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Synthesis and pharmacological activity of 1,3,6-trisubstituted-4-oxo-1,4-dihydroquinoline-2-carboxylic acids as selective ET_A antagonists

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ABSTRACT

A series of 1,3,6-trisubsituted-4-oxo-1,4-dihyroquinoline-2-carboxylic acid analogs (**2a**–**m**) were designed and synthesized and their pharmacological activity determined, with the objective to better understand their SAR as potential ET_A selective inhibitors. Most of the compounds displayed significant ET_A antagonist activity having IC_{50} for inhibition of binding of the [^{125}I]ET-1 to ET_A receptor <10 nM, with good selectivity for ET_A antagonism over ET_B receptor. Based on the in vitro results, SAR of this series of compounds requires an alkoxy substituent at the 6-position to be a straight and saturated chain up to three carbons long, since substitution of unsaturated and branched alkyloxy groups results in decrease in ET_A antagonist activity. In this series, compound **2c** (6-*O*-*n*-propyl analog) was found to be most potent (IC_{50} = 0.11 nM) with ET_B/ET_A selectivity of 8303.

Endothelins are divided into three structurally similar subtypes: endothelin-1, 2, and 3 (ET-1, ET-2, and ET-3), which are members of 21 amino acid peptide families.[1] Among them, ET-1 is the major isoform involved in human cardiovascular and non-cardiovascular physiology and pathophysiology. ET-1 is a very potent vasoconstrictor, 10 times more potent than angiotensin II and 100 times more potent than epinephrine and also has inotropic, pro-inflammatory, and mitogenic properties. It also influences the salt-water homeostasis, and stimulates the renin–angiotensin–aldosterone and sympathetic nervous systems.[2,3] Increased level of the plasma concentration of ET-1 has been implicated in several diseases such as hypertension, pulmonary hypertension, acute myocardial infarction, congestive heart failure, renal failure, atherosclerosis, pulmonary fibrosis, and cancer.[4]

ET-1 exerts its physiological action by binding to the specific receptors called endothelin receptor type A (ET_A) and B (ET_B), belonging to the heptahelical G-protein-coupled receptor superfamily.[5] Endothelin receptors are widely expressed in most of the physiological systems, and interaction of ET_A expressed on VSMC with ET-1 results in vasoconstriction and cell proliferation.[6] On the other hand, ET_B activation is mainly responsible for vasodilation depending on tissue location[7] and clearance of endogenous endothelins.[8]

Endothelin receptor antagonists (ERAs), both selective ET_A antagonist and non-selective ET_A/ET_B antagonists, are novel therapeutics in clinical development for various diseases like pulmonary arterial hypertension, chronic heart failure, vascular remodeling (restenosis, atherosclerosis), renal failure, cancer, and lung fibrosis.[9] Though theoretically it seems, selective ET_A receptor antagonists would be useful as therapeutic agents for the treatment of the aforementioned chronic pathological conditions. Advantages of a selective antagonist of the ET_A receptor[10] are:

- Vasoconstriction in the human cardiovascular system by ET-1 appears to be predominantly mediated by the ET_A receptor.
- The mitogenic and pro-inflammatory effects induced by ET-1 are mediated by ET_A receptor stimulation.
- Blockade of the ET_B receptor would prevent the putative beneficial effects like vasodilation of ET-1-induced NO and PGI_2 release from the endothelium.
- Since the ET_B receptor in the lung is involved in clearance of ET-1, ET_B-antagonism will reduce the rate of clearance of exogenous ET-1 from the circulation.

Most non-peptidic endothelin receptor antagonists have the following common structural features: a carboxylic acid group or an acidic sulfonamide moiety between two aromatic or hetero-aromatic ring systems (Fig. 1).[10] These pharmacophore groups are positioned so that they mimic amino acids of the ET-1 C-terminal, which is in a helical form. Different central core units like indane (enrasentan),[11] chromene,[12] cyclopentenopyridine (L-753037),[13,14] and pyrrolidine (atrasentan)[15] have been incorporated into endothelin antagonists currently in the clinical trials (Fig. 2).

