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SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIPS OF 9-SUBSTITUTED ACRIDINES AS ENDOTHELIN-A RECEPTOR ANTAGONISTS

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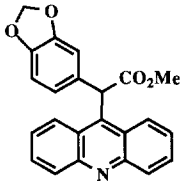
Abstract. Screening of a compound library against endothelin receptors (ET_A and ET_B) revealed PD 102566 (compound **1**) as an ET_A selective antagonist. Synthesis and structure-activity relationships (SAR) of a series of analogs are described.

Introduction. Endothelin-1 (ET-1) is a 21-amino acid peptide that was originally isolated from endothelial cells.[1] Along with ET-2 and ET-3, this relatively new class of peptides are potent vasoconstrictors with a range of additional biological activities.[2] Endothelin exerts its biological activity by interaction with endothelin receptors, of which two distinct subtypes, known as ET_A and ET_B, have been cloned and expressed from human tissues.[3] The ET_A receptor subtype is selective for ET-1 and mainly resides in vascular smooth muscle cells mediating vasoconstriction. The ET_B receptor is isopeptide non selective and mediates both vasoconstriction and vasodilatation in different tissues. A number of non peptide ET antagonists have been reported in recent years including ET_A selective agents PD 156707,[4] BMS-182874,[5] A-127722,[6] and ET_A/ET_B balanced antagonists Bosentan,[7] SK 209670,[8] L-754142.[9] Development of ET antagonists offers a potentially novel approach to the treatment of a variety of human diseases such as essential hypertension, acute myocardial infarction, pulmonary hypertension, cerebral ischemia, congestive heart failure, and subarachnoid hemorrhage.[10] In view of the fact that the ET_B receptor mediates vasodilatation and inhibition of platelet aggregation and that the ET_B receptor has been reported to play a role in clearance, its blockade may not always be beneficial. In addition, the ET_A receptor is widely localized in human tissues and mediates certain known vasoconstriction responses.[11] Development of ET_A selective antagonists may prove to be advantageous in treating human diseases.

Screening of the Parke-Davis compound library using the rabbit ET_A receptor (rET_A, rabbit renal artery vascular smooth muscle cells) identified PD 102566 (compound **1**) as an ET_A selective antagonist with moderate potency. Compound **1** showed no binding affinity to the human ET_B receptor (CHO cells) up to concentration of 250 μM. In order to evaluate the importance of various portions of the molecule in compound **1** to ET_A receptor binding affinity, a SAR study was carried out.



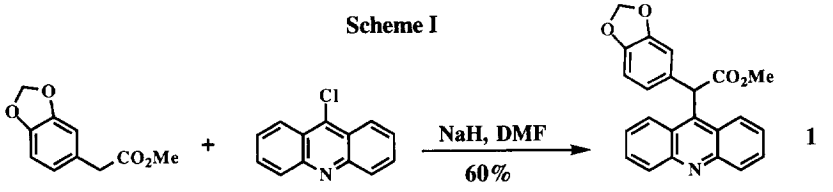
PD 102566 (1)

IC_{50} (rET_A) = 2.8 μM
IC_{50} (hET_A) = 4.3 μM
IC_{50} (hET_B) > 250 μM

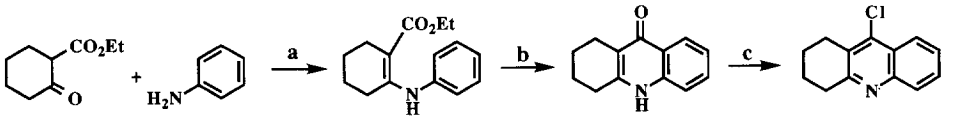
Chemistry. As shown in Scheme I, compounds **1** and **3-8** were synthesized in good yields by mixing the anion of a specific phenyl acetic acid ester, generated by NaH in DMF, with 9-chloroacridine through an addition-elimination process. Syntheses of **10** and **11** required preparation of substituted 4-chloro-quinolines via the route exemplified in Scheme II. Condensation of aniline with an appropriately substituted β-keto ester occurred smoothly in toluene with a catalytic amount of TsOH. The product was directly refluxed in Dowtherm at 220 °C to afford the quinolone, which was subsequently converted to the 4-chloroquinoline by refluxing in $POCl_3$ in

