Synthesis of New Imidazole Derivatives as Potential Inhibitors of Thromboxane Synthetase

Aldo Banfi*, Alberto Sala and P. Angelo Soresinetti

Italfarmaco Research Center, Via dei Lavoratori 54,
20092 Cinisello Balsamo, Milan, Italy

Giovanni Russo

Dipartimento di Chimica Organica e Industriale, Università degli Studi and Centro di Studio per le Sostanze Organiche Naturali del C.N.R., Milan, Italy

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The preparation of new imidazole derivatives containing a carboxylic moiety such as succinic, adipic or benzoic into the side chain, is reported starting from the suitable imidazole intermediates.

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Introduction.

Thromboxane A2 (TXA2), discovered by Hamberg [1], is a potent pro-aggregatory and vasoconstrictor compound produced by the metabolism of arachidonic acid in blood platelets and other tissues. TXA2 is considered to play an important role in the maintenance of vascular homeostasis and may contribute to the pathogenesis of a variety of vascular disorders.

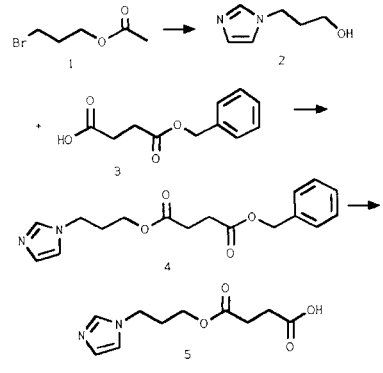
During the last few years a great deal of synthetic effort has been focussed on either inhibiting its synthesis or blocking its action at its receptor site by means of an antagonist. Several inhibitors of TXA2-synthetase, which catalyzes the synthesis of thromboxane from prostaglandin H2 in blood platelets, have been reported [2-5]. In particular, since the selective inhibition properties of imidazole derivatives were discovered [6], a variety of compounds containing the imidazole ring have been screened for inhibitory effects [7-9]. The structure-activity relationship studies [10] have shown some important features of an imidazole derivative as a TXA2-synthetase inhibitor: a) the side chain on the imidazole ring must be at position 1; b) the carboxylic function should be preferred as terminal group of 1-substituted imidazoles; c) the introduction of various substituents, particularly an aromatic group, into the carboxy-bearing side chain increases the inhibitory potency; d) the distance between the nitrogen atom at position 1 of the imidazole ring and the carboxylic function for the most interesting compounds, is concentrated in a very limited range (8.5-9.0 Å).

Our interest in the cardiovascular field prompted us to synthesize a series of new imidazole derivatives introducing an ester function into the alkylene side chain in order to evaluate their possible inhibitory activity.

Chemistry.

Shown in Scheme 1 is the synthetic route followed for the preparation of succinic acid derivatives **4** and **5**. In order to improve the obtainment of already reported 3-(1-imidazolyl-)1-propanol **2** [11] we started from 3-bromopropyl acetate **1** which was prepared from 1,3-dibromopropane and potassium acetate in ethanol. The reaction between compound **1** and the sodium salt of imidazole in *N,N*-dimethylformamide gave intermediate **2** after basic hydrolysis. A solution of succinic acid monobenzyl ester **3** in tetrahydrofuran was treated with carbonyldiimidazole and, then, with alcohol **2** in the presence of a catalytic amount of sodium methoxide to give derivative **4** which was hydrogenated to acid **5** in ethanol using 10% palladium on activated charcoal as catalyst. Analytical data of compounds **4** and **5** are presented in Table 1; the ^{1}H-nmr of these molecules are reported in Table 2.

