Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 7, No. 14, pp. 1883-1886, 1997
© 1997 Elsevier Science Ltd
All rights reserved. Printed in Great Britain
0960-894X/97 $17.00 + 0.00

PII: S0960-894X(97)00319-3

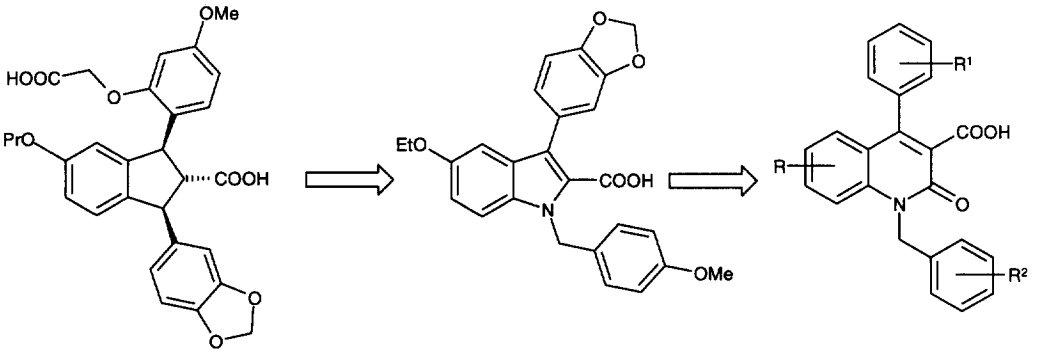
1,4-DIARYL-2-OXO-1,2-DIHYDRO-QUINOLINE-3-CARBOXYLIC ACIDS AS ENDOTHELIN RECEPTOR ANTAGONISTS

Werner W. K. R. Mederski*, Mathias Osswald, Dieter Dorsch, Maria Christadler, Claus-Jochen Schmitges, and Claudia Wilm
Merck KGaA, Preclinical Pharmaceutical Research, 64271 Darmstadt, Germany

Abstract: The discovery, synthesis and structure-activity relationships of a series of novel 1,4-diaryl-2-oxo-1,2-dihydro-quinoline-3-carboxylic acids as non-selective endothelin ET_A / ET_B receptor antagonists are described. The most potent inhibitor **3m** displayed an IC_{50} of 260 nM and 200 nM for ET_A and ET_B receptors, respectively. © 1997 Elsevier Science Ltd.

Introduction: The endothelins (ET-1, ET-2 and ET-3) are a peptide family of potent endogenous vasoconstrictor and pressor agents.[1] The ETs exert their biological effects by interacting with at least two specific G-protein coupled receptors (ET_A and ET_B) which are distinguished by their relative affinities for these peptides.[2] The ET_A subtype, which is selective for ET-1 over ET-3, is mainly found in vascular smooth muscle tissues and mediates vasoconstriction while the non-selective ET_B receptor appears to mediate either vasodilation or vasoconstriction, depending upon the tissue type.[3] Regarding the potential pathophysiological role of ET in cardiovascular disease, there is good evidence that ET regulates vascular tone and blood pressure. Studies with endothelin receptor antagonists in conditions associated with chronic vasoconstriction such as hypertension and heart failure, as well as in vasospastic disorders, such as subarachnoid haemorrhage and Raynaud's disease support the importance of endothelin in several diseases.[4]

Chart 1.



