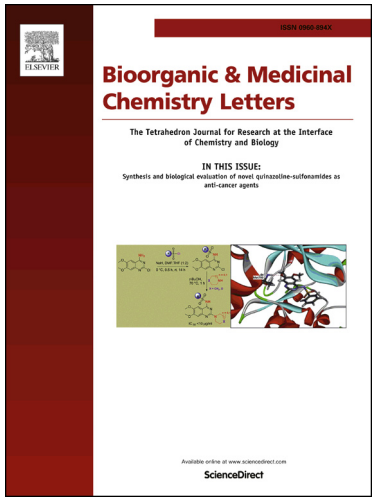


Design, synthesis and evaluation of 1,3,6-trisubstituted-4-oxo-1,4-dihydroquinoline-2-carboxylic acid derivatives as ET_A receptor selective antagonists using FRET assay

Nikhil Khadtare, Ralph Stephani, Vijaya Korlipara

PII: S0960-894X(17)30426-2
DOI: http://dx.doi.org/10.1016/j.bmcl.2017.04.049
Reference: BMCL 24902

To appear in: *Bioorganic & Medicinal Chemistry Letters*

Received Date: 6 March 2017
Revised Date: 14 April 2017
Accepted Date: 15 April 2017

Please cite this article as: Khadtare, N., Stephani, R., Korlipara, V., Design, synthesis and evaluation of 1,3,6-trisubstituted-4-oxo-1,4-dihydroquinoline-2-carboxylic acid derivatives as ET_A receptor selective antagonists using FRET assay, *Bioorganic & Medicinal Chemistry Letters* (2017), doi: http://dx.doi.org/10.1016/j.bmcl.2017.04.049

Bioorganic & Medicinal Chemistry Letters
journal homepage: www.elsevier.com

Design, synthesis and evaluation of 1,3,6-trisubstituted-4-oxo-1,4-dihydroquinoline-2-carboxylic acid derivatives as ET_A receptor selective antagonists using FRET assay

Nikhil Khadtare, Ralph Stephani, and Vijaya Korlipara*

Department of Pharmaceutical Sciences, College of Pharmacy and Health Sciences, St. John's University, Queens, NY 11439

ARTICLE INFO

Article history:
Received
Revised
Accepted
Available online

Keywords:
Endothelin receptor antagonists
ET_A receptor selectivity
FRET assay
4-oxo-1,4-dihydroquinoline-2-carboxylic acid derivatives

ABSTRACT

The endothelin axis and in particular the two receptor subtypes, ET_A and ET_B, are under investigation for the treatment of various diseases such as pulmonary arterial hypertension, fibrosis, renal failure and cancer. Previous work in our lab has shown that 1,3,6-trisubstituted-4-oxo-1,4-dihydroquinoline-2-carboxylic acid derivatives exhibit noteworthy endothelin receptor antagonist activity. A series of analogues with modifications centered around position 6 of the heterocyclic quinolone core and replacement of the aryl carboxylic acid group with an isosteric tetrazole ring was designed and synthesized to further optimize the structure activity relationship. The endothelin receptor antagonist activity was determined by *in vitro* Förster resonance energy transfer (FRET) using GeneBLAzer® assay technology. The most potent member of this series exhibited ET_A receptor antagonist activity in the subnanomolar range with an IC_{50} value of 0.8 nM, and was 1000-fold selective for the ET_A receptor compared to the ET_B receptor. Its activity and selectivity profile resembles that of the most recently approved drug, macitentan.

