Syntheses of Substituted Pyrrolo[2,3-*d*]imidazole-5-carboxylates and Substitued Pyrrolo[3,2-*d*]imidazole-5-carboxylates

A. Shafiee*, J. Shahbazi Mojarrad, M. A. Jalili, H. R. Adhami and F. Hadizadeh

Department of Chemistry, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran

Received September 14, 2001

Starting from readily available *p*-substituted-benzylamines a series of ethyl 2-alkylthio-1-substituted-benzylpyrrolo[2,3-*d*]imidazole-5-carboxylates was prepared. In addition, starting from 2-alkyl-4(or 5)-formylimidazoles and methyl 4'-bromomethylbiphenyl-2-carboxylate a series of methyl substituted-pyrrolo[2,3-*d*]imidazole-5-carboxylates and methyl substituted-pyrrolo[3,2-d]imidazole-5-carboxylates was prepared.

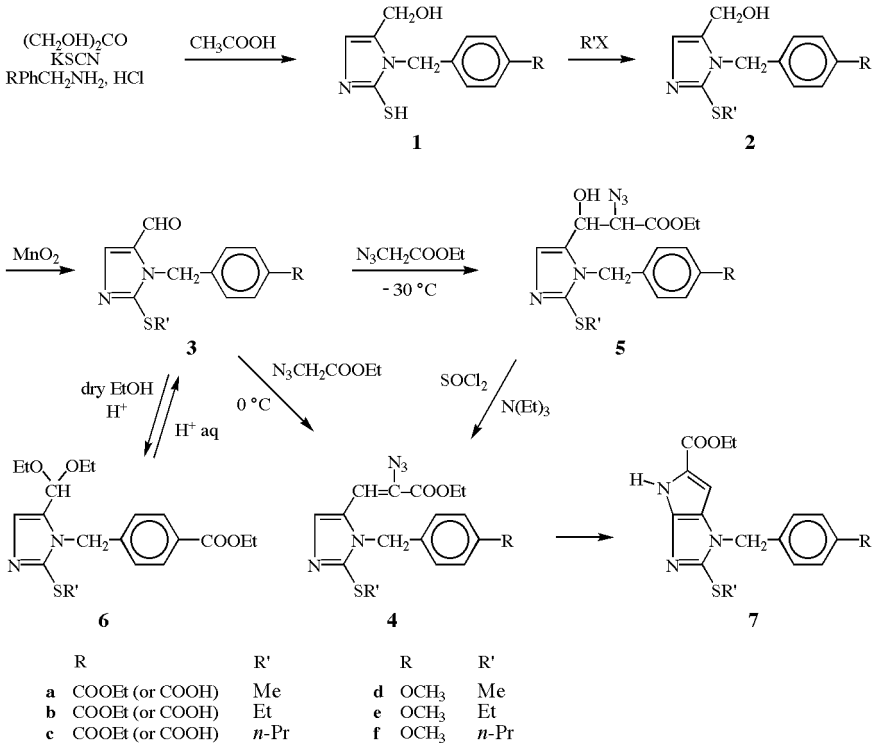
J. Heterocyclic Chem., **39**, 367 (2002).

The renin angiotensin system (RAS) plays a key role in the regulation of cardiovascular homeostasis and blood pressure in mamelians [1,2]. Since the angiotensin converting enzyme inhibitors (ACEIs) have side effects such as dry cough and angioderma, caused by potentiation of bradykinin, substance P and other active peptides, nonpeptide angiotensin II receptor antagonists are of interest [3,4].

In view of the antihypertensive activity of 2-alkyl-*N*-benzyl fused imidazoles [5] and 2-alkyl-*N*-biphenyl fused imidazoles as angiotensin II receptor antagonists [6,7], it was our interest to prepare the title compounds as potential antagonists of the angiotensin II receptor. The synthesis of the desired ethyl 2-alkylthio-1-substituted-benzyl-pyrrolo[2,3,*d*]imidazole-5-carboxylates (**7**) was accomplished according to Scheme 1.

The starting 5-hydroxymethyl-2-mercapto-1-substituted-benzylimidazoles (**1**) could be obtained from benzylation of 2-mercapto-5-formylimidazole according to the procedure reported previously [8]; however, this reaction would give a mixture of two compounds. Therefore, we have decided to use a direct method for the preparation of **1**. Reaction of 1,3-dihydroxyacetone, potassium thiocyanate and substituted-benzylamine hydrochlorides in acetic acid gave **1** [4]. Alkylation of **1** with alkyl halides afforded 2-alkylthio-5-hydroxymethyl-1-substituted benzylimidazoles (**2**) [9,10]. Oxidation of **2** with manganese dioxide [11] gave 2-alkylthio-5-formyl-1-substituted-benzylimidazoles (**3**). Condensation of **3** with ethyl azidoacetate at -30 °C, according to the procedure reported previously gave ethyl α-azido-β-hydroxy-β-(2-alkylthio-1-sub-

Scheme 1



	R	R'		R	R'
a	COOEt (or COOH)	Me	**d**	OCH_3	Me
b	COOEt (or COOH)	Et	**e**	OCH_3	Et
c	COOEt (or COOH)	*n*-Pr	**f**	OCH_3	*n*-Pr

stituted-benzylimidazol-5-yl)propionates (**5**) [12] as mixtures of threo and erythro isomers.

The structures of **5** were confirmed by ^{1}H-nmr. The α-hydrogen appeared at 4.87-4.89 and 4.98-5.01 ppm as two doublets for the erythro and threo isomers (J=7.2 Hz and J=4.8 Hz).

The reaction of **5** with thionyl chloride in triethylamine yielded the desired ethyl α-azido-β-(2-alkylthio-1-substituted-benzylimidazol-5-yl)acrylates (**4**)[14]. Alternatively, **4** could be obtained from condensation of **3** with ethyl azidoacetate at zero degree [13]. Compounds **4a-c** (R=COOEt) were a mixture of *E* and *Z* isomers (Scheme 1).