Scheme 1



Illustrated in Scheme 2 is the synthetic approach used for the preparation of adipic acid derivatives **7a,b**, **8a,b**, **9** and **10**. Carbonyldiimidazole was added to a solution of adipic acid monoesters **6a,b** in dichloromethane and each of the resulting imidazolides **7a,b** was treated in acetonitrile with paraformaldehyde in the presence of a catalytic amount of zinc chloride affording 1-imidazolylmethyl adipates **8a,b**. Benzyl ester **8b** was hydrogenated in ethanol using 10% palladium on activated charcoal as the catalyst to obtain the desired derivative **9** which was

Table 1

Compound	Yield %	MP, °C (Crystallization solvent)	Molecular Formula	Analysis, % (Calcd./Found) C	H	N
4	45	oil	$C_{17}H_{20}N_2O_4$	64.54 64.26	6.37 6.48	8.85 8.90
5	84	81-83° (acetone)	$C_{10}H_{14}N_2O_4$	53.09 53.30	6.24 6.28	12.38 12.40
7a	66	45-47° (diethyl ether/pentane)	$C_{11}H_{16}N_2O_3$	58.90 58.61	7.19 7.04	12.49 12.26
7b	77	50-52° (diethyl ether/pentane)	$C_{16}H_{18}N_2O_3$	67.12 66.87	6.37 6.59	9.78 9.65
8a	45	oil	$C_{12}H_{18}N_2O_4$	56.68 56.41	7.13 6.83	11.01 10.72
8b	65	40-41° (hexane)	$C_{17}H_{20}N_2O_4$	64.54 64.29	6.37 6.31	8.85 8.73
9	75	101-103° (diethyl ether/ethanol)	$C_{10}H_{14}N_2O_4$	53.09 53.05	6.24 6.21	12.38 12.18
10	73	oil	$C_{17}H_{27}N_3O_3$	63.53 63.25	8.47 8.73	13.07 12.88
13a	50	oil	$C_{20}H_{34}N_2O_4$	65.54 65.25	9.35 9.15	7.64 7.35
13b	33	oil	$C_{25}H_{36}N_2O_4$	70.06 69.99	8.47 8.38	6.54 6.41
13c	80	oil	$C_{25}H_{28}N_2O_5$	68.79 68.50	6.46 6.29	6.41 6.28
13d	67	oil	$C_{24}H_{26}N_2O_4$	70.91 70.70	6.44 6.38	6.89 6.72
14a	45	61° (diisopropyl ether/ethanol)	$C_{18}H_{30}N_2O_4$	63.88 63.62	8.93 9.07	8.28 8.16
14b	63	65° (diethyl ether/hexane/acetone)	$C_{18}H_{22}N_2O_5$	62.41 62.34	6.40 6.52	8.09 7.96
17	32	82° (ethyl acetate/hexane)	$C_{19}H_{18}N_2O_3$	70.78 70.65	5.62 5.68	8.68 8.56
18	72	184-185° (ethyl acetate/methanol)	$C_{12}H_{12}N_2O_3$	62.06 61.89	5.21 5.32	12.06 11.92