The endothelin peptides (ETs) consist of three structurally similar subtypes ET-1, ET-2 and ET-3 each consisting of 21 amino acids. They produce their effects by binding to the two endothelin receptor subtypes ET_A and ET_B, and have been implicated in the pathophysiology of various human diseases.[1–4] Endothelin receptor antagonists have been evaluated extensively for the treatment of pulmonary arterial hypertension (PAH) and other hypertensive conditions, cancer, and fibrogenic diseases of the kidney.[2,5–10] The FDA approved agents and the compounds in clinical trials are either ET_A-selective antagonists with ET_A/ET_B > 100 or dual ET_A/ET_B receptor antagonists. The role of ET_B receptor has not been fully elucidated and very few ET_B selective antagonists have been developed for evaluation in clinical trials.[2,11]

The three clinically available endothelin receptor antagonists, bosentan (Tracleer®),[12] ambrisentan (Letairis®) and macitentan (Opsumit®)[12] have been approved for the treatment of PAH (Figure 1). Sitaxsentan (Thelin®) was also approved for PAH in 2006 but was withdrawn in 2010 due to fatal hepatotoxicity.[3,5,6,13,14] Many other compounds are under phase II or phase III clinical trials and include clazosentan for aneurysmal subarachnoid hemorrhage, darusentan for coronary artery disease, tezosentan for acute heart failure, and atrasentan for hormone refractory prostate cancer metastatic to bone and for diabetic neuropathy treatment (Figure 2).[15–18] More recently, clinical trials have been conducted to study the efficacy of the combination of some endothelin receptor antagonists with other cardiovascular drugs in improving the therapeutic outcome for PAH and cancer patients.[16,19]

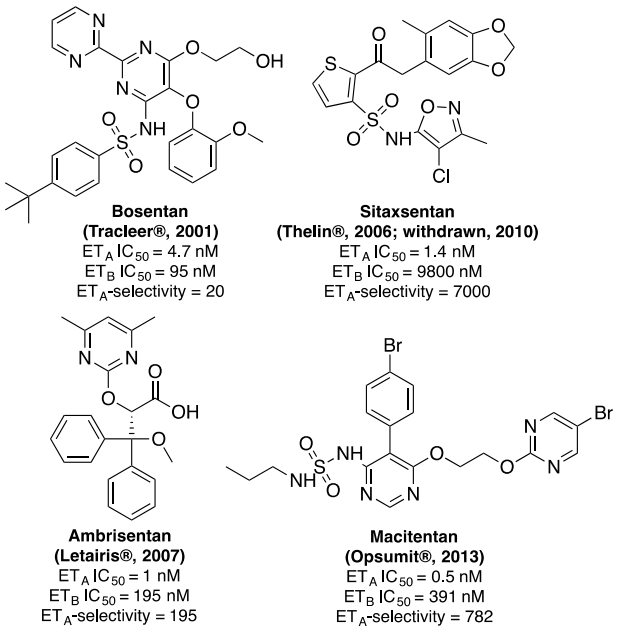


Figure 1. FDA approved endothelin receptor antagonists for PAH.

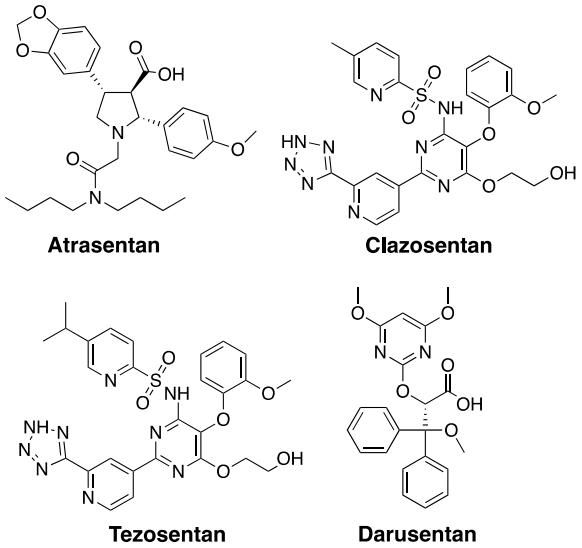


Figure 2. Structures of endothelin receptor antagonists in clinical trials.