The ^{1}H-nmr spectra of compounds **4a-c** are in agreement with the suggested structure. The CH_2 benzylic protons appeared as two singlets at 5.56-5.59 and 5.20-5.24 ppm for the *E* and *Z* isomers. In addition, the β vinylic proton of **4** appeared as a singlet at 6.52-6.66 ppm. This value is similar to the one reported previously [13].

In the case of compounds **3a-c** (R=COOH), before condensation with ethyl azidoacetate, the carboxylic acids were estrified with ethanol and sulfuric acid. Under the latter conditions, in addition to the conversion of the carboxylic acids to the corresponding ethyl esters, the aldehydes were converted to diethylacetals **6a-c**.

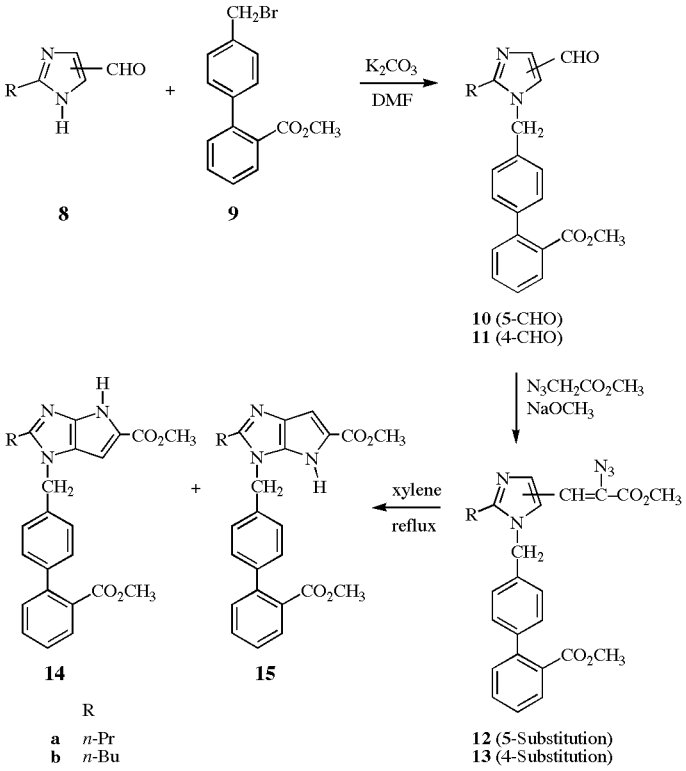
The ^{1}H-nmr spectra of **6** were in agreement with the suggested structure. The CH of acetal appeared as a singlet at 5.27 ppm. Compounds **6a-c** were hydrolyzed to compounds **3a-c** (R=COOEt) in aqueous acid.

Cyclization of **4** to the desired pyrrolo[2,3-*d*]imidazoles **7** was accomplished *via* heating in xylene.

Methyl substituted-pyrrolo[2,3-*d*]imidazole-5-carboxylates (**14**) and methyl substituted-pyrrolo[3,2-*d*]imidazole-5-carboxylates (**15**) were prepared according to Scheme 2.

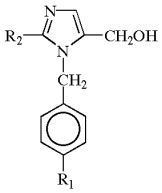
Alkylation [14] of 2-alkyl-4 (or 5)-formylimidazoles (**8**)[15,16] with methyl 4'-bromomethylbiphenyl-2-carboxylate (**9**)[17] gave a 30:70 mixture of 2-alkyl-1-[(2'-carbomethoxylbiphenyl-4-yl)methyl]-5-formylimidazoles (**10**) and 2-alkyl-1-[(2'-carbomethoxybiphenyl-4-yl)methyl]-4-formylimidazoles (**11**) respectively. These compounds were separated by column chromatography on silica gel.

Scheme 2



The structures of compounds **10** and **11** were confirmed by ^{1}H-nmr. The N-CH_2 resonance of **10** (5.6 ppm) is more deshielded than that of **11** (5.15 ppm). In addition, ^{1}H-nmr spectral data of **10** were similar to previously reported data [8].

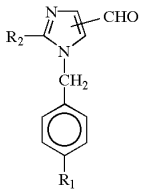
Table 1



Comp.	R_1	R_2	mp, °C [a]	Yield	Formula [b]	Calcd C%	Found C%	Calcd H%	Found H%	Calcd N%	Found N%
2a	COOH	SMe	168-171	89	$C_{13}H_{14}N_2O_3S$	56.12	55.88	5.03	5.07	10.07	10.43
2b	COOH	SEt	164-166	86	$C_{14}H_{16}N_2O_3S$	57.53	57.80	5.48	5.13	9.59	9.26
2c	COOH	SPr	140-142	82	$C_{15}H_{18}N_2O_3S$	58.82	58.52	5.88	6.13	9.15	8.79
2d	OCH_3	SMe	127-128	91	$C_{13}H_{16}N_2O_2S$	59.10	59.54	6.06	5.70	10.61	10.22
2e	OCH_3	SEt	99-101	89	$C_{14}H_{18}N_2O_2S$	60.43	60.85	6.47	6.20	10.07	9.81
2f	OCH_3	SPr	57-58	94	$C_{15}H_{20}N_2O_2S$	61.64	61.80	6.85	6.52	9.59	9.87

[a] All compounds were crystallized from ether. [b] Microanalytical analyses were within ±0.4% of theoretical values, except for compounds **2d**: C +0.44% and **2e**: C +0.42%.

