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Nonpeptide Endothelin Antagonists: from Lower Affinity Pyrazol-5-ols to Higher Affinity Pyrazole-5-carboxylic Acids

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Abstract—Random screening of compounds in endothelin receptor (ET_A and ET_B) binding assays led to the discovery of a new class of pyrazol-5-ol ligands. Characterization of structural features crucial for binding activities of these pyrazol-5-ols, by structure–activity-relationship (SAR) studies, allowed us to design a novel class of pyrazole-5-carboxylic acids as more potent ET antagonists.

Introduction

The endothelins (ET-1, 2 and 3) constitute a family of homologous 21-amino acid peptides, with ET-1 being one of the most potent vasoconstrictors identified to date.[1] Although originally isolated from endothelial cells, these peptides are also produced by a number of other cell types.[2] The ETs exert their biological effects by interacting with at least two specific G-protein coupled membrane receptors (ET_A and ET_B) which are differentiated by their relative affinities for these peptides.[3] ET_A receptors are mainly found in the vascular smooth muscle tissues and can mediate both vasodilation[4] or vasoconstriction,[5] depending on their tissue localization. As a result of their potent and long-lasting vasoconstrictor effects, endothelin receptor blockade has been proposed as a target for therapeutic intervention in numerous diseases, such as myocardial infarction, hypertension, heart failure, atherosclerosis, cerebral and coronary vasospasm, acute renal failure and asthma.[6] The discovery of both potent subtype selective and nonselective ET antagonists should be extremely useful in clarifying the physiological and pathological roles of endothelins, and thereby providing useful chemotherapeutic agents.[7]

The screening of our in house compound library on ET receptor binding assays allowed us to identify a series of pyrazol-5-ols with modest affinities to both ET_A and ET_B subtypes.

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These pyrazol-5-ols are structurally different from most of the other endothelin antagonists reported in the literature.[8] We wish to describe herein the synthesis and SAR studies of this pyrazol-5-ol series, which led us to the more potent pyrazole-5-carboxylic acid series.

Chemistry

The pyrazol-5-ol compounds used in this study were prepared by two methods outlined in Scheme 1.[9] All the 3-polyfluoroalkyl pyrazol-5-ols **5**–**25** (Tables 1–4) were synthesized by route **A:** the commercially available β-ketoesters **1** were deprotonated by NaH in toluene and then alkylated with the appropriate benzyl halides in the presence of NaI, using aliquat-336 as phase transfer agent. The corresponding α-alkylated β-ketoesters **2** were then refluxed in acetic acid with the appropriate salt-free benzyl hydrazines to afford the desired pyrazol-5-ols **5**–**25**. The salt-free benzyl hydrazines were obtained by neutralization with NaOH (1N) in water of the corresponding benzyl hydrazine hydrochlorides which were prepared according to a literature method.[10] The other pyrazol-5-ols **26**–**29** (Table 4) were prepared by route **B:** the commercially available β-ketoesters **1** were transformed to the corresponding pyrazolones **3** under similar conditions to the second step of route **A**. Refluxing of these pyrazolones **3** with piperonal in toluene in the presence of $ZnCl_2$ as catalyst afforded the compounds **4**, which were hydrogenated over Pd/C in ethyl acetate, to yield the final pyrazol-5-ols **26**–**29**.

Several *O*-alkylated derivatives **5a**–**f** of pyrazol-5-ol **5** were prepared as depicted in Scheme 2. Alkylation of **5**

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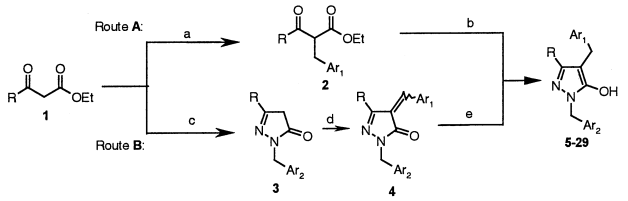
with methyl iodide, ethyl bromoacetate, ethyl 4-bromobutyrate and 2-bromoethanol in the presence of K_2CO_3 in DMF afforded the compounds **5a**,**b**,**d**,**f** respectively. The acids **5c** and **5e** were obtained by saponification of corresponding **5b** and **5d** with NaOH (2N) in ethanol.