Heterocyclic quinolone derivative **44** in the carboxylic acid series with the *n*-propoxy substituent at position 6 has been reported to be a potent and selective ET_A receptor antagonist (Figure 3, Table 1).[20,21] It exhibited an ET_A and ET_B receptor IC_{50} values of 4 nM and 2870 nM, respectively with ET_A-selectivity of 717 in receptor membrane preparations using a radioligand assay.[20] It also antagonized [^{125}I]ET-1 with an IC_{50} value of 0.11 nM in monkey renal cells (CCL-81) expressing the ET_A receptor.[21] Based on the previous structure activity relationship studies reported by Patel et al., target compounds were designed to expand the SAR on the oxygen atom at position 6 of the quinolone core by substitution of alicyclic rings of varying sizes and introduction of a polar 2-aminoethyl group. The carboxylic acid at position 3 of the benzyl substituent was replaced with an isosteric tetrazole ring to obtain a parallel series of eleven compounds. The R^1 substituents in the tetrazole series included those previously explored in the carboxylic acid series as well as the new R^1 substituents being explored in this project for the carboxylic acid series. Endothelin receptor antagonist activities and selectivity against ET_A and ET_B receptors were evaluated using a whole cell based GeneBLAzer® FRET assay. This is a functional assay which uses HEK293T cells containing a mammalian-optimized β-lactamase reporter gene combined with a FRET-enabled substrate under the control of the Nuclear Factor of Activated T-cell (NFAT) response element. This assay has been validated for EC_{50} concentrations of ET-1.[22,23] The FRET assay was chosen as an alternative to the radioligand [^{125}I] ET-1 binding assay to avoid the generation of radioactive waste and also the need for a secondary functional assay to identify whether the compounds are agonists or antagonists.[24] To our knowledge, this is the first reported use of a FRET assay for the evaluation of endothelin receptor antagonist activity. All 22 compounds belonging to the tetrazole series and carboxylic acid series were evaluated by this assay for direct comparison of their activities and ET_A/ET_B selectivity.

Compounds **41-62** were synthesized as illustrated in schemes 1-5. 3-(1*H*-tetrazole-5-yl)benzaldehyde **1** was obtained in 95% yield via [2 + 3] cycloaddition of sodium azide to commercially available 3-cyanobenzaldehyde in presence of triethylamine as reported in the literature.[25] Nitration of 3-hydroxyacetophenone with nitric acid in presence of acetic acid resulted in the desired regioisomer 1-(5-hydroxy-2-nitrophenyl)ethan-1-one **2** in 14% yield.[26]

Aldol condensation of 1-(5-hydroxy-2-nitrophenyl)ethan-1-one **2** with 3-carboxybenzaldehyde followed by esterification resulted in chalcone **4** while aldol condensation of **2** with 3-(1*H*-tetrazole-5-yl)benzaldehyde **1** resulted in chalcone **5** (Scheme 1). Protection of the phenolic hydroxyl group of **4** and **5** provided TBDMS-protected chalcones derivatives **6** and **7**.[27] Hydrogenation of compounds **6** and **7** with PtO_2 as a catalyst reduced both the nitro group and the olefinic double bond of the TBDMS-protected chalcone derivatives to yield compounds **8** and **9** (Scheme 2).

Palladium catalyzed reduction of 3,4-methylenedioxy acetophenone **10** followed by formylation with α,α-dichloromethyl methyl ether resulted in the key intermediate **12** (Scheme 3). Palladium catalyzed reduction of acetophenone **10** was more efficient than the previously reported method using Wolff-Kishner reduction. Reductive amination of **12** with chalcones **8** and **9** using sodium triacetoxyborohydride yielded the corresponding secondary amines **13** and **14**, respectively (Scheme 4). N-acylation of **13** and **14** with ethyl oxalyl chloride led to compounds **15** and **16** in excellent yields. Cyclization of compounds **15** and **16** in presence of the hindered base DBU yielded TBDMS-protected-4-quinolone ester derivatives **17** and **18**, respectively. Deprotection of the TBDMS group under acidic conditions resulted in free phenolic derivatives **19** and **20**.[27] As shown in Scheme 5, alkylation of compounds **19** and **20** with various alkyl halides led to the corresponding O-alkylated derivatives **21-30** and **31-40,** respectively. Saponification of the ester group at position 2 of the quinolone ring led to the target compounds **41, 43-52** in the carboxylic acid series and **42, 53-62** in the tetrazole series.