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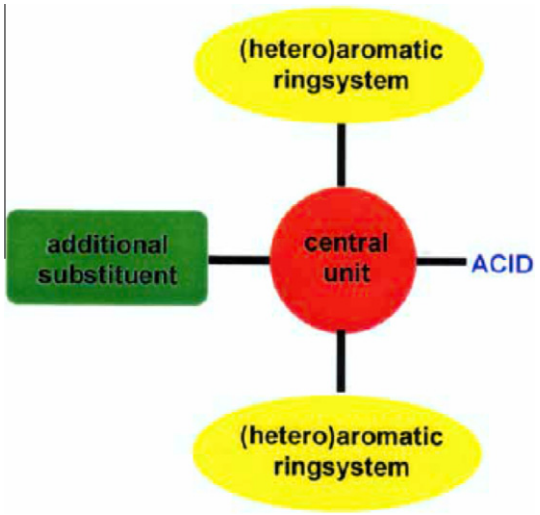


Figure 1. General structure of endothelin receptor antagonists.[10]

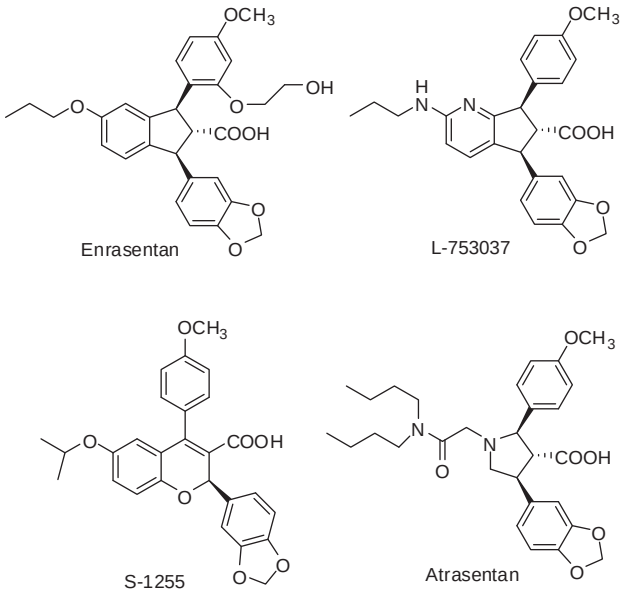


Figure 2. Examples of endothelin receptor antagonists in clinical trials.

Earlier, when the indane ring of SB-209670 was superimposed on the quinolone ring, a good overlap was obtained with 1,3-disubstituted-2-carboxylic quinolones (**1**). Preliminary SAR resulted in compound **1** having potent ET_A antagonist activity and was 800 times more selective for ET_A.[16] Also, it had been reported that introduction of an alkylamino or alkoxy was beneficial to potency and selectivity in analogs belonging to indane,[11] chromene,[12] and cyclopenteno[1,2*b*]pyridine[13,14] carboxylic acid series. Therefore it was hypothesized that introducing an alkoxy substituent at the 6th position of the A ring of quinolone would lead to a new series of compounds with increased potency and selectivity towards ET_A receptor (Fig. 3). This hypothesis was validated by generating the CoMFA model of endothelin receptor antagonists having IC_{50} values between 0.19 and 780 nM, which showed steric groups favorable at the 6 position of the quinolone ring.

In the synthesis of the target compounds 1,3,6-trisubstituted-4-oxo-1,4-dihydro-quinoline-2-carboxylic acids (**2a**–**m**), compound **15** is the key intermediate. Alkylation of **15** with various alkyl halides led to analogs with different substituents at the 6-position of

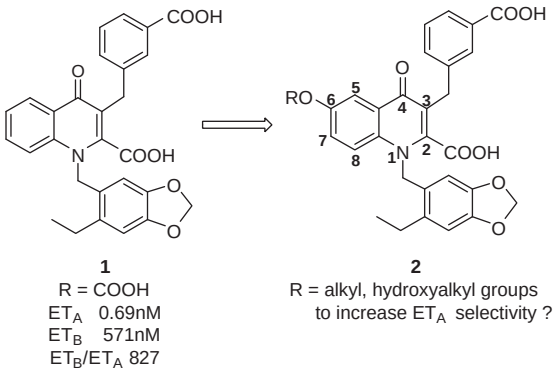


Figure 3. Hypothesis for the synthesis of 1,3,6-trisubstituted-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid as selective ET_A antagonists.

