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Synthesis and antitumor activity of N^1-acetylamino-(5-alkyl/aryl-1,3,4-thiadiazole-2-yl)-5-fluorouracil derivatives

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Abstract

A new series of N^1-acetylamino-(5-alkyl/aryl-1,3,4-thiadiazole-2-yl)-5-fluorouracil derivatives were designed and synthesized. These compounds have not been reported in literature, and their structure chemical were confirmed by IR, ^{1}H NMR and MS (HRMS). The results of antitumor inhibitory activity test showed that some compounds possess more potent antitumor inhibitory activity than 5-fluorouracil.

Keywords: 5-Fluorouracil derivatives; 1,3,4-Thiadiazole; Synthesis; Antitumor

5-Fluorouracil (5-Fu) as antineoplastic agents has received much attention because of their antitumor activities. It has been widely used in the therapy of different solid tumor types, such as cancers of the stomach, liver, intestine, etc. In order to achieve therapeutic drug levels, 5-Fu is currently administered weekly at 400–600 mg/m^2, however, tumor cells are only exposed to the formation-rate limited active metabolites for a brief time, due to the short half-life of 5-Fu locally within tissues, as well as systemically (15–20 min) [1], moreover, it may cause some adverse effects: bone marrow depression, gastrointestinal tract reaction, or even leucopenia and thrombocytopenia [2]. Therefore, it is essential to design a valuable formulation to improve the therapeutic index of 5-Fu. In the past years, novel of 5-Fu derivatives possessing a broader spectrum of antitumor activity and fewer toxicity have been sought diligently by many researchers [3,4].

Here, we wished to introduce thiadiazole ring into 5-Fu, improve antitumor activities and decrease toxicities. Since 1,3,4-thiadiazole derivatives are well known as compounds of a wide range of anticancer activity[5,6], for this type of derivatives a different mechanism of action is assigned, depending on the type of modification of 1,3,4-thiadiazole ring [7,8]. At the same time, many amides display some pharmacological activities, and easily formation hydrogen bond with tissues. The synthesis of N^1-acetylamino-(5-alkyl/aryl-1,3,4-thiadiazole-2-yl)-5-fluorouracil derivatives **3** are described in this paper.

The synthesis of 2-amino-alkyl/aryl-1,3,4-thiadiazoles **1** [9] was achieved conveniently by treating carboxylic acid directly with thiosemicarbazide in the presence of phosphorus oxychloride, and reaction resulted in a increase in yield

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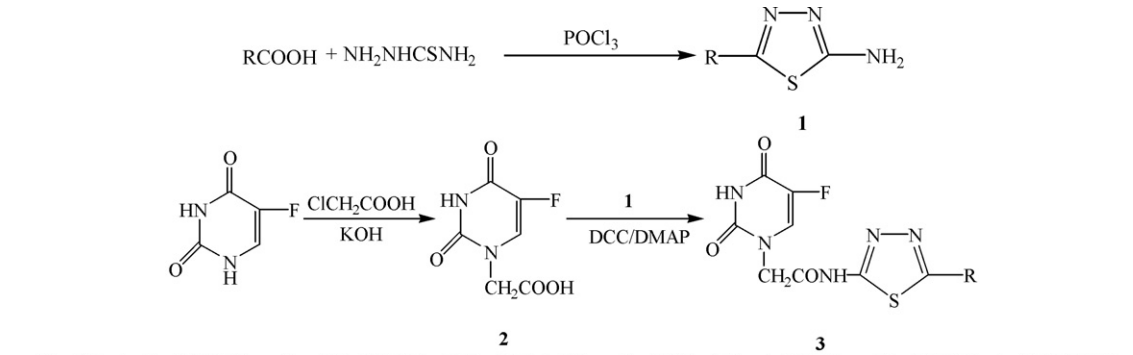
Table 1
Characterization data of 2-amino-5-substituted-1,3,4-thiadiazoles **1a–1k**

