Synthesis of New Imidazole Derivatives as Potential Inhibitors of Thromboxane Synthetase. II.

Aldo Banfi, Francesca Benedini and Alberto Sala*

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

Received July 20, 1990

The preparation of new imidazole derivatives containing ether or amide functions into the side chain, is reported starting from the suitable imidazole intermediates.

J. Heterocyclic Chem., **28**, 401 (1991).

Introduction.

Thromboxane A2 (TxA2) is a powerful proaggregatory and vasoconstrictor compound derived from the TxA2-synthetase catalyzed rearrangement of the endoperoxide PGH2 in the arachidonic acid cascade.

After Needleman discovered in 1977 [1] that imidazole selectively inhibited the enzyme TxA2-synthetase, a large number of molecules containing the imidazole moiety was synthesized in order to obtain selective inhibitors [2-10]. In a previous paper [11] we reported the preparation of imidazole derivatives containing a carboxylic moiety, such as succinic, adipic or benzoic acid, into the alkylene side chain at position 1 of the imidazole ring.

Even though such molecules showed a good *in vitro* activity as TxA2-synthetase inhibitors, their bioavailability was limited by the *in vivo* hydrolysis of the carboxylic function.

On the basis of this knowledge we turned our attention to the synthesis of imidazole derivatives containing ether or amide functions into the alkylene side chain, in order to evaluate how the polarity change and the improved stability of the molecules could influence the inhibitory properties.

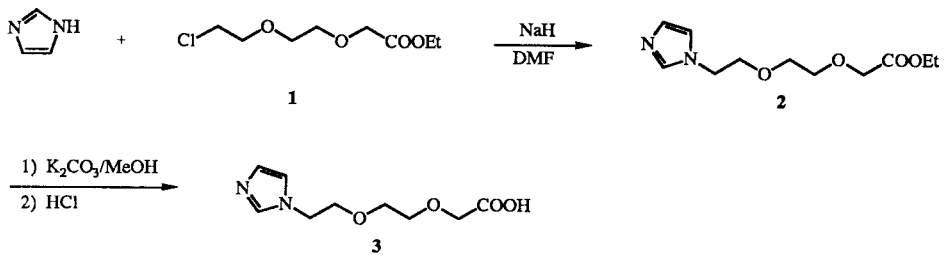
Chemistry.

The synthesis of compounds **2** and **3** was carried out, according to Scheme A, by treating sodium salt of imidazole with ethyl 8-chloro-3,6-dioxaoctanoate **1** [12] in dry *N,N*-dimethylformamide for 24 hours at 90°. The hydrolysis of **2** with 1 *M* aqueous potassium carbonate in methanol afforded compound **3**.

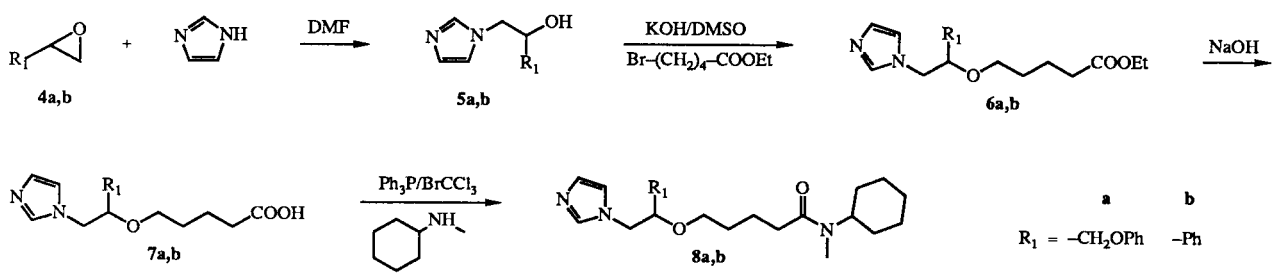
The synthesis of compounds **6a,b**, **7a,b** and **8a** was carried out according to Scheme B.

