

# 氟乙酰胺类新型抗血吸虫药的 合成及其杀虫作用

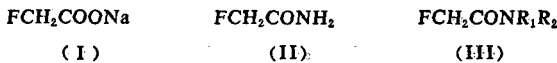
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**提要** 我所生化代谢的研究发现氟乙酸钠有显著的杀日本血吸虫的作用, 作者等据此合成了125个氟乙酰胺类化合物。动物实验治疗结果证明, 122个化合物有抗血吸虫作用, 其中21个化合物的减虫率达90~100%, 而毒性较之氟乙酸大幅度地降低; 有些化合物剂量可高达5~10mg/鼠, 但离进行临床试验还有一定的差距。

**关键词** 日本血吸虫; 氟乙酸钠; 氟乙酰胺

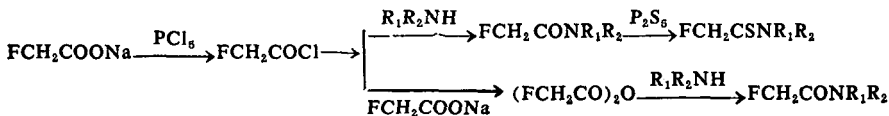
1964年, 我所生化研究室<sup>(1)</sup>在研究日本血吸虫的代谢时, 曾观察到某些药物对日本血吸虫的柠檬酸代谢有一定的抑制作用。因而用了有“致死合成”作用的氟乙酸钠I<sup>(2)</sup>, 以抑制日本血吸虫的柠檬酸代谢。进行小白鼠实验治疗的结果, 发现氟乙酸钠有显著的杀虫作用, 但毒性也显著。据Phillips等<sup>(3~5)</sup>报道氟乙酰胺(II)对哺乳动物的毒性低于氟乙酸及氟乙酰乙酯。因此, 作者等于1965年除合成了几个不同系列的氟乙酰胺类化合物(III), 以探讨其构效关系外, 还选择了一些已用于临床的具有氨基的药物, 特别是抗寄生虫药物进行氟乙酰化, 以期找到高效低毒的这类药物。



我们共合成了125个氟乙酰胺类化合物, 经小白鼠日本血吸虫病实验治疗试验, 除一个化合物无效(化合物30)和二一个化合物未得药理结果外, 都有不同程度的抗血吸虫作用。其中21个化合物的减虫率高达90~100%, 有些化合物的剂量可高达5~10mg/鼠(化合物26、43), 化合物3、89和108等连续给药三天, 均可达到杀虫而使小鼠基本不死<sup>(6,7)</sup>。这些结果说明, 氟乙酰胺类与氟乙酸钠之间在对宿主的毒性及抗血吸虫的作用上都存在着显著的差别; 这也说明了化学结构的改变, 是有可能使药物的疗效提高和毒性降低的。但是, 要试用于临床, 还须作进一步的努力。

据文献报道<sup>(8)</sup>, 硫代氟乙酰胺的毒性较氟乙酰胺为低。我们所合成的硫代氟乙酰胺的毒性并不低于相应的氟乙酰胺, 而抗血吸虫作用却比后者为差。








氟乙酰胺类的合成是以氟乙酰氯或氟乙酸乙酯和胺作用而得。硫代氟乙酰胺的合成是用相应的氟乙酰胺和五硫化二磷反应而制得。氟乙酰氯的制备方法, 文献上报道颇多<sup>(9,10)</sup>。



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表 1 FCH<sub>2</sub>CONR<sub>1</sub>R<sub>2</sub>

