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

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**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  $\text{ET}_A$  /  $\text{ET}_B$  receptor antagonists are described. The most potent inhibitor **3m** displayed an IC<sub>50</sub> of 260 nM and 200 nM for  $\text{ET}_A$  and  $\text{ET}_B$  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.<sup>1</sup> The ETs exert their biological effects by interacting with at least two specific Gprotein coupled receptors ( $ET_A$  and  $ET_B$ ) which are distinguished by their relative affinities for these peptides.<sup>2</sup> 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.<sup>3</sup> 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.<sup>4</sup>



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.<sup>5</sup> 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.<sup>6</sup> Of particular interest to us in the design of non-selective antagonists was the indane derivative SB 209670 (1) [chart 1].<sup>7</sup> 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<sup>8</sup> 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<sup>TM</sup>. 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.<sup>9</sup> Scheme 1



a. (*t*-BuOCO)<sub>2</sub>O, THF, 65%; b. *t*-C<sub>4</sub>H<sub>9</sub>Li, 4-MeOC<sub>6</sub>H<sub>4</sub>CHO, THF, 20%; c. DMP (Dess-Martin periodinane), CH<sub>2</sub>Cl<sub>2</sub>, 80%; d. 5N HCl, dioxane, 90%; e. ClCOCH<sub>2</sub>COOCH<sub>3</sub>, EtNH(*i*-Pr)<sub>2</sub>, DMF, 90%; f. NaOMe, MeOH, 87%; g. 2,5-(MeO)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>CH<sub>2</sub>Cl, K<sub>2</sub>CO<sub>3</sub>, 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<sup>10</sup> 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*.-butyscarbonyl) 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<sup>11</sup> followed by Dess-Martin oxidation<sup>12</sup> 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.<sup>13</sup> 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 [<sup>125</sup>I]-ET-1 binding to rat aorta membranes ( $ET_A$ ) and porcine kidney (inner medulla) membranes ( $ET_B$ ).<sup>14</sup> The receptor binding affinities of compounds **3a-n** are summarized in table 1.

**Table I.**Endothelin Receptor Binding Affinity [IC50 (µM)]



Cpd	R	R <sup>1</sup>	R <sup>2</sup>	n	ETA	ETB
3a	Н	3,4-OCH <sub>2</sub> O-	Н	0	>10.0	>10.0
3b	Н	3,4-OCH <sub>2</sub> O-	4-OMe	0	2.4	6.8
3c	Н	3,4-OCH <sub>2</sub> O-	3-OMe	0	>10.0	>10.0
3d	Н	3,4-OCH <sub>2</sub> O-	3,4-OCH <sub>2</sub> O-	0	2.6	2.7
3e	Н	3,4-OCH <sub>2</sub> O-	2-OMe	0	2.0	0.94
3f	Н	3,4-OCH <sub>2</sub> O-	2-OMe	1	>10.0	>10.0
3g	6-OEt	3,4-OCH <sub>2</sub> O-	2-OMe	0	0.38	0.45
3ĥ	6-Et	3,4-OCH <sub>2</sub> O-	2-OMe	0	1.5	1.3
3i	5,6-diOMe	3,4-OCH <sub>2</sub> O-	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<sup>1</sup> = 3,4-OCH<sub>2</sub>O-) and varied the benzyl substituent R<sup>2</sup> at N-1. Of the aforementioned compounds the *ortho* methoxy derivative 3e showed affinities which was the best for both ET<sub>A</sub> and ET<sub>B</sub> 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.<sup>15</sup> 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 4phenyl ring (**3n**) afforded no advantage for binding.

For quinolinone **3m**, functional  $\text{ET}_A$  antagonism was determined by generating an ET-1 concentrationresponse curve in isolated rat aortic rings without endothelium.<sup>16</sup> Compound **3m** is a functional antagonist of the ET<sub>A</sub> receptor with a pA<sub>2</sub> value of 5.2. This is about an order of magnitude larger than expected from the IC<sub>50</sub> 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<sub>A</sub> 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.

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## References and notes:.

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- 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<sup>-1</sup>; <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) 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<sup>+</sup>). Anal. calcd. for C<sub>28</sub>H<sub>27</sub>NO (489.53): C, 68.70; H, 5.56; N, 2.86; found: C, 68.5; H, 5.7; N, 2.9.
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