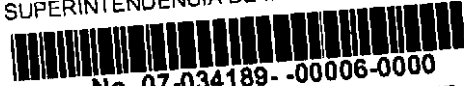


AS. 103.509

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Señores

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES**

E. S. D.

REF: Expediente No. 07 034189- Solicitud de Patente de Invención a favor
de **ROMARK LABORATORIES, L.C.**

JUAN PABLO CADENA SARMIENTO, portador de la tarjeta profesional No. 57.492 del C.S.J., obrando en calidad de apoderado de la Sociedad ROMARK LABORATORIES, L.C., de acuerdo con el artículo 46 de la Decisión 486 de la Comisión de la Comunidad Andina, me permito anexar copia de las siguientes publicaciones, para dar cumplimiento al requerimiento notificado por fijación en lista del 23 de diciembre de 2010.

1. IMTIAZ H, MISRA SN: "Search for potent anthelmintics Part XIII".
Journal of the Indian Chemical Society (1979) Vol. 56 (9) pp. 917-18.

Del Señor Jefe atentamente,


JUAN PABLO CADENA SARMIENTO
T.P. No. 57.492 del C.S.J.
C.C. 80.410.337 de Usaquén
Calle 70A No. 4-41

Bogotá, 07 de marzo de 2011
MXB/LMA
Anexo

Search for Potent Anthelmintics—Part XIII

2-(3,5-Substituted Salicylamido/Cinnamido)-4,5-Substituted Thiazoles

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Manuscript received 27 November 1978, revised 28 February 1979; accepted 24 August 1979

Twenty one new 2-(3,5-substituted salicylamido)-4,5-substituted thiazoles and ten 2-(substituted cinnamido)-4,5-substituted thiazoles have been prepared. Eight of them, when screened against *Nippostrongylus brasiliensis* in rats and *Hymenolepis nana* in mice at doses of 250 mg/kg $\times$ 3 and 250 mg/kg $\times$ 1 respectively, were found to be inactive.

3.5-SUBSTITUTED salicylamide derivatives like Niclosamide¹, Rafoxamide² and Clfoxamide³ have recently emerged as a new class of anthelmintics. Some 2-substituted thiazoles⁴⁻⁷ have shown strong anthelmintic efficacy in mice. Some cinnamic acid derivatives^{8,9} have been known to be active against *S. ovelata* and *A. suum*. Keeping this in view the title compounds were synthesised.

These were prepared according to the procedure
A or B.

Procedure A :

A mixture consisting of 3, 5-substituted salicyloyl chloride^{10,11} (.01 mole), chloroform (30 ml) and anhydrous potassium carbonate (.01 mole) was cooled in ice and an appropriate amino thiazole¹²⁻¹⁴ (.01 mole) gradually added to it. The resulting mixture was refluxed on a steam bath for 6 to 8 hr, cooled and filtered. Concentration of the filtrate afforded a solid which was washed successively with NaHCO₃ solution, dil HCl and water. It

Experimental

All melting points are uncorrected.

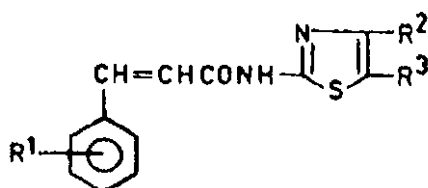
2-(3, 5-Substituted salicylamido)-4, 5-substituted thiazoles (Table 1) :

