Synthesis and Anticancer Activity Of Novel Benzimidazole Chromenes, ThiadiazolylChromenes Under Microwave Irradiation Conditions

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Abstract A series of 3-(1H-Benzimidazol-2-yl)-chromen-2-ones (3a-g), 3-(8H-imidazo[4',5':3,4]benzo[1,2,C][1,2,5]thiadiazol –7- yl)chromen-2-ones (6a-f) have been synthesized and evaluated for anticancer activity in vitro. The compounds showed very good activity against different tumor cell lines.

Introduction

A number of chromene imidazoles (**3**a-g) and imidazobenzthiadiazoyl chromenes (**6**a-f) were prepared and evaluated for cytotoxic activity. Several compounds were inhibitory to the proliferation of murine leukemia cells (LI210/0) and human lymphotic cells (Molt 4/C8; CEM/0) in vitro. Among all the compounds **3**b and **3**c have shown maximum inhibitory activity.

Coumarin derivatives are associated with wide variety of physiological activities such as estrogenic[1], anti-cancer[2] and other biological activities. Benzimidazole posses diversified therapeutic activities such as anti-cancer, anti-inflammatory[3], anti-helmitic, anti-ulcer[4], and anti-fungal activities[5]. In the light of these interesting biological activities, it appeared to be of interest to synthesize imidazobezothiadiazolyl chromen-2-one/3-one **3**a-g and chromen-2-one benzimidazoles under microwave irradiation in *p*-toluene sulphonic acid (PTSA). Microwave irradiation of organic reactions has rapidly gained popularity as it accelerates variety of synthetic transformations[6].

Here we would like to report our preliminary investigation, concerning the direct synthesis of benzimidazole chromenes, thiadiazolyl benzimidazole chromenes. In this paper, we describe microwave irradiation in PTSA. All the reactions were carried out in an open pyrex beaker. Compared with the conventional reaction in polyphosphoric acid (PPA), PTSA in microwave reaction conditions were mild and isolated in high yields in less time. In our on going search for potential anti-cancer agents, here we present our results on the synthesis of benzimidazole chromenes, thiadiazolyl benzimidazole chromenes. Some of the title compounds presented here were annoyed in vitro for their anti-cancer activity.

Simple and substituted coumarin 3- carboxylic acids[7] and benzo [1,2,5] thiadiazolyl-4,5 diamine was prepared as per the literature method[8]. Reaction of coumarin –3-carboxylic acids with benzene-1,2- diamine and benzo [1,2,5]thiadiazolyl-

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4,5 diamine in PTSA/PPA in microwave oven for 3-4.5mints at 300 watt power level, resulted in the formation the title compounds **3**, **6** respectively (**Scheme I**). The compounds **3**a and **6**a were fully characterized by IR, NMR and mass spectra.

Experimental

All the melting points are taken in open capillary in liquid paraffin bath and are uncorrected. Purity of all compounds were checked by TLC. IR spectra (KBr) were recorded on Shimadzu FTIR Model 8010 Spectrometer and the ^{1}H NMR spectra in $CDCl_3$ on Varian C17-20-ZM-390-200 MH_Z NMR spectrometer using TMS as an internal standard (Chemical shifts in δ ppm). The C, H, N and S analysis of the compounds was done on a Carlo Erba Model EA1108 C H N and S elemental analyser.

Synthesis of 3-(1H-benzimidazol-2-yl)-chromen-2-one: (3a)

Method-A (Microwave irradiation method): A mixture of coumarin-3-carboxylic acid (0.19g, 0.001mol/l) and benzene-1,2-diamine (0.108g, 0.001mol/l) mixed in toluene and PTSA (0.001mol) dried and irradiated in domestic microwave oven at 300 watts power level for 2.5 minutes (**Scheme I**). The reaction was monitored over TLC. It was poured in cold water filtered, the crude product was crystallised from chloroform to yield **3**a.

Yield: 80%, m.p.244-245^{0}C (lit. m.p.243-244^{0}C)[9]

IR(KBr, υ_{max} cm^{-1}) 1140 (C-O-C) 1570 (C=C), 1630 (C=N), 1720 (lactone-C=O), 3375 (N-H).

^{1}H-NMR (200MHz, $CDCl_3$): δ 8.9(s, 1H, C-4'H), 7.24-7.82 (m, 8H, C-4, C-5, C-6, C-7, C-5', C-6', C-7'&C-8'H), 11.26 (bs, 1H, N-H, D_2O exchangeable). MS: m/z 262 (30%), 234(100%), 206(70%), 179(20%)

Synthesis of 3-(6H-imidazo[4',5':3,4]benzo[1,2-C][1,2,5]thiadiazol –7- yl)chromen-2-one:6a

Method-A (Microwave irradiation method): A mixture of coumarin-3-carboxylic acid (0.19g, 0.001mol/l) and benzo[1,2,5]thiadiazolyl-4,5-diamine (1.66g, 0.001mol/l) mixed in toluene and PTSA (0.001mol) dried and irradiated in domestic microwave oven at 300 watts power level for 3 minutes (**Scheme I**). The reaction was monitored over TLC. It was poured in cold water filtered, the crude product was crystallised from chloroform to yield **6a**.

