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The synthesis of novel 1-alkyl or 1-aryl-2-(4-substituted-1-piperazinyl)-1*H*-benzothieno[2,3-*d*]imidazoles **7e-x** starting from 2-nitro-3-bromobenzo[*b*]thiophene is described. These compounds were prepared as potential H_1 -antihistaminic agents.

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As part of a program designed to investigate the biological activity of tricyclic heterocyclic systems containing a thiophene ring as the central nucleus [1-6], recently we have put forward a convenient way to synthesize 1[H] and 1-methyl-1*H*-benzothieno[2,3-*d*]imidazoles [2].

A survey of the literature showed that derivatives of benzoimidazole and pyridoimidazole possessed H_1 -antihistaminic activity [7-10]; among these compounds are derivatives of 2-(4-substituted-1-piperazinyl)benzimidazole which have shown potent H_1 -antihistaminic activity [10], although its structure was appreciably different from that of typical H_1 -antihistaminic agents.

In light of these facts, and as a continuation of our investigations on tricyclic systems we decided to synthesize a series of 1-alkyl or 1-aryl-2-(4-substituted-1-piper-

azinyl)-1*H*-benzothieno[2,3-*d*]imidazoles **7e-x** to evaluate their pharmacological profile as H_1 -antihistaminic agents.

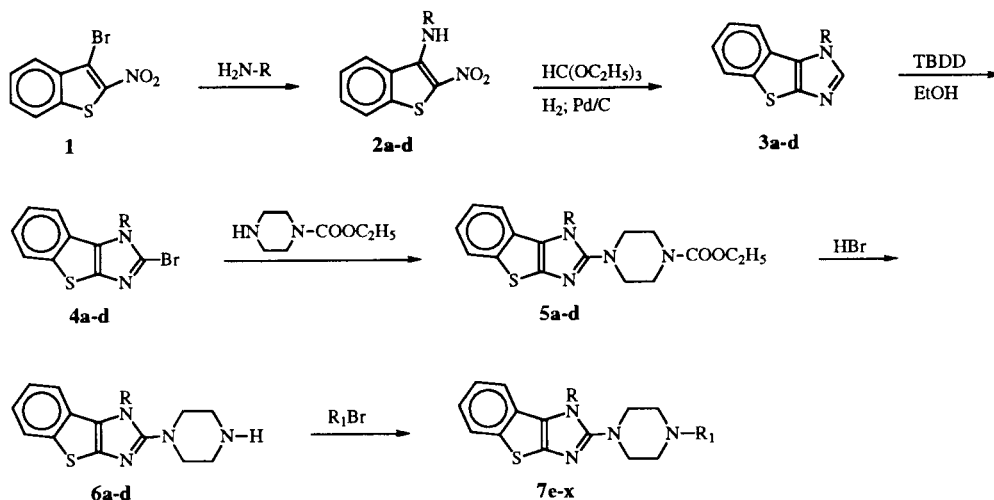
The synthetic method for 1-alkyl or 1-aryl-2-(4-substituted-1-piperazinyl)-1*H*-benzothieno[2,3-*d*]imidazoles **7e-x** is outlined in Scheme 1.

The started compounds, 1-alkyl or 1-aryl-1*H*-benzothieno[2,3-*d*]imidazoles **3a-d** were prepared according to the method we previously reported [2].

The 1-substituted-1*H*-benzothieno[2,3-*d*]imidazoles were converted into 1-substituted-2-bromo-1*H*-benzothieno[2,3-*d*]imidazoles **4a-d** in ethanolic solution with 2,4,4,6-tetrabromocyclohexa-2,5 dienone (TBDD), reactive as a selective monobrominating agent [11-12].