The reaction between imidazole and epoxides **4a,b** in *N,N*-dimethylformamide at 80° for 24 hours afforded alcohols **5a,b**. These compounds were converted into the corresponding potassium salts with a slight excess of powdered potassium hydroxide in dry dimethylsulfoxide and treated with an equimolar amount of ethyl 5-bromovalerate to obtain derivatives **6a,b**. The hydrolysis of compounds **6a,b** with 1 *M* aqueous sodium hydroxide afforded good yields of products **7a,b**. Compound **7a** was treated

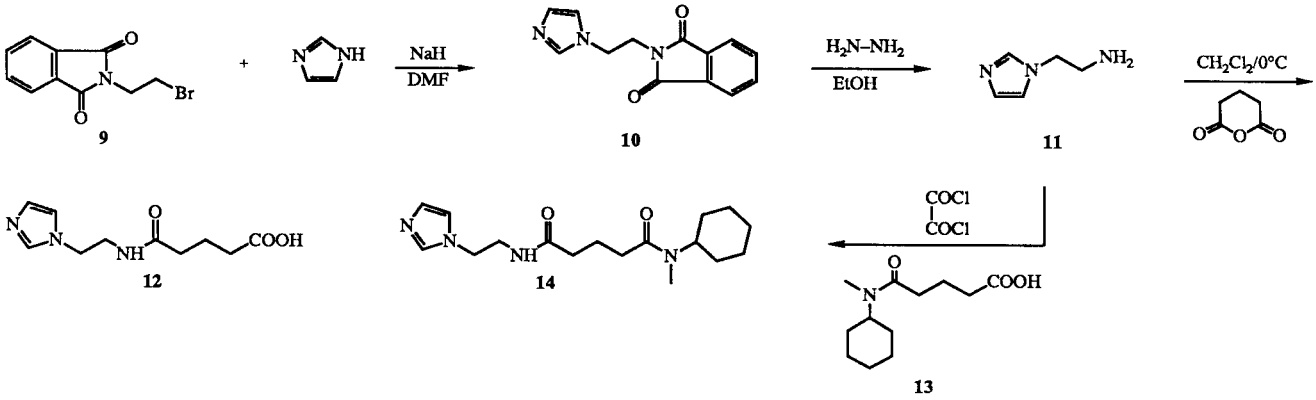
Scheme A



Scheme B



Scheme C



with triphenylphosphine, bromotrichloromethane and *N*-cyclohexyl-*N*-methylamine in refluxing tetrahydrofuran [13] to give amide **8a**.

Illustrated in Scheme C is the syunthesis of amides **12** and **14**.

The reaction between *N*-(2-bromoethyl)phtalimide **9** and sodium salt of imidazole gave compound **10** which was cleaved with hydrazine to afford amine **11**. Compound **12** was obtained by treating amine **11** with glutaric anhydride in cold dichloromethane. Diamide **14** was obtained from amine **11** with glutaric acid mono *N*-cyclohexyl-*N*-methylamide and oxalyl chloride.

The imidazole derivatives described in this paper show a remarkable TxA2-synthetase inhibition (IC50 between 6 x 10-6 and 3 x 10-7 *M*) in rabbit PRP. In addition, in the *in vivo* model of sudden death by arachidonic acid in rat, these compounds have a better protective activity compared to imidazole derivatives reported in our previous ar-