Method-B (Conventional method): A mixture of coumarin-3-carboxylic acid **5**a (1.9g, 0.01mole) and [1,2,5]thiadiazolyl-4,5 diamine (1.66g, 0.01mol) were taken in PPA (40gr) and gently refluxed for 7 hours (**Scheme I**). The reaction mixture was cooled to room temperature and poured over crushed ice, the solid which separates was filtered, washed

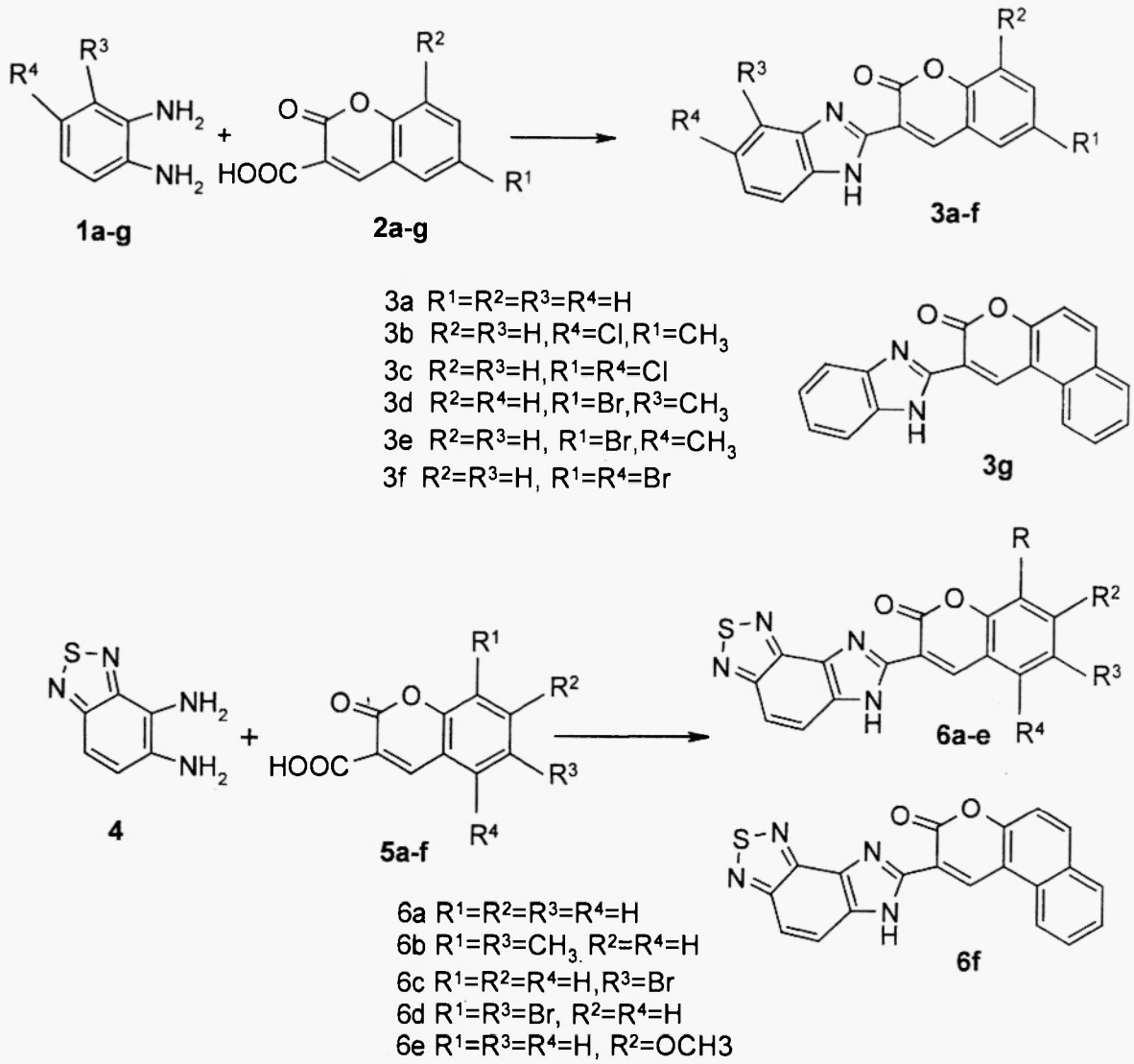
with aqueous sodium carbonate solution, then with water and dried. The crude product was crystallised from chloroform as shining needles. Yield: 86%, m.p.180-181^{0}C

IR(KBr, υ_{max} cm^{-1}) 1570 (C=C), 1680 (C=N), 1790 (lactone-C=O), 3400 (N-H).

