Synthesis of Novel 1-Alkyl or 1-Aryl-2-(4-substituted-1-piperazinyl)-1*H*-benzothieno[2,3-*d*]imidazoles

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

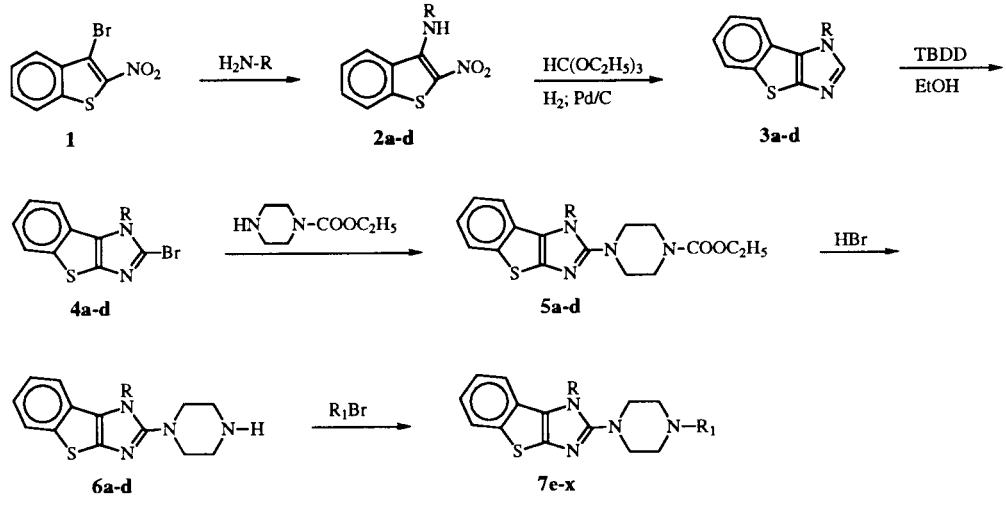
The synthetic method for 1-alkyl or 1-aryl-2-(4-substituted-1-piperazinyl)-1*H*-benzothieno[2,3-*d*]imidazoles **7e-x** is outlined in Scheme 1.

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 = CH_3
b, R = $CH(CH_3)_2$
c, R = $CH_2C_6H_5$
d, R = $CH_2C_6H_4(p)F$

e, R = CH_3, R_1 = CH_3
f, R = CH_3, R_1 = $CH_2CH_2CH_3$
g, R = CH_3, R_1 = CH_2CH_2OH
h, R = CH_3, R_1 = $CH_2CH(OH)CH_3$
i, R = CH_3, R_1 = $CH_2CH_2C_6H_5$
j, R = $CH(CH_3)_2$, R_1 = CH_3
k, R = $CH(CH_3)_2$, R_1 = $CH_2CH_2CH_3$
l, R = $CH(CH_3)_2$, R_1 = CH_2CH_2OH
m, R = $CH(CH_3)_2$, R_1 = $CH_2CH(OH)CH_3$
n, R = $CH(CH_3)_2$, R_1 = $CH_2CH_2C_6H_5$

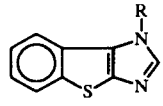
o, R = $CH_2C_6H_5$, R_1 = CH_3
p, R = $CH_2C_6H_5$, R_1 = $CH_2CH_2CH_3$
q, R = $CH_2C_6H_5$, R_1 = CH_2CH_2OH
r, R = $CH_2C_6H_5$, R_1 = $CH_2CH(OH)CH_3$
s, R = $CH_2C_6H_5$, R_1 = $CH_2CH_2C_6H_5$
t, R = $CH_2C_6H_4(p)F$, R_1 = CH_3
u, R = $CH_2C_6H_4(p)F$, R_1 = $CH_2CH_2CH_3$
v, R = $CH_2C_6H_4(p)F$, R_1 = CH_2CH_2OH
w, R = $CH_2C_6H_4(p)F$, R_1 = $CH_2CH(OH)CH_3$
x, R = $CH_2C_6H_4(p)F$, R_1 = $CH_2CH_2C_6H_5$

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

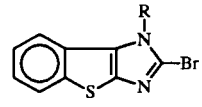
Pharmacological data are not reported because the tested compounds did not show meaningful activity.