化合物	NR <sub>1</sub> R <sub>2</sub>	熔点或沸点 (°C)	重结晶溶剂	分子式	元素分析	减虫率 (%)
1	*NH <sub>2</sub>	108~9	水	C <sub>2</sub> H <sub>4</sub> FNO	FN	47.5
2	NHCH <sub>3</sub>	62~4	乙醇-乙醚	C <sub>3</sub> H <sub>6</sub> FNO	FN	30
3	NHC <sub>2</sub> H <sub>5</sub>	70/4 mm	—	C <sub>4</sub> H <sub>8</sub> FNO	FN	94
4	*NHC <sub>3</sub> H <sub>7-n</sub>	37	乙醇-乙醚	C <sub>6</sub> H <sub>10</sub> FNO	FN	90.2
5	NHC <sub>3</sub> H <sub>7-i</sub>	36	乙醇-乙醚	C <sub>6</sub> H <sub>10</sub> FNO	FN	93.6
6	*NHC <sub>4</sub> H <sub>9-n</sub>	64/2 mm	—	C <sub>8</sub> H <sub>12</sub> FNO	FN	100
7	NHC <sub>4</sub> H <sub>9-i</sub>	35	乙醇-乙醚	C <sub>8</sub> H <sub>12</sub> FNO	FN	64.5
8	NHC <sub>5</sub> H <sub>11-n</sub>	86/5 mm	—	C <sub>9</sub> H <sub>14</sub> FNO	FN	60.9
9	NHC <sub>5</sub> H <sub>11-i</sub>	96/8 mm	—	C <sub>9</sub> H <sub>14</sub> FNO	FN	69.1
10	NHC <sub>6</sub> H <sub>13-n</sub>	97~8/1 mm	—	C <sub>9</sub> H <sub>16</sub> FNO	FN	92.8
11	*NH— 	93~4	稀乙醇	C <sub>8</sub> H <sub>14</sub> FNO	FN	86.6
12	NHC <sub>7</sub> H <sub>15-n</sub>	50	乙 醇	C <sub>9</sub> H <sub>18</sub> FNO	FN	24.4
13	*NHCH <sub>2</sub> OH	96~8	醋酸乙酯	C <sub>3</sub> H <sub>6</sub> FNO <sub>2</sub>	FN	87.1
14	NHCH <sub>2</sub> OCH <sub>3</sub>	86~9/18 mm	—	C <sub>4</sub> H <sub>8</sub> FNO <sub>2</sub>	FN	76.2
15	NHCH <sub>2</sub> OC <sub>2</sub> H <sub>5</sub>	76/15 mm	—	C <sub>6</sub> H <sub>10</sub> FNO <sub>2</sub>	FN	61.2
16	NHCH <sub>2</sub> OOC <sub>2</sub> H <sub>5</sub>	96~8	乙 醇	C <sub>10</sub> H <sub>10</sub> FNO <sub>3</sub>	FN	88.3
17	NHCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	73~4	乙 醇	C <sub>9</sub> H <sub>10</sub> FNO	FN	89.2
18	*NH—CH <sub>2</sub> — 	115~8/3 mm	—	C <sub>7</sub> H <sub>8</sub> FNO <sub>2</sub>	FN	29.7
19	NHC <sub>2</sub> H <sub>4</sub> OH	150~52/8 mm	—	C <sub>4</sub> H <sub>8</sub> FNO <sub>2</sub>	FN	84.6
20	NHC <sub>2</sub> H <sub>4</sub> OOCCH <sub>2</sub> Cl	164~7/15 mm	—	C <sub>6</sub> H <sub>8</sub> ClFNO <sub>3</sub>	FN	62.8
21	NHC <sub>2</sub> H <sub>4</sub> OOCCH=CH— 	152~5	乙 醇	C <sub>11</sub> H <sub>11</sub> FN <sub>2</sub> O <sub>6</sub>	FN	74.2
22	NHC <sub>2</sub> H <sub>4</sub> Cl	60~63	氯 仿	C <sub>4</sub> H <sub>7</sub> ClFNO	FN	76.5