The subsequent reaction of **4a-d** with 1-carboxyethylpiperazine gave the 1-substituted-2-(4-carboxy-

Scheme 1



- a, R = CH₃
b, R = CH(CH₃)₂
c, R = CH₂C₆H₅
d, R = CH₂C₆H₄(*p*)F

- e, R = CH₃, R₁ = CH₃
f, R = CH₃, R₁ = CH₂CH₂CH₃
g, R = CH₃, R₁ = CH₂CH₂OH
h, R = CH₃, R₁ = CH₂CH(OH)CH₃
i, R = CH₃, R₁ = CH₂CH₂C₆H₅
j, R = CH(CH₃)₂, R₁ = CH₃
k, R = CH(CH₃)₂, R₁ = CH₂CH₂CH₃
l, R = CH(CH₃)₂, R₁ = CH₂CH₂OH
m, R = CH(CH₃)₂, R₁ = CH₂CH(OH)CH₃
n, R = CH(CH₃)₂, R₁ = CH₂CH₂C₆H₅

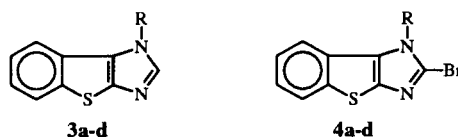
- o, R = CH₂C₆H₅, R₁ = CH₃
p, R = CH₂C₆H₅, R₁ = CH₂CH₂CH₃
q, R = CH₂C₆H₅, R₁ = CH₂CH₂OH
r, R = CH₂C₆H₅, R₁ = CH₂CH(OH)CH₃
s, R = CH₂C₆H₅, R₁ = CH₂CH₂C₆H₅
t, R = CH₂C₆H₄(*p*)F, R₁ = CH₃
u, R = CH₂C₆H₄(*p*)F, R₁ = CH₂CH₂CH₃
v, R = CH₂C₆H₄(*p*)F, R₁ = CH₂CH₂OH
w, R = CH₂C₆H₄(*p*)F, R₁ = CH₂CH(OH)CH₃
x, R = CH₂C₆H₄(*p*)F, R₁ = CH₂CH₂C₆H₅

ethyl-1-piperazinyl)-1*H*-benzothieno[2,3-*d*]imidazoles **5a-d**; deprotection of **5a-d** with 48% aqueous hydrobromic acid solution gave derivatives **6a-d**, which were readily converted to **7e-x** by reaction with the appro-

priate alkyl halide in ethanol in the presence of sodium carbonate.

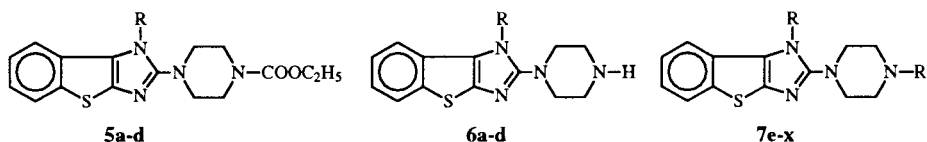
Pharmacological data are not reported because the tested compounds did not show meaningful activity.

Table 1
Analytical Data for 1-Substituted-1*H*-benzothieno[2,3-*d*]imidazoles **3a-d** and
1-Substituted 2-Bromo-1*H*-benzothieno[2,3-*d*]imidazoles **4a-d**



Compound	R	X	Yield %	Mp °C (solvent)	Molecular Formula	Analyses (%)		
						Calcd./Found C	H	N
3a	CH ₃	H	67	96-97 (C ₆ H ₁₂)	C ₁₀ H ₈ N ₂ S (188.04)	63.82 63.80	4.29 4.25	14.89 14.83
3b	CH(CH ₃) ₂	H	74	76-77 (Ligroin)	C ₁₂ H ₁₂ N ₂ S (216.30)	66.64 66.60	5.59 5.47	12.95 13.02
3c	CH ₂ C ₆ H ₅	H	67	96-97 (C ₆ H ₁₂)	C ₁₆ H ₁₂ N ₂ S (264.07)	72.71 72.69	4.58 4.61	10.61 10.76
3d	CH ₂ C ₆ H ₄ (<i>p</i>)F	H	74	76-77 (C ₆ H ₁₂)	C ₁₆ H ₁₁ FN ₂ S (282.34)	68.07 68.00	3.93 3.89	9.93 9.91
4a	CH ₃	Br	74	160-162 (C ₆ H ₁₂)	C ₁₀ H ₇ BrN ₂ S (267.14)	44.96 44.98	2.64 2.52	10.49 10.56
4b	CH(CH ₃) ₂	Br	98	119-120 (C ₆ H ₁₂)	C ₁₂ H ₁₁ BrN ₂ S (295.20)	48.83 48.68	3.76 3.63	9.49 9.33
4c	CH ₂ C ₆ H ₅	Br	74	160-162 (C ₆ H ₁₂)	C ₁₆ H ₁₁ BrN ₂ S (343.24)	55.99 55.98	3.23 3.13	8.16 8.22
4d	CH ₂ C ₆ H ₄ (<i>p</i>)F	Br	98	119-120 (C ₆ H ₁₂)	C ₁₆ H ₁₀ FBrN ₂ S (361.23)	53.20 53.19	2.79 2.67	7.75 7.67