Table 1

Analitycal 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**



3a-d

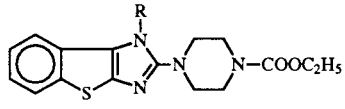


4a-d

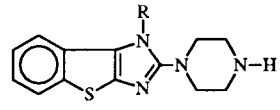
Compound	R	X	Yield %	Mp °C (solvent)	Molecular Formula	Analyses (%) Calcd./Found C	H	N
3a	CH_3	H	67	96-97 (C_6H_{12})	$C_{10}H_8N_2S$ (188.04)	63.82 63.80	4.29 4.25	14.89 14.83
3b	$CH(CH_3)_2$	H	74	76-77 (Ligroin)	$C_{12}H_{12}N_2S$ (216.30)	66.64 66.60	5.59 5.47	12.95 13.02
3c	$CH_2C_6H_5$	H	67	96-97 (C_6H_{12})	$C_{16}H_{12}N_2S$ (264.07)	72.71 72.69	4.58 4.61	10.61 10.76
3d	$CH_2C_6H_4(p)F$	H	74	76-77 (C_6H_{12})	$C_{16}H_{11}FN_2S$ (282.34)	68.07 68.00	3.93 3.89	9.93 9.91
4a	CH_3	Br	74	160-162 (C_6H_{12})	$C_{10}H_7BrN_2S$ (267.14)	44.96 44.98	2.64 2.52	10.49 10.56
4b	$CH(CH_3)_2$	Br	98	119-120 (C_6H_{12})	$C_{12}H_{11}BrN_2S$ (295.20)	48.83 48.68	3.76 3.63	9.49 9.33
4c	$CH_2C_6H_5$	Br	74	160-162 (C_6H_{12})	$C_{16}H_{11}BrN_2S$ (343.24)	55.99 55.98	3.23 3.13	8.16 8.22
4d	$CH_2C_6H_4(p)F$	Br	98	119-120 (C_6H_{12})	$C_{16}H_{10}FBrN_2S$ (361.23)	53.20 53.19	2.79 2.67	7.75 7.67

Table 2

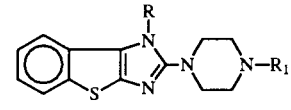
Analitycal Data for 1-Substituted-2-(4-carboxyethylpiperazinyl)-1*H*-benzothieno[2,3-*d*]imidazoles **5a-d**, 1-Substituted-2(4*H*-piperazinyl)-1*H*-benzothieno[2,3-*d*]imidazoles **6a-d** and 1-Alkyl or 1-Aryl-2-(4-substitutedpiperazinyl)-1*H*-benzothieno[2,3-*d*]imidazoles **7e-x**