^{1}H-NMR (200MHz, $CDCl_3$): δ 8.9(s, 1H, C-4'H), 7.6-7.8 (m, 4H C-5', C-6', C-7'&C-8'H), 7.5 (d, 1H, J=6.5Hz, C-7H), 7.3 (d, 1H, J=6.5Hz, C-8H), 4.2 (bs, 1H, N-H, D_2O exchangeable). MS: m/z 320 (70%), 146 (100%), 118 (40%).

Table 1: Physical data of compounds synthesized

Compound	M.P (^{0}C)	Yield (%)	Mol.formula (mol.wt)	Found (Cal) (%) C	H	N	S
3a	247-248	80	$C_{16}H_{10}N_2O_2$ (262)	73.12 (73.27)	3.52 (3.84)	10.3 (10.7)	
3b	253-254	76	$C_{17}H_{12}N_2O_2$ (276)	73.49 (73.47)	4.58 (4.86)	10.21 (10.14)	
3c	321-322	78	$C_{16}H_8Cl_2N_2O_2$ (330)	58.16 (58.08)	2.36 (2.44)	8.45 (8.46)	
3d	269-270	82	$C_{17}H_{11}BrN_2O_2$ (355)	57.27 (57.49)	3.05 (3.12)	7.85 (7.89)	
3e	262-263	78	$C_{17}H_{11}BrN_2O_2$ (355)	57.18 (57.49)	3.17 (3.12)	7.86 (7.89)	
3f	275-276	67	$C_{16}H_8Br_2N_2O_2$ (420)	45.65 (45.75)	1.95 (1.92)	6.64 (6.67)	–
3g	270-271	72	$C_{20}H_{12}N_2O_2$ (312)	76.87 (76.91)	3.79 (3.87)	8.99 (8.97)	–
6a	180-181	86	$C_{16}H_8O_2N_4S$ (320)	60.05 (60.00)	2.48 (2.50)	17.49 (17.50)	10.01 (10.00)
6b	175-176	84	$C_{18}H_{12}O_2N_4S$ (348)	62.04 (62.06)	3.58 (3.47)	16.18 (16.08)	9.40 (9.20)
6c	196-197	78	$C_{16}H_7O_2BrN_4S$ (399)	48.20 (48.14)	1.75 (1.77)	14.06 (14.03)	8.11 (8.03)
6d	240-241	75	$C_{16}H_6O_2Br_2N_4S$ (478)	40.26 (40.19)	1.26 (1.26)	11.73 (11.72)	6.70 (6.71)
6e	161-162	71	$C_{17}H_{10}O_3N_4S$ (350)	58.26 (58.28)	2.88 (2.86)	16.02 (16.00)	9.12 (9.14)
6f	290-291	66	$C_{20}H_{10}O_2N_4S$ (370)	64.84 (64.86)	2.71 (2.70)	15.13 (15.13)	8.65 (8.64)



Scheme-I

Anti-Cancer Activity

The compounds **3b**, **3c**, **3d**, **3f**, **6a-6d** were evaluated for anticancer activity against several cell lines like Murine leukemia (L1210/0), human T-Lymphocyte cells (Molt 4/C8) and CEM/0. The results of the compounds are expressed as IC_{50} %, which is the drug concentration (μg/ml) producing 50% inhibition of cell growth. No reference compound was used for testing activity along with the synthesized compounds. The mean (± SD) activities of different compounds against these cell lines are given in the **Table 2**. All the compounds (**3b**, **3c**, **3d**, **3f**, **6a**, **6b**, **6c**, **6d**) exhibited potent anti cancer activity in different cell lines. Comparison the activities of these compounds revealed that **3b** and **3c**

have shown significant inhibitory effect on the proliferation of the solid human tumor derived cell lines with the lowest $IC_{50\%}$ values for Murine leukemia.

Table 2: Anticancer activity of different compounds tested against different cell lines $IC_{50\%}$ (μg/ml)

compound	Murine leukemia(L1210/0)	Molt 4/C8	CEM/0
3b	5.1±0.5	3.6±1.5	1.9±0.4
3c	0.67±0.08	0.44±0.23	0.42±0.17
3d	≥200	≥200	121±48
3f	32±22	7.0±5.4	7.0±2.3
6a	24±2	34±3	49±9
6b	76±8	80±9	56±19
6c	12±4	14±4	17±1
6d	11±0	5.3±0.4	7.0±2.3

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