23	N(C <sub>2</sub> H <sub>4</sub> Cl) <sub>2</sub>	141~5/4 mm	—	C <sub>6</sub> H <sub>10</sub> Cl <sub>2</sub> FNO	FN	71.2
24	*NHCHOHCCl <sub>3</sub>	112~5	甲醇-水	C <sub>4</sub> H <sub>5</sub> Cl <sub>3</sub> FNO <sub>2</sub>	FN	47.8
25	*NHCH(OOCCH <sub>3</sub> )CCl <sub>3</sub>	130~32/3 mm	—	C <sub>6</sub> H <sub>6</sub> Cl <sub>3</sub> FNO <sub>3</sub>	FN	68.9
26	*NHCH(OOCC <sub>2</sub> H <sub>5</sub> )CCl <sub>3</sub>	70	乙 醇	C <sub>8</sub> H <sub>11</sub> Cl <sub>3</sub> FNO <sub>3</sub>	FN	91
27	*NHCHClCCl <sub>3</sub>	78~80	石油醚	C <sub>4</sub> H <sub>5</sub> Cl <sub>4</sub> FNO	FN	70.7
28	*NHCHOHCBBr <sub>3</sub>	128~30	甲醇-水	C <sub>4</sub> H <sub>4</sub> Br <sub>3</sub> FNO	FN	96.2
29	NHCH <sub>2</sub> CHOHCH <sub>3</sub>	126~8/5 mm	—	C <sub>5</sub> H <sub>10</sub> FNO <sub>2</sub>	FN	46.7
30	NHC <sub>2</sub> H <sub>4</sub> N(C <sub>2</sub> H <sub>5</sub> )·HCl	125~7	无水乙醇	C <sub>8</sub> H <sub>18</sub> ClFNO	FN	无效
31	NHC <sub>2</sub> H <sub>4</sub> 	88~9	无水乙醇	C <sub>8</sub> H <sub>16</sub> FN <sub>2</sub> O <sub>2</sub>	FN	54.6
32	NHCH <sub>2</sub> COOH	175~8	水	C <sub>4</sub> H <sub>6</sub> FNO <sub>3</sub>	FN	98.8
33	NHCH <sub>2</sub> COOC <sub>2</sub> H <sub>5</sub>	136~40/20 mm	—	C <sub>6</sub> H <sub>10</sub> FNO <sub>3</sub>	FN	58.8
34	NHCONH <sub>2</sub>	208~211	苯	C <sub>3</sub> H <sub>5</sub> FN <sub>2</sub> O <sub>2</sub>	FN	90.4
35	NHCONHCH <sub>2</sub> CH <sub>2</sub> Cl	142~5	甲 醇	C <sub>5</sub> H <sub>8</sub> ClFN <sub>2</sub> O <sub>2</sub>	FN	70.4
36	NHCONHC <sub>6</sub> H <sub>5</sub>	156~8	苯	C <sub>8</sub> H <sub>9</sub> FN <sub>2</sub> O <sub>2</sub>	FN	36.2
37	NHNHCONHCH <sub>2</sub> CH <sub>2</sub> Cl	136~8	四氢呋喃	C <sub>6</sub> H <sub>9</sub> ClFN <sub>3</sub> O <sub>2</sub>	FN	40.6
38	*NHNHCONHC <sub>6</sub> H <sub>5</sub>	174~6	四氢呋喃	C <sub>9</sub> H <sub>10</sub> FN <sub>3</sub> O <sub>2</sub>	FN	86.4
39	NHNHCSNH <sub>2</sub>	186(分解)	50%乙醇	C <sub>3</sub> H <sub>6</sub> FN <sub>3</sub> OS	FN	71.3
40	NH(CH <sub>2</sub> ) <sub>4</sub> CH(CH <sub>2</sub> ) <sub>2</sub> N— 	112~4	乙 醇	C <sub>19</sub> H <sub>26</sub> FN <sub>3</sub> O <sub>3</sub>	FN	47.7
41		110/2 mm	—	C <sub>8</sub> H <sub>10</sub> FN <sub>2</sub> O <sub>2</sub>	FN	44.9
42	 ·HCl	170~2	无水乙醇	C <sub>7</sub> H <sub>14</sub> ClFN <sub>2</sub> O	FN	100