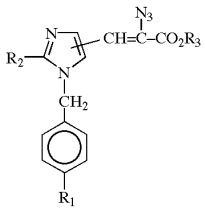
Table 2



Comp.	R_1	R_2	Substitution	mp, °C [a]	Yield	Formula	Calcd C%	Found C%	Calcd H%	Found H%	Calcd N%	Found N%
3a	COOH	SMe	5-yl	176-177	89	$C_{13}H_{12}N_2O_3S$	56.52	56.79	4.35	4.11	10.15	9.85
3b	COOH	SEt	5-yl	164-166	90	$C_{14}H_{14}N_2O_3S$	57.93	58.26	4.83	4.53	9.66	9.29
3c	COOH	SPr	5-yl	148-150	91	$C_{15}H_{16}N_2O_3S$	59.22	58.91	5.26	5.02	9.21	8.88
3d	OCH_3	SMe	5-yl	77-79	91	$C_{13}H_{14}N_2O_2S$	59.54	59.27	5.34	5.50	10.69	10.43
3e	OCH_3	SEt	5-yl	Oil	92	$C_{14}H_{16}N_2O_2S$	60.87	60.56	5.80	5.59	10.15	10.41
3f	OCH_3	SPr	5-yl	Oil	95	$C_{15}H_{18}N_2O_2S$	62.07	61.80	6.21	5.93	9.66	9.32
10a	Phenyl-2'-CO_2Me	Pr	5-yl	Oil	27	$C_{22}H_{22}N_2O_3$	72.93	73.15	6.08	6.02	7.73	7.61
10b	Phenyl-2'-CO_2Me	Bu	5-yl	Oil	23	$C_{23}H_{24}N_2O_3$	73.40	73.63	6.38	6.52	7.45	7.30
11a	Phenyl-2'-CO_2Me	Pr	4-yl	Oil	52	$C_{22}H_{22}N_2O_3$	72.93	72.67	6.08	5.99	7.73	7.59
11b	Phenyl-2'-CO_2Me	Bu	4-yl	Oil	48	$C_{23}H_{24}N_2O_3$	73.40	73.05	6.38	6.31	7.45	7.34

[a] Unless otherwise mentioned the compound was crystallized from ether.

Table 3



Comp.	R_1	R_2	R_3	Substitution	mp, °C	Yield	Formula	Calcd C%	Found C%	Calcd H%	Found H%	Calcd N%	Found N%
4a	COOEt	SMe	Et	5-yl	Oil	51	$C_{19}H_{21}N_5O_4S$	54.94	55.19	5.06	5.31	16.87	16.60
4b	COOEt	SEt	Et	5-yl	Oil	60	$C_{20}H_{23}N_5O_4S$	55.94	56.19	5.36	5.66	16.32	16.08
4c	COOEt	SPr	Et	5-yl	Oil	63	$C_{21}H_{25}N_5O_4S$	56.89	56.61	5.64	5.88	15.80	15.54
4d	OCH_3	SMe	Et	5-yl	61-63	59	$C_{17}H_{19}N_5O_3S$	54.69	54.92	5.09	4.87	18.77	18.50
4e	OCH_3	SEt	Et	5-yl	Oil	61	$C_{18}H_{21}N_5O_3S$	55.81	56.07	5.43	5.20	18.09	18.35
4f	OCH_3	SPr	Et	5-yl	Oil	59	$C_{19}H_{23}N_5O_3S$	56.86	57.04	5.74	5.41	17.46	17.19
12a	Phenyl-2'-CO_2Me	Pr	Me	5-yl	Oil	40	$C_{25}H_{25}N_5O_4$	65.36	64.99	5.45	5.37	15.25	15.50
12b	Phenyl-2'-CO_2Me	Bu	Me	5-yl	Oil	42	$C_{26}H_{27}N_5O_4$	65.96	65.63	5.71	5.83	14.80	14.52
13a	Phenyl-2'-CO_2Me	Pr	Me	4-yl	Oil	40	$C_{25}H_{25}N_5O_4$	65.36	65.11	5.45	5.29	15.25	14.98
13b	Phenyl-2'-CO_2Me	Bu	Me	4-yl	Oil	40	$C_{26}H_{27}N_5O_4$	65.96	66.23	5.71	5.55	14.80	15.05

Condensation of compounds **10** and **11** with methyl azidoacetate under the condition reported above, afforded methyl α-azido-β-[1-(2'-carbomethoxybiphenyl-4-yl)methyl]-2-alkyl-5-imidazolyl]acrylates (**12**) and methyl α-azido-β-[1-(2'-carbomethoxybiphenyl-4-yl)methyl]-2-alkyl-4-imidazolyl]acrylates (**13**).

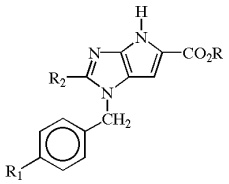
Cyclization of compounds **12** and **13** to the desired compounds **14** and **15** was accomplished through heating in xylene.

The structures of all compounds were confirmed by elemental analysis, ir, nmr and mass spectroscopy. The physical constants of compounds prepared are summarized in Tables 1 to 4.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. The ir spectra were obtained using a Perkin-Elmer Model 781 or Nicolet FT-IR Magna 550 spectrographs. The ^{1}H-nmr spectra were obtained on a Bruker FT-80 spectrometer and chemical shifts (δ) are in ppm relative to internal tetramethylsilane. Mass spectra were obtained on a Finnigan MAT TSQ 70 spectrometer at 70 eV.

