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1,3-Disubstituted-2-carboxy Quinolones: Highly Potent and Selective Endothelin A Receptor Antagonists

Jean-Luc Haesslein,[a,*] Isabelle Baholet,[a] Michel Fortin,[b] Alain Iltis,[a] Jean Khider,[a] Anne Marie Periers,[a] Christine Pierre[a] and Jean-Paul Vevert[a]

[a]*Medicinal Chemistry, Hoechst Marion Roussel, 102 route de Noisy, 93235 Romainville Cedex, France*
[b]*Central Research, Hoechst Marion Roussel, 102 route de Noisy, 93235 Romainville Cedex, France*

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Abstract—The design, synthesis, and in vitro biological activity of a series of 2-carboxy quinolone antagonists selective for the endothelin A receptor are presented. Introduction of a second acid group in position 3 of the quinolone ring increases dramatically the selectivity for ET_A.

Introduction

Endothelin 1 (ET-1), a 21 amino-acid peptide, belongs to a family of highly potent endogenous vasoconstrictor agents along with ET-2 and ET-3.[1] It exerts its action by interacting with at least two specific G protein coupled receptors, ET_A and ET_B.[2]

ET_A, which is selective for ET-1 and ET-2 over ET-3, is mainly found in vascular smooth muscle cells (VSMC) and mediates vasoconstriction[3] and VSMC proliferation.[4] ET_B, which is non-selective for the three isoforms, mediates either vasoconstriction or vasorelaxation, depending on its tissue location.[5,6]

Endothelin has been implicated in a number of human diseases, including hypertension, congestive heart failure, acute renal failure, pulmonary hypertension, restenosis, stroke and cerebral vasospasm.[7]

Several peptidic as well as non-peptidic endothelin antagonists have been reported in the literature, being either ET_A selective (i.e., BQ 123,[8] BMS 182874,[9] A-127772,[10]) ET_B selective (BQ 788 [11]) or non selective (i.e., PD 142893,[12] Bosentan,[13] SB 209670 [14]).

During the course of our screening of G-protein coupled receptor antagonists, we discovered that 6-substituted quinolones, which were fairly good antagonists of the AT1 receptor,[15] also showed moderate affinity for both ET_A and ET_B receptors (Fig. 1).

Struck by the high affinity level of SB 209670 (**1**) for both ET_A and ET_B receptors, and by the major contribution of a methylenedioxyphenyl group and an acid function, we superimposed the indane ring of SB 209670 with the quinolone ring. A good overlap could be obtained with 1,3-disubstituted-2-carboxylic quinolones (**2**) (Fig. 2).

Herein we describe the synthesis and structure activity relationships of this series, yielding highly potent and selective ET_A antagonists.

Chemistry

As no synthesis of 1,3-disubstituted-2-carboxy quinolones had been described, we envisaged to create the quinolone ring by cyclisation of the corresponding oxamate **6**. Thus, *o*-nitroacetophenone was reacted with the appropriate aldehyde at room temperature overnight, in the presence of 2N sodium hydroxide in methanol.[16] As few as 0.1 to 0.5 equiv of sodium hydroxide are sufficient for the reaction to occur. For base sensitive aldehydes, the reaction was performed in the presence of a catalytic amount of piperidine and acetic acid in refluxing toluene, yielding the corresponding chalcones in 80 to 95% yield. Both the double bond and the nitro group were cleanly reduced over platinum oxide, giving compound **4** (Scheme 1).

The resulting aminoketones **4** were then submitted to reductive amination with the corresponding aldehyde

*Corresponding author. Tel.: +33-1-49-91-53-80; fax: +33-1-49-91-50-87; e-mail: jean-luc.haesslein@aventis.com

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yielding compounds **5** in 50 to 70% yield. Condensation of **5** with ethyl oxalyl chloride proceeded smoothly to give compound **6** quantitatively.

The key step of the synthesis was the cyclization of **6** into the corresponding quinolone ring. This could in fact be achieved in high yield under a variety of conditions (K_2CO_3, MeOH; DBU, EtOH; EtONa, EtOH; tBuOK, THF), the two first leading to cleaner reaction mixtures. Finally, the ester group was saponified with 2 equiv of 6N KOH in EtOH under heating, and the compounds tested as their potassium salts.

Most of the derivatives showed good aqueous solubility (>20 mg/mL).

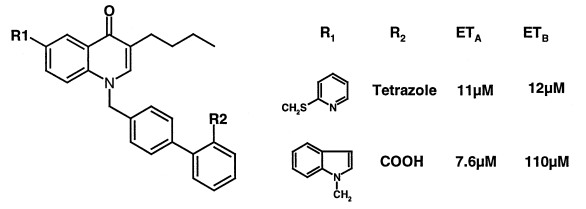


Figure 1.