Scheme 2

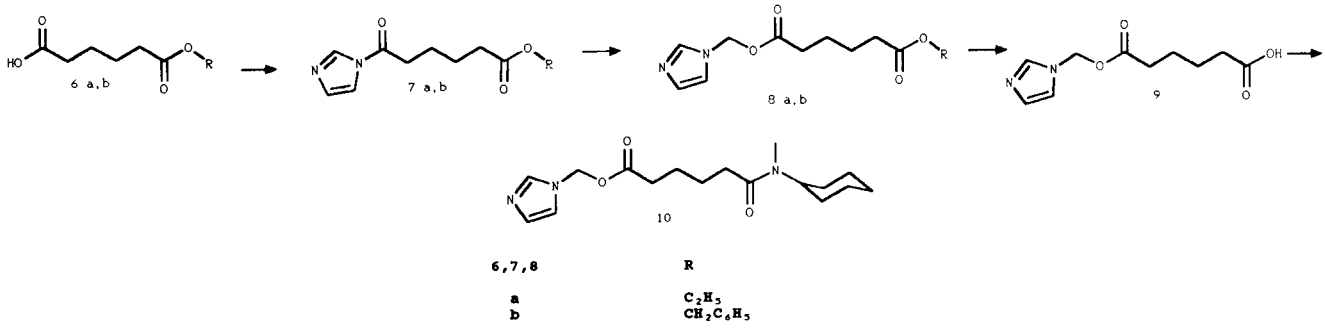


Table 2

^{1}H-NMR Data of Compounds **4-5, 7-10, 13-14** and **17-18**

Compound	δ (ppm) Deuteriochloroform [a]
4	7.53 (s, 1H), 7.42 (s, 5H), 7.11 (d, 1H), 6.97 (d, 1H), 5.17 (s, 2H), 4.05 (t, 2H), 3.99 (t, 2H), 2.68 (s, 4H), 2.02 (quintet, 2H)
5	14.21 (s, 1H), 7.82 (s, 1H), 7.07 (s, 1H), 6.97 (s, 1H), 4.08 (t, 4H), 2.61 (s, 4H), 2.07 (quintet, 2H)
7a	8.18 (d, 1H), 7.44 (t, 1H), 7.35 (s, 5H), 7.08 (d, 1H), 5.12 (s, 2H), 2.96-2.73 (m, 2H), 2.53-2.23 (m, 2H), 1.98-1.57 (m, 4H)
7b	8.20 (s, 1H), 7.51 (s, 1H), 7.11 (s, 1H), 4.14 (q, 2H), 3.09-2.73 (m, 2H), 2.51-2.25 (m, 2H), 2.05-1.60 (m, 4H), 1.27 (t, 3H)
8a	7.67 (s, 1H), 7.07 (s, 2H), 5.83 (s, 2H), 4.10 (q, 2H), 2.30 (m, 4H), 1.62 (m, 4H), 1.21 (t, 3H)
8b	7.67 (s, 1H), 7.33 (s, 5H), 7.06 (s, 2H), 5.83 (s, 2H), 5.12 (s, 2H), 2.30 (m, 4H), 1.63 (m, 4H)
9 [b]	11.25 (s broad, 1H), 7.93 (s, 1H), 7.37 (s, 1H), 7.03 (s, 1H), 6.03 (s, 2H), 2.30 (m, 4H), 1.53 (m, 4H)
10	7.74 (s, 1H), 7.23 (d, 1H), 6.89 (d, 1H), 5.91 (s, 2H), 4.18 (m, 0.58H), 3.53 (m, 0.42H), 2.74 (s, 1.74H), 2.65 (s, 1.26H), 2.29 (m, 4H), 1.50 (m, 14H)
13a	7.48 (s, 1H), 7.03 (d, 1H), 6.89 (d, 1H), 5.08 (m, 1H), 4.09 (m, 4H), 2.26 (m, 4H), 1.69-0.83 (m, 22H)
13b	7.45 (s, 1H), 7.33 (s, 5H), 7.03 (d, 1H), 6.88 (d, 1H), 5.08 (s, 2H), 5.07 (m, 1H), 4.00 (d, 2H), 2.32 (m, 4H), 1.80-1.07 (m, 19H)
13c	7.70 (s, 1H), 7.50-6.83 (m, 12H), 5.26 (m, 1H), 5.12 (s, 2H), 4.32 (d, 2H), 3.95 (m, 2H), 2.35 (m, 4H), 1.62 (m, 4H)
13d	7.68 (s, 1H), 7.36 (m, 10H), 7.03 (d, 1H), 6.83 (d, 1H), 5.97 (t, 1H), 5.10 (s, 2H), 4.25 (d, 2H), 2.36 (m, 4H), 1.62 (m, 4H)
14a	12.99 (s, 1H), 7.79 (s, 1H), 7.17 (s, 1H), 7.01 (s, 1H), 5.18 (m, 1H), 4.15 (d, 2H), 2.39 (m, 4H), 1.86-1.03 (m, 19H)
14b	11.53 (s, 1H), 7.78 (s, 1H), 7.50-6.83 (m, 7H), 5.37 (m, 1H), 4.35 (d, 2H), 3.95 (m, 2H), 2.32 (m, 4H), 1.64 (m, 4H)
17	8.10-6.97 (m, 12H), 5.14 (s, 2H), 4.58 (t, 2H), 4.32 (t, 2H)
18 [b]	7.84-6.76 (m, 7H), 4.40 (s, 4H)

