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One-Pot Synthesis of Novel 3-(2-Oxo-2*H*-chromen-3-yl)-[1,3,4] Thiadiazino [2,3-*b*] Quinazolin-6 (2*H*)-ones Under Microwave Irradiation

V. Naveen Kumar
Department of Chemistry, National Institute of Technology, Warangal, India

E. De Clercq
Rega Institute of Medical Research, Belgium

B. Rajitha
Department of Chemistry, National Institute of Technology, Warangal, India

An efficient one-pot synthesis of 3-(2-oxo-2H-chromen-3-yl)-[1,3,4] thiadiazino [2,3-b] quinazolin-6(2H)-ones in high yields has been developed by microwave-induced heterocyclization of 3-amino-2mercapto-3H-quinazolin-4-one when irradiated with 3-(2-bromo-acetyl)-chromen-2-one in ethanol and anhydrous potassium carbonate. A comparative study of conventional and MW methods is briefly discussed.

Keywords Chromen; microwave; one-pot synthesis; quinazolin

INTRODUCTION

Quinazolinones and coumarins constitute an important class of heterocyclic molecules. Both moieties have been found to be of great interest in view of their varied biological and pharmacological properties. Various substituted quinazolinones are reported to possess a wide range of biological activities, which include analgesic and antinflammatory,[1–3] antibacterial,[4–7] antiviral,[8,9] antihistamine,[10] antihypertensive,[11,12] and anticancer[13] activity. Coumarins are common in nature and find their main applications as fragrances, pharmaceuticals, and agrochemicals.[14]

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Address correspondence to B. Rajitha, National Institute of Technology, Department of Chemistry; Warangal, 506 004 India. E-mail: rajitabhargavi@yahoo.com

In the last few years there has been increased interest in the use of microwave irradiation in organic synthesis. Some of the interesting features of this method are milder reaction conditions, reduction of reaction times, enhanced selectivity, and associated ease of manipulation.[15] Earlier we reported the synthesis of desyl ethers,[16] benzofurans,[17] benzodifurans,[18] quinolines,[19] and xanthenes[20] under MW irradiation. Keeping in view the biological importance of quinozolin and coumarin derivatives and in continuation of our work on coumarin derivatives using microwave irradiation, we have desired to synthesize a rapid, convenient, and efficient microwave-assisted synthesis of 3-(2-oxo-2H-chromen-3-yl)-[1,3,4] thiadiazino [2,3-b] quinazolin-6(2H)-ones that contain both quinazolinone and coumarin moieties in their structures.

RESULTS AND DISCUSSION

A mixture of 3-amino-2mercapto-3H-quinazolin-4-one and 3-(2-bromoacetyl)-chromen-2-one in the presence of ethanol & K_2CO_3 was refluxed for about 4–6 hours and furnished **3a–f**. Alternatively, when **2a–f** with **1**, taken in a domestic MW oven at 400 W level, was irradiated in an open vessel for 4–6 min in ethanol & K_2CO_3, they furnished **3a–f** in good yields (Scheme 1).

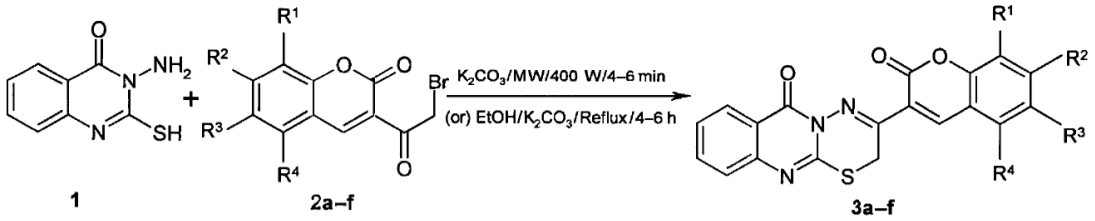
EXPERIMENTAL SECTION

All melting points were determined in an open capillary in a liquid paraffin bath and are uncorrected. The purity of the compounds was checked by TLC. ^{1}H NMR spectra on Varian Gemini 200 MHZ Spectrometer using TMS as an internal standard. The C, H, and N analysis of the compounds was done on a Carlo Erba model EA1108. Mass spectra was done on a jeol JMS D-300 spectrometer. For the microwave irradiation experiments, BPL 800T was used.

Biological Results

All the newly synthesized compounds were tested for their cytotoxicity and antiviral activity HFI HeLa, Vero, and murine-leukemia cells. The results are summarized in Tables II–V. Other biological activities are still in progress.

As shown in Tables II–V, some compounds (e.g., **3b** and **3f**) showed significant cytotoxic and antiviral activities, while others (e.g., **3c** and



1 2a–f 3a–f

Compound	R^1	R^2	R^3	R^4
3a	H	H	H	H
3b	H	H	Br	H
3c	Br	H	Br	H
3d	H	H	NO_2	H
3e	NO_2	H	NO_2	H
3f	H	H	Cl	H

SCHEME 1

3e) displayed medium cytotoxic and antiviral activities, and others (e.g., **3a** and **3d**) only had marginal or no cytotoxic and antiviral activities against HEL, Hela, Vero cell cultures, and murine leukemia cells.