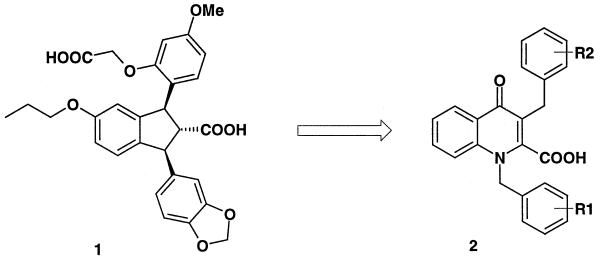


Figure 2.

Biological results

All the compounds were tested for their ability to inhibit ^{125}I-ET1 binding to rat ventricle (ET_A) or to rat cerebellum (ET_B).[17]

From the results in Table 1, it appears that the position of the methylenedioxyphenyl group is very important in this series, **9** being 25 times more potent than **10** both on ET_A and ET_B. We then investigated the effect of various substituents on the methylenedioxyphenyl group in R_1 (cpds **11a–16**); of these, derivatives with a substituent (Cl, vinyl, Et) next to the methylene group showed the highest activity, five to ten times more potent than compound **9**, giving rise to low nanomolar derivatives. In addition, all these compounds showed a good selectivity for ET_A, **11a** being the most dissociated.

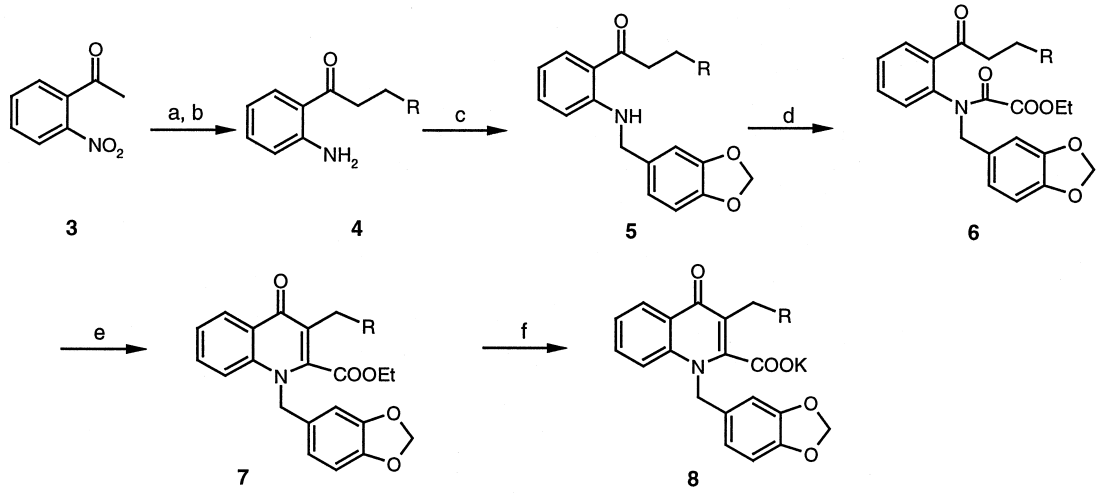
Therefore this group was retained in position 1 of the quinolone ring and the influence of R_2 was investigated (Table 2).

Several types of substituents were evaluated as R_2: aromatic (**11c–11k**), heteroaromatic (**11l–11n**) and non-aromatic (**11o–11r**).

Clearly, the deletion of CH_2R_2 leads to a loss of activity (**11b**). All the aromatic analogues tested are in the same range of activity, except compound **11e**, which incorporates the side chain of SB 209670 and is surprisingly far less active. The selectivity on ET_A which is always good, increases dramatically through the introduction of an acid function in **11f** making this compound 4000 times more potent on ET_A than on ET_B.[18]

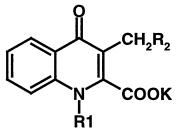
The same phenomena is observed for non-aromatic compounds: introduction of an acid or an ester (**11p**, **11q** and **11r**) function increases the selectivity (>1000).

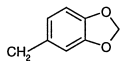
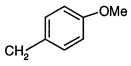
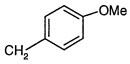
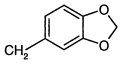
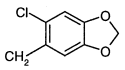
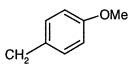
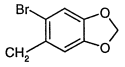
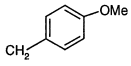
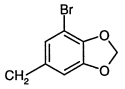
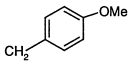
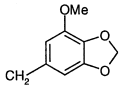
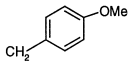
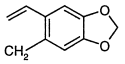
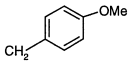
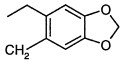
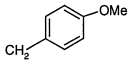
However, introduction of an acid function in the *meta* position does not lead to such a boosting in selectivity (**11i**).