Endothelin receptor antagonist activity of compounds **41-62** was determined by *in vitro* Förster Resonance Energy Transfer (FRET) using GeneBLAzer® assay technology (Table 1). Besides the target compounds, BQ-123, a selective ET_A receptor antagonist and BQ-788, a selective ET_B receptor antagonist were used as positive controls for ET_A and ET_B receptors, respectively.

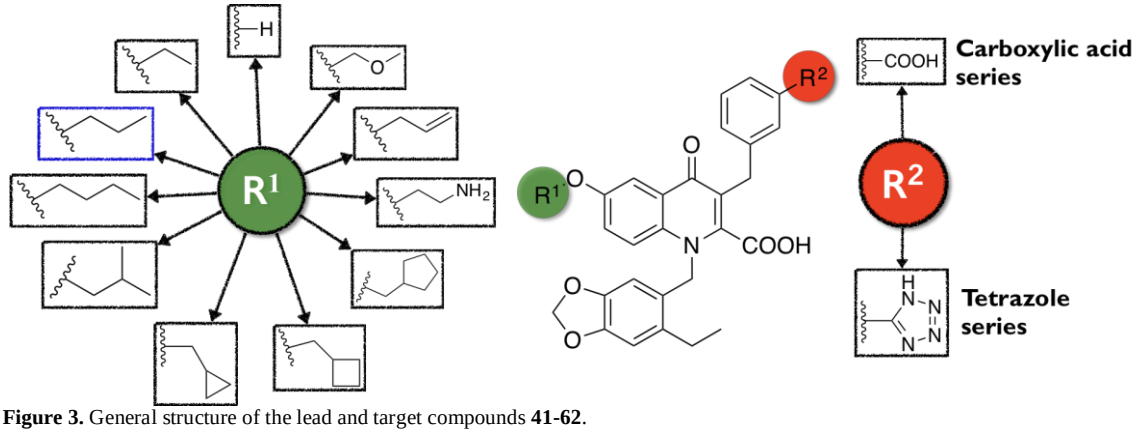
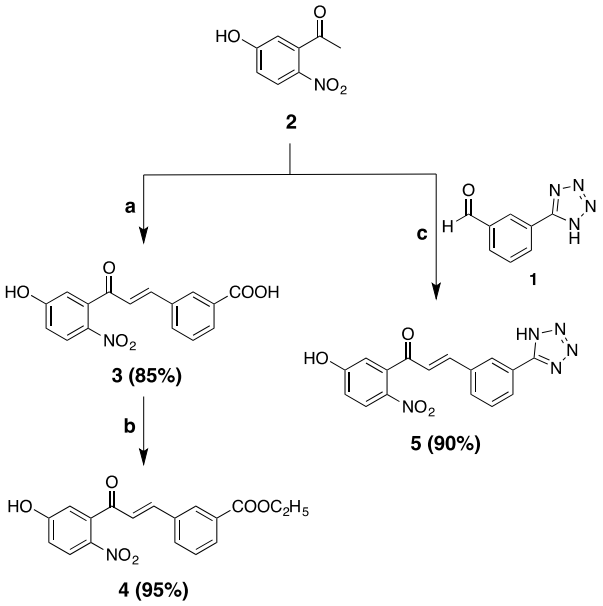
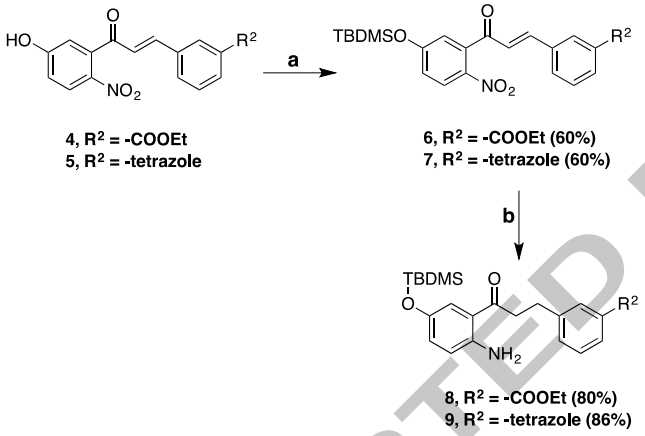