TABLE I Analytical Data of Title Compounds 3a–f

Compound	Mol formula (Mol. Wt.)	Method A		Method B		Calcd. (Found) %		
		Yield (%)	Time (min)	Yield (%)	Time (h)	C	H	N
3a	$C_{19}H_{11}N_3O_3S$ (361)	90	4.15	82	4.00	63.15 (63.25	3.07 3.00	11.63 11.60)
3b	$C_{19}H_{10}BrN_3O_3S$ (440)	89	4.00	79	4.00	1.83 (51.80	2.29 2.30	18.15 18.10)
3c	$C_{19}H_9Br_2N_3O_3S$ (519)	72	4.30	66	4.00	43.96 (43.90	1.75 1.79	8.09 8.01)
3d	$C_{19}H_{10}N_4O_5S$ (406)	75	5.30	70	5.00	56.16 (56.16	2.48 2.48	13.79 13.79)
3e	$C_{19}H_9N_5O_7S$ (452)	78	5.30	70	6.00	57.14 (57.15	2.88 2.85	13.33 13.40)
3f	$C_{19}H_{10}ClN_3O_3S$ (395)	74	6.00	69	6.00	72.58 (72.56	3.78 3.76	2.92 2.90)

TABLE II Cytotoxicity and Antiviral Activity of Compounds (6a–f) in HEL Cell Cultures

		Minimum Inhibitory Concentration[b] (ug/mL)				
Compound	Minimum Cytotoxic Concentration (ug/mL)	Herpes Simplex Virus-1 (KOS)	Herpes Simplex Virus-2(G)	Vesicular Virus	Vesicular Stomatitis Virus	Herpes Simplex Virus-1 TK KOS ACV^r
3a	>100	>100	>100	>100	>100	>100
3b	20	>4 (20)	>4	>4	>4	>4
3c	100	>20	>20	>20	>20	>20
3d	100	>100	>100	>100	>100	>100
3e	100	>20	>20	>20	>20	>20
3f	20	>4	>4	>4	>4	>4
Brivudin	>400	0.0768	240	0.64	>400	>400
Ribavirin	>400	9.6	240	48	240	240
Acyclovir	>400	0.128	0.0768	240	>400	9.6
Ganciclovir	>100	0.0192	0.0192	>100	>100	0.16

[a]Required to cause a microscopically detectable alteration of normal cell morphology.
[b]Required to reduce virus-induced cytopathogenicity by 50%.

General Procedure: Synthesis of 3-(2-oxo-2H-chromen-3-yl)-[1,3,4] thiadiazino [2,3-b] quinazolin-6 (2H)-ones

Method A (Microwave Irradiation Method)

A mixture of 3-amino-2mercapto-3H-quinazolin-4-one **la** (0.001 mole), 3-(2-bromo-acetyl)-chromene-2-one **2a** (0.001 mole), anhydrous K_2CO_3 (0.001 mole), and ethanol (2 ml) was irradiated in microwave irradiation at 450W level for 4.15 min. Progress of the reaction was monitored over TLC. After completion of the reaction, it was poured over crushed ice, and the resulting solid was crystallized from ethanol as shining needles.

Compounds **3b–f** were prepared similarly.

Method B (Conventional Method)

3-amino-2mercapto-3H-quinazolin-4-one **1a** (0.001 mole) was treated with 3-(2-bromo-acetyl)-chromene-2-one **2a** (0.001 mole) and baked K_2CO_3 (0.001 mole), ethanol (5 mL) was added, and the reaction mixture was refluxed for 10.30 h. Progress of the reaction was monitored over TLC. After completion of the reaction, it was poured over crushed ice, and the resulting solid was crystallized from ethanol as shining needles.

Compounds **3b–f** were prepared similarly.

TABLE III Cytotoxicity and Antiviral Activity of Compounds (6a–f) in HeLa Cell Cultures

Compound	Minimum Cytotoxic Concentration (ug/mL)	Minimum Inhibitory Concentration[b] (ug/mL)		
		Vesicular Stomatitis Virus	Coxsackie Virus B4	Respiratory Syncytical Virus
3a	100	>20	>20	>20
3b	20	>4	>4	>4
3c	100	>20	>20	>20
3d	>100	>100	>100	>100
3e	100	>20	>20	>20
3f	20	>4	>4	>4
Brivudin	>400	>400	>400	>400
(S)-DHPA	>400	>400	>400	>400
Ribavirin	>400	48	240	9.6

[a]Required to cause a microscopically detectable alteration of normal cell morphology.
[b]Required to reduce virus-induced cytopathogenicity by 50%.

3a. 3-(2-oxo-2H-chromen-3-yl)-[1,3,4] thiadiazino [2,3-b] quinazolin-6 (2H)-one. Colorless crystals, m.p. 230–232°C. IR (KBr): 1720 (Coumarin C=0), 1640 (C=0), 1570 (C=N), 1530 (C=C), cm^{-1}. ^1H NMR (DMSO-d_6): δ 7.61–8.20 (m, 8H, Ar-H), 8.51 (s,1H, Coumarin C-4), 2.84 (s, 2H, CH_2). MS (FAB^+): m/z: 362 (M + 1).