Table 2
Analytical Data for 1-Substituted-2-(4-carboxyethylpiperazinyl)-1*H*-benzothieno[2,3-*d*]imidazoles **5a-d**,
1-Substituted-2(4*H*-piperazinyl)-1*H*-benzothieno[2,3-*d*]imidazoles **6a-d** and 1-Alkyl or
1-Aryl-2-(4-substitutedpiperazinyl)-1*H*-benzothieno[2,3-*d*]imidazoles **7e-x**



Compound	R	R ₁	Yield %	Mp °C (solvent)	Molecular Formula	Analyses (%)		
						Calcd./Found C	H	N
6a	CH ₃	H	56	152-154 (CH ₃ CN)	C ₁₄ H ₁₆ N ₄ S (272.36)	61.73 61.74	5.92 5.87	20.57 20.31
7e	CH ₃	CH ₃	52	135-137 (H ₂ O)	C ₁₅ H ₁₈ N ₄ S (286.39)	62.91 62.80	6.33 6.30	19.56 19.37
5a	CH ₃	COOC ₂ H ₅	81	186-187 (CH ₃ CN)	C ₁₇ H ₂₀ N ₄ O ₂ S (344.43)	59.28 59.59	5.85 6.00	16.26 16.19
7f	CH ₃	CH ₂ CH ₂ CH ₃	73	158-159 (Ligroin)	C ₁₇ H ₂₂ N ₄ S (314.15)	64.94 64.93	7.06 7.05	17.82 17.81
7g	CH ₃	CH ₂ CH ₂ OH	65	140-142 (AcOEt)	C ₁₆ H ₂₀ ON ₄ S (316.42)	60.73 60.74	6.37 6.34	17.70 17.94
7h	CH ₃	CH ₂ CH(OH)CH ₃	98	125-127 (Ligroin)	C ₁₇ H ₂₂ ON ₄ S (330.449)	61.79 61.81	6.71 6.68	16.95 16.89
7i	CH ₃	CH ₂ CH ₂ C ₆ H ₅	83	132-134 (Ligroin)	C ₂₂ H ₂₄ N ₄ S (376.52)	70.17 70.09	6.42 6.24	14.88 14.81

Table 2 (continued)