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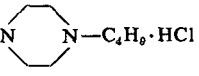
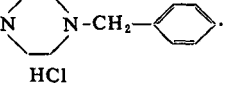
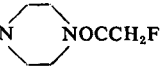
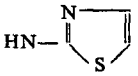

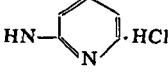
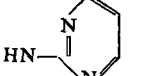

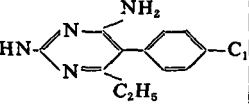
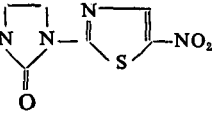
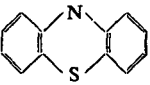

化合物	NR <sub>1</sub> R <sub>2</sub>	熔点或沸点 (°C)	重结晶溶剂	分子式	元素分析	减虫率 (%)
43	 N-C <sub>4</sub> H <sub>9</sub> ·HCl	111~4	无水乙醇	C <sub>10</sub> H <sub>20</sub> ClFN <sub>2</sub> O	FN	66.4
44	 N-CH <sub>2</sub> -C <sub>6</sub> H <sub>5</sub> HCl	220~22	乙醇	C <sub>13</sub> H <sub>18</sub> ClFN <sub>2</sub> O	FN	58.1
45	 NOCCH <sub>2</sub> F	152~4	乙醇	C <sub>8</sub> H <sub>12</sub> F <sub>2</sub> N <sub>2</sub> O <sub>2</sub>	FN	59.9
46	 HN-	160~63	乙醇	C <sub>5</sub> H <sub>5</sub> FN <sub>2</sub> OS	FN	69.3
47	 NH-NO <sub>2</sub>	240(分解)	乙醇	C <sub>5</sub> H <sub>4</sub> FN <sub>3</sub> O <sub>2</sub> S	FN	50.8
48	 HN·HCl	217~9(分解)	乙醇	C <sub>7</sub> H <sub>7</sub> ClFN <sub>2</sub> O	FN	81.2
49	 HN-	99~101	乙醇	C <sub>8</sub> H <sub>8</sub> FN <sub>3</sub> O	FN	99
50	 NH-OH	>300	D M F	C <sub>5</sub> H <sub>6</sub> FN <sub>2</sub> O <sub>2</sub>	FN	57.6
51	 NH-NH <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> -C <sub>1</sub> -C <sub>2</sub> H <sub>5</sub>	220~23	乙醇	C <sub>14</sub> H <sub>14</sub> ClFN <sub>3</sub> O	FN	58.3
52	 NH-NO <sub>2</sub>	190~93	乙醇	C <sub>8</sub> H <sub>7</sub> FN <sub>2</sub> O <sub>2</sub> S	FN	81.2
53		170~73	乙醇	C <sub>14</sub> H <sub>10</sub> FNOS	FN	99

表 2 

化合物	X <sub>n</sub>	熔 点 (°C)	分子式	元素分析	减虫率 (%)
54	H	74~6	C <sub>8</sub> H <sub>8</sub> FNO	FN	58.9
*55	4-CH <sub>3</sub>	128~30	C <sub>9</sub> H <sub>10</sub> FNO	FN	22
56	4-OH <sup>a</sup>	144~7	C <sub>8</sub> H <sub>8</sub> FNO <sub>2</sub>	FN	98.3
57	*4-Cl	127~9	C <sub>8</sub> H <sub>7</sub> ClFNO	FN	82.5
58	*4-Br <sup>b</sup>	132~3	C <sub>8</sub> H <sub>7</sub> BrFNO	FN	46.2
59	2,4-(CH <sub>3</sub> ) <sub>2</sub> <sup>c</sup>	78~80	C <sub>10</sub> H <sub>12</sub> FNO	FN	71.9
60	3,4-(CH <sub>3</sub> ) <sub>2</sub>	64~6	C <sub>10</sub> H <sub>12</sub> FNO	FN	33.9
61	3-OH, 4-COOH	226(分解)	C <sub>9</sub> H <sub>8</sub> FNO <sub>4</sub>	FN	82.2
62	2,4-Cl <sub>2</sub>	96~8	C <sub>8</sub> H <sub>6</sub> Cl <sub>2</sub> FNO	FN	21.4
63	2,5-Cl <sub>2</sub>	105~7	C <sub>8</sub> H <sub>6</sub> Cl <sub>2</sub> FNO	FN	56.7
64	3,4-Cl <sub>2</sub>	94~6	C <sub>8</sub> H <sub>6</sub> Cl <sub>2</sub> FNO	FN	98.8