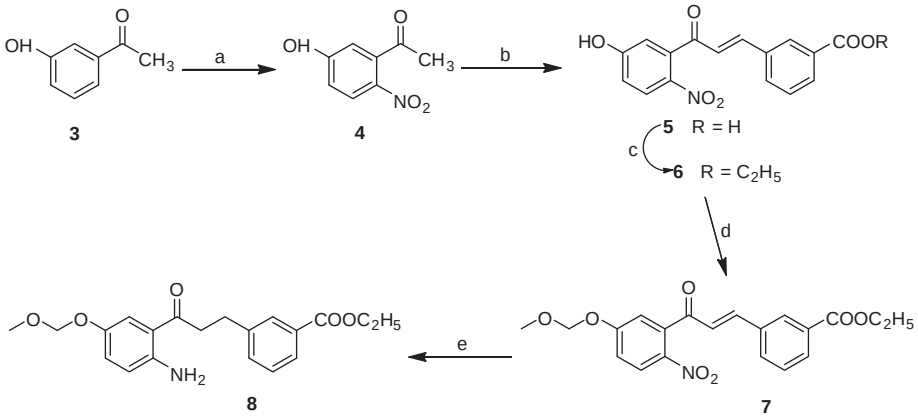
the quinolone. As shown in Scheme 1, nitration of 3-hydroxyacetophenone with nitric acid in the presence of acetic acid resulted in the desired regioisomer 3-hydroxy-6-nitroacetophenone, **4**, which had the reported melting point.[17,18] Compound **4** was condensed with 3-carboxybenzaldehyde to yield *E*-configuration chalcone **5**. Carboxylic acid **5** was converted into ester **6** by reaction with anhydrous ethanol saturated with HCl gas followed by MOM protection of the hydroxyl group resulting in compound **7**. Hydrogenation at 45 psi with PtO_2 catalyst for 45 minutes reduced both the nitro group and the double bond of chalcone **7** to give amine **8**.

For the synthesis of intermediate 6-ethylpiperonal, **11**, Scheme 2 was followed. Wolff–Kishner reduction of 3,4-methylenedioxyacetophenone (**9**) resulted in crude product, which was purified by vacuum-distillation at 130 °C and 27 mm/Hg to yield 63.4% of pure **10**. Formylation of 3,4-methylenedioxy ethylbenzene (**10**) with α,α-dichloromethyl methyl ether as precursor of the formyl group, via alkylation catalyzed by titanium tetrachloride, resulted in 6-ethylpiperonal (**11**) in excellent yield.[19]

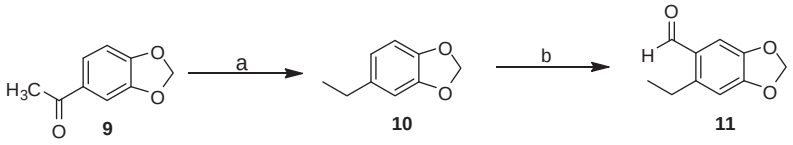
Reductive amination of 6-ethylpiperonal, **11** with aromatic amine **8** was then carried out by using hydride reducing agents such as sodium cyanoborohydride ($NaBH_3CN$),[20] or titanium (IV) isopropoxide ($Ti(OiPr)_4$)/sodium cyanoborohydride ($NaBH_3CN$),[21] or sodium triacetoxyborohydride ($NaBH(OAc)_3$).[22] Among these three methods, reductive amination with $NaBH(OAc)_3$ gave the best yield of product **12**. N-acylation of **12** with ethyl oxalyl chloride gave an excellent yield of compound **13**, which on cyclization by the hindered base 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) in ethanol gave MOM-protected-4-quinolone diester **14**. Deprotection of MOM-group under acidic condition resulted in key intermediate **15** (Scheme 3).

Alkylation of **15** with various alkyl halides in presence of sodium hydride and potassium carbonate led to derivatives with different substituents at the 6-position of the quinolone **16a**–**k** (Scheme 4). The synthesis of the target compounds (**2a**–**m**) was accomplished by potassium hydroxide treatment of the 4-oxo-quinoline diesters in moderate yields. The general synthetic scheme along with the physical properties is described in Supplementary data.