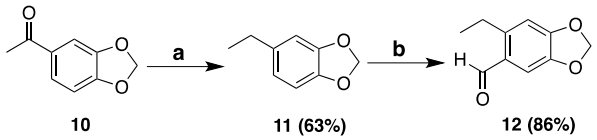
Figure 3. General structure of the lead and target compounds **41-62**.



Scheme 1. Synthesis of compounds **4** and **5**. **(a)** 3-Carboxybenzaldehyde, 10N NaOH, CH_3OH, Reflux. **(b)** Ethanolic HCl, rt. **(c)** 10N NaOH, CH_3OH, Reflux.



Scheme 2. Synthesis of compounds **8** and **9**. **(a)** Imidazole, TBDMSCl, DMF, 48 h, rt. **(b)** PtO_2, H_2, 70 psi, Ethanol, 2-3 h, rt.

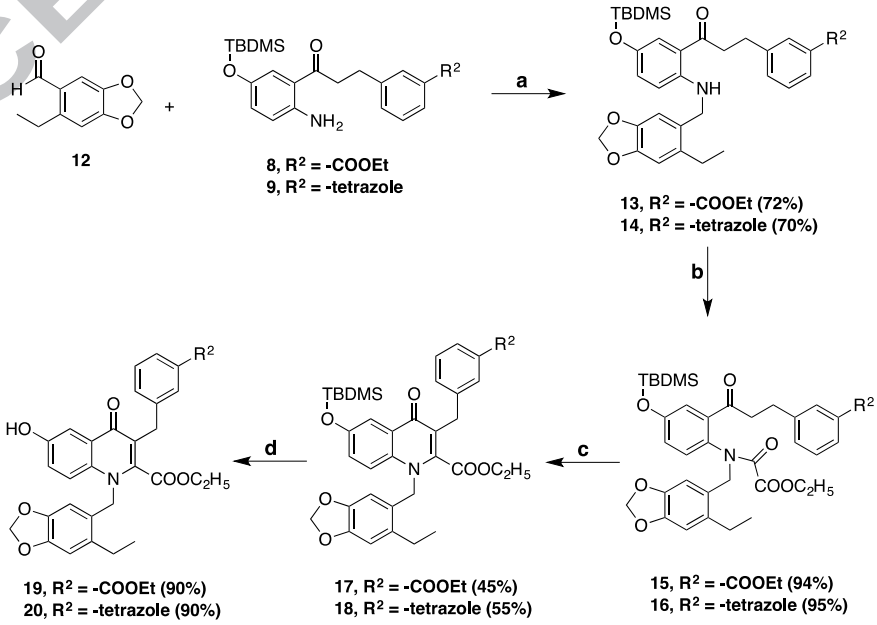


Scheme 3. Synthesis of 6-Ethylpiperonal **12**. **(a)** 10% Pd/C, Ammonium formate, Acetic acid, 110 °C, N_2. **(b)** α,α-dichloromethyl methyl ether, $TiCl_4$, 0 °C to rt.