Table 4



Comp.	R_1	R_2	R_3	mp, °C[a]	Yield	Formula	Calcd C%	Found C%	Calcd H%	Found H%	Calcd N%	Found N%
7a	COOEt	SMe	Et	109-111	42	$C_{19}H_{21}N_3O_4S$	58.92	59.18	5.43	5.23	10.85	10.56
7b	COOEt	SEt	Et	111-113	44	$C_{20}H_{23}N_3O_4S$	59.85	59.59	5.74	5.96	10.47	10.68
7c	COOEt	SPr	Et	81-83	40	$C_{21}H_{25}N_3O_4S$	60.72	60.97	6.02	6.29	10.12	9.86
7d	OCH_3	SMe	Et	132-134	45	$C_{17}H_{19}N_3O_3S$	59.13	59.37	5.51	5.79	12.17	12.37
7e	OCH_3	SEt	Et	136-138	51	$C_{18}H_{21}N_3O_3S$	60.17	60.41	5.85	6.06	11.70	11.45
7f	OCH_3	SPr	Et	110-112	49	$C_{19}H_{23}N_3O_3S$	61.13	60.88	6.17	5.90	11.26	11.03

[a] All compounds were crystallized from ether.

5-Hydroxymethyl-2-mercapto-1-substitutedbenzylimidazoles (**1**).

A mixture of the substituted benzylamine hydrochloride (40 mmoles), dihydroxy- acetone dimer (3.06 g, 17 mmoles), potassium thiocyanate (5.19 g, 53 mmoles), 1-butanol (25 ml) and glacial acetic acid (4 ml) was stirred for 72 hours. The suspension was diluted with water and filtered. The precipitate was washed with water (3×30 ml) to give compounds **1**.

1-(4-Carboxybenzyl)-5-hydroxymethyl-2-mercaptoimidazole (**1**, R=COOH).

This compound was obtained as a white powder in 72% yield, mp 241-243 °C; ^{1}H-nmr (dimethylsulfoxide–d_6): δ 12.17 (bs, 1H, SH),7.89 (d, 2H, aromatic, J=8Hz), 7.29 (d, 2H, aromatic, J=8Hz), 6.68 (s, 1H, H-C_4 imidazole), 5.38 (s, 2H, NCH_2), 4.15 ppm (s, 2H, CH_2O); ms: m/z (%) 264 (M^+, 87), 246 (35), 213 (21), 201 (28), 135 (100), 129 (34), 107 (71), 98 (26), 57 (25).

Anal. Calcd. for $C_{12}H_{12}N_2O_3S$: C, 54.54; H, 4.55; N, 10.61; Found: C, 54.29; H, 4.71; N, 10.88.

5-Hydroxymethyl-2-mercapto-1-(4-methoxybenzyl)imidazole (**1**, R=OCH_3).

This compound was obtained as a white powder in 74% yield, mp 194-196 °C; ^{1}H-nmr (deuteriochloroform): δ 12.08 (bs, 1H, SH), 7.23 (d, 2H, aromatic, J=8Hz), 6.87 (d, 2H, aromatic, J=8Hz), 6.82 (s, 1H, H-C_4 imidazole), 5.25 (s, 2H, NCH_2), 4.16 (s, 2H, CH_2O), 3.73 ppm (s, 3H, OCH_3); ms: m/z (%) 250 (M^+, 63), 121 (100), 91 (50), 77 (62), 65 (17), 58 (18).

Anal. Calcd. for $C_{12}H_{14}N_2O_2S$: C, 57.60; H, 5.60; N, 11.20. Found: C, 57.83; H, 5.28; N, 11.15.

1-(4-Carboxybenzyl)-5-hydroxymethyl-2-methylthioimidazole (**2a**).

Compound **1** (R=COOH, 3 g, 11.43 mmoles) was dissolved in a minimum quantity of water and the solution was basified with a solution of 20% aqueous sodium hydroxide. Methyl iodide (1.89 g, 13.38 mmoles) was added to the stirring solution. The stirring was continued for 6 hours. The pH of the solution was brought to 7 with dilute hydrochloric acid and was extracted with ethyl acetate. The organic layer was washed with brine, dried (sodium sulfate) and evaporated under reduced pressure. The residue was crystallized from ether to give 2.83 g (89%) of compound **2a** as a pale yellow solid, mp 168-171 °C. ^{1}H-nmr (dimethylsulfoxide-d_6): δ 7.91 (d, 2H, aromatic, J=8Hz), 7.16 (d, 2H, aromatic, J=8Hz), 6.96 (s, 1H, H-C_4 imidazole), 5.29 (s, 2H, NCH_2), 4.34 (s, 2H, CH_2O), 2.44 ppm (s, 3H, CH_3); ms: m/z (%) 278 (M^+, 17), 263 (22), 249 (46), 135 (100), 109 (78), 76 (25).

Anal. Calcd. for $C_{13}H_{14}N_2O_3S$: C, 56.12; H, 5.03; N, 10.07. Found: C, 55.88; H, 5.07; N, 10.43.

Compounds **2b** and **2c** were prepared similarly (Table 1).

5-Hydroxymethyl-1-(4-methoxybenzyl)-2-methylthioimidazole (**2d**).

Compound **1** (R=OCH_3, 2.85 g, 11.43 mmoles) was dissolved in a minimum quantitiy of water and the solution was basified with a solution of 20% aqueous sodium hydroxide. Methyl iodide (1.89 g, 13.38 mmoles) was added to the stirring solution. The stirring was continued for 6 hours. The precipitate was isolated by filtration, washed with water and crystallized from ether to give 2.74 g (91%) of compound **2d** as a white solid, mp 127-128 °C; ^{1}H-nmr (deuteriochloroform): δ 7.04 (d, 2H, aromatic, J=8Hz), 6.88 (s, 1H, H-C_4 imidazole), 6.81 (d, 2H, aromatic, J=8Hz), 5.19 (s, 2H, NCH_2), 4.45 (s, 2H, CH_2O), 3.77 (s, 3H, OCH_3), 2.82 (bs, 1H, OH), 2.52 ppm (s, 3H, SCH_3); ms: m/z (%) 264 (M^+, 100), 247 (10), 121 (100), 78 (17).

Anal. Calcd. for $C_{13}H_{16}N_2O_2S$: C, 59.10; H, 6.06; N, 10.61. Found: C, 59.54; H, 5.70; N, 10.22.