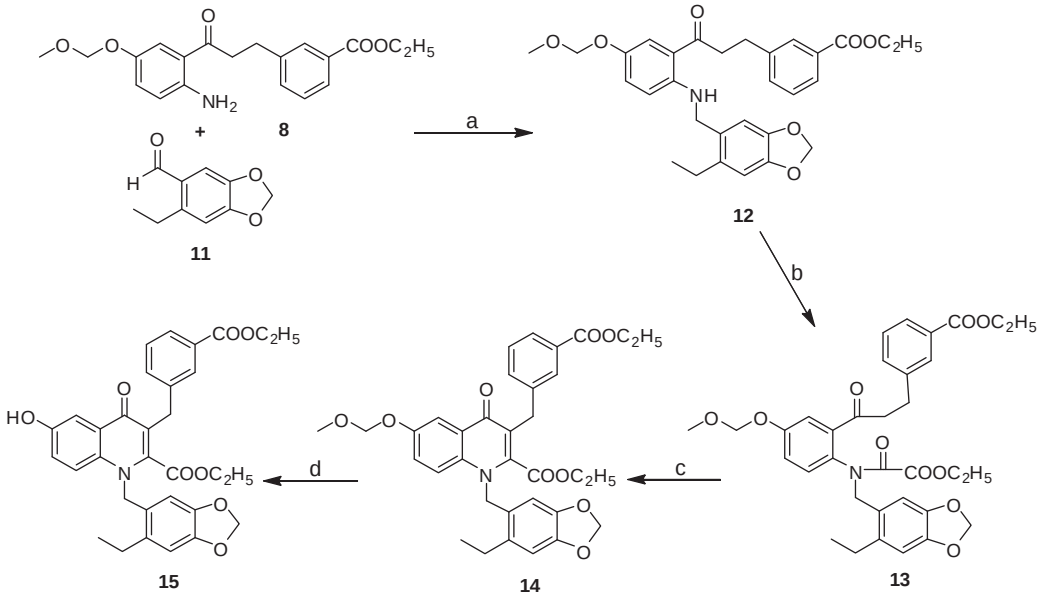
All compounds listed in Table 1 were evaluated for their ability to inhibit endothelin-A (ET_A) and endothelin-B (ET_B) receptors in vitro. The results are summarized in Table 1. For each compound, eight concentrations were tested in the presence of fixed concentration of radio-labeled ET-1([^{125}I] ET-1) on green monkey renal tubular (Vero) cells expressing ET_A receptors[23] and membrane expressing ET_B receptor. Besides thirteen proposed compounds, BQ-123 (selective ET_A antagonist) was taken as a positive control to validate the method. The IC_{50} values, which are the concentrations that reduce the [^{125}I] ET-1 binding to the



Scheme 1. Preparation of intermediate **8**. Reagents and conditions: (a) HNO_3, glacial CH_3COOH, 70 ± 2 °C; (b) 3-carboxybenzaldehyde, 10 N NaOH (3 equiv), CH_3OH, reflux; (c) dry HCl gas, anhydrous C_2H_5OH; (d) MOMCl, NaH, dry K_2CO_3, dry DMF; (e) 45 psi H_2 gas, PtO_2, anhydrous CH_3OH.



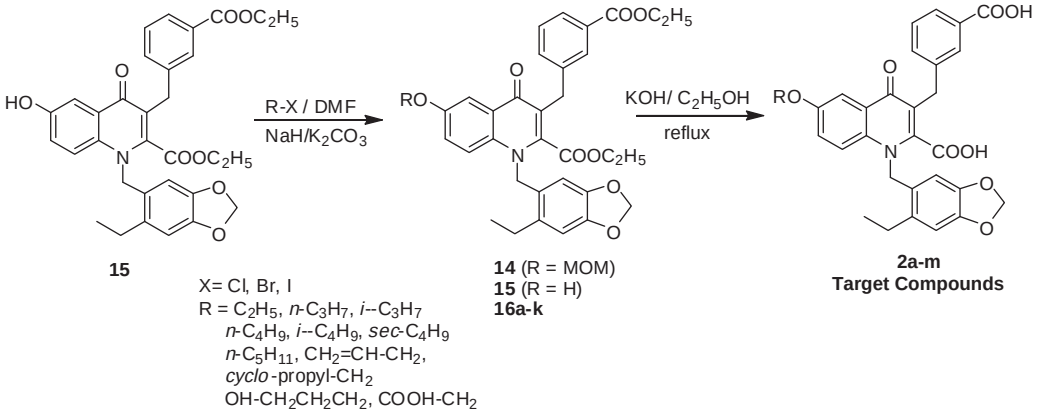
Scheme 2. Synthesis of 6-ethylpiperonal, **11**. Reagents and conditions (a) (i) $NH_2NH_2{\cdot}H_2O$, ethanol, reflux, (ii) KOH, 160 °C; (b) $TiCl_4$, α,α-dichloromethyl methyl ether, dichloroethane, 0 °C to rt.



Scheme 3. Preparation of intermediate **15**. Reagents: (a) $NaBH(OAc)_3$, DCE; (b) ethyl oxalyl chloride, NEt_3, dry DMF; (c) DBU, ethanol; (d) dry HCl gas, anhydrous C_2H_5OH.