1 SB 209670

2 IC_{50} (ET_A) = 130.0 nM
IC_{50} (ET_B) = 300.0 nM
pA_2 (ET_A) = 6.4

3

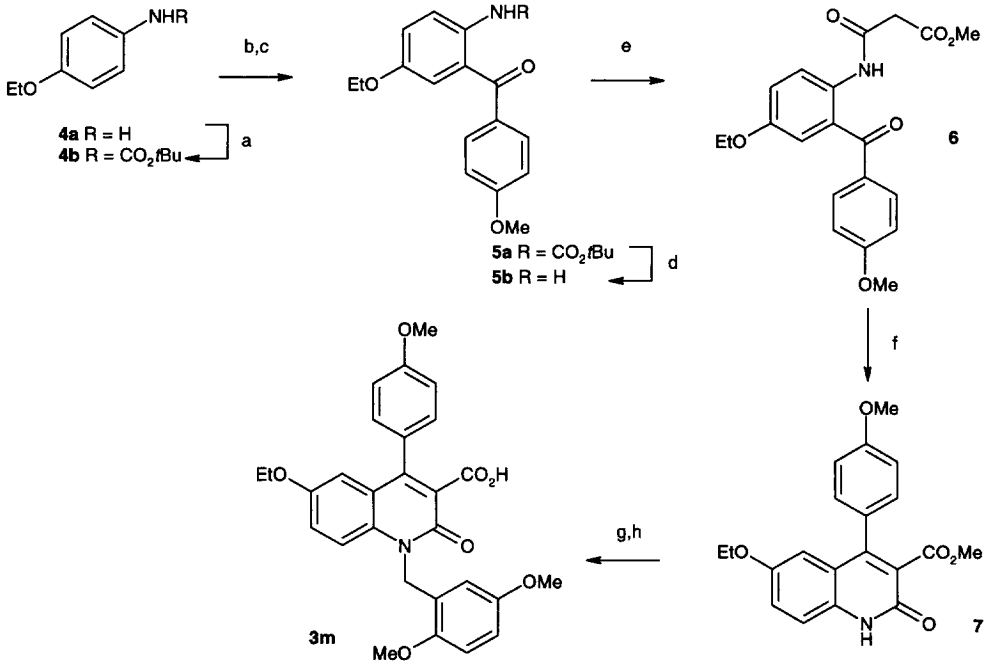
Previously several ET_A-selective non-peptide antagonists including BMS-182874 and PD 156707 were discovered as well as mixed ET_A / ET_B antagonists such as Bosentan, SB 209670 and L-749,329.[5] However, it is still not clear which of these will prove to be of greatest therapeutic value. Therefore we decided to investigate both classes of compounds. Recently, we described the identification of the potent ET_A-selective antagonist

* Fax: +49-6151-7315041; E-mail: mederski@merck.de

EMD 94246.[6] Of particular interest to us in the design of non-selective antagonists was the indane derivative SB 209670 (**1**) [chart 1].[7] We directed our attention to a series of *N*-1 substituted indoles and discovered compound **2**, which has moderate affinity for both the ET_A and ET_B receptor [chart 1]. Due to the disclosure of a series of indoles[8] we decided to replace the indole core structure by 6-membered rings. We superimposed the indole ring of **2** on different similarly substituted heterocycles after having determined the minimum energy conformations of these derivatives using the modelling program HyperChem™. A good overlap with indole **2** was achieved with 1,2-diaryl-2-oxo-1,2-dihydro-quinoline-3-carboxylic acids **3** [chart 1]. Herein, we report on their synthesis and structure-activity relationships.

Synthesis: The synthesis of the 2-oxo-1,2-dihydro-quinoline-based antagonists bearing an aryl group in 1 and 4 position is outlined in scheme 1. This general method is well illustrated by the preparation of compound **3m**.[9]

Scheme 1



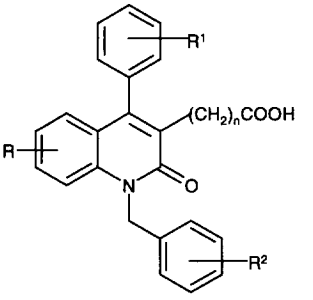
a. (t-BuOCO)$_2$O, THF, 65%; b. t-C_4H_9Li, 4-$MeOC_6H_4CHO$, THF, 20%; c. DMP (Dess-Martin periodinane), CH_2Cl_2, 80%; d. 5N HCl, dioxane, 90%; e. $ClCOCH_2COOCH_3$, $EtNH(i\text{-}Pr)_2$, DMF, 90%; f. NaOMe, MeOH, 87%; g. 2,5-$(MeO)_2C_6H_3CH_2Cl$, K_2CO_3, DMF, 72%; h. 1N NaOH, MeOH, THF, 82%.

Key step in the synthesis of 3-carboxylic acid of 2-quinolinone **3m** was the aromatic directed *ortho* metalation (DOM) reaction[10] of carbamic acid *tert.*-butyl ester **4b** to an *ortho*-lithiated species which undergoes reaction with electrophilic agents to yield 1,2-disubstituted products. *Para*-phenetidine **4a** was *N*-BOC (*tert.*-butoxycarbonyl) protected with di-*tert.*-butyl dicarbonate to give **4b**. *Ortho* alkylation of **4b** with 4-methoxybenzaldehyde in the presence of *tert.*-butyllithium to the corresponding alcohol[11] followed by Dess-Martin oxidation[12] afforded the BOC-amido benzophenone **5a**. The BOC group was subsequently removed by treatment with hydrochloric acid to generate 2-amino benzophenone **5b** in modest overall yield. The quinolone nucleus was formed *via* an intramolecular Knoevenagel condensation. Therefore, benzophenone **5b** was acylated with methyl malonyl chloride to give compound **6** and then cyclised with sodium methoxide to give