Compounds **2e** and **2f** were prepared similarly (Table 1).

1-(4-Carboxybenzyl)-5-formyl-2-methylthioimidazole (**3a**).

A stirred suspension of compound **2a** (2.78 g, 10 mmoles) and activated manganese dioxide (4.35 g, 50 mmoles) in chloroform (40 ml) was refluxed for 12 hours. The reaction mixture was cooled to room temperature and filtered. The chloroform was evaporated and the residue was crystallized from ether-petroleum ether to give 2.6 g (89%) of compound **3a** as a pale yellow solid; mp 176-177 °C; ^{1}H-nmr (deuteriochloroform): δ 9.60 (s, 1H, CHO), 8.02 (s, 1H, H-C_4 imidazole), 7.90 (d, 2H, aromatic, J=8Hz), 7.18 (d, 2H, aromatic, J=8Hz), 5.53 (s, 2H, NCH_2), 2.64 ppm (s, 3H, SCH_3); ms: m/z (%) 276 (M^+, 25), 135 (54), 107 (100), 89 (47), 77 (55), 63 (26), 45 (56).

Anal. Calcd. for $C_{13}H_{12}N_2O_3S$: C, 56.52; H, 4.35; N, 10.15. Found: C, 56.79; H, 4.11; N, 9.85.

Compounds **3b-3f** were prepared similarly (Table 2).

Ethyl 2-Azido-3-[1-(4-ethoxycarbonylbenzyl)-2-methylthioimidazol-5-yl]arcrylate (**4a**, R=COOEt).

To a stirred solution of sodium (0.46 g, 20 mmoles) in absolute ethanol (20 ml) at 0 °C was added dropwise a solution of compound **3a** (1.50 g, 4.93 mmoles) and ethyl azidoacetate (2.58 g , 20 mmoles) in absolute ethanol (10 ml). The reaction mixture was stirred for 2.5 hours, poured into a cold solution of saturated ammonium chloride (80 ml) and extracted with diethyl ether. The organic layer was washed with brine, dried (sodium sulfate) and evaporated to dryness under reduced pressure. The residue was purified by column chromatography (silica gel, chloroform as eluent) to give 1.04 g (51%) of compound **4a** as an colorless oil as a mixture of *Z* and *E* isomers; ir (chloroform): ν 2129 (N_3), 1712 cm^{-1} (C=O); ^{1}H-nmr (deuteriochloroform): δ 7.98 (m, 2H, aromatic), 7.79 (s, 1H, H-C_4 imidazole), 7.20 (m, 2H, aromatic), 6.52 (s, 1H, =CH), 5.56 & 5.20 (2s, 2H, NCH_2), 4.30 (m, 4H, OCH_2), 2.66 (s, 3H, SCH_3), 1.33 ppm (m, 6H, OCH_2CH_3); ms: m/z (%) 387 (M^+-N_2, 3), 303 (25), 271 (21), 185 (58), 163 (100), 135 (71), 107 (64), 90 (33).

Anal. Calcd. for $C_{19}H_{21}N_5O_4S$: C, 54.94; H, 5.06; N, 16.87. Found: C, 55.19; H, 5.31; N, 16.60.

Compounds **4b-4f** were prepared similarly (Table 3).

Ethyl α-Azido-β-hydroxy-β-[1-(4-methoxybenzyl)-2-methylthioimidazol-5-yl]propionate (**5d**).

To a stirred solution of sodium (0.46 g , 20 mmoles) in absolute ethanol (20 ml) at –30 °C was added dropwise a solution of compound **3d** (1.29 g, 4.93 mmoles) and ethyl azidoacetate (2.58 g, 20 mmoles) in absolute ethanol (10 ml). The reaction mixture was stirred for 2.5 hours. It was poured into a cold solution of saturated ammonium chloride (80 ml) and was extracted with diethyl ether. The organic layer was washed with brine, dried (sodium sulfate) and evaporated to dryness under reduced pressure. The residue was purified by column chromatography (silica gel, chloroform as eluent) to give 1.27 g of **5d** as an colorless oil (66%) as a mixture of *erythro* and *threo* isomers; ir (chloroform): ν 3476 (OH), 2119 (N_3), 1740 cm^{-1}(C=O); ^{1}H-nmr (deuteriochloroform): δ 6.96 (s, 1H, H-C_4 imidazole), 7.00 (d, 2H, aromatic, J=8Hz), 6.81 (d, 2H, aromatic, J=8Hz), 5.20 (s, 2H, NCH_2), 5.01 & 4.89 (2d, 1H, H-C_β, J=4.8 Hz & J= 7.2Hz), 4.18 (m, 3H, OCH_2 & H-C_α), 3.77 (s, 3H, OCH_3), 2.50 (s, 3H, SCH_3), 1.24 (t, 3H, OCH_2CH_3); ms: m/z (%) 391 (M^+,12), 263 (100), 121 (21).

Anal. Calcd. for $C_{17}H_{21}N_5O_4S$: C, 52.17; H, 5.37; N, 17.90.Found: C, 52.36; H, 5.02; N, 18.14.

Ethyl α-Azido-β-hydroxy-β-[2-ethylthio-1-(4-methoxybenzyl)-imidazol-5-yl]propionate (**5e**).

This compound was prepared similarly, ir (chloroform): ν 3483 (OH), 2115 (N_3), 1744 cm^{-1} (C=O); ^{1}H-nmr (deuteriochloroform): δ 7.08 (s, 1H, H-C_4 imidazole), 6.99 (d, 2H, aromatic, J=8Hz), 6.81 (d, 2H, aromatic, J=8Hz), 5.24 (s, 2H, NCH_2), 4.99 & 4.88 (2d, 1H, H-C_β, J=4.8 Hz & J=7.2 Hz), 4.17 (m, 3H, OCH_2 & H-C_α), 3.77 (s, 3H, OCH_3), 3.05 (q, 2H, SCH_2), 1.33 (t, 3H, OCH_2CH_3), 1.20 (t, 3H, SCH_2CH_3); ms: m/z (%) 405 (M^+, 10), 277 (100), 121 (19).