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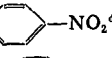
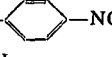



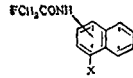
化合物	Xn	熔 点 (°C)	分 子 式	元素分析	减 虫 率 (%)
65	2,6-Cl <sub>2</sub>	114~6	C <sub>8</sub> H <sub>6</sub> Cl <sub>2</sub> FNO	FN	87.5
66	2-Cl, 4-NO <sub>2</sub>	126~9	C <sub>8</sub> H <sub>6</sub> ClFN <sub>2</sub> O <sub>3</sub>	FN	58
67	2,4,6-(CH <sub>3</sub> ) <sub>3</sub>	157~9	C <sub>11</sub> H <sub>14</sub> FNO	FN	25.7
68	2,4,5-Cl <sub>3</sub>	125~7	C <sub>8</sub> H <sub>6</sub> Cl <sub>3</sub> FNO	FN	80
69	2,4,6-Br <sub>3</sub>	193~5	C <sub>8</sub> H <sub>6</sub> Br <sub>3</sub> FNO	FN	42.4
70	2-NO <sub>2</sub> , 3,4-(CH <sub>3</sub> ) <sub>2</sub>	131~3	C <sub>10</sub> H <sub>11</sub> FN <sub>2</sub> O <sub>3</sub>	FN	64.9
71	2-NO <sub>2</sub> , 3,4-Cl <sub>2</sub>	116~8	C <sub>8</sub> H <sub>6</sub> Cl <sub>2</sub> FN <sub>2</sub> O <sub>3</sub>	FN	46.2
72	2,4,6-(CH <sub>3</sub> ) <sub>3</sub> , 3-F	135~7	C <sub>11</sub> H <sub>13</sub> F <sub>2</sub> NO	FN	64.6
73	2,4,6-(CH <sub>3</sub> ) <sub>3</sub> , 3-Cl	152~5	C <sub>11</sub> H <sub>13</sub> ClFNO	FN	17.3
74	2,4,6-(CH <sub>3</sub> ) <sub>3</sub> , 3-Br	157~9	C <sub>11</sub> H <sub>13</sub> BrFNO	FN	78.2
75	2,4,6-(CH <sub>3</sub> ) <sub>3</sub> , 3-NO <sub>2</sub>	144~6	C <sub>11</sub> H <sub>13</sub> FN <sub>2</sub> O <sub>3</sub>	FN	87.1
76	4-CH=NNHCONH <sub>2</sub> <sup>d</sup>	232(分解)	C <sub>10</sub> H <sub>11</sub> FN <sub>2</sub> O <sub>2</sub>	FN	50.8
77	4-CH=NNHCSNH <sub>2</sub> <sup>e</sup>	224~6	C <sub>10</sub> H <sub>11</sub> FN <sub>2</sub> OS	FN	44.4
78	4-S-  -NO <sub>2</sub> <sup>d</sup>	139~41	C <sub>14</sub> H <sub>12</sub> FN <sub>2</sub> O <sub>3</sub> S	FN	59
79	4-SO <sub>2</sub> -  -NO <sub>2</sub> <sup>d</sup>	233~5	C <sub>14</sub> H <sub>12</sub> FN <sub>2</sub> O <sub>6</sub> S	FN	23.2
80	4-SO <sub>2</sub> NH <sub>2</sub>	213~6	C <sub>8</sub> H <sub>10</sub> FN <sub>2</sub> O <sub>3</sub> S	FN	63.1
81	4-SO <sub>2</sub> NH-C(=NH)-NH <sub>2</sub>	233~5	C <sub>9</sub> H <sub>12</sub> FN <sub>2</sub> O <sub>3</sub> S	FN	89.9
82	4-SO <sub>2</sub> NH- 	238~41	C <sub>11</sub> H <sub>10</sub> FN <sub>3</sub> O <sub>3</sub> S <sub>2</sub>	FN	49.7
83	4-SO <sub>2</sub> NH- 	248(分解)	C <sub>12</sub> H <sub>11</sub> FN <sub>2</sub> O <sub>3</sub> S	FN	47.3
84	4-SO <sub>2</sub> NH- 	260(分解)	C <sub>11</sub> H <sub>10</sub> FN <sub>2</sub> O <sub>3</sub> S <sub>2</sub>	FN	53.4