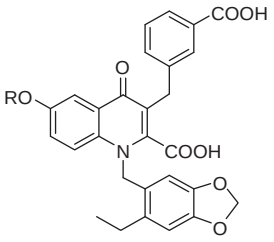
receptors by 50%, were determined for each drug and are listed in Table 1.

On the basis of this study, the following structure–activity relationships are proposed for the 1,3,6-trisubstituted-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid analogs, **2a**–**m** as an ET_A antagonists. Among the compounds tested, 6-*O*-ethyl (**2b**), 6-*O*-*n*-propyl (**2c**), 6-*O*-*n*-butyl (**2g**), 6-*O*-*i*-butyl (**2h**), 6-*O*-*sec*-butyl (**2i**), 6-*O*-propan-3-ol (**2l**), 4-oxo-1,4-dihydroquinoline diacids displayed significant ET_A antagonist activity having IC_{50} for inhibition of binding of the [^{125}I]ET-1 to ET_A receptor <10 nM. As shown in Table 1, when the 6-OH group of **2a** is replaced by a 6-alkoxy group of two carbons (**2b** IC_{50}: 6.6 nM), there is a sixfold increase in ET_A antagonist activity and a slight increase in selectivity for ET_A over ET_B, i.e., 473 for **2b** versus 399 for **2a**. Increase in chain length by one more carbon to 3 carbons (**2c**) resulted in 60-fold increase in ET_A (IC_{50}: 0.11 nM) and threefold increase in ET_B (IC_{50}: 913 nM) antagonist activity compared to **2b**. Although there is increase in binding affinity for both the receptors, a *n*-propoxy group at 6-position of quinoline is more beneficial for ET_A receptor binding as seen in selectivity of more than 8000 for ET_A over ET_B. There is 10-fold decrease in ET_A antagonist activity compared to **2c** when the side chain length is increased by one carbon to butyl (**2g**;



Scheme 4. Synthesis of 6-*O*-substituted-4-oxo-quinoline-dicarboxylic acids (**2a**–**m**). Reagents and conditions: (a) alkyl halides, NaH, dry K_2CO_3, dry DMF; (b) 6 N KOH (6 equiv), C_2H_5OH, reflux.

Table 1
In vitro inhibitory binding assay (IC_{50}) of 1,3,6-trisubstituted-4-oxo-1,4-dihydroquinoline-2-carboxylic acids, **2a**–**m**



2a-m

No.	R	Mp (°C)	ET_A IC_{50}[a] (nM)	ET_B IC_{50}[b] (nM)	ET_B/ET_A
2a	H	198–199	38.9 ± 2.6	15561.5 ± 162.7	399
2b	C_2H_5	213–215	6.6 ± 1.1	3119 ± 54.3	473
2c	*n*-C_3H_7	162–163	0.11 ± 0.02	913.4 ± 27.2	8304
2d	*i*-C_3H_7	199–200	13.5 ± 1.5	677 ± 9.6	50
2e	CH_2═CH–CH_2	165–166	38.1 ± 3.6	1131 ± 24.8	30
2f	CH_3–O–CH_2	176–177	24.4 ± 2.9	1030 ± 17.3	43
2g	*n*-C_4H_9	161–162	1.44 ± 0.6	548.2 ± 14.5	381
2h	*i*-C_4H_9	229–231	6.3 ± 1.5	1983 ± 35.7	315
2i	*sec*-C_4H_9	185–186	9.9 ± 1.7	—	—
2j	*cyclo*-C_3H_5–CH_2	173–174	115.9 ± 11.4	—	—
2k	*n*-C_5H_{11}	153–155	610 ± 54	—	—
2l	HO–$CH_2CH_2CH_2$	192–194	7.4 ± 0.9	4387 ± 63.7	593
2m	HOOC–CH_2	177–180	284.5 ± 3.5	1453 ± 20.7	5
	BQ123	—	24.8 ± 1.3[c] (25)	—	—

[a] Monkey renal cells CCL-81 grown as monolayer.[23] $n = 3$.
[b] Endothelin-B receptor precursor (human) membranes. $n = 2$.
[c] Literature IC_{50} value, *ibid*.