Table 1

Analytical Data of Compounds **2, 3, 5a,b-7a,b, 8a, 12, 14**

Compound	δ (ppm) in deuteriochloroform	Molecular Formula	Elemental Analysis % (Calcd./Found)		
			C	H	N
2	s, 7.46 (1H), s, 6.93 (1H), s, 6.91 (1H), q, 4.12 (2H), t, 4.03 (2H), s, 4.01 (2H), m, 3.68-3.50 (6H), t, 1.19 (3H)	$C_{11}H_{18}N_2O_4$	54.53 54.48	7.49 7.40	11.56 11.48
3 [a]	s, 8.66 (1H), s, 7.46 (1H), s, 7.35 (1H), t, 4.34 (2H), t, 3.83 (2H), s, 3.79 (2H), m, 3.58 (4H)	$C_9H_{14}N_2O_4 \cdot H_2O$	46.55 46.39	6.94 6.91	12.06 11.98
5a	m, 7.50 (8H), m, 4.85-4.55 (1H), m, 4.20-3.70 (4H)	$C_{12}H_{14}N_2O_2$	66.04 66.01	6.46 6.53	12.83 12.73
5b	m, 7.41-7.25 (6H), s, 6.94 (1H), s, 6.87 (1H), X part of ABX system, 4.92 (1H), AB part of ABX system, 4.09 (2H)	$C_{11}H_{12}N_2O$	70.19 70.06	6.42 6.44	14.88 14.71
6a	s, 7.47 (1H), m, 7.31-7.20 (2H), m 7.00-6.81 (5H), m 4.28-3.87 (5H), m, 3.83-3.70 (2H), t, 2.25 (2H), m, 1.70-1.45 (4H), t, 1.21 (3H)	$C_{19}H_{26}N_2O_4$	65.87 65.56	7.56 7.44	8.08 7.89
6b	s, 7.36 (1H), m 7.34-7.15 (5H), s, 6.95 (1H), s, 6.86 (1H), dd, 4.38 (1H), q, 4.08 (2H), m, 4.03 (2H), m, 3.24 (2H), t, 2.22 (2H), m, 1.68-1.43 (4H), t, 1.20 (3H)	$C_{18}H_{24}N_2O_3$	68.37 68.01	7.65 7.71	8.86 8.57
7a	s, 12.63 (1H), s, 7.71 (1H), m, 7.31-7.21 (2H), s, 7.04 (1H), m, 6.99-6.82 (4H), m, 4.30-3.68 (5H), m, 3.48 (2H), t, 2.28 (2H), m, 1.72-1.47 (4H)	$C_{17}H_{22}N_2O_4$	64.13 64.01	6.96 7.02	8.80 8.72
7b	s, 12.58 (1H), s, 7.68 (1H), m, 7.32-7.16 (5H), s, 7.00 (1H), s, 6.89 (1H), t, 4.41 (1H), d, 4.05 (2H), m, 3.24 (2H), t, 2.25 (2H), m, 1.70-1.45 (4H)	$C_{16}H_{20}N_2O_3$	66.64 66.42	6.99 6.90	9.71 9.53
8a	s, 7.49 (1H), m, 7.32-7.21 (2H), m, 7.00-6.82 (5H), m, 4.47-3.35 (8H), s, 2.76 (3H), m, 2.33-2.20 (2H), m, 1.85-1.20 (14H)	$C_{24}H_{35}N_3O_3$	69.70 69.61	8.53 8.50	10.16 10.02
12 [a]	s, 8.51 (1H), s, 7.32 (1H), s, 7.25 (1H), m, 4.16 (2H), m, 3.45 (2H), m, 2.04-1.89 (4H), quintet, 1.53 (2H)	$C_{10}H_{15}N_3O_3$	53.32 53.57	6.71 6.68	18.65 18.74
14	t, 7.40 (1H), s, 7.38 (1H), s, 6.93 (1H), s, 6.87 (1H), m, 4.38-4.23 (0.55H), t, 4.04 (2H), m, 3.61-3.27 (2.45H), s, 2.76 (1.65H), s, 2.71 (1.35H), m, 2.34-2.15 (4H), m, 1.91-0.88 (12H)	$C_{17}H_{28}N_4O_2$	63.72 63.71	8.80 8.75	17.48 17.42

[a] Spectra recorded in deuterium oxide.

ticle [11]. This probably due to the improved *in vivo* stability of the new compounds.

EXPERIMENTAL

The ^{1}H nmr spectra were recorded at 200 MHz (Varian Gemini 200); chemical shifts are given in ppm. Elemental analysis were carried out on Perkin Elmer 240. Melting points were determined on a Büchi 530 apparatus and are uncorrected. The analytical data of all new compounds are presented in Table 1.

1-(3,6-Dioxa-7-ethoxycarbonylheptyl)imidazole **2**.