The pyrazole 5-carboxylic acids **37a**,**b** were synthesized according to the method outlined in Scheme 3.[9] The α,γ-diketoester **30** prepared from acetophenone by a literature method,[11] was treated with hydrazine monohydrate in EtOH at reflux to afford the corresponding pyrazole **31**. Bromination of **31** with NBS in CH_2Cl_2 yielded the bromopyrazole **32** which was then alkylated with 3-methoxybenzyl chloride in the presence of NaH in DMF at room temperature to give the desired compound **33**. Stille coupling of **33** with the corresponding stannanes **35a**,**b** in the presence of $Pd_2(dba)_3CHCl_3$-(dppf) in DMF at 60 °C afforded the compounds **36a**,**b**. The requisite stannanes were prepared from the corresponding benzyl chlorides **34a**,**b** with $(Bu_3Sn)_2$ in the presence of $Pd(PPh_3)_4$.[12] The final pyrazole carboxylic acids **37a**,**b** were obtained by saponification of **36a**,**b**.

Results and Discussion

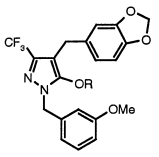
The inhibition of endothelin binding to ET_A and ET_B receptors was measured using ^{125}-I labeled ET-1 competition assays.[9] Despite the large number of pyrazol-5-ols tested before starting this work, only a few compounds (Table 2: **5**, **6** and **7**; Table 3: **15**) were identified by initial screening as weak endothelin receptor ligands, with IC_{50}s superior to 1 μM. They all contained a 3-trifluoromethyl group and two different substituted benzyl groups at position 1 and 4 of the pyrazol-5-ol. Indeed, other pyrazol-5-ols with either hydrogen atom or a small alkyl group (i.e., *n*-propyl) replacing one of the two benzyl groups did not show any affinity at all. These findings suggested that the 1,4-dibenzyl-pyrazol-5-ol was the minimum structure necessity for ET receptor binding affinities. Moreover, structural analysis (NMR and IR),[13] revealed that most of these compounds were in the enol-form (i.e., the pyrazol-5-ol), and not in the pyrazolone form.

Among the various structural features of the initial weakly active pyrazol-5-ols, the hydroxy function is the most likely to give a hydrogen bond or an ionic interaction within the ET receptors. Therefore, it was decided to investigate its contribution to the binding affinities. Thus, several *O*-alkylated derivatives of the pyrazol-5-ol **5**, which displayed the highest binding affinities (IC_{50}s: 1.5 μM/ET_A; 11 μM/ET_B) in our screening assays, were synthesized (Table 1). The lack of affinities of the *O*-methyl analogue **5a** highlighted the importance of this hydroxy group. pK_a Measurement in ethanol:water (1:1) system showed this hydroxy function to be slightly acidic ($pK_a = 6$). More acidic functions were then introduced at various distances from the pyrazole nucleus. Compound **5c** showed improved affinities for both ET receptors, whereas its precursor, ester **5b**, did not show any affinity at all. This result indicated that an acid group was required for potent binding in this region within the ET receptors. Increasing the length of the spacer between



Scheme 1. Reagents and conditions: (a) (i) NaH/toluene; (ii) Ar_1CH_2Cl, NaI and aliquat-336, reflux; (b) (i) $Ar_2CH_2NHNH_2$.HCl, NaOH (1N); (ii) **2**/AcOH, reflux; (c) (i) $Ar_2CH_2NHNH_2$.HCl, NaOH (1N); (ii) **1**/AcOH, reflux; (d) Ar_1CHO, $ZnCl_2$, toluene, reflux; (e) H_2, Pd/C, AcOEt.