Anal. Calcd. for $C_{18}H_{23}N_5O_4S$: C, 53.33; H, 5.68; N, 17.28. Found: C, 53.14; H, 5.41; N, 17.08.

5-Formyl-1-(4-carbethoxybenzyl)-2-methylthioimidazole Diethylacetal (**6a**).

To a solution of compound **3a** (1.75 g, 6.34 mmoles) in absolute ethanol (20 ml) was slowly added concentrated sulfuric acid (1.5 ml). The solution was refluxed for 12 hours. The ethanol was evaporated. The residue was dissolved in chloroform (20 ml) and washed with a solution of 50% aqueous sodium bicarbonate (3×30 ml). The organic layer was dried (sodium sulfate) and concentrated to give 1.38 g (58%) of compound **6a** as an colorless oil; ^{1}H-nmr (deuteriochloroform): δ 7.99 (d, 2H, aromatic, J=8Hz), 7.79 (s, 1H, H-C_4 imidazole), 7.21 (d, 2H, aromatic, J=8Hz), 5.33 (s, 2H, NCH_2), 5.27 (s, 1H, CH), 4.36 (q, 2H, OCH_2), 3.49 (m, 4H, OCH_2), 2.54 (s, 3H, SCH_3), 1.36 (t, 3H, OCH_2CH_3), 1.09 (t, 6H, OCH_2CH_3); ms: m/z (%) 378 (M^+, 23), 288 (43), 163 (100), 135 (36), 90 (21).

Anal. Calcd. for $C_{19}H_{26}N_2O_4S$: C, 60.32; H, 6.88; N, 7.41 .Found: C, 60.43; H, 6.90; N, 7.63.

Ethyl 1-(4-Ethoxycarbonylbenzyl)-2-methylthiopyrrolo[2,3-*d*]-imidazole-5-carboxylate (**7a**).

A solution of compound **4a** (1 g, 2.41 mmoles) in xylene (20 ml) was added to boiling xylene (100 ml). The reaction mixture was refluxed for 2 hours. The solvent was evaporated and the residue was purified by column chromatography (silica gel, chloroform-ethyl acetate, 1:1 as eluent) to give 0.39 g (42%) of compound **7a** as a white solid, mp 109-111 °C (ether); ir (potassium bromide): ν 3151 (NH), 1699 cm^{-1} (C=O); ^{1}H-nmr (deuteriochloroform): δ 9.05 (bs, 1H, NH), 8.02 (d, 2H, aromatic, J= 8Hz), 7.27 (d, 2H, aromatic, J=8Hz), 6.41 (s, 1H, HC pyrrole), 5.23 (s, 2H, N-CH_2), 4.33 (m, 4H, OCH_2), 2.68 (s, 3H, SCH_3), 1.43 (t, 3H, OCH_2CH_3), 1.27 ppm (t, 3H, OCH_2CH_3); ms: m/z (%) 387 (M^+, 100), 224 (63), 178 (100), 163 (78), 135 (25), 107 (36), 90 (25).

Anal. Calcd. for $C_{19}H_{21}N_3O_4S$: C, 58.92; H, 5.43; N, 10.85.Found: C, 59.18; H, 5.23; N, 10.56.

Compounds **7b-7f** were prepared similarly (Table 4).

2-(*n*-Propyl)-1-[(2'-carbomethoxybiphenyl-4-yl)methyl]imidazole-5-carboxaldehyde (**10a**) and 2-(*n*-Propyl)-1-[(2'-carbomethoxybiphenyl-4-yl)methyl] imidazole-4-carboxaldehyde (**11a**).

A solution of **8a** (2.42 g, 17.5 mmoles), **9** (5.88 g, 19.3 mmoles), potassium carbonate (4.83 g, 35 mmoles) and dimethylformamide (100 ml) was stirred at 25 °C for 24 hours. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was diluted with water, and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated. Column chromatography on silica gel (petroleum ether-ethyl acetate, 70:30 and then 10:90 as eluent) afforded respectively 1.71 g (27%) of **10a** and 3.30 g (52%) of **11a** as pale yellow oils.

Compound **10a** has ir (sodium chloride disk): ν 2960 (CH, CHO), 1725 (C=O, ester), 1670 cm^{-1} (C=O, CHO); ^{1}H-nmr(deuteriochloroform): δ 9.70 (s, 1H, CHO), 7.90 (d, 1H, aromatic, J=8Hz), 7.84 (s, 1H, HC_4 imidazole), 7.50-7.10 (m, 7H, aromatic), 5.65 (s, 2H, NCH_2), 3.65 (s, 3H, OCH_3), 2.70 (t, 2H, CH_2, J=7.4 Hz), 1.80-1.50 (m, 2H, CH_2), 1.00 ppm (t, 3H, CH_3, J=7.4 Hz)

Anal. Calcd. for $C_{22}H_{22}N_2O_3$: C, 72.93; H, 6.08; N, 7.73. Found: C, 73.15; H, 6.02; N, 7.61.

Compound **11a** has ir (sodium chloride disk): ν 2960 (CH, CHO), 1720 (C=O, ester), 1680 cm^{-1} (C=O, CHO); ^{1}H-nmr (deuteriochloroform): δ 9.84 (s, 1H, CHO), 7.92 (d, 1H, aromatic J=8Hz), 7.58 (s, 1H, HC_5 imidazole), 7.50-7.10 (m, 7H, aromatic), 5.15 (s, 2H, NCH_2), 3.70 (s, 3H, OCH_3), 2.75 (t, 2H, CH_2, J=7.4 Hz), 1.80-1.40 (m, 2H, CH_2), 1.00 ppm (t, 3H, CH_3, J=7.4 Hz).