To a suspension of 80% sodium hydride (3.38 g, 0.113 mole) in dry *N,N*-dimethylformamide (200 ml), imidazole (7.67 g, 0.113 mole) was added and after heating at 90° for 1 hour under nitrogen atmosphere, compound **1** (23.75 g, 0.113 mole) in dry *N,N*-dimethylformamide (250 ml) was slowly dropped. The reaction mixture was stirred at 90° for 22 hours, washed with water and extracted with dichloromethane (400 ml). After evaporation of the solvent at reduced pressure the residue was purified by silica gel flash-chromatography eluting with dichloromethane/methanol 9/1 to give 20.22 g (74%) of compound **1** as an oil.

1-(3,6-Dioxa-7-carboxyheptyl)imidazole monohydrate **3**.

To a solution of compound **2** (3.3 g, 0.0136 mole) in methanol (15 ml) 1 *M* aqueous solution of potassium carbonate (14.3 ml) was added and the reaction mixture was stirred at room temperature for 3 hours. After evaporation of the solvent the crude product was purified by silica gel chromatography eluting with propanol/33% ammonium hydroxide 4/1 to give 2.68 g (85%) of compound **3** as an oil.

1-(3-Phenyloxy-2-hydroxypropyl)imidazole **5a**.

Imidazole (13.3 g, 0.195 mole) and epoxide **4a** (30.0 g, 0.195 mole) in dry *N,N*-dimethylformamide (135 ml) were heated at 90° for 50 hours under stirring. After cooling at room temperature the mixture was diluted with water (2 l) and extracted with ethyl ether. Concentration of organic layer afforded a crude solid which was crystallized from ethyl ether to give 32.8 g of pure **5a** (77%, mp 108°).

1-(2-Hydroxy-2-phenylethyl)imidazole **5b**.

This compound was similarly prepared starting from styrene oxide (74%, mp 146°).

1-[2-(4-Ethoxycarbonylbutoxy)-3-phenoxy]propylimidazole **6a**.

To a suspension of powdered potassium hydroxide (5.05 g, 0.0902 mole) in dry dimethyl sulfoxide (10 ml) under inert atmosphere, a solution of compound **5a** (5.00 g, 0.0229 mole) in dry dimethyl sulfoxide (10 ml) was added at room temperature under stirring. After 90 minutes ethyl 5-bromovalerate (9.67 g, 0.0458 mole) in dimethyl sulfoxide (10 ml) was dropped at 10° and the reaction mixture was stirred at room temperature for 12 hours, diluted with water (2 l) neutralized with 2 *M* sulphuric acid and extracted with methylene chloride (3 x 200 ml). The organic layer was dried under sodium sulphate, evaporated at reduced pressure and the residue was chromatographed on silica gel column eluting with ethyl acetate/methanol 9/1 to give 3.0 g (38%) of compound **6a** as an oil.

Ethyl 7-Phenyl-8-(1-imidazolyl)-6-oxaoctanoate **6b**.

This compound was similarly prepared starting from alcohol **5b** (25%, oil).

7-Phenoxymethyl-6-oxa-8-(1-imidazolyl)octanoic Acid **7a**.

A solution of compound **6a** (7.6 g, 0.0219 mole) in 1 *M* aqueous sodium hydroxide (22.5 ml) was stirred at room temperature for 24 hours and then washed with dichloromethane (30 ml). The aqueous layer was neutralized with 5% sulphuric acid and extracted with dichloromethane (4 x 50 ml). The organic phase was dried with sodium sulphate and concentrated at reduced pressure to give 6 g of pure acid **7a** after recrystallization from dichloromethane/ethyl ether (86%, mp 64°).

7-Phenyl-8-(1-imidazolyl)-6-oxaoctanoic Acid **7b**.

This compound was similarly prepared starting from ester **6b** (85%, oil).

7-Phenoxymethyl-8-(1-imidazolyl)-6-oxaoctanoil-*N*-cyclohexyl-*N*-methylamide **8a**.

Triphenylphosphine (3.15 g, 0.012 mole), bromotrichloromethane (4.78 g, 0.024 mole), compound **7a** (3.87 g, 0.012 mole) and *N*-cyclohexyl-*N*-methylamine (2.77 g, 0.024 mole) were dissolved in tetrahydrofuran (50 ml). The reaction mixture was refluxed for 5 hours and stirred at room temperature for 18 hours. The solvent was evaporated and the residue was treated with dichloromethane, washed with water and dried over sodium sulphate. After evaporation of the solvent the crude was chromatographed on silica gel column eluting with dichloromethane/methanol/hexane 10/1/1 to give 3 g (60%) of compound **8a** as an oil.