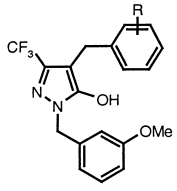
Table 1. In vitro endothelin receptor binding affinity (IC_{50} (μM)) for compounds **5**, **5a**–**f**



No.	R	IC_{50} (μM)	
		ET_A[a]	ET_B[b]
5	H	1.5	11
5a	Me	*n*[c]	*n*
5b	CH_2COOEt	*n*	*n*
5c	CH_2COOH	0.45	2.2
5e	$(CH_2)_3COOH$	64	*n*
5f	CH_2CH_2OH	40	>25

[a]Rat heart ventricles.
[b]Rat cerebellum.
[c]*n* = No measurable affinity.

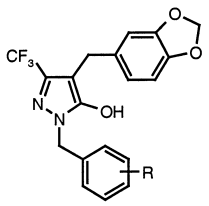
Table 2. In vitro endothelin receptor binding affinity (IC_{50} (μM)) for compounds **5**–**14**



No.	R	IC_{50} (μM)	
		ET_A[a]	ET_B[b]
5	3,4-Methylenedioxy	1.5	11
6	H	98	*n*[c]
7	4-F	40	*n*
8	4-Cl	4.3	22
9	3,4-diCl	10	8.4
10	3,4-Methylenedioxy-5-Cl	1.3	5.4
11	3,4-Methylenedioxy-6-Cl	0.6	2.4
12	4-OMe	48	39
13	3,4-$(OMe)_2$	*n*	*n*
14	3,4,5-$(OMe)_3$	*n*	*n*

[a]Rat heart ventricles.
[b]Rat cerebellum.
[c]*n* = No measurable affinity.

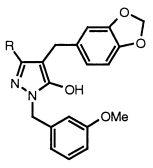
Table 3. In vitro endothelin receptor binding affinity (IC_{50} (μM)) for compounds **5**, **15**–**23**



No.	R	IC_{50} (μM)	
		ET_A[a]	ET_B[b]
5	3-OMe	1.5	11
15	H	10	24
16	2-Cl	3.8	25
17	3-Cl	1.9	14
18	2-OMe	1.8	33
19	4-OMe	2.1	9.2
20	2-(OCH_2COOH)-4-OMe	3.8	12
21	3-OH	1.7	36
22	3-OCH_2COOH	3.5	29
23	3,4-methylenedioxy	5.6	17

[a]Rat heart ventricles.
[b]Rat cerebellum.

Table 4. In vitro endothelin receptor binding affinity (IC_{50} (μM)) for compounds **5**, **24**–**29**

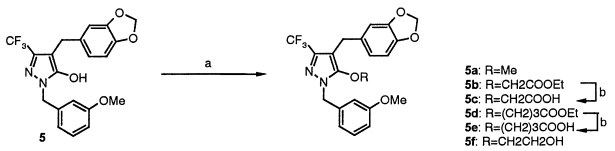


No.	R	IC_{50} (μM)	
		ET_A[a]	ET_B[b]
5	CF_3	1.5	11
24	CF_2CF_3	0.11	3.3
25	$CF_2CF_2CF_3$	0.14	1.0
26	Me	20	*n*[c]
27	4-MeO-$PhCH_2$	7.5	24
28	Ph	0.42	3.2
29	4-NO_2-Ph	3.1	15

[a]Rat heart ventricles.
[b]Rat cerebellum.
[c]n = No measurable affinity.

the acid function and the pyrazole nucleus resulted in decreased potency (**5e**). The extremely poor affinities of the corresponding alcohol analogue **5f**, nearly 100 times less potent than **5c** towards ET_A receptor, provided further evidence for an ionic interaction between the hydroxy group of these pyrazol-5-ols and the ET receptors.