TABLE IV Cytotoxicity and Antiviral Activity of Compounds (6a–f) in Vero Cell Cultures

Compound	Minimum Cytotoxic Concentration (ug/mL)	Minimum Inhibitory Concentration[b] (ug/mL)				
		Para Influenza-3 Virus	Reovirus-1	Sindbis Virus	Coxsackie Virus B4	Punta Toro Virus
3a	>100	>100	>100	>100	>100	>100
3b	20	>4	>4	>4	>4	>4
3c	100	>20	>20	>20	>20	>20
3d	100	>20	>20	>20	>20 (60)	>20
3e	100	>20	>20	>20	>20	>20
3f	20	>4	>4	>4	>4	>4
Brivudin	>400	>400	>400	>400	>400	>400
(S)-DHPA	>400	>400	>400	>400	>400	>400
Ribavirin	>400	48	48	240	>400	48

[a]Required to cause a microscopically detectable alteration of normal cell morphology.
[b]Required to reduce virus-induced cytopathogenicity by 50%.

TABLE V Proliferation of Murine-Leukemia Cells (L1210/0) and Human t-Lymphocyte Cells (Molt4/C8,CEM/0)

	IC50 (ug/mL)		
Compound	L1210/0	Molt4/C8	CEM/0
3a	161 ± 40	>200	>200
3b	2.4 ± 0.1	1.3 ± 0.2	1.7 ± 0.5
3c	15 ± 2	5.5 ± 0.6	5.5 ± 1.1
3d	>200	>200	≥ 200
3e	15 ± 1	6.6 ± 1.2	1.6 ± 0.6
3f	2.4 ± 0.1	1.3 ± 0.5	1.7 ± 0.6

50% inhibitory concentration.

3b. 3-(6-bromo-2-oxo-2H-chromen-3-yl)-[1,3,4] thiadiazino [2,3-b] quinazolin-6 (2H)-one. Colorless crystals, m.p. 200–202°C. IR (KBr): 1720 (Coumarin C=0), 1640 (C=0), 1540 (C=N), 1530 (C=C) cm^{-1}. ^1H NMR (DMSO-d_6): δ 7.10–7.82 (m, 7H, Ar-H), 8.21 (s, 1H, Coumarin C-4), 2.91 (s, 2H, CH_2). MS (FAB^+): m/z: 441 (M + 1).

3c. 3-(6,8-dibromo-2-oxo-2H-chromen-3-yl)-[1,3,4] thiadiazino [2,3-b] quinazolin-6 (2H)-one. Colorless crystals, m.p. 251–253°C. IR (KBr): 1720 (Coumarin C=0), 1640 (C=0), 1570 (C=N), 1530 (C=C) cm^{-1}. ^1H NMR (DMSO-d_6): δ 6.91–7.80 (m, 6H, Ar-H), 8.25 (s, 1H, Coumarin C-4), 2.85 (s, 2H, CH_2). MS (FAB^+): m/z: 520 (M + 1).

3d. 3-(6-nitro-2-oxo-2H-chromen-3-yl)-[1,3,4] thiadiazino [2,3-b] quinazolin-6 (2H)-one. Colorless crystals, m.p. 190–192°C. IR (KBr): 1720 (Coumarin C=0), 1640 (C=0), 1570 (C=N), 1530 (C=C)cm^{-1}. ^1H NMR (DMSO-d_6): δ 7.21–8.30 (m, 7H, Ar-H), 8.50 (s, 1H, Coumarin C-4), 2.90 (s, 2H, CH_2). MS (FAB^+): m/z: 406 (M^+).

3e. 3-(6,8-dinitro-2-oxo-2H-chromen-3-yl)-[1,3,4] thiadiazino [2,3-b] quinazolin-6 (2H)-one. Colorless crystals, m.p. >300. IR (KBr): 1720 (Coumarin C=0), 1640 (C=0), 1570 (C=N), 1530 (C=C)cm^{-1}. ^1H NMR (DMSO-d_6): δ 7.21–7.80 (m, 6H, Ar-H), 8.20 (s, 1H, Coumarin C-4), 2.85 (s, 2H, CH_2). MS (FAB^+): m/z: 453 (M + 1).

3f. 3-(6-chloro-2-oxo-2H-chromen-3-yl)-[1,3,4] thiadiazino [2,3-b] quinazolin-6 (2H)-one. Colorless crystals, m.p. >300. IR (KBr): 1720 (Coumarin C=0), 1640 (C=0), 1570 (C=N), 1530 (C=C)cm^{-1}. ^1H NMR (DMSO-d_6): δ 7.10–7.80 (m, 7H, Ar-H), 8.20 (s, 1H, Coumarin C-4), 2.90 (s, 2H, CH_2). MS (FAB^+): m/z: 396 (M + 1).

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