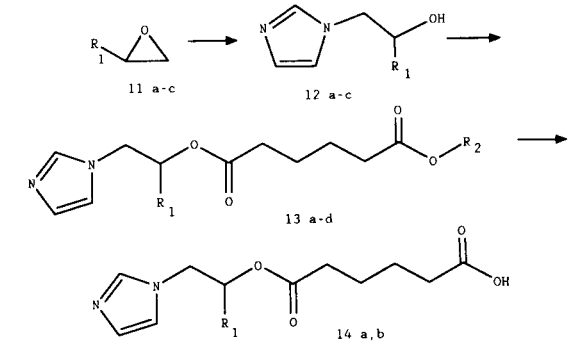
[a] TMS as internal standard.
[b] Spectra recorded in dimethyl sulfoxide-d_6

transformed into amide **10** with *N*-methyl-*N*-cyclohexylamine in tetrahydrofuran in the presence of triphenylphosphine and bromotrichloromethane [12].

Analytical data of compounds **7a,b, 8a,b, 9** and **10** are reported in Table 1; the ^{1}H-nmr of these molecules are shown in Table 2.

The synthesis of adipic acid derivatives **13a-d** and **14a,b** prepared to investigate the change in the inhibitory activity by the introduction of various substituents, such as alkyl, phenyl or phenyloxymethyl into the side chain is shown in Scheme 3. The reaction between suitable ethylene oxides **11a-c** and imidazole in *N,N*-dimethylformamide, afforded 2-imidazolylethanol intermediates **12a-c** which were dropped into a mixture of adipic acid monoesters and carbonyldiimidazole in tetrahydrofuran in the presence of a catalytic amount of sodium methoxide to

Scheme 3



11,12	R_1
a	n-C_7H_{15}
b	$CH_2OC_6H_5$
c	C_6H_5

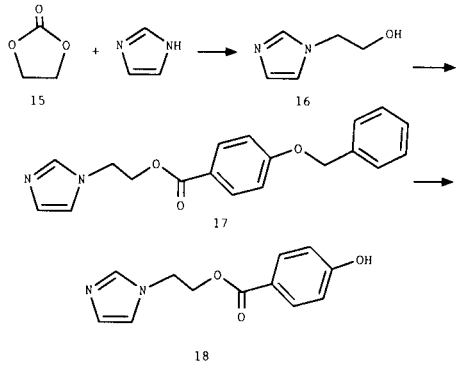
13	R_1	R_2
a	n-C_7H_{15}	C_2H_5
b	n-C_7H_{15}	$CH_2C_6H_5$
c	$CH_2OC_6H_5$	$CH_2C_6H_5$
d	C_6H_5	$CH_2C_6H_5$

14	R_1
a	n-C_7H_{15}
b	$CH_2OC_6H_5$

give compounds **13a-d**. Derivatives **13b,c** were hydrogenated in ethanol using 10% palladium on activated charcoal as catalyst obtaining acids **14a,b**. Analytical data of compounds **13a-d** and **14a,b** are presented in Table 1; the ^{1}H-nmr of these molecules are reported in Table 2.

Illustrated in Scheme 4 is the synthetic route followed for the preparation of benzoic acid compounds **17** and **18**. In particular derivative **18** was conceived to investigate the change in the inhibitory activity introducing a phenyl group into the side chain and substituting, as the terminal group, the carboxylic function with a phenolic hydroxyl. The synthesis was carried out starting from ethylene carbonate **15** which, reacting with imidazole, gave 2-imidazolylethanol **16**. 4-Benzyloxybenzoyl chloride was treated with alcohol **16** in dichloromethane affording benzoic acid derivative **17** which was hydrogenated in ethanol using 10% palladium on activated charcoal as catalyst to obtain phenol **18**. Analytical data of compounds **17** and **18** are presented in Table 1; the ^{1}H-nmr of these molecules are reported in Table 2.