excellent yield. The coupling reaction with **2** required heating at 70 °C due to the reduced reactivity of 4-chloroquinoline compared with 9-chloroacridine. To study SAR on the side chain, the route we initially proposed was to hydrolyze **1** to the acid **30** followed by functional group manipulations. However, under various saponification conditions, we were unable to isolate the acid due to immediate decarboxylation (Scheme III). Alternatively, several esters of 3,4-methylenedioxyphenyl acetic acid were synthesized and further reacted through the anion, generated by NaH, with 9-chloroacridine (**17-22**). Alcohol **23** was obtained in 91% yield by reduction of **1** with DIBAL-H and it was converted to the aldehyde **24** by Swern oxidation. Attempts to obtain the acid **30** by Jones oxidation of **24**, hydrogenation (Pd/C) of **17**, acid hydrolysis of **22** (TFA or HCl), or by DDQ oxidation[12] of **20** were all unsuccessful due to the inherent instability of the product. The amides **25** and **26** were synthesized by reacting **1** and **9** in NH_3 under pressure. The tether-modified analogs **27-29** were successfully synthesized by similar coupling reactions. Noticeably, **28** was synthesized by reaction of the alkoxide, generated from the corresponding mandelate with *n*-BuLi, with 9-chloroacridine. Saponification of **28** under mild conditions (1 eq. LiOH, rt) again led to decarboxylated product.

Scheme I

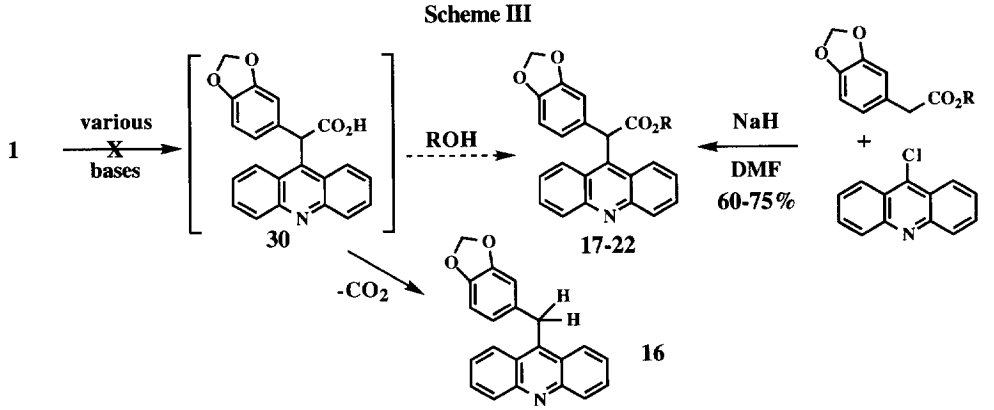


Scheme II



(a) TsOH, toluene, reflux, 55%. (b) Dowtherm, 220 °C, 67%. (c) $POCl_3$, reflux, 75%. 2-Ph-9-Cl-quinoline was made similarly from ethyl benzoylacetate and aniline.

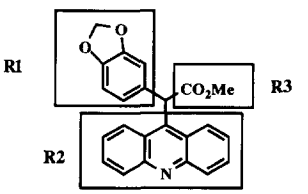
Scheme III



Results and Discussion. Table I summarizes biological activity of the compounds in this study. The endothelin receptor binding assays have been described previously.[13] In addition to using rET_A, compounds were also tested with cloned human receptors, hET_A and hET_B, expressed in Ltk$^-$ cells and CHO-K1 cells, respectively. Several analogs in this study demonstrated reasonable binding affinity and good selectivity to ET_A receptors although the whole series showed a rather flat SAR. Activity was very sensitive to substitutions at the R_1 position. It was found that 3,4-methylenedioxyphenyl was the only group tolerated here. The nitrogen atom in the acridine ring is required for binding activity possibly due to an important H-bonding interaction. The acridine ring could be successfully replaced by a quinoline ring while maintaining activity (compounds **9** and **11**). Modification of the ester to other oxygen-containing functional groups afforded several analogs (**17** and **20-26**)

with similar or slightly improved activity. Benzyl ester **17** showed an IC_{50} of 7.5 μM affinity to rET_A. An electron withdrawing group (**19**) or a bulky substituent (**18**) at the benzene ring decreased activity while electron donating groups at the para position retained activity. The alcohol analog **23** demonstrated the best binding affinity in this series (IC_{50} = 0.9 μM), indicating that hydrogen bonding interaction with the receptors may be important at this site. In compound **28**, an oxygen atom was inserted between the northern and southern parts of **1** while retaining activity.