表 3




化合物	FCH <sub>2</sub> CONH	X	熔 点 (°C)	分 子 式	元素分析	减 虫 率 (%)
85	1	*H	129~31	C <sub>12</sub> H <sub>10</sub> FNO	FN	94
86	2	*H	88~90	C <sub>12</sub> H <sub>10</sub> FNO	FN	68
87	1	Cl	136~7	C <sub>12</sub> H <sub>9</sub> ClFNO	FN	50.7
88	1	4-NH <sub>2</sub>	169~71	C <sub>12</sub> H <sub>11</sub> FN <sub>2</sub> O	FN	61.2
89	1	4-NO <sub>2</sub>	175~7	C <sub>12</sub> H <sub>9</sub> FN <sub>2</sub> O <sub>3</sub>	FN	91.7
90	1	4-NH-  -NO <sub>2</sub>	250(分解)	C <sub>15</sub> H <sub>11</sub> FN <sub>3</sub> O <sub>3</sub> S	FN	54.9

表 4  $(FCH_2CONH)_2C_6H_4-X^n$ 

化合物	X <sub>n</sub>	熔 点 (°C)	分 子 式	元素分析	减 虫 率 (%)
91	H	208~10	C <sub>11</sub> H <sub>12</sub> F <sub>2</sub> N <sub>2</sub> O <sub>2</sub>	FN	45
92	2-Cl	188~90	C <sub>11</sub> H <sub>11</sub> ClF <sub>2</sub> N <sub>2</sub> O <sub>2</sub>	FN	94.2
93	3-NO <sub>2</sub>	218~20	C <sub>11</sub> H <sub>11</sub> F <sub>2</sub> N <sub>2</sub> O <sub>4</sub>	FN	59
94	4-NO <sub>2</sub>	229~30	C <sub>11</sub> H <sub>11</sub> F <sub>2</sub> N <sub>2</sub> O <sub>4</sub>	FN	43.7
95	4-Br	227~9	C <sub>11</sub> H <sub>11</sub> BrF <sub>2</sub> N <sub>2</sub> O <sub>2</sub>	FN	77.8
96	2,4-(NO <sub>2</sub> ) <sub>2</sub>	184~6	C <sub>10</sub> H <sub>10</sub> F <sub>2</sub> N <sub>2</sub> O <sub>6</sub>	FN	57.9