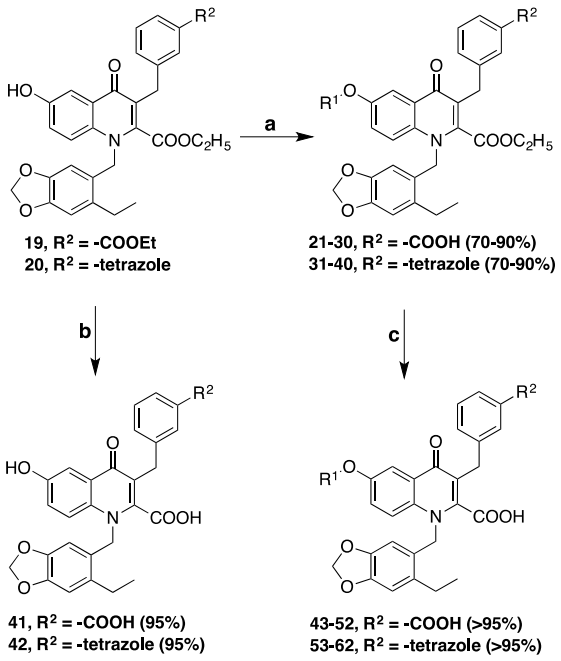
The structure activity relationship deduced for the carboxylic acid series was found to parallel that of the tetrazole series very closely. Among the compounds tested, *n*-propoxy analogue **54** in the tetrazole series was found to be the most potent ET_A receptor antagonist with an IC_{50} value of 0.8 nM. Compound **54** was also the most selective ET_A receptor antagonist with an ET_A-selectivity of 1004. In the carboxylic acid series, the lead molecule **44** with *n*-propoxy substituent was found to be the most potent ET_A receptor antagonist with an IC_{50} value of 4.2 nM. As in case of the corresponding tetrazole analogue **54**, it was also the most selective member of its series with an ET_A-selectivity of 683.

Increasing the chain length to obtain *n*-butoxy analogue **45** (IC_{50} = 1.88 nM) in the carboxylic acid series led to a slight improvement in ET_A receptor antagonist activity but was accompanied by reduction in ET_A-selectivity by a factor of 2. A similar reduction in ET_A-selectivity for *n*-butoxy analogue **55** (IC_{50} = 1.2 nM) in the tetrazole series was observed although the ET_A receptor antagonist activity was slightly reduced in this series.

Truncating the alkyl chain to two carbon atoms at position 6 of the quinolone ring resulted in the ethoxy analogue **43** (IC_{50} = 6.6 nM) in the carboxylic acid series. This led to 1.5-fold reduction in activity and selectivity against the ET_A receptor compared to the lead molecule **44**. Similar modification in the tetrazole series led to the ethoxy analogue **53** (IC_{50} = 7.1 nM) which showed 10-fold decrease in the ET_A receptor antagonist activity and the ET_A-selectivity also reduced to 581 compared to the most potent compound **54**. Substitution of a branched alkyl chain to obtain *i*-butoxy analogue **46** (IC_{50} = 9.9 nM) of the carboxylic acid series led to a 5-fold decrease in the ET_A receptor antagonist activity and was accompanied by 4-fold reduction in ET_A-selectivity compared to the straight chain analogue **45**.



Scheme 4. Synthesis of compounds **19** and **20**. **(a)** $NaBH(OAc)_3$, DCE, rt. **(b)** Ethyl oxalyl chloride, Triethylamine, DMF, 0 °C to rt. **(c)** DBU, Ethanol, rt. **(d)** Ethanolic HCl, rt.



Scheme 5. Synthesis of compounds **41**-**62**. **(a)** R^1-X, DMF, NaH, K_2CO_3, 0 °C to rt. **(b)** & **(c)** 6N KOH, Ethanol, Reflux.

Branched alkyl, *i*-butoxy analogue **56 (**IC_{50} = 6.2 nM) of the tetrazole series had 5-fold lower ET_A receptor antagonist activity and selectivity in comparison with straight chain analogue **55**. Elimination of the alkyl chain entirely to obtain 6-OH analogue **41** (IC_{50} = 37.01 nM) in the carboxylic acid series led to 10-fold decrease in ET_A receptor antagonism and was accompanied by 1.6 times decrease in ET_A-selectivity compared to the most potent analogue **44** in this series. Removal of the alkyl chain in the tetrazole series to obtain analogue **42** caused the reduction of ET_A receptor antagonist activity by 40-fold and selectivity by 1.8 times compared to the most potent compound **54** in this series.