Scheme 1. Reagents and conditions: (a) RCHO, 0.1–0.5 equiv 2N NaOH, MeOH or cat. Piper; AcOH, Toluene, reflux, 80–95%; (b) H_2, PtO_2, EtOAc, 100%; (c) 3,4-methylenedioxybenzaldehyde, $NaBH_3CN$, AcOH, MeOH, 50–70%; (d) ClCOCOOEt, THF, NEt_3, rt, 100%; (e) K_2CO_3, EtOH or DBU, EtOH, 80–90%; (f) 6N KOH, EtOH, reflux, 90%.

Table 1. Endothelin receptor binding affinity (nM)

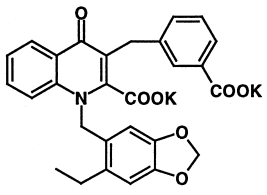


Compound	R_1	CH_2R_2	ET_A	ET_B
9			10.7	606
10			255	16000
11a			1.6	216
12			7.8	244
13			18.9	187
14			9.5	244
15			1.8	70
16			1	69

At the receptor level, there is no difference in activity or selectivity while going from the acid to the ester (**11i** versus **11k**, **11q** versus **11r**). When introducing an acid function, there is no improvement on ET_A activity (**11c** versus **11f**) but only a strong drop in ET_B activity, suggesting a significant difference between ET_A and ET_B receptor structure in this region.

In vivo, compounds of type **11** and **16** gave the best results in the pithed rat assay[19] ($ED_{50} = 1$ mg/kg IV), therefore the best substituents found in **11** as R_2 were introduced in **16**. This led to compound **16i** which shows an ED_{50} of 0.1mg/kg IV in the pithed rat, together with a sub-nanomolar affinity for ET_A. Moreover, this compound is orally active in the ET-1 induced death in mice[20] ($ED_{50} = 10$ mg/kg po).

16i

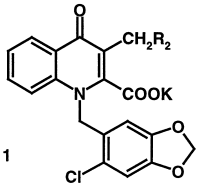


ET_A: 0.69nM

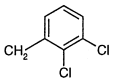
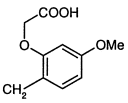
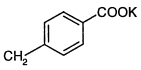
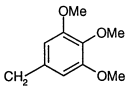
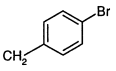
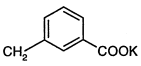
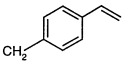
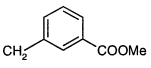
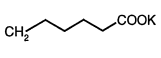
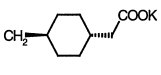
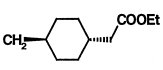
ET_B: 571nM

In conclusion, we have found a new series of highly potent and selective ET_A antagonists, which are valuable tools for further understanding the physiological and pathophysiological role of endothelin.

Table 2. Endothelin receptor binding affinity for compounds **11**



11

Compound	CH_2R_2	ET_A	ET_B
11b	H	8700	29,000
11c		4.1	157
11d		10.9	570
11e		54.3	549
11f		4.6	17,100
11g		1.9	789
11h		5.7	166
11i		3	500
11j		5.6	190
11k		8.2	747
11l		20.4	1603
11m		5.7	1890
11n		29	1900
11o		1.1	100
11p		93	9500
11q		3.4	6630
11r		4.7	5000