表 5 FCH<sub>2</sub>CONH-X-NHCOCH<sub>2</sub>F



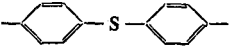
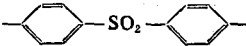
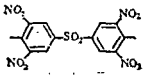
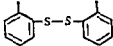
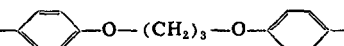
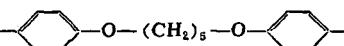
化合物	X	熔 点 (°C)	分 子 式	元素分析	减 虫 率 (%)
97	-S-	179	C <sub>4</sub> H <sub>6</sub> F <sub>2</sub> N <sub>2</sub> O <sub>2</sub> S	FN	73.9
98	-(CH <sub>2</sub> ) <sub>2</sub> -	184~7	C <sub>6</sub> H <sub>10</sub> F <sub>2</sub> N <sub>2</sub> O <sub>2</sub>	FN	89.5
99	-(CH <sub>2</sub> ) <sub>3</sub> -	128~30	C <sub>7</sub> H <sub>12</sub> F <sub>2</sub> N <sub>2</sub> O <sub>2</sub>	FN	53.1
100	-(CH <sub>2</sub> ) <sub>5</sub> -	127~9	C <sub>9</sub> H <sub>16</sub> F <sub>2</sub> N <sub>2</sub> O <sub>2</sub>	FN	-
101	-(CH <sub>2</sub> ) <sub>6</sub> -	128~31	C <sub>10</sub> H <sub>18</sub> F <sub>2</sub> N <sub>2</sub> O <sub>2</sub>	FN	84.6
102		255~6	C <sub>10</sub> H <sub>10</sub> F <sub>2</sub> N <sub>2</sub> O <sub>2</sub>	FN	25.2
103		153~6	C <sub>10</sub> H <sub>10</sub> F <sub>2</sub> N <sub>2</sub> O <sub>2</sub>	FN	54.2
104		220~22	C <sub>18</sub> H <sub>14</sub> F <sub>2</sub> N <sub>2</sub> O <sub>2</sub> S	FN	80.9
105		264~7	C <sub>18</sub> H <sub>14</sub> F <sub>2</sub> O <sub>2</sub> S	FN	96
106		>300	C <sub>18</sub> H <sub>10</sub> F <sub>2</sub> N <sub>6</sub> O <sub>12</sub> S	FN	58
107		118~20	C <sub>18</sub> H <sub>14</sub> F <sub>2</sub> N <sub>2</sub> O <sub>2</sub> S <sub>2</sub>	FN	82.9
108		179~82	C <sub>19</sub> H <sub>20</sub> F <sub>2</sub> N <sub>2</sub> O <sub>4</sub>	FN	32.3
109		196~8	C <sub>21</sub> H <sub>24</sub> F <sub>2</sub> N <sub>2</sub> O <sub>4</sub>	FN	29.4

表 6 FCH<sub>2</sub>CONHN=X







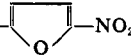


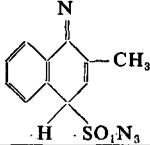

化合物	N=X	熔 点 (°C)	分 子 式	元素分析	减 虫 率 (%)
110	NH <sub>2</sub>	117~20	C <sub>2</sub> H <sub>6</sub> FN <sub>2</sub> O	FN	74.7
111	NH- 	96~8	C <sub>8</sub> H <sub>9</sub> FN <sub>2</sub> O	FN	—
112	N=CH- 	129~30	C <sub>8</sub> H <sub>7</sub> FN <sub>2</sub> O	FN	50.6
113	N=CH- 	166~8	C <sub>9</sub> H <sub>6</sub> ClFN <sub>2</sub> O	FN	40.6
114	N=CH- 	164~6	C <sub>9</sub> H <sub>6</sub> FN <sub>2</sub> O <sub>3</sub>	FN	37.2
115	N=CH- 	187~9	C <sub>9</sub> H <sub>7</sub> FN <sub>2</sub> O <sub>2</sub>	FN	34.8
116	N=CH- 	199~200	C <sub>9</sub> H <sub>7</sub> FN <sub>2</sub> O <sub>3</sub>	FN	75.1
117	N=C(CH <sub>3</sub> )-CH=CH- 	201~3	C <sub>11</sub> H <sub>9</sub> FN <sub>2</sub> O <sub>4</sub>	FN	24.6
118	 N=CH-CHO	241~3	C <sub>10</sub> H <sub>8</sub> FN <sub>2</sub> O <sub>2</sub>	FN	50.2
119	(HOCH <sub>2</sub> ) <sub>3</sub> -C(=O)- 	132~4	C <sub>9</sub> H <sub>11</sub> FN <sub>2</sub> O <sub>6</sub>	FN	50.2
120		>300	C <sub>12</sub> H <sub>10</sub> FNO <sub>3</sub> SNa	FN	23.3

