazolium hydrogen sulphate	RT	74
14	Acetonitrile	1-Ethyl-3-methylimidazolium hydrogen sulphate	Sonication	81
15	Acetonitrile	1-Ethyl-3-methylimidazolium hydrogen sulphate	78	82
16	Ethanol	1-Ethyl-3-methylimidazolium hydrogen sulphate	RT	84
17	Ethanol	1-Ethyl-3-methylimidazolium hydrogen sulphate	Sonication	90
18	Ethanol	1-Ethyl-3-methylimidazolium hydrogen sulphate	78	94
19	Ethanol	1-Ethyl-3-methylimidazolium hydrogen sulphate, 15 %	78	94
20	Ethanol	1-Ethyl-3-methylimidazolium hydrogen sulphate, 20 %	78	94

Table 2. Reaction of 2-anthranilamide and various aldehydes for the preparation of 2,3-dihydroquinazolinone.



1 2a-p 3a-p, A1-16

Entry	Aldehydes (2)	R1	R2	R3	2,3-Dihydroquinazolinone (3a-p)	Code	Time (min)	Yield [a] (%)
1	4-Fluorobenzaldehyde	H	H	-F	3a	A1	142	93
2	3-Nitrobenzaldehyde	H	NO_2	H	3b	A2	155	89
3	4-Hydroxy-3-methoxybenzaldehyde	H	OCH_3	OH	3c	Â3	163	84
4	1-Naphthaldehyde	H	H	H	3d	A4	161	87
5	4-Methylbenzaldehyde	H	H	Me	3e	A5	154	89
6	4-Bromobenzaldehyde	H	H	Br	3f	A6	130	91
7	4-Hydroxybenzaldehyde	H	H	OH	3g	A7	150	87
8	3-Hydroxybenzaldehyde	H	OH	H	3h	A8	167	81
9	2-Nitrobenzaldehyde	NO_2	H	H	3i	A9	168	86
10	2,4-Dichlorobenzaldehyde	Cl	Cl	H	3j	A10	150	89
11	3-Bromobenzaldehyde	H	Br	H	3k	A11	160	84
12	2,3-Dichlorobenzaldehyde	Cl	Cl	H	3l	A12	150	87
13	Benzaldehyde	H	H	H	3m	A13	180	80
14	4-Nitrobenzaldehyde	H	H	NO_2	3n	A14	140	94
15	3-Chlorobenzaldehyde	H	NO_2	H	3o	A15	120	93
16	2,4,6-Trimethoxybenzaldehyde	OCH_3	OCH_3	OCH_3	3p	A16	170	78

[a] Isolated yield.

The use of camphor sulphonic acids in acetonitrile solvents with different reaction conditions has been carried out (Table 1, Entry 7-9). It indicates, there is a scope to increase yield of product by changing the solvent as ethanol with different reaction conditions (Table 1, Entry 9-12). Our interest in the area of developing green and sustainable method, has forced us to investigate an alternate milder method for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-one derivatives (Table 2).

Herein, we report a green protocol for the synthesis of synthesis of 2,3-dihydroquinazolin-4(1*H*)-one derivatives under reflux conditions by using cheap and readily available ionic liquids as catalyst under milder reaction conditions (Table 1, Entry 13). To change the reaction conditions with acetonitrile at sonifaction and reflux condition, good yield of product were obtained (Table 1, Entry 14-15). The reaction solvent has been replaced to ethanol at room temperature reaction conditions gave the good yield of product (Table 1, Entry 16-17). The best result was obtained at reflux conditions (Table 1, Entry 18). Increasing the amount of catalyst (15 mol%) did not improve the yield (Table 1, Entry 19-20). Whereas in the absence of catalyst less amount product was obtained.

3.1. Biological activity

3.1.1. Determination of IC_{50}

A lung carcinoma cells (A549) were treated with screening compounds and antiproliferative effect was evaluated by MTT assay. A dose dependant, decreases the growth of cancer cells with increasing concentration of the compounds. IC_{50} value of compounds in A549 cells are shown in Figure 2.

The results obtained by MTT assay at 490 nm by addition of compounds to cancer cells and incubated for 24 h at 37 °C in CO_2 incubator (5 % CO_2) where a) **A2**, **A3**, **A4**, **A5** compounds, b) **A6**, **A7**, **A8**, **A9** compounds, c) **A10**, **A11**, **A12**, **A13** and d) **A14**, **A15**, **A16**, **Dox**. The IC_{50} calculated by using the GraphPad Prism software.