As we demonstrated the crucial role of the hydroxy group, we turned our attention toward the two-benzyl groups, which also appeared to be important for ET receptor binding affinities as shown by preliminary screening results. Table 2 summarizes the IC_{50}s of derivatives with a range of different substituents on the 4-benzyl



Scheme 2. Reagents and conditions: (a) K_2CO_3, DMF, rt, MeI (**5a**); $BrCH_2COOEt$ (**5b**); $Br(CH_2)_3COOEt$ (**5d**); $BrCH_2CH_2OH$ (**5f**); (b) NaOH (2N), EtOH.

group. Compound **6** with an unsubstituted benzyl showed very poor affinity for ET_A and no affinity for ET_B subtype. A slightly better affinity for ET_A receptor was obtained with a 4-fluorine atom (**7**). A similar effect for ET_A was observed with a 4-methoxy group, together with a gain in affinity for the ET_B receptor (**12**). However introduction of additional methoxy substituents had deleterious effects on binding (**13**, **14**). Replacing the 4-fluorine substituent by chlorine resulted in a modest affinity for ET_B subtype while increasing affinity for ET_A receptor by one order of magnitude. Introduction of a second chlorine at 3-position slightly improved ET_B but not ET_A binding. However, the highest affinities for both receptors were observed with compounds **5**, **10** and **11** which all contain a 3,4-methylenedioxybenzyl group (i.e., piperonyl). The most potent derivative was pyrazol-5-ol **11**, which possessed a 3,4-methylenedioxy-6-chloro-benzyl group. Interestingly, changing the 3,4-methylenedioxy for a 3,4-dimethoxy resulted in a complete loss of affinity for both ET receptor subtypes as already mentioned (**5** versus **13**). This remarkable contribution of the 3,4-methylenedioxy substituent to potency has also been observed by other groups.[14] One possible explanation is the oxygen atoms in the methylenedioxy functionality are rigid and well orientated for binding interaction with ET receptors while those in the two methoxy groups could not give this kind of interactions, perhaps because of steric effects resulting from the two methyl groups.

Since the 3,4-methylendioxybenzyl group is such an important contributor to the binding potency, it was maintained for the investigation of the second benzyl moiety (Table 3). IC_{50} Data examination of these compounds suggested that all substituted benzyl groups (compounds **5**, **16**–**23**) improved the ET_A receptor binding affinities by 2 to 6 fold compared to the unsubstituted benzyl (**15**), but had less effect on the ET_B receptor binding affinities.

All the compounds described above incorporated the hydrophobic and electron-withdrawing 3-trifluoromethyl. Therefore, this group could not only contribute to stabilize the enol-form but also to increase the acidity of the hydroxy group. In order to define the optimal structural requirement for the substituent at 3 position of these pyrazol-5-ol derivatives, several analogues (**24**–**29**) were prepared (Table 4).

Replacement of the CF_3 by more hydrophobic pentafluoroethyl (**24**) or heptafluoropropyl (**25**) of similar electron-withdrawing potency, improved significantly both ET receptor binding affinities. On the other hand,