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References and Notes

1. Yanagisawa, M.; Kurihara, H.; Kimura, S.; Tomobe, Y.; Kobayashi, M.; Mitsui, Y.; Yazaki, Y.; Goto, K.; Masaki, T. *Nature* **1988**, *332*, 411.
2. Arai, H.; Hori, S.; Aramori, I.; Ohkubo, H.; Nakanishi, S. *Nature* **1990**, *348*, 730.
3. Panek, R. L.; Major, T. C.; Hingorani, G. P.; Doherty, A. M.; Taylor, D. G.; Rapundalo, S. T. *Biochem. Biophys. Res. Comm.* **1992**, *183*, 566.
4. Ohlstein, E. H.; Arleth, A.; Bruyan, H.; Elliott, J. D.; Sung, C. P. *Eur. J. Pharmacol.* **1992**, *225*, 347.
5. DeNucci, G.; Thomas, R.; D'Orleans-Juste, P.; Antunes, E.; Walder, C.; Warner, T. D.; Vane, J. R. *Proc. Natl. Acad. Sci. USA* **1988**, *85*, 9797.
6. Moreland, S.; Mc Mullen, D. M.; Delaney, C. L.; Lee, V. G.; Hunt, J. T. *Biochem. Biophys. Res. Comm.* **1992**, *184*, 100.
7. (**a**) Doherty, A. M.; *J. Med. Chem.* **1992**, *35,* 1493. (**b**) Webb, M. L.; Meck, T. D. *Med. Res. Rev.* **1997**, *17*, 17. (**c**) Giaid, A.; Yanagisawa, M.; Langleben, D.; Michel, R. P.; Levy, R.; Shennib, H.; Kimura, S.; Masaki, T.; Duguid, W. P.; Path, F. R. C.; Stewart, D. J. *N. Engl. J. Med.* **1993**, 328, 1732. (**d**) Azuma, H.; Hidehisa, H.; Yasunari, N.; Takahido, T.; Osamu, M. *Am. J. Physiol.* **1994**, *267*, (Heart Circ.Physiol. 36): H2259-H2267. (**e**) Dao, H. H.; Moreau, P. *Expert Opin. Invest. Drugs* **1999**, *8*, 1807.
8. Ishikawa, K.; Fukami, T.; Nagase, T.; Fujita, K.; Hayama, T.; Niiyama, K.; Mase, T.; Ihara, M.; Yano, M. *J. Med. Chem.* **1992**, *35*, 2139.
9. Stein, P. D.; Hunt, J. T.; Floyd, D. M.; Moreland, S.; Dickinson, K. E. J.; Mitchell, C.; Liu, E. C. K.; Webb, M. L.; Murugesan, N.; Dickey, J.; Mc Mullen, D.; Zhang, R.; Lee, V. G.; Serafino, R.; Delaney, C.; Schaeffer, T. R.; Kozlowski, M. *J. Med. Chem.* **1994**, *37*, 329.
10. Winn, M.; Tasker, A. S.; Boyd, S. A.; Jae, H. S.; Von Geldern, T. N.; Bal, R. B.; Mantei, R. A.; Wu-Wong, J. R.; Chiou, W. J.; Dixon, D.; Opgenorth, T. J. In *210th National Meeting of the American Chemical Society*; Chicago, IL, 1995; Medi 030.
11. Ishikawa, K.; Ihara, M.; Noguchi, K.; Mase, T.; Mino, N.; Saeki, T.; Fukuroda, T.; Fukami, T.; Ozaki, S.; Nagase, T.; Nishikibe, M.; Yano, M. *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 4892.
12. Cody, W. L.; Doherty, A. M.; He, J. X.; De Pue, P. L.; Rapundalo, S. T.; Hingorani, G. A.; Major, T. C.; Panek, R. L.; Dudley, D. T.; Haleen, S. J.; La Douceur, D.; Hill, K. E.; Flynn, M. A.; Reynolds, E. F. *J. Med. Chem.* **1992**, *35*, 3301.
13. Clozel, M.; Breu, V.; Gray, G. A.; Kalina, B.; Loffler, B. M.; Burri, K.; Cassal, J. M.; Hirth, G.; Muller, M.; Neidhart, W.; Ramuz, H. *J. Pharmacol. Exp. Ther.* **1994**, *270*, 228.
14. Elliott, J. D.; Lago, M. A.; Cousins, R. D.; Gao, A.; Leber, J. D.; Erhard, K. F.; Nambi, P.; Elshourbagy, N. A.; Kumar, C.; Lee, J. A.; Bean, J. W.; De Brosse, C. W.; Eggleston, D. S.; Brooks, D. P.; Feuerstein, G.; Ruffolo, R. R. J.; Weinstock, J.; Gleason, J.; Peishoff, C. E.; Ohlstein, E. H. *J. Med. Chem.* **1994**, *37*, 1553.
15. Clemence, F.; Fortin, M.; Haesslein, J. L.. EP 498723, *Chem. Abstr* **1993**, *118*, 22154.
16. (a) Engler, C.; Dorant, K. *Ber.* **1895**, *28*, 2497. (b) Tokes, A. L.; Szilagyi, L. *Synth. Comm.* **1987**, *17*, 1235.
17. Haesslein, J. L., WO 9633190, *Chem. Abstr.* **1996**, *126*, 31277.
18. Very recently, highly selective (>10,000) ET_A receptors antagonists have been described: Wu, C.; Decker, E. R.; Blok, N.; Bui, H.; Chen, Q.; Raju, B.; Bourgoyne, A. R.; Knowles, V.; Biediger, R. J.; Market, R. V.; Lin, S.; Dupré, B.; Kogan, T. P.; Holland, G. W.; Brock, T. A.; Dixon, A. F. *J. Med. Chem.* **1999**, *42*, 4485.
19. Antagonists were injected as a bolus (1 mL/kg), ten min before endothelin was injected in a cumulative dose manner every two min (0.1–10 μg/kg, 0.1 mL/dose/rat) in pithed rats (male Sprague-Dawley).
20. ET-1 (10 nmol/kg IV) was used to induce sudden death in female Swiss mice ($n = 10$). Drugs were administered 10 min before ET-1 for iv administration and 30 min for po administration.