IC_{50}: 1.6 nM), but still shows better activity than **2b**. Further increase in length to 5 carbons (**2k**; IC_{50} 610 nM) resulted in 6000-fold loss in activity compared to 6-*O*-*n*-propyl analog (**2c**), also seen in the cyclopenteno[1,2-*b*]pyridine series as ET_A receptor antagonist.[14]

Replacement of the saturated 6-*O*-*n*-propyl group with the unsaturated 6-*O*-allyl group resulted in **2e** analog (IC_{50} = 38.11 nM) 380 times less active than the *n*-propyl analog **2c**. This suggests that a saturated alkyl chain is required at the 6-position of the 4-oxo-1,4-dihydroquinoline diacids for better ET_A antagonist activity. Also, when the second atom of the *n*-propyl chain in **2c** is replaced by isosteric O (**2f**; IC_{50}: 24.4 nM), there is 240-fold decrease in activity compared to **2c**.

Substitutions at the C1 of the 6-*O*-alkyl chain are not well tolerated. There is a twofold decrease in ET_A antagonist activity compared to **2b** when the methylene group of the ethyl chain is substituted, **2d** (*i*-propyl, IC_{50} = 13.5 nM). Similarly, substitution of the methylene group at C1 of the 6-*O*-*n*-propyl chain resulted in compound **2i** (6-*O*-*sec*-butyl) which is 90-fold less active, than **2c**, in inhibition of binding of the [^{125}I]ET-1 to ET_A receptor (IC_{50} = 9.9 nM). Likewise, branching at C2 of the alkyl chain is not tolerated, as substitution of a methyl group at C2 of the 6-*O*-*n*-propyl chain resulted in analog **2h** (6-*O*-*i*-butyl) which is 60 times less active as ET_A receptor antagonist (IC_{50} = 6.6 nM) than **2c**. Also, compound **2j** (6-*O*-cyclopropylmethyl) which is a cyclic analog of **2h**, shows 1000 times less ET_A receptor antagonist activity than **2c**. These results suggest that straight chain saturated alkoxy groups are required at the 6-position of the 4-oxo-1,4-dihydroquinoline diacids for good ET_A receptor antagonism.

Introduction of a hydroxyl group (**2l**; IC_{50}: 7.4 nM) at C3 of the 6-*O*-*n*-propyl side chain resulted in 70-fold reduction in ET_A receptor antagonist activity compared with **2c**. Also, substitution of a carboxylic acid group (**2m**; IC_{50}: 284.46 nM) for a methyl group in **2b** causes a 43-fold decrease in binding affinity for ET_A receptor compared with **2b**. These results are consistent with the previously reported SAR of cyclopenteno[1,2-*b*]pyridine analogs as ET_A receptor antagonists.[14]

Compound **2a** was found to reduce lung inflammation induced by lipopolysaccharide (LPS),[24] cigarette smoke, and ET-1[25] in a hamster animal model by reducing the recruitment of broncoalveolar lavage fluid (BALF) leukocytes (neutrophils and macrophages). Therefore, reducing ET-1 activity with selective ET_A receptor antagonists could potentially decrease neutrophil derived enzymes and oxidants in the lung, thereby decreasing or inhibiting the progression of lung injury. Compound **2a** was also effective in controlling preterm delivery induced by lipopolysaccharide (LPS) in a pregnant mouse animal model.[26] This result, in accordance with previous literature, suggests the role of ET-1 in both normal parturition and premature birth.

In summary, a new series of 1,3,6-trisubstituted-4-oxo-1,4-dihydroquinoline-2-carboxylic acid analogs were synthesized and evaluated for their ET_A antagonist activity and selectivity for ET_A receptor over ET_B receptor. Among the compounds tested, **2b**, **2c**, **2g**, **2h**, **2i**, and **2l** 4-oxo-1,4-dihydroquinoline diacids displayed significant ET_A antagonist activity with IC_{50} values of inhibition of binding of the [^{125}I]ET-1 to ET_A receptor <10 nM. These compounds also showed good selectivity for ET_A antagonism over ET_B receptor. Initial SAR at C6 of the quinolone ring indicates straight, unbranched, and saturated alkyl chain up to three carbons long, with hetero atom spacer required for good ET_A antagonist activity and selectivity. Also, polar hydrophilic groups at the 6-position are unfavorable for ET_A antagonist activity, as seen with a decrease in activity when substituted by 6-*O*-propan-3-ol (**2l**) and 6-*O*-carboxymethyl (**2m**) of the quinoline ring. The 6-*O*-*n*-propyl-4-oxo-1,4-dihydroquinoline diacids analog, **2c** was found to be most potent (IC_{50}: 0.11 nM) with ET_B/ET_A selectivity of 8303. In vivo, compound **2a** (6-OH), a prototype of this 4-oxo-1,4-dihydroquinolone diacid series was shown to reduce LPS-induced lung inflammation and preterm labor in two different animal models.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.08.074.

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