Synthesis and Bioevaluation of Tetrahydroquinazolones as Chemotherapeutical Agents

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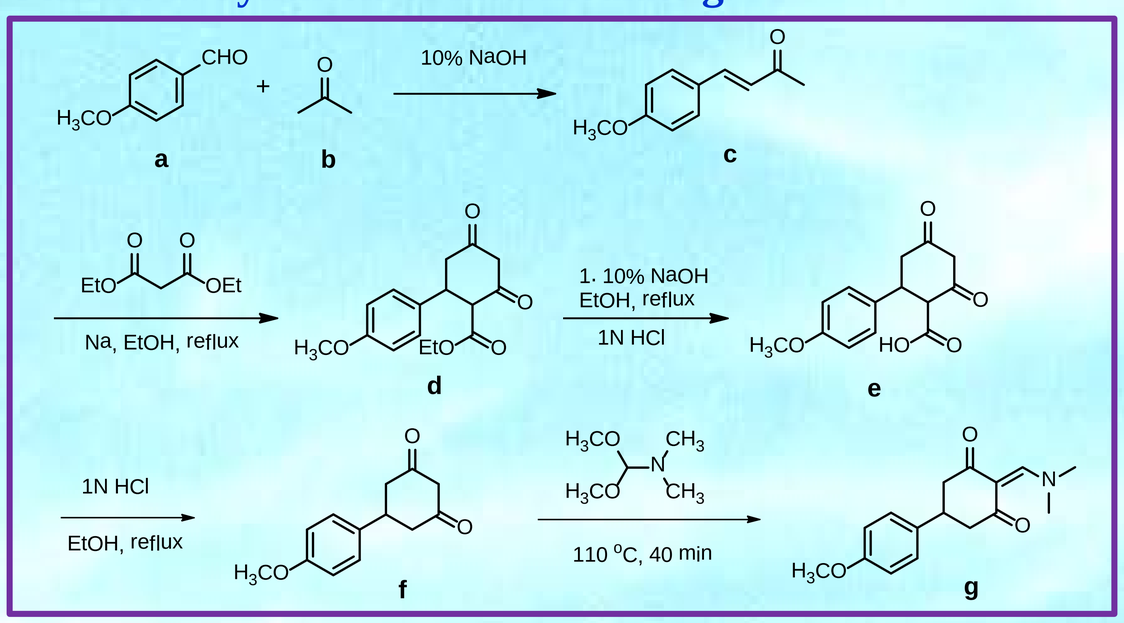
Abstract

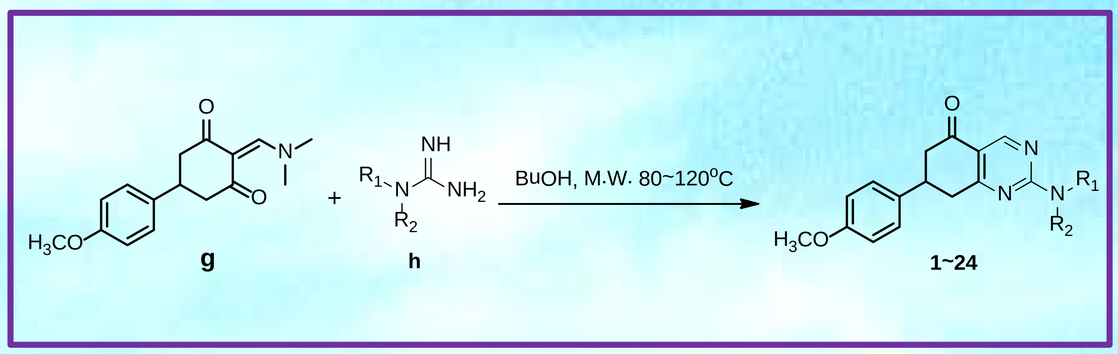
Nuclear factor E2-related factor 2 (Nrf-2), a transcriptional factor, responds to cellular oxidative stress or environmental carcinogens, which drives a variety of downstream cytoprotective genes. Generally, the Nrf-2 protein is restrained in cytoplasm by the Kelch-like ECH-associated protein 1 (Keap1) which is also known as the inhibitor of Nrf-2 (INrf2). Although Nrf-2 protein was initially considered as a cellular redox sensor, accumulating reports indicated that it played controversial roles both in chemoprevention and carcinogenesis. Nrf-2 protein functions as an oncoprotein or induces chemoresistance for its cytoprotective property. However, Nrf-2 protein is able to suppress oxidative or inflammatory stress and the DNA mutation, and therefore prevents occurrence of several diseases, including cancer, diabetes, obesity and organ injury by hypoxia or chemical toxins. Hence, development of Nrf-2-activating drugs could be applied to prevent numerous diseases. A cell-based luciferase activity system was established and applied to screen a series of tetrahydroquninzaolinone derivatives. The IC_{50} value of each compound was also determined at the same time. Only 14 showed cytotoxicity on Jurkat and TW01 cells, but not acted as a Nrf-2/ARE activator. Among twenty-four compounds tested, 1, 3 and 17 treatment significantly showed ~1.4 fold, ~1.6 fold and ~2.8 up-regulation in the luciferase activity through the Nrf-2/ARE manner, respectively.

Chemical Synthesis

Scheme 1. Synthesis of intermediate g.



Scheme 2. Synthesis of tetrahydroquninzaolinone derivatives.



Results

Table 1. The Nrf2 and cytotoxic activity of tetrahydroquninzaolinone derivatives.

Compound	R_1	R_2	Nrf2 (Fold)	IC_{50} (μM)-H226	IC_{50} (μM)-Jurkat	IC_{50} (μM)-TW01
1	H	H	1.37	138.4	7935.0	174.7
2	H	Me	0.86	227.2	784.8	396.8
3	phenyl	H	1.59	174.1	96.1	86.9
4	phenyl	Me	1.16	4459.2	108.2	155.3
5	2-chlorophenyl	H	0.81	453.7	841.7	71.9
6	2-fluorophenyl	H	1.09	758.6	186.2	68.6
7	2-methoxyphenyl	H	1.13	1819.6	296.7	93.9
8	3-chlorophenyl	H	1.19	126.6	80.1	40.7
9	3-fluorophenyl	H	1.42	306.0	278.0	69.6
10	3-methoxyphenyl	H	1.62	57.7	82.6	58.8
11	4-chlorophenyl	H	1.13	114.5	355.0	44.3
12	4-fluorophenyl	H	1.11	132.2	155.5	42.3
13	4-methoxylphenyl	H	1.13	933.8	187.0	439.1
14	2,5-dimethoxylphenyl	H	1.05	96.5	14.8	18.0
15	3,5-dimethoxylphenyl	H	0.78	129.9	204.0	41.5
16	3,4-methylenedioxyphenyl	H	1.22	290.8	733.6	167.2
17	3-pyridine	H	2.85	52.2	864.1	74.0
18	4-pyridine	H	1.15	75.3	858.1	43.0
19	acetyl	H	1.24	109.2	374.3	220.4
20	propionyl	H	ND	ND	ND	ND
21	isobutyryl	H	1.20	146.9	176.4	614.1
22	succinic	H	1.38	184.5	187.4	240.6
23	glutamic	H	1.23	714.9	146.0	181.9
24	4-methoxybenzoyl	H	ND	ND	ND	ND