5a-d



6a-d



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_3CN)	$C_{14}H_{16}N_4S$ (272.36)	61.73 61.74	5.92 5.87	20.57 20.31
7e	CH_3	CH_3	52	135-137 (H_2O)	$C_{15}H_{18}N_4S$ (286.39)	62.91 62.80	6.33 6.30	19.56 19.37
5a	CH_3	$COOC_2H_5$	81	186-187 (CH_3CN)	$C_{17}H_{20}N_4O_2S$ (344.43)	59.28 59.59	5.85 6.00	16.26 16.19
7f	CH_3	$CH_2CH_2CH_3$	73	158-159 (Ligroin)	$C_{17}H_{22}N_4S$ (314.15)	64.94 64.93	7.06 7.05	17.82 17.81
7g	CH_3	CH_2CH_2OH	65	140-142 (AcOEt)	$C_{16}H_{20}ON_4S$ (316.42)	60.73 60.74	6.37 6.34	17.70 17.94
7h	CH_3	$CH_2CH(OH)CH_3$	98	125-127 (Ligroin)	$C_{17}H_{22}ON_4S$ (330.449)	61.79 61.81	6.71 6.68	16.95 16.89
7i	CH_3	$CH_2CH_2C_6H_5$	83	132-134 (Ligroin)	$C_{22}H_{24}N_4S$ (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)	$C_{16}H_{20}N_4S$ (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_6H_{12})	$C_{17}H_{22}N_4S$ (314.45)	64.93 65.05	7.05 7.29	17.81 17.81
5b	$CH(CH_3)_2$	$COOC_2H_5$	90	173-175 (CH_3CN)	$C_{19}H_{24}N_4O_2S$ (372.161)	61.26 61.03	6.50 6.45	15.05 14.99
7k	$CH(CH_3)_2$	$CH_2CH_2CH_3$	65	181-183 (Ligroin)	$C_{19}H_{26}N_4S$ (342.50)	66.63 66.50	7.65 7.52	16.36 16.23
7l	$CH(CH_3)_2$	CH_2CH_2OH	67	178-179 (Ligroin)	$C_{18}H_{24}N_4OS$ (344 47)	62.76 62.66	7.02 6.98	16.26 16.15
7m	$CH(CH_3)_2$	$CH_2CH(OH)CH_3$	61	182-184 (Ligroin)	$C_{19}H_{26}N_4OS$ (358.18)	63.65 63.54	7.32 7.22	15.64 15.49
7n	$CH(CH_3)_2$	$CH_2CH_2C_6H_5$	52	160-162 (CH_3CN)	$C_{24}H_{28}N_4S$ (404.57)	71.25 71.00	6.98 6.88	13.85 13.68
6c	$CH_2C_6H_5$	H	56	152-154 (Ligroin)	$C_{20}H_{20}N_4S$ (348.47)	68.94 68.83	5.79 5.73	16.08 16.02
7o	$CH_2C_6H_5$	CH_3	52	135-137 (CH_3CN)	$C_{21}H_{22}N_4S$ (362.15)	69.58 69.47	6.12 6.07	15.47 15.35
5c	$CH_2C_6H_5$	$COOC_2H_5$	81	186-187 (CH_3CN)	$C_{23}H_{24}N_4O_2S$ (420.53)	65.69 65.57	5.75 5.63	13.32 13.27
7p	$CH_2C_6H_5$	$CH_2CH_2CH_3$	74	158-159 (CH_3CN)	$C_{23}H_{26}N_4S$ (390.18)	70 74 70.68	6.72 6.65	14.36 14.20
7q	$CH_2C_6H_5$	CH_2CH_2OH	67	140-142 (Ligroin)	$C_{22}H_{24}N_4OS$ (392.52)	67.32 67.05	6.16 6.12	14.27 14.13
7r	$CH_2C_6H_5$	$CH_2CH(OH)CH_3$	98	125-127 (Ligroin)	$C_{23}H_{26}N_4OS$ (406.18)	67.95 67.88	6.45 6.42	13.79 13.74
7s	$CH_2C_6H_5$	$CH_2CH_2C_6H_5$	83	132-134 (Ligroin)	$C_{28}H_{28}N_4S$ (452.62)	74.30 74.25	6.24 6.19	12.38 12.12
6d	$CH_2C_6H_4(p)F$	H	46	165-167 (Ligroin)	$C_{20}H_{19}FN_4S$ (366.13)	65.55 65.45	5.23 5.17	15.30 15.15
7t	$CH_2C_6H_4(p)F$	CH_3	82	150-151 (Ligroin)	$C_{21}H_{21}FN_4S$ (380.48)	66.29 66.10	5.56 5.45	14.73 14.53
5d	$CH_2C_6H_4(p)F$	$COOC_2H_5$	70	173-175 (C_6H_{12})	$C_{23}H_{23}FN_4O_2S$ (438.15)	62.99 62.85	5.29 5.10	12.78 12.68
7u	$CH_2C_6H_4(p)F$	$CH_2CH_2CH_3$	65	181-183 (Ligroin)	$C_{23}H_{25}FN_4S$ (408.54)	67.62 67.71	6.17 6.10	13.71 13.68
7v	$CH_2C_6H_4(p)F$	CH_2CH_2OH	67	178-179 (Ligroin)	$C_{22}H_{23}FN_4OS$ (410.15)	64.37 64.25	5.65 5.59	13.66 13.62
7w	$CH_2C_6H_4(p)F$	$CH_2CH(OH)CH_3$	61	182-184 (Ligroin)	$C_{23}H_{25}FN_4OS$ (424.54)	65.07 65.01	5.94 5.87	13.20 13.10
7x	$CH_2C_6H_4(p)F$	$CH_2CH_2C_6H_5$	52	160-161 (CH_3CN)	$C_{28}H_{27}FN_4S$ (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 ±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} (NO_2).

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} (NO_2).

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} (NO_2).

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-

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

A mixture of **3a-d** (10 mmoles) and 2,4,4,6-tetrabromo-2,5-cycloexadienone (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 1*N* 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)-1*H*-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-(4*H*-piperazinyl)-1*H*-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 *p*H 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)-1*H*-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 1*N* sodium hydroxide to *p*H 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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