N-[2-(1-Imidazolyl)ethyl]glutarylamide **12**.

To a chilled solution (0°) of glutaric anhydride (2.56 g, 0.0225 mole) in dichloromethane (55 ml) amine **11** (2.50 g, 0.0225 mole) in dichloromethane (20 ml) was added dropwise. After 1 hour at room temperature under stirring compound **11** was collected by filtration and recrystallized from dichloromethane (2.53 g, 50%, mp 70°).

N-[2-(1-Imidazolyl)ethyl]-*N'*-cyclohexyl-*N'*-methylglutarylamide **14**.

To a stirred suspension of amide **13** (4.10 g, 0.018 mole) in toluene (150 ml) and *N,N*-dimethylformamide (2 ml) at 5-10° oxalyl chloride (2.85 g, 0.0225 mole) was added dropwise. After 2 hours at room temperature the solvent was distilled off and tetrahydrofuran was twice added to the residue and evaporated. The obtained acyl chloride was dissolved in tetrahydrofuran and added dropwise to a chilled solution (0°) of amine **11** (2.40 g, 0.0216 mole) and sodium carbonate (2.51 g, 1 mole) in tetrahydrofuran (30 ml) and water (30 ml). After 2 hours the organic solvent was evaporated under reduced pressure and the aqueous layer was extracted with dichloromethane. The organic layer was washed with water, dried over sodium sulphate and evaporated to give a crude product which was purified by silica gel chromatography eluting with dichloromethane/methanol 10/1. Pure derivative **14** (4.0 g, 69%) was obtained as an oil.

REFERENCES AND NOTES

[1] P. Needleman, H. Raz, J. A. Ferrendelle and M. Mines, *Proc. Natl. Acad. Sci. U.S.A.*, **74**, 1716 (1977).

[2] K. Iizuka, K. Akahane, D. Momose and M. Nakazawa, *J. Med.*

Chem., **24**, 1139, (1981).

[3] P. E. Cross, R. P. Dickinson, M. J. Parry and M. J. Randall, *J. Med. Chem.*, **28**, 1427 (1985).

[4] P. E. Cross, R. P. Dickinson, M. J. Parry and M. J. Randall, *J. Med. Chem.*, **29**, 342 (1986).

[5] P. E. Cross, R. P. Dickinson, M. J. Parry and M. J. Randall, *J. Med. Chem.*, **29**, 1637 (1986).

[6] P. E. Cross, R. P. Dickinson, M. J. Parry and M. J. Randall, *J. Med. Chem.*, **29** 1643 (1986).

[7] P. W. Manley, D. P. Tuffin, N. M. Allanson, P. E. Buckle, N. Lad, S. M. F. Lai, D. O. Lunt, R. A. Porter and P. J. Wade, *J. Med. Che.*, **30**, 1812 (1987).

[8] G. R. Martinez, K. A. M. Walker, D. R. Hirschfeld, P. J. Maloney, D. S. Yang and R. P. Rosenkranz, *J. Med. Chem.*, **32**, 890 (1989).

[9] Y. Amemiya, A. Terado, K. Wachi, H. Miyazawa, N. Hatakeyama, K. Matsuda and T. Oshima, *J. Med. Chem.*, **32**, 1265 (1989).

[10] M. Kanao, Y. Watanabe, Y. Klimura, J. Saegusa, K. Yamamoto, H. Kanno, N. Kanaya, H. Kubo, S. Ashida and F. Ishikawa, *J. Med. Chem.*, **32**, 1326 (1989).

[11] A. Banfi, A. Sala, P. A. Soresinetti and G. Russo, *J. Heterocyclic Chem.*, **27**, 215 (1990).

[12] E. Müller and H. Huber-Emden, *Liebigs Ann. Chem.*, **649**, 70 (1961).

[13] L. E. Barstow and V. J. Hruby, *J. Org. Chem.*, **36**, 1305 (1971).