quinolinone **7** in high yield.[13] Alkylation of **7** with 2,5-dimethoxybenzyl chloride in the presence of potassium carbonate gave a mixture of *N*- and *O*-alkylated products which were easily separated by silica gel chromatography. Alkaline hydrolysis of the resulting *N*-alkylated ethyl ester provided the targeted acid **3m** in good yield.

Results and discussion: The compounds were screened for their ability to inhibit specific [^{125}I]-ET-1 binding to rat aorta membranes (ET_A) and porcine kidney (inner medulla) membranes (ET_B).[14] The receptor binding affinities of compounds **3a-n** are summarized in table 1.

Table I. Endothelin Receptor Binding Affinity [IC_{50} (μM)]



Cpd	R	R^1	R^2	n	ET_A	ET_B
3a	H	3,4-OCH_2O-	H	0	>10.0	>10.0
3b	H	3,4-OCH_2O-	4-OMe	0	2.4	6.8
3c	H	3,4-OCH_2O-	3-OMe	0	>10.0	>10.0
3d	H	3,4-OCH_2O-	3,4-OCH_2O-	0	2.6	2.7
3e	H	3,4-OCH_2O-	2-OMe	0	2.0	0.94
3f	H	3,4-OCH_2O-	2-OMe	1	>10.0	>10.0
3g	6-OEt	3,4-OCH_2O-	2-OMe	0	0.38	0.45
3h	6-Et	3,4-OCH_2O-	2-OMe	0	1.5	1.3
3i	5,6-diOMe	3,4-OCH_2O-	2-OMe	0	3.3	2.6
3k	6-OEt	4-OMe	2-OMe	0	1.3	0.50
3m	6-OEt	4-OMe	2,5-diOMe	0	0.26	0.20
3n	6-OEt	2,4-diOMe	2-OMe	0	1.2	0.54

The effects of electron donating substituents at each aromatic ring were investigated. We began our studies with the unsubstituted quinolinones **3a** - **3e** (R = H, R^1 = 3,4-OCH_2O-) and varied the benzyl substituent R^2 at *N*-1. Of the aforementioned compounds the *ortho* methoxy derivative **3e** showed affinities which was the best for both ET_A and ET_B receptor in the micromolar range. Therefore, the *ortho* methoxy substitution on this ring was kept constant. Replacement of the carboxy function in **3e** by an acetic acid moiety led to compound **3f**, which was inactive. To improve the binding affinity, molecules with additional substituents at the phenyl ring of the quinolinone nucleus were synthesized. We expected that analogues with electron donating groups in 5- or 6-position (R in table 1) exhibit higher affinity. Substituting the quinolinone ring in 6-position with an ethoxy ether (**3g**) caused an additional increase in binding affinity for both receptors whereas substitution with ethyl (**3h**) or dimethoxy (**3i**) retained activity relative to compound **3e**.

In vivo a methylendioxyphenyl moiety is suspected to inhibit and induce cytochrome P450, and therefore can cause unfavourable drug interactions.[15] For this reason, we synthesized the 4-methoxy analogue **3k**. This deri-

vative showed diminished affinity for the ET_A receptor in comparison with **3g**. However, introducing a second methoxy group in 5-position of the benzyl ring led to analogue **3m** with nearly balanced affinity in the submicromolar range for both receptors. On the contrary, a second methoxy substituent in 2-position of the 4-phenyl ring (**3n**) afforded no advantage for binding.

For quinolinone **3m**, functional ET_A antagonism was determined by generating an ET-1 concentration-response curve in isolated rat aortic rings without endothelium.[16] Compound **3m** is a functional antagonist of the ET_A receptor with a pA_2 value of 5.2. This is about an order of magnitude larger than expected from the IC_{50} value for the receptor binding and is different from the finding in the indole series (*cf.* compound **2**), where both parameters correlate well for the ET_A receptor.

In summary, we have developed a series of novel quinolinone derivatives that display low micromolar binding affinity for both the ET_A and ET_B receptor. However, the most potent compound in this series **3m** demonstrated diminished functional ET_A antagonistic activity.