Compound	R	M.P. (°C)	Yield (%)	MS (ESI) *m/z*
1a	CH_3–	234–236 (234–235)	77.8 (64.3)	116.1 ($M+H^+$)
1b	CH_3CH_2–	196–198 (198)	72.2 (66.5)	130.2 ($M+H^+$)
1c	$CH_3CH_2CH_2$–	212–214 (215–216)	75.2 (74.9)	166.4 ($M+Na^+$)
1d	$(CH_3)_2CH$–	180–182 (182–185)	60.4 (49.2)	166.1 ($M+Na^+$)
1e	C_6H_5–	220–222 (222–223)	70.1 (63.7)	200.1 ($M+Na^+$)
1f	4-ClC_6H_4–	226–228 (227–229)	80.1 (70.0)	212.3 ($M+H^+$)
1g	4-FC_6H_4–	210–212 (211)	69.2 (58.0)	196.1 ($M+H^+$)
1h	4-$CH_3C_6H_4$–	212–214 (214–215)	72.3 (62.0)	192.2 ($M+H^+$)
1i	4-$CH_3OC_6H_4$–	188–190 (187–188)	71.5 (60.0)	208.1 ($M+H^+$)
1j	3,5-$(NO_2)_2C_6H_3$–	212–214 (210)	88.9 (78.0)	268.1 ($M+H^+$)
1k	3-Py-	236–238 (238–239)	76.2 (70.0)	179.2 ($M+H^+$)

Yields and M.P. in parenthesis are those reported in Refs. [12–15].

(Table 1). The condensation of 5-Fu with α-chloroacetic acid in the presence of potassium hydroxide in water afforded 5-fluorouracil-1-acetic acid **2** [10]. Compounds **3** [11] were produced by reaction of **1** with **2** using DCC as condensation reagent and a catalytic amount of DMAP in DMF solution (Scheme 1). The structures of target compounds were confirmed by IR, ^1H NMR and MS (HRMS). Some analytical data of **3a–3k** were shown in Ref. [17].



a, R= CH_3; b, R= CH_3CH_2; c, R= $CH_3CH_2CH_2$; d, R= $(CH_3)_2CH$; e, R= C_6H_5; f, R= 4-ClC_6H_4; g, R= 4-FC_6H_4; h, 4-$CH_3C_6H_4$; i, R= 4-$CH_3OC_6H_4$; j, R= 3,5-$(NO_2)_2C_6H_3$, k, R= 3-Py;

Scheme 1. Synthesis route of compounds **3a–3g**.

Table 2
Structural, physical, and IC_{50} data of A-549 and Bcap-37 of *in vitro* for 5-fluorouracil derivatives **3a–3k**

Compound	R	Yield (%)	M.P. (°C)	MS (ESI)	IC_{50} (μg/mL)	
				m/z	A-549	Bacp-37
3a	CH_3–	83	>300	286.1 ($M+H^+$)	120.07	101.17
3b	CH_3CH_2–	86	>300	300.1 ($M+H^+$)	77.16	69.23
3c	$CH_3CH_2CH_2$–	84	286–288	314.2 ($M+H^+$)	59.39	19.31
3d	$(CH_3)_2CH$–	80	282–284	314.3 ($M+H^+$)	90.20	78.92
3e	C_6H_5–	86	>300	348.1 ($M+H^+$)	27.39	9.18
3f	4-ClC_6H_4–	88	>300	382.1 ($M+H^+$)	34.10	24.37
3g	4-FC_6H_4–	80	>300	366.1 ($M+H^+$)	12.07	20.67
3h	4-$CH_3C_6H_4$–	90	>300	384.2 ($M+Na^+$)	103.23	11.23
3i	4-$CH_3OC_6H_4$–	87	>300	400.2 ($M+Na^+$)	32.00	8.43
3j	3,5-$(NO_2)_2C_6H_3$–	80	>300	438.1 ($M+H^+$)	25.17	3.87
3k	3-Py-	84	>300	349.3 ($M+H^+$)	32.19	29.20
5-Fu					33.01	9.91