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

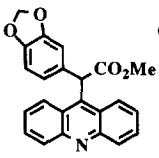
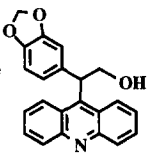
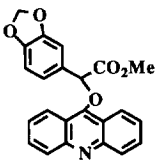
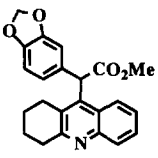
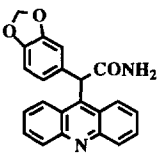


cpd	R1	R2	R3	rET_A	hET_A*
1	(3,4-OCH_2O)-Ph	acridin-9-yl	CO_2Me	2.8	4.3
3	4-OMe-Ph	"	"	>25	>25
4	3,4-$(OMe)_2$-Ph	"	"	>25	>25
5	4-Cl-Ph	"	"	>25	>25
6	3,4-Cl_2-Ph	"	"	>25	>25
7	4-NO_2-Ph	"	"	>25	>25
8	(3,4-$OC(Me)_2O$)-Ph	"	"	>25	>25
9	(3,4-OCH_2O)-Ph	2-Me-quinolin-4-yl	"	2.8	61
10	"	2-Ph-quinolin-4-yl	"	>25	>25
11	"	2,3,4,5-tetrahydro-acridin-9-yl	"	7.3	11
12	"	3,4-$(OMe)_2$-acridin-9-yl	"	>25	>25
13	"	10-oxy-acridin-9-yl	"	>25	>25
14	"	$(Ph)_2CH$-	"	>25	>25
15	"	5-dibenzosuberyl	"	>25	>25
16	"	acridin-9-yl	H	>25	>25
17	"	"	CO_2Bn	7.5	57
18	"	"	CO_2(*p*-*t*-Bu-Bn)	>25	>25
19	"	"	CO_2(*p*-Cl-Bn)	>25	>25
20	"	"	CO_2(*p*-OMe-Bn)	8.2	34
21	"	"	CO_2(3,4-OCH_2O-Bn)	8.7	33
22	"	"	CO_2*t*-Bu	5.6	66
23	"	"	CH_2OH	0.9	0.9
24	"	"	CHO	20	1.5
25	"	"	$CONH_2$	8.5	7.9
26	"	2-Me-quinolin-4-yl	$CONH_2$	13	37
27	"	9-anthrylmethyl	CO_2Me	>25	76
28	"	acridin-9-yloxy	"	--	2.2
29	(3,4-OCH_2O)-$PhCH_2$	acridin-9-yl	"	>25	>25

* All compounds showed no significant binding affinity to the human ET_B receptor up to 200 μM.

Functional Activity of Selected Compounds. Selected compounds were evaluated in an ET_A functional assay[13] measuring their ability to inhibit ET-1 induced arachidonic acid release (AAR_A) in rabbit renal artery vascular smooth muscle cells. As shown in Table II, reasonable antagonist activity was observed for compounds **1**, **28**, and **11**, which correlated well with their binding activities.

Table II. ET_A Functional Activity (AAR_A in rabbit VSMC)

cpd	1	23	28	11	25
Structure					
hET_A IC_{50} (μM)	4.3	0.9	2.2	11	7.9
AAR_A IC_{50} (μM)	5.8	10	4.6	12	77

In summary, we have developed a series of novel acridine and quinoline derivatives that have low micromolar affinity and selectivity for binding to human ET_A receptors. Several compounds also demonstrated functional antagonist activity. Studies of this series and other ET antagonists reported should prove useful in understanding the role of endothelin in human diseases.

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