Replacement of the saturated *n*-propoxy group in compound **44** with the unsaturated allyloxy group to obtain compound **47** resulted in 10-fold decrease in ET_A receptor antagonism and more than 20-fold decrease in ET_A-selectivity. Analogous unsaturated allyloxy compound **57** in the tetrazole series was found to have diminished ET_A receptor antagonist activity by 60-fold and ET_A-selectivity by 50-fold compared to *n*-propoxy compound **54**. This suggests that a saturated alkyl chain at position 6 of 4-oxo-1,4-dihydro-quinoline-2-carboxylic acid is beneficial for ET_A receptor antagonist activity. Also, when the *n*-propoxy chain in **44** is replaced by isosteric methoxymethyoxy chain in the carboxylic acid series to obtain analogue **48**, there is 6 fold loss of ET_A receptor antagonism and 15 fold loss of ET_A-selectivity.

A similar reduction in ET_A-selectivity for methoxymethoxy analogue **58** in the tetrazole series was observed although the ET_A receptor antagonist activity reduced by nearly 20-fold. Replacement of the terminal methyl group of the *n*-propoxy side chain of **44** in the carboxylic acid series with an amino group led to compound **49** which exhibited 85-fold reduction in ET_A receptor antagonism. ET_A-selectivity also declined drastically from 683 to 4 compared to **44**. The 2-aminoethoxy analogue **59** in the tetrazole series resulted in more than 450-fold reduction in ET_A receptor antagonist activity and a virtual loss of ET_A-selectivity compared to **54**. This suggests that substitution of an amino group in place of the terminal methyl group of the *n*-propoxy side chain is detrimental for ET_A receptor antagonism and selectivity.

A series of analogues with alicyclic side chains were synthesized to determine tolerance of steric bulk at position 6 of the 4-oxo-1,4-dihydro-quinoline-2-carboxylic acid. Cyclopropylmethoxy analogue **50** in the carboxylic acid series showed more than 10 times lower ET_A receptor antagonist activity and selectivity compared to the corresponding open chain *i*-butyl analogue **46**. Reduction in ET_A receptor antagonist activity and selectivity of cyclopropylmethoxy analogue **60** (IC_{50} = 78.4 nM) of the tetrazole series compared to the *i*-butyl compound **56** were found to parallel the effects of the carboxylic acid derivatives **50** and **46**. This considerable reduction in antagonist activity and receptor selectivity could be due to the fact that C-C bonds in cyclopropane have more π character than σ character, resulting in cyclopropylmethoxy substituent acting like an unsaturated allyloxy substituent at position 6 of the quinolone ring. This behavior resembles the ET_A receptor binding nature of the unsaturated allyloxy derivatives **47** and **57** compared to the corresponding saturated *n*-propoxy derivatives **1** and **54**.

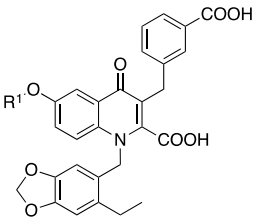
ET_A receptor antagonist activity was found to decrease by 3-fold with the increment of each methylene group to increase the ring size of the alicyclic analogue **50** to obtain cyclobutylmethoxy analogue **51** and cyclopentylmethoxy **52** in the carboxylic acid series. Compounds **51** and **52** also exhibited poor ET_A-selectivity. A similar reduction of 3-fold in ET_A receptor antagonist activity and poor ET_A-selectivity was observed with an increase in the ring size of cyclopropylmethoxy analogue **60** in the tetrazole series to yield cyclobutylmethoxy analogue **61** and cyclopentylmethoxy **62**.

In conclusion, a series of endothelin receptor antagonists was synthesized and evaluated for their ET_A and ET_B receptor antagonist activity and selectivity using GeneBLAzer® FRET assay technology. The structure activity relationship deduced for the carboxylic acid series was found to parallel that of the tetrazole series. The *n*-propoxy analogue **54** in the tetrazole series was found to be