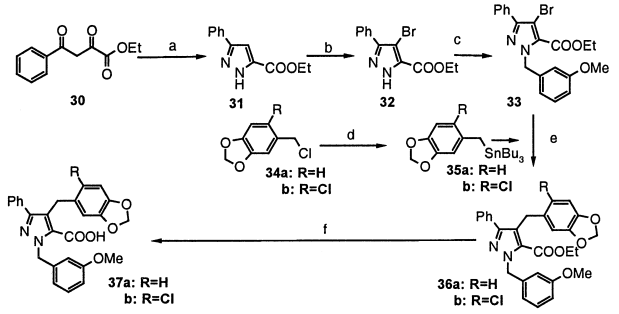
its replacement by a CH_3 group (**26**) had the opposite effect (IC_{50}s of **25** decreased while those of **26** increased, both by one order of magnitude). This could be either due to the low lipophilicity of this methyl or to its electron-donating effect which, in contrast to the CF_3 group, favours the keto- over the enol-form, as confirmed by NMR and IR spectra analysis.[15] Compound **27** with a more lipophilic 4-methoxybenzyl group, despite the predominance of the keto-form, displayed better affinities than the methyl analogue **26**, but nevertheless lower affinities than compound **5**. Compound **28**, with a lipophilic phenyl group which at the same time favours the enol-form by conjugation effect, displayed better affinities than compound **5**. Introduction of a nitro group at the 4-position of this phenyl decreased the binding affinities, probably by repulsive effect between the dipole of the NO_2 group and the ET receptors. These studies clearly indicated, not only the crucial role of the substituent at the 3 position of the pyrazole ring, but also the importance of its liphophilic properties. They also highlighted the influence of their inductive effects on the acidity of the hydroxyl at the 5 position. Therefore, they confirmed our initial hypothesis on the existence of a strong and specific ionic interaction between the hydroxy and the ET receptors.

From these SAR studies, four structural features on the pyrazole ring were identified as key requirements for the ET receptor binding: an acidic functionality flanked by two benzyl groups (one of them being piperonyl), and a hydrophobic substituent located next to the piperonyl. Based on this pharmacophore hypothesis, we synthesized two pyrazole-5-carboxylic acids **37a**,**b** (Table 5) (Scheme 3).

Table 5. In vitro endothelin receptor binding affinity (IC_{50} (μM)) for compounds **37a**,**b**

No.	R	IC_{50} (μM)	
		ET_A[a]	ET_B[b]
37a	H	0.028	0.040
37b	Cl	0.018	0.034

[a]Rat heart ventricles.
[b]Rat cerebellum.



Scheme 3. Reagents and conditions: (a) $NH_2NH_2.H_2O$, EtOH, reflux; (b) NBS, CH_2Cl_2, rt; (c) 3-MeO-PhCH_2Cl, NaH, DMF, rt; (d) $(Bu_3Sn)_2$, $Pd(PPh_3)_4$, toluene, reflux; (e) $Pd_2(dba)_3CHCl_3$-(dppf), DMF, 60 °C; (f) NaOH (2N), EtOH.

The pyrazole-5-carboxylic acid **37a** displayed 10-fold improved ET_A and nearly 100-fold improved ET_B binding affinity compared to the corresponding pyrazol-5-ol **28**. Introduction of the 6-chloropiperonyl, which was shown to be the best substituent in the pyrazol-5-ol series, gave the most potent pyrazole-5-carboxylic acid **37b**. These encouraging results were in complete agreement with our pharmacophore model obtained from the SAR studies of the pyrazol-5-ols. Additional results concerning this novel class of ET antagonists will be communicated in due course.

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References and Notes

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13. Data for compound **5**: ^{1}H NMR (250 MHz, CD_3OD, ppm): δ 3.76 (s, 5H), 5.09 (s, 2H), 5.96 (s, 2H), 6.65.85 (m, 6H), 7.21 (m, 1H); IR (Nujol PE580): 3500–3200 (OH), 1612, 1590, 1576, 1492 cm^{-1}.

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15. Data for compound **26**: ^{1}H NMR (250 MHz, CD_3OD, ppm): keto-form (I): δ 2.0 (s, 3H), 3.28 (t, 1H), 3.78 (s, 3H), 4.62.78 (dd, 2H), 5.91 (S, 2H), 6.57.88 (m, 6H), 7.16 (t, 1H); enol-form (II): δ 1.99 (s, 3H), 3.55 (s, 2H), 3.76 (s, 3H), 4.82 (s, 2H), 5.89 (s, 2H), 6.57.88 (m, 6H), 7.25 (m, 1H); keto-form (I): enol-form (II) = 2:1 ; IR ($CHCl_3$): 1698, 1602, 1590, 1504, 1492 cm^{-1}.