Compound	R	R ₁	Yield %	Mp °C (solvent)	Molecular Formula	Analyses (%)		
						Calcd./Found	C	H N
6b	CH(CH ₃) ₂	H	50	165-167 (Ligroin)	C ₁₆ H ₂₀ N ₄ S (300.42)	63.97 63.85	6.72 6.60	18.66 18.59
7j	CH(CH ₃) ₂	CH ₃	82	150-151 (C ₆ H ₁₂)	C ₁₇ H ₂₂ N ₄ S (314.45)	64.93 65.05	7.05 7.29	17.81 17.81
5b	CH(CH ₃) ₂	COOC ₂ H ₅	90	173-175 (CH ₃ CN)	C ₁₉ H ₂₄ N ₄ O ₂ S (372.161)	61.26 61.03	6.50 6.45	15.05 14.99
7k	CH(CH ₃) ₂	CH ₂ CH ₂ CH ₃	65	181-183 (Ligroin)	C ₁₉ H ₂₆ N ₄ S (342.50)	66.63 66.50	7.65 7.52	16.36 16.23
7l	CH(CH ₃) ₂	CH ₂ CH ₂ OH	67	178-179 (Ligroin)	C ₁₈ H ₂₄ N ₄ OS (344.47)	62.76 62.66	7.02 6.98	16.26 16.15
7m	CH(CH ₃) ₂	CH ₂ CH(OH)CH ₃	61	182-184 (Ligroin)	C ₁₉ H ₂₆ N ₄ OS (358.18)	63.65 63.54	7.32 7.22	15.64 15.49
7n	CH(CH ₃) ₂	CH ₂ CH ₂ C ₆ H ₅	52	160-162 (CH ₃ CN)	C ₂₄ H ₂₈ N ₄ S (404.57)	71.25 71.00	6.98 6.88	13.85 13.68
6c	CH ₂ C ₆ H ₅	H	56	152-154 (Ligroin)	C ₂₀ H ₂₀ N ₄ S (348.47)	68.94 68.83	5.79 5.73	16.08 16.02
7o	CH ₂ C ₆ H ₅	CH ₃	52	135-137 (CH ₃ CN)	C ₂₁ H ₂₂ N ₄ S (362.15)	69.58 69.47	6.12 6.07	15.47 15.35
5c	CH ₂ C ₆ H ₅	COOC ₂ H ₅	81	186-187 (CH ₃ CN)	C ₂₃ H ₂₄ N ₄ O ₂ S (420.53)	65.69 65.57	5.75 5.63	13.32 13.27
7p	CH ₂ C ₆ H ₅	CH ₂ CH ₂ CH ₃	74	158-159 (CH ₃ CN)	C ₂₃ H ₂₆ N ₄ S (390.18)	70.74 70.68	6.72 6.65	14.36 14.20
7q	CH ₂ C ₆ H ₅	CH ₂ CH ₂ OH	67	140-142 (Ligroin)	C ₂₂ H ₂₄ N ₄ OS (392.52)	67.32 67.05	6.16 6.12	14.27 14.13
7r	CH ₂ C ₆ H ₅	CH ₂ CH(OH)CH ₃	98	125-127 (Ligroin)	C ₂₃ H ₂₆ N ₄ OS (406.18)	67.95 67.88	6.45 6.42	13.79 13.74
7s	CH ₂ C ₆ H ₅	CH ₂ CH ₂ C ₆ H ₅	83	132-134 (Ligroin)	C ₂₈ H ₂₈ N ₄ S (452.62)	74.30 74.25	6.24 6.19	12.38 12.12
6d	CH ₂ C ₆ H ₄ (<i>p</i>)F	H	46	165-167 (Ligroin)	C ₂₀ H ₁₉ FN ₄ S (366.13)	65.55 65.45	5.23 5.17	15.30 15.15
7t	CH ₂ C ₆ H ₄ (<i>p</i>)F	CH ₃	82	150-151 (Ligroin)	C ₂₁ H ₂₁ FN ₄ S (380.48)	66.29 66.10	5.56 5.45	14.73 14.53
5d	CH ₂ C ₆ H ₄ (<i>p</i>)F	COOC ₂ H ₅	70	173-175 (C ₆ H ₁₂)	C ₂₃ H ₂₃ FN ₄ O ₂ S (438.15)	62.99 62.85	5.29 5.10	12.78 12.68
7u	CH ₂ C ₆ H ₄ (<i>p</i>)F	CH ₂ CH ₂ CH ₃	65	181-183 (Ligroin)	C ₂₃ H ₂₅ FN ₄ S (408.54)	67.62 67.71	6.17 6.10	13.71 13.68
7v	CH ₂ C ₆ H ₄ (<i>p</i>)F	CH ₂ CH ₂ OH	67	178-179 (Ligroin)	C ₂₂ H ₂₃ FN ₄ OS (410.15)	64.37 64.25	5.65 5.59	13.66 13.62
7w	CH ₂ C ₆ H ₄ (<i>p</i>)F	CH ₂ CH(OH)CH ₃	61	182-184 (Ligroin)	C ₂₃ H ₂₅ FN ₄ OS (424.54)	65.07 65.01	5.94 5.87	13.20 13.10
7x	CH ₂ C ₆ H ₄ (<i>p</i>)F	CH ₂ CH ₂ C ₆ H ₅	52	160-161 (CH ₃ CN)	C ₂₈ H ₂₇ FN ₄ S (470.19)	71.46 71.35	5.79 5.72	11.91 11.85

EXPERIMENTAL

Melting points were determined on a Buchi 510 apparatus and are uncorrected. Elemental analysis were carried out on a Perkin-Elmer 1106 and the results obtained were within $\pm 0.4\%$ of the calculated values. The ir spectra were recorded on a Perkin Elmer spectrophotometer 281. Thin layer chromatography was used for monitoring the completion of reactions.