The MTT assay was used to evaluates the antiproliferative action of compounds at different concentrations (0, 5, 10, 25, 50 µg/L) on A549 cells. After 24 h exposure to compounds; approximately 2-fold decrease in cell survival between the control (0 µg/L) and compounds treated cells has been reported (Figure 2).

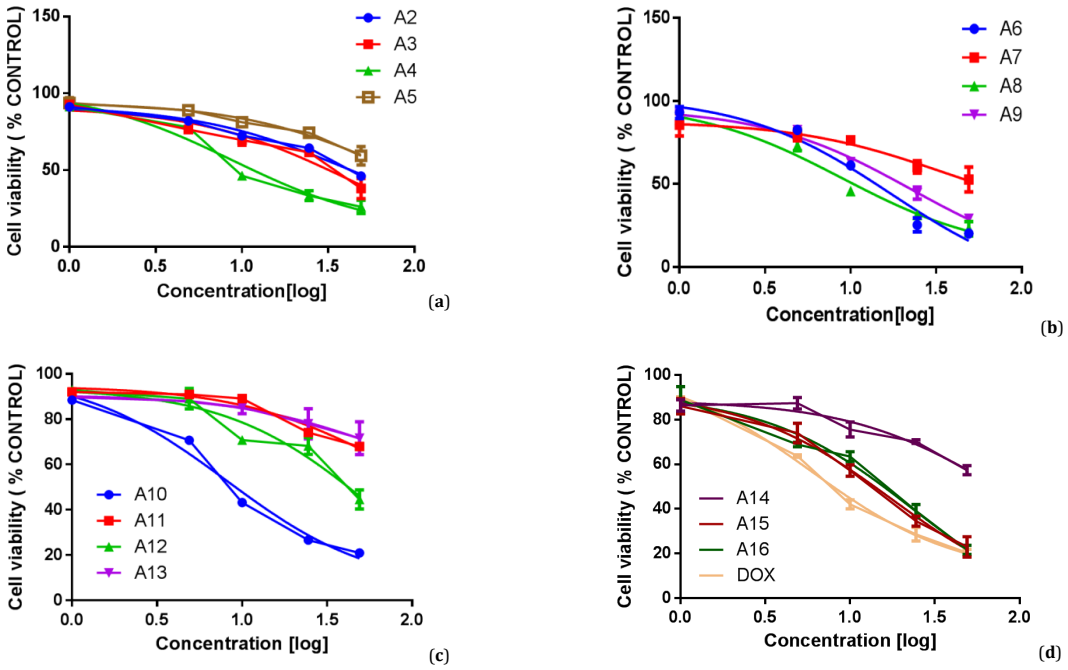


Figure 2. Dose dependent effect of quinazolinones derivatives on the growth of cancer cells (A 549) where a) **A2**, **A3**, **A4**, **A5** compounds, b) **A6**, **A7**, **A8**, **A9** compounds, c) **A10**, **A11**, **A12**, **A13** and d) **A14**, **A15**, **A16**, **Dox**.

Compound **A4**, **A8**, **A10** were found to be more promising antiproliferative against the lung carcinoma A549 cells. The IC_{50} values for compounds **A4**, **A8** and **A10** were found to be 8.133, 9.056 and 9.169 µg/L in A549 cells, respectively. Doxorobucin was used as a standard reference drug for this assay.

4. Conclusion

In conclusion, we have successfully developed a greener protocol for the synthesis of 2, 3-dihydroquina-zolin-4(1*H*)-ones using 1-Ethyl-3-Methylimidazolium hydrogen sulphate as an expeditious and reusable catalyst at reflux conditions. A wide range of products bearing different functionalized groups are easily isolated. The method offers several advantages including, high yield of products, short reaction time, recyclability of catalyst, and the fact that the crude is recrystallized from methanol to give the pure product without further column purification. Compounds showed the inhibitory effect on the growth of cancer cells (A549). Compounds **A4**, **A8** and **A10** were found to be more promising antiproliferative against the lung carcinoma A549 cells.

Acknowledgements

Authors thankful to Principal, Dr. Shivajirao Nivrattirao Thore, Deogiri College, Aurangabad, India.

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