Acknowledgement: We would like to thank Martina Germann and Karin Rauschenbach-Ruess for preparing the compounds mentioned in this paper and Christina Heiner, Patric Kriesch, Gabriele Mahr, Rolf Löffler and Lydia Schulze for measuring the biological data.

References and notes:.

1. Yanagisawa, M.; Kurihara, H.; Kimura, H.; Tomobe, Y.; Kobayashi, M.; Mitsui, Y.; Yazaki, Y.; Goto, K.; Masaki, T. *Nature* **1988**, *332*, 411.
2. (a) Arai, H.; Hori, S.; Aramori, I.; Ohkubo, H.; Nakanishi, S. *Nature* **1990**, *348*, 730. (b) Sakurai, T.; Yanagisawa, M.; Takuwa, Y.; Miyazaki, H.; Kimura, S.; Goto, K.; Masaki, T. *Nature* **1990**, *348*, 732.
3. (a) Miller, R. C.; Pelton, J. T.; Huggins, J. P. *Trends Pharm. Sci.* **1993**, *14*, 54. (b) Lüscher, T. F.; Oemar, B. S.; Boulanger, C. M.; Hahn, W. A. *Journal of Hypertension* **1993**, *11*, 7.
4. Rubanyi, G. M.; Polokoff, M. *Pharmacol. Rev.* **1994**, *46*, 325.
5. Webb, M. L.; Meek, T. D. *Medicinal Research Reviews* **1997**, *17*, 17.
6. Osswald, M.; Mederski, W. W. K. R.; Dorsch, D.; Christadler, M.; Wilm, C.; Schmitges, C.-J.; Ladtstetter, B. J. *Abstract of Papers*, 211th Am. Chem. Soc. Natl. Mtg., New Orleans, March 24-29, **1996**, MEDI 143.
7. 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.; DeBrosse, C. W.; Eggleston, D. S.; Brooks, D. P.; Feuerstein, G.; Ruffolo, Jr., R. R.; Weinstock, J.; Gleason, J. G.; Peishoff, C. E.; Ohlstein, E. H. *J. Med. Chem.* **1994**, *37*, 1553.
8. Elliott, J. D.; Leber, J. D. *PCT Int. Appl.*, WO 94 14,434 (Chem. Abstr. **1994**, *121*, 205207).
9. All new compounds were characterized by IR, NMR and mass spectra and afforded correct combustion data. For **3m**: mp 178-180°C; IR (KBr) 1736, 1605 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ ppm: 13.08 (sbr, 1H), 7.35 (d, J = 8.7 Hz, 2H), 7.23 (d, J = 2.9 Hz, 2H), 7.10 (d, J = 8.7 Hz, 2H), 7.03 (d, J = 9.0 Hz, 1H), 6.84 (dd, J = 9.0 Hz, J = 3.0 Hz, 1H), 6.66 (d, J = 2.5 Hz, 1H), 6.19 (d, J = 3.0 Hz, 1H), 5.42 (s, 2H), 3.90 (s, 3H), 3.86 (q, J = 7.0 Hz, 2H), 3.84 (s, 3H), 3.59 (s, 3H), 1.23 (tr, J = 7.0 Hz, 3H); MS (FAB), m/z = 490 (M^+). Anal. calcd. for $C_{28}H_{27}NO$ (489.53): C, 68.70; H, 5.56; N, 2.86; found: C, 68.5; H, 5.7; N, 2.9.
10. Snieckus , V. *Chem. Rev.* **1990**, *90*, 879.
11. Muchowski, J. M.; Venuti, M. C. *J. Org. Chem.* **1980**, *45*, 4798.
12. Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.
13. Robl, J. A. *Synthesis* **1991**, 56.
14. Sograbe, K.; Nirei, H.; Shoubo, M.; Nomoto, A.; Ao, S.; Notsu, Y.; Ono, T.; *J. Pharmacol. Exp. Therap.* **1993**, *264*, 1040.
15. Kumagai, Y.; Fukuto, J. M.; Cho, A. K. *Curr. Med. Chem.* **1994**, *4*, 254.
16. Clozel, M.; Breu, V.; Burri, K.; Cassal, J.-M.; Fischli, W.; Gray, G. A.; Hirth, G.; Löffler, B.-M.; Müller, M.; Neidhart, W.; Ramuz, H. *Nature* **1993**, *365*, 759.

(*Received in Belgium* 6 *March* 1997; *accepted* 16 *June* 1997)