General Procedure for the Synthesis of 2-Nitro-3-substituted-aminobenzo[*b*]thiophenes **2a-d**.

The title compounds were synthesized according to the method previously described by us [4].

2-Nitro-3-methylaminobenzo[*b*]thiophene (**2a**) was reported [3].

2-Nitro-3-isopropylaminobenzo[*b*]thiophene (**2b**).

This compound was obtained in 70% yield, mp 120-121° (from ethanol); ir: ν 3365 (N-H), 1540, 1365 cm⁻¹ (NO₂).

2-Nitro-3-benzylaminobenzo[*b*]thiophene (**2c**).

This compound was obtained in 90% yield, mp 179-180° (from dioxane); ir: ν 3360 (N-H), 1540, 1370 cm⁻¹ (NO₂).

2-Nitro-3-(4-fluorobenzylaminobenzo[*b*]thiophene (**2d**).

This compound was obtained in 70% yield, mp 188-189° (from dioxane); ir: ν 3365 (N-H), 1540, 1365 cm⁻¹ (NO₂).

General Procedure for the Synthesis of 1-Substituted-1*H*-benzothieno[2,3-*d*]imidazoles **3a-d**.

The title compounds were synthesized according to the method previously described [3]. In Table I are reported the analytical data for derivatives **3a-d**.

General Procedure for the Synthesis of 1-Substituted-2-bromo-

1H-Benzothieno[2,3-d]imidazoles 4a-d.

A mixture of **3a-d** (10 mmoles) and 2,4,4,6-tetrabromo-2,5-cyclohexadienone (10 mmoles) in ethanol (99%, 150 ml) was stirred at room temperature under nitrogen. The completion of the reaction was checked by tlc. After the solution was evaporated *in vacuo* the residue was treated with 1N sodium hydroxide solution, filtered and the solid was crystallized from a suitable solvent.

In Table 1 are reported analytical data for **4a-d**.

General Procedure for the Synthesis of 1-Substituted-2-(4-carboxyethylpiperazinyl)-1H-benzothieno[2,3-d]imidazoles 5a-d.

A mixture of **4a-d** (10 mmoles) and 1-carboxyethylpiperazine (150 ml) was heated at 120° with stirring for 48 hours. The completion of the reaction was checked by tlc. To the cooled mixture was added water, filtered and the residue was crystallized from a suitable solvent.

In Table 2 are reported the analytical data for **5a-d**.

General Procedure for the Synthesis of 1-Substituted-2-(4H-piperazinyl)-1H-benzothieno[2,3-d]imidazoles 6a-d.

A solution of **5a-d** (10 mmoles) in 70 ml of hydrobromic acid (48%) was refluxed for 3 hours. The completion of the reaction was checked by tlc. The reaction mixture was evaporated *in vacuo* and this residue was solubilized with water and aqueous 37% ammonia was added to pH 10. The mixture was extracted with chloroform and the extract was evaporated *in vacuo*. The residue was recrystallized from a suitable solvent. In Table 2 are reported analytical data of **6a-d**.

General Procedure for the Synthesis of 1-Alkyl or 1-Aryl-2-(4-substitutedpiperazinyl)-1H-benzothieno[2,3-d]imidazoles 7e-x.

A mixture of **6a-d** (10 mmoles), an appropriate alkyl derivative (12 mmoles), and potassium carbonate (6 mmoles) in ethanol (20 ml) was stirred at 65° for 12 hours. The completion

of reaction was checked by tlc. After cooling, the reaction made basic with 1N sodium hydroxide to pH 12. The residue which separated was filtered and crystallized from a suitable solvent. In Table 2 are reported the analytical data for **7e-x**.

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