Scheme 4



The inhibition of TXA2-synthetase performed by these new imidazole derivatives was investigated, but, even though a satisfactory *in vitro* activity was found, there were only slight inhibitory properties *in vivo*.

EXPERIMENTAL

Melting points were determined on a Buchi SMP-20 apparatus and are uncorrected. The ^{1}H-nmr spectra were recorded with a Varian EM-360 L spectrometer, except the spectrum of derivative **10** that was recorded with a Varian CFT-20 spectrometer.

3-Bromopropyl Acetate (**1**).

Into a refluxing solution of 1,3-dibromopropane (370 g, 1.83 moles) in ethanol (800 ml) a solution of potassium acetate (60 g, 0.61 mole) in ethanol (800 ml) was added dropwise during 2 hours. The reaction mixture was heated for 2 hours and then stirred overnight at room temperature. The crude product obtained after evaporation of the solvent was dissolved in diethyl ether (500 ml), washed with water (2 x 500 ml) and dried with sodium sulphate. After evaporation of the solvent the residue was chromatographed on silica gel column (hexane/chloroform = 10/1 as eluent) to give 50 g of **1** as a colorless oil.

3-(1-Imidazolyl)propanol (**2**).

In to a suspension of sodium hydride (9.93 g, 0.33 mole) in *N,N*-dimethylformamide (200 ml) under an inert atmosphere a solution of imidazole (22.54 g, 0.33 mole) in *N,N*-dimethylformamide (150 ml) was slowly added dropwise at room temperature. After heating at 100° under stirring, a solution of **1** (60 g, 0.33 mole) in *N,N*-dimethylformamide (200 ml) was added dropwise during 2 hours and the heating was carried on for 2 hours. The solvent was evaporated and the residue was dissolved in chloroform and washed with water to give, after evaporation of the chloroform, 53 g of crude product, which was treated with 10% aqueous sodium hydroxide (280 ml) for 1 hour at room temperature under stirring. Water was evaporated and the residue, extracted with chloroform, was chromatographed on silica gel column (eluent: chloroform/methanol = 9/3) to give 13 g of desired product **2**.

Benzyl 3-(1-imidazolyl)propyl Succinate (**4**).

Adipic acid monobenzyl ester **3** (7.03 g, 0.028 mole) was added at room temperature to a stirred solution of N,N'-carbonyldiimidazole (4.59 g, 0.0028 mole) in dry tetrahydrofuran (35 ml). A solution of the sodium salt of **2** (4.19 g, 0.028 mole) in dry tetrahydrofuran (28 ml) was slowly added dropwise and the reaction mixture was stirred for 24 hours at room temperature. After evaporation of the solvent, the residue was treated with ethyl acetate, washed with water, 3% aqueous sodium hydrogen carbonate solution, water and dried over sodium sulphate. The solvent was evaporated and the crude reaction product (6.5 g) was chromatographed on silica gel column (eluent: ethyl acetate/methanol = 85/15) to give 4 g of desired compound **4**.

Succinic Acid Mono 3-(1-Imidazolyl)propyl Ester (**5**).

Derivative **4** (7.0 g, 0.022 mole) in ethanol (100 ml) was hydrogenated at room temperature under vigorous stirring for 3 hours in the presence of 0.70 g of 10% palladium on activate charcoal. The catalyst was filtered off and the residue, after evaporation of the solvent, was recrystallized from acetone to give 4.2 g of compound **5**.

Compound **9**, **14a**, **14b** and **18** were similarly prepared.

Ethyl 5-(1-Imidazolylcarbonyl)pentanoate (**7a**).

To a solution of **6a** (21.48 g, 0.121 mole) in methylene chloride (250 ml), *N,N'*-carbonyldiimidazole (20 g, 0.120 mole) was added portionwise under stirring at room temperature. The reaction mixture was stirred for 1 hour and then poured into water (100 ml). The organic layer was dried over sodium sulphate to give 29.5 g of crude product as a yellow oil. After crystallization from diethyl ether/pentane = 1/1 18 g of compound **7a** was obtained.