Anal. Calcd. for $C_{22}H_{22}N_2O_3$: C, 72.93; H,6.08; N, 7.73. Found: C, 72.67; H, 5.99; N, 7.59.

Compounds **10b** and **11b** were prepared similarly (Table 2).

Methyl α-Azido-β-[1-[(2'-carbomethoxybiphenyl-4-yl)methyl]-2-propylimidazol-5-yl]acrylate (**12a**).

To a stirred solution of sodium (0.46 g, 20 mmoles) in absolute methanol (8 ml) at -15 °C was added dropwise a solution of **10a** (1.8 g, 5 mmoles) and methyl azido acetate (1.3 g, 20 mmoles) in absolute methanol (4 ml). After two hours at -15 °C, the mixture was added to a saturated solution of ammonium chloride. The mixture was extracted with ether. The organic layer was washed once with water and dried (anhydrous sodium sulfate). The ether was evaporated and the residue was purified by column chromatography on silica gel (petroleum ether-chloroform; 80:20 as eluent) to give 0.9 g (40%) of **12a** as an pale yellow oil. ir (sodium chloride disk): ν 2120 (N_3), 1720 (C=O, esters), 1620 cm^{-1} (C=C); ^{1}H-nmr (deuteriochloroform): δ 8.00 (s, 1H, HC_4 imidazole), 7.92 (d, 1H, aromatic, J=8 Hz), 7.50-7.10 (m, 7H, aromatic), 6.74 (s, 1H, H_β), 5.25 (s, 2H, NCH_2), 3.85 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 2.72 (t, 2H, CH_2, J=7.4 Hz), 1.90-1.50 (m, 2H, CH_2), 1.00 ppm (t, 3H, CH3, J=7.4 Hz).

Anal. Calcd. fo\r $C_{25}H_{25}N_5O_4$: C, 65.36; H, 5.45; N, 15.25. Found: C, 64.99; H, 5.37; N, 15.50.

Compounds **12b** and **13a,b** were prepared similarly (Table 3).

Methyl 2-(*n*-Propyl)-1-[(2'-carbomethoxybiphenyl-4-yl)methyl]-pyrrolo[2,3-*d*]imidazole-5-carboxylate (**14a**).

A solution of **12a** (2.8 g, 6.1 mmoles) in xylene (40 ml) was refluxed for 2 hours. The solvent was evaporated and the residue was purified by column chromatography on silica gel (petroleum ether-chloroform 50:50) and then it was crystallized from diethyl ether to give 0.84 g (32%) of **14a** as a white solid, mp188-190 °C; ir (potassium bromide): ν 3380 (NH), 1730 (C=O), 1690 cm^{-1} (C=O); ^{1}H-nmr (deuteriochloroform): δ 10.61 (bs, 1H, NH), 7.85 (d, 1H, aromatic, J=8 Hz), 7.50-7.20 (m, 7H, aromatic): 6.32 (s, 1H, HC pyrrole), 5.31 (s, 2H, NCH_2), 3.83 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 2.81 (t, 2H, CH_2, J=7.4 Hz), 1.90-1.50 (m, 2H, CH_2), 1.00 ppm (t, 3H, CH_3, J=7.4 Hz); ms: m/z (%) 431 (M^+, 14), 225 (100), 165 (50), 152 (11).

Anal. Calcd. for $C_{25}H_{25}N_3O_4$: C, 69.60; H, 5.80; N, 9.74. Found: C, 69.37; H, 5.69; N, 9.92.

Methyl 2-(*n*-Pyropyl)-1-[2'-carbomethoxybiphenyl-4-yl)-methyl]pyrrolo[3,2-*d*]imidazole-5-carboxylate (**15a**).

This compound was prepared in a similar fashion to **14a** affording **15a** as a white solid in 39% yield; mp 196-198 °C; ir (potassium bromide): ν 3280 (NH), 1720 (C=O), 1645 cm^{-1} (C=O); ^{1}H-nmr (deuteriochloroform): δ 11.40 (bs, 1H, NH), 7.72 (d, 1H, aromatic, J=8Hz) 7.50-7.10 (m, 7H, aromatic), 6.84 (s, 1H, HC pyrrole), 5.25 (s, 2H, NCH_2), 3.75 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 2.71 (t, 2H, CH_2, J=7.4 Hz), 1.90-1.50 (m, 2H, CH_2), 0.95 ppm (t, 3H, CH_3, J=7.4 Hz); ms: m/z (%) 431 (M^+, 8), 225 (100), 165 (54), 152 (13).

Anal. Calcd. for $C_{25}H_{25}N_3O_4$: C, 69.60; H, 5.80; N, 9.74. Found: C, 69.23; H, 5.97; N, 9.93.

Methyl 2-(*n*-Butyl)-1-[(2'-carbomethoxybiphenyl-4-yl)methyl]-pyrrolo[2,3-*d*]imidazole-5-carboxylate (**14b**).

This compound was prepared in a similar fashion to **14a** affording **14b** as a white solid in 32% yield; mp 174-175 °C; ir (potassium bromide): ν 3380 (NH), 1715 (C=O), 1700 cm^{-1} (C=O); ^{1}H-nmr (deuteriochloroform): δ 9.85 (bs, 1H, NH), 7.85 (d, 1H, aromatic, J=8 Hz), 7.50-7.20 (m, 7H, aromatic), 6.44 (s, 1H, HC pyrrole), 5.25 (s, 2H, NCH_2), 3.83 (s, 3H, OCH_3) 3.61 (s, 3H, OCH_3), 2.93 (t, 2H,CH_2, J=7.4 Hz), 2.10-1.70 (m, 2H, CH_2), 1.60-1.30 (m, 2H, CH_2), 0.90 ppm (t, 3H, CH_3, J=7.2 Hz); ms: m/z (%) 445 (M^+, 14), 225 (100), 178 (83), 165 (46), 152 (11), 44 (17).