表 7 FCH<sub>2</sub>CSNHR

化合物	R	熔点或沸点 (°C)	分 子 式	元素分析	减 虫 率 (%)
121	*H <sup>a</sup>	43~6	C <sub>2</sub> H <sub>4</sub> FNS	FN	55.6
122	C <sub>2</sub> H <sub>5</sub>	55~7/2 mm	C <sub>4</sub> H <sub>8</sub> FNS	FN	95.1
123	C <sub>3</sub> H <sub>7</sub> -i	66~9/7 mm	C <sub>5</sub> H <sub>10</sub> FNS	FN	50.6
124	C <sub>4</sub> H <sub>9</sub> -n	98~101/9 mm	C <sub>6</sub> H <sub>12</sub> FNS	FN	57.4
125		121~4	C <sub>12</sub> H <sub>10</sub> FNS	FN	76

注 本表所载熔点均未校正

附有\* 者为已知化合物

未知物 FN 元素分析值与理论值误差在 ±0.5% 范围内

表 2~7 重结晶溶剂: a 水; b 甲醇; c 丙醇; d 丙酮; e 丙酮+水; f DMF; g DMF+水; h 苯; 其他均用乙醇重结晶。

## 实 验 部 分

### 一、氟乙酰脂肪胺类的合成

1. 取 0.03 M 的脂肪胺，溶在适量无水溶剂中，用冰水冷却，在搅拌下，滴加 0.05 M 氟乙酰氯（溶在 5 ml 无水溶剂中）。加毕，在室温搅拌 2 小时。过滤，滤液除去溶剂后，进行减压蒸馏或用溶剂重结晶，即得产物。

2. 将 0.04 M 的氟乙酸乙酯和 0.06 M 的脂肪胺混合，在 50°C 加热 4 小时后，减压蒸馏或用溶剂重结晶，即可得产物。

### 二、氟乙酰芳香或杂环胺类的合成

取 0.015 M 的芳香或杂环胺类，溶在适量的无水溶剂中。加入少量无水吡啶或三乙胺，外用冰水冷却，在搅拌下滴加 0.016 M 氟乙酰氯。加毕，继续搅拌 2 小时，除去溶剂后，产物用水洗，重结晶得产物。

### 三、硫代氟乙酰胺类的合成

将相应的氟乙酰胺与过量的五硫化二磷加热制得硫代氟乙酰胺。

### 四、氟乙酰胍类的合成

取 0.5 M 氟乙酸乙酯和 25 ml 85% 水合胍混合，在室温放置 48 小时后，减压蒸馏得产物。

### 五、氟乙酰脲类的合成

将 0.02 M 的氟乙酰胍，溶在适量乙醇或四氢呋喃中。在搅拌下，加入 0.02 M 醛或酮类（溶在适量溶剂中），在 50°C 加热 2 小时，放冷，滤集固体，重结晶得产物。

### 六、氟乙酰甘氨酸的合成

取 0.05 M 的甘氨酸，溶在适量水中，在搅拌下，将 0.1 M 的氟乙酸酐分二次加入，再搅拌 1~2 小时，滤集固体，用水重结晶，即得产物。

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# SYNTHESIS AND SCHISTOSOMICIDAL ACTIVITY OF FLUOROACETAMIDES—A NEW CLASS OF ANTISCHISTOSOMAL AGENTS

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## ABSTRACT

Huang T Y and coworkers had observed the significant schistosomicidal effect of sodium fluoroacetate in the study of carbohydrate metabolism of *S. japonicum*. This fact led us to synthesize the fluoroacetic acid derivatives of lower toxicity. One hundred and twenty-five fluoroacetamides were prepared and submitted for animal screening tests and experimental therapy. Most of the fluoroacetamides showed prominent antischistosomal activity and much lower toxicity than that of fluoroacetic acid. However, they were still rather toxic for clinical trial.

**Key words** *S. japonicum*; Sodium fluoroacetate; Fluoroacetamides