Compound **7b** was similarly prepared.

Ethyl 1-Imidazolylmethyladipate (**8a**).

A solution of **7a** (18 g, 0.080 mole) and trioxymethylene (2.41 g, 0.027 mole) in dry acetonitrile (90 ml) with a catalytic amount of zinc chloride was stirred at 65° for 24 hours. The solvent was distilled off and the crude mixture was treated with 10% aqueous sodium carbonate (100 ml). The insoluble material was filtered off, the product was extracted with ethyl acetate and purified on silica gel column (eluent: methylene chloride/acetone = 6/4) to

give 9 g of derivative **8a**.

Compound **8b** was similarly prepared.

N-Cyclohexyl-*N*-methyl 5-(1-imidazolyl)methyloxycarbonyl pentanoilamide (**10**).

N-Cyclohexyl-*N*-methylamine (5.8 ml, 0.044 mole), derivative **9** (5 g, 0.022 mole), triphenylphosphine (5.8 g, 0.022 mole) and bromotrichloromethane (4.3 ml, 0.044 mole) were refluxed in tetrahydrofuran (125 ml) for 5 hours. The reaction mixture was cooled at room temperature, the amine hydrobromide was filtered off and the solvent was evaporated under reduced pressure. The residue (18 g) was purified by flash chromatography on silica gel column (eluent: chloroform/ethyl acetate = 1/1) to give 5.17 g of **10** as a brown oil.

1-(2-Hydroxyethyl)imidazole (**16**).

Imidazole (20 g, 0.294 mole) and ethylene carbonate (40.4 g, 0.456 mole) were stirred at 80° for 20 hours and then the reaction mixture was chromatographed on silica gel column (eluent: chloroform/methanol = 8/2) to give 17.1 g of **16** as a colorless oil.

2-(1-Imidazolyl)ethyl 4-Benzyloxybenzoate (**17**).

To a chilled solution of 4-benzyloxybenzoylchloride (14.25 g, 0.062 mole) in methylene chloride (150 ml) derivatives **16** (7.0 g, 0.062 mole) was added and the reaction mixture was stirred for 2 hours at 0°. After washing with 1*N* aqueous sodium hydroxide (50 ml), the organic layer was separated, dried, evaporated under reduced pressure and chromatographed on silica gel column (eluent: chloroform/methanol = 20/1) to give 7 g of pure **17** after recrystallization from ethyl acetate/hexane.

1-(3-Phenyloxy-2-hydroxypropyl)imidazole (**12b**).

Imidazole (13.3 g, 0.20 mole) and compound **11b** (30 g, 0.18 mole) were dissolved in dry *N*,*N*-dimethylformamide (135 ml) and stirred at 90° for 70 hours. The reaction mixture was cooled at room temperature, diluted with water (2 *l*) and extracted with diethyl ether (2 × 200 ml). Evaporation of the solvent and recrystallization of the residue from diethyl ether afforded 33 g of pure **12b**.

Compounds **12a** and **12c** were similarly prepared.

Benzyl 2-[3-(1-Imidazolyl)-1-phenyloxy]propyladipate (**13c**).

To a solution of monobenzoyl adipate (7.0 g, 0.030 mole) in methylene chloride (250 ml) *N*,*N*'-carbonyldiimidazole (4.8 g, 0.030 mole) in methylene chloride (100 ml) was added dropwise during 15 minutes under stirring. After 30 minutes a catalytic amount of sodium methoxide (500 mg) and derivative **12b** (7.17 g, 0.030 mole) were added protionwise. The reaction mixture was refluxed for 4 hours, cooled at room temperature, washed with 3% aqueous sodium hydrogen carbonate solution and water, dried over sodium sulphate and evaporated under reduced pressure to give 16 g of a yellow oil. The chromatography on silica gel column (eluent: methylene chloride/methanol = 20/1) afforded 10.35 g of pure **13c**.

Compounds **13a**, **13b** and **13d** were similarly prepared.

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