Anal. Calcd. for $C_{26}H_{27}N_3O_4$: C, 70.11; H, 6.07; N, 9.44; Found: C, 69.71; H, 6.28; N, 9.67.

Methyl 2-(*n*-Butyl)-1-[(2'-carbomethoxybiphenyl-4-yl)methyl]-pyrrolo[3,2-*d*]imidazole-5-carboxylate (**15b**).

This compound was prepared in a similar fashion to **14a** affording **15b** as a white solid in 35% yield; mp 187-188 °C; ir (potassium bromide): ν 3280 (NH), 1725 (C=O), 1650 cm^{-1} (C=O); ^{1}H-nmr (deuteriochloroform): δ 9.15 (bs, 1H, NH), 7.85 (d, 1H, aromatic J=8 Hz), 7.50-7.20 (m, 7H, aromatic), 6.92 (s, 1H, HC pyrrole), 5.23 (s, 2H, NCH_2), 3.77 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3),2.83 (t, 2H, CH_2, J=7.4 Hz), 2.10-1.70 (m, 2H, CH_2), 1.65-1.35 (m, 2H, CH_2), 0.95 ppm (t, 3H, CH_3, J=7.2 Hz); ms: m/z (%) 445 (M^+, 6), 225 (100), 178 (92), 165 (46), 97 (7).

Anal. Calcd. for $C_{26}H_{27}N_3O_4$: C, 70.11; H, 6.07; N, 9.44. Found: C, 69.81; H, 6.29; N, 9.27.

Acknowledgements.

This work was supported by grants from the Research Council of Tehran University of Medical Sciences and the International Organization for Chemical Sciences in Development (IOCD).

REFERENCES AND NOTES

[1] H. Yanagisawa, Y. Amemiya, T. Kanazaki, Y. Shimajy, K. Fujimoto, Y. Kitahara, T. Sada, M. Mizuno, M. Ikeda, S. Migamoto, Y. Furukawa and H. Koike, *J. Med. Chem*., **39**, 323 (1996).

[2] C. Almansa, L. A. Gomes, F. L. Gavalcanti, A. F. de Arriba, J. Garcia-Rafanell and J. Forn, *J. Med. Chem*., **40**, 547 (1997).

[3] R. M. Keenan, J. Weinstock, J. A. Finkelstein, R. G. Franz, D. E. Gaitanopoulos, G. R. Girard, D. T. Hill, T. M. Morgan, J. M. Samanen, C. E. Peishoff, L. M. Tucker, N. Aiyar,E. Griffin, E. H. Ohlstein, E. J. Stack, E. F. Weidley and R. M. Edwards, *J. Med. Chem*., **36**, 1880 (1993).

[4] J. V. Duncia, A. T. Chiu, D. J. Carini, G. B. Gregory, A. L. Johnson, W. A. Price, G. J. Wells, P.C. Wong, J.C. Calabrese and P.B.M.W.M. Timmermans, *J. Med. Chem.*, **33**, 1312 (1990).

[5] M. Fortin, D. Frechet, G. Hamon,S. Jouquey, J.P. Veven; Eur. Pat. Appl. Ep 461, 040 (1991), *Chem. Abstr*. **116**; 151760n (1992).

[6] N. B. Mantlo, P. K. Chakravarty, D. L. Ondeyka, P. K. S. Sieg, R. S. Chang, V. J. Lotti, K. A. Faust, T. B.Chen, T. W. Schorn, C. S. Sweet, S. E.Emmert, A. A.Patchett, W. J.Greenlee, *J. Med. Chem*. **34**, 2919 (1991).

[7] A. P. Thomas, C. P. Allott, K. H. Gibson, J. S. Major, B. B. Masek, A. A. Oldham, A. H. Ratcliffe, D. A. Roberts, S. T. Russell, and D. A. Thomason, *J. Med. Chem*. **35**, 877 (1992).

[8] A. Shafiee, F. Hadizadeh and A. Foroumadi, *Ind. J. Chem*., **36B**, 813 (1997).

[9] A. Shafiee, T. Akbarzadeh, A. Foroumadi, F. Hadizadeh, *J. Heterocyclic Chem*., **35**, 141 (1998).

[10] D. J. Carini and J. V. Duncia, Eur. Pat. Appl. Ep 253, 310 (1988); *Chem. Abstr*., **109**, 129008 g (1988).

[11] A. Shafiee and F. Hadizadeh, *J. Heterocyclic Chem*., **34**, 549 (1997).

[12] Y. Murakami, T. Watanobe, H. Suzuki, N. Kotake, T. Takahashi, K. Togonary, M. Ohno, K. Takase, T. Suzuki and K. Kondo, *Chem. Pharm. Bull*., **45**, 1739 (1997).

[13] A. Shafiee, A. Mazloumi and V. I. Cohen, *J. Heterocyclic Chem*., **16**, 1563 (1979).

[14] S. C. Shilcrat, M. K. Mokhallalati, J. M. D. Fortunak, and L. N. Pridgen, *J. Org. Chem*. **62**, 8449 (1997).

[15] I. Sircar, G. Bobowski, J. A. Bristol, R. E. Weishaar and D. B. Evans, *J. Med. Chem*., **29,** 261 (1986).

[16] S. P. Watson, *Synthetic Communications*, **22**, 2971 (1992).

[17] D. J. Carini, J. V. Duncia, P. E. Aldrich, A. T. Chiu, A. L. Johnson, M. E. Pierce, W. A. Price, J. B. Santella III, G. J. Wells, R. R. Wexler, P. C. Wong, S. E. Yoo, and P. B. M. W. M. Timmermans, *J. Med. Chem*., **34**, 2525 (1991).