TABLE 1-2-(SUBSTITUTED SALICYLAMIDO)-4,5-SUBSTITUTED THIAZOLES

EL No.	R	R'	R''	R'''	M.P. °C	Yield %	Mol. Formula	% Nitrogen	
								Found	Calcd.
1.	Cl	Cl	H	NO ₂	148	50	C ₁₀ H ₄ Cl ₂ N ₂ SO ₂	12.24	12.68
2.	Cl	Cl	H	Br	115	56	C ₁₀ H ₃ BrCl ₂ N ₂ SO ₂	7.84	7.00
3.	Cl	Cl	H	Cl	122	48	C ₁₀ H ₃ Cl ₃ N ₂ SO ₂	8.92	8.85
4.	Cl	Cl	C ₆ H ₅	H	140	45	C ₁₆ H ₁₁ Cl ₂ N ₂ SO ₂	7.38	7.67
5.	Cl	Cl	p-ClC ₆ H ₄	H	260	40	C ₁₆ H ₉ Cl ₃ N ₂ SO ₂	6.78	7.01
6.	Cl	Cl	p-OHC ₆ H ₄	H	214	52	C ₁₆ H ₉ Cl ₂ N ₂ SO ₂	7.02	7.35
7.	Cl	Cl	OH	COOC ₂ H ₅	215	58	C ₁₇ H ₁₁ Cl ₂ N ₂ SO ₂	7.05	7.47
8.	Br	Br	H	NO ₂	172	45	C ₁₀ H ₃ Br ₂ N ₂ SO ₂	9.38	9.93
9.	Br	Br	H	Br	160	48	C ₁₀ H ₂ Br ₃ N ₂ SO ₂	5.82	6.13
10.	Br	Br	H	Cl	145	58	C ₁₀ H ₂ Br ₂ ClN ₂ SO ₂	7.18	6.79
11.	Br	Br	C ₆ H ₅	H	174	51	C ₁₆ H ₁₀ Br ₂ N ₂ SO ₂	6.44	6.17
12.	Br	Br	p-ClC ₆ H ₄	H	190	54	C ₁₆ H ₈ Br ₂ ClN ₂ SO ₂	5.45	5.73
13.	Br	Br	p-OHC ₆ H ₄	H	105	50	C ₁₆ H ₉ Br ₂ N ₂ SO ₂	6.94	6.96
14.	Br	Br	CH ₃	COOC ₂ H ₅	205	52	C ₁₇ H ₁₁ Br ₂ N ₂ SO ₂	6.28	6.04
15.	H	NO ₂	H	NO ₂	176	46	C ₁₀ H ₇ N ₂ SO ₂	17.60	18.07
16.	H	NO ₂	H	Br	120	48	C ₁₀ H ₆ BrN ₂ SO ₂	12.55	12.21
17.	H	NO ₂	H	Cl	230	52	C ₁₀ H ₆ ClN ₂ SO ₂	14.48	14.02
18.	H	NO ₂	C ₆ H ₅	H	168	56	C ₁₆ H ₁₁ N ₂ SO ₂	11.80	12.31
19.	H	NO ₂	p-ClC ₆ H ₄	H	190	42	C ₁₆ H ₉ ClN ₂ SO ₂	10.75	11.18
20.	H	NO ₂	p-OHC ₆ H ₄	H	250	46	C ₁₆ H ₉ ClN ₂ SO ₂	11.42	11.77
21.	H	NO ₂	CH ₃	COOC ₂ H ₅	180	50	C ₁₇ H ₁₁ N ₂ SO ₂	11.53	11.97

* Screened for anthelmintic activity.

TABLE 2—2-(SUBSTITUTED CINNAMIDO)-4,5-SUBSTITUTED THIAZOLES



Sl. No.	R ¹	R ²	R ³	M.P. °C	Yield %	Mol. Formula	% Nitrogen	
							Found	Calcd.
1.	H	C ₆ H ₅	H	903	65	C ₁₈ H ₁₅ N ₂ SO	8.76	9.13
2.	H	CH ₃	COOC ₂ H ₅	140	55	C ₁₈ H ₁₇ N ₂ SO	8.41	8.86
3.	p-Cl	C ₆ H ₅	H	215	59	C ₁₈ H ₁₃ ClN ₂ SO	8.63	8.22
4.	p-Cl	CH ₃	COOC ₂ H ₅	280	56	C ₁₈ H ₁₅ ClN ₂ SO	7.68	7.99
5.	p-Cl	H	NO ₂	248	60	C ₁₈ H ₁₃ ClN ₂ SO	12.14	12.57
6.	o-Cl	C ₆ H ₅	H	200	68	C ₁₈ H ₁₃ ClN ₂ SO	8.58	8.22
7.	o-Cl	H	NO ₂	210	60	C ₁₈ H ₁₃ ClN ₂ SO	14.10	12.57
8.	o-Cl	CH ₃	COOC ₂ H ₅	257	62	C ₁₈ H ₁₅ ClN ₂ SO	8.29	7.99
9.	p-N(CH ₃) ₂	C ₆ H ₅	H	190	55	C ₂₀ H ₁₇ N ₃ SO	11.60	12.04
10.	p-N(CH ₃) ₂	H	NO ₂	290	54	C ₂₀ H ₁₇ N ₃ SO	17.19	17.61

* Screened for anthelmintic activity.

was recrystallised from benzene-petroleum ether or ethanol.

Procedure B :

To an ice cold mixture of 3, 5-substituted salicyloyl chloride (.01 mole) and pyridine (30 ml), an appropriate amino thiazole (.01 mole) was added slowly with stirring. The contents were refluxed for 6 hr and excess of solvent distilled off. The residue was poured into ice cold water whereupon a solid separated out. It was filtered and recrystallised from ethanol.

2-(Substituted cinnamido)-4,5-substituted thiazoles (Table 2) :

These were prepared analogously from an appropriately substituted cinnamoyl chloride¹⁵ and an amino thiazole by following the procedure B. The compounds were recrystallised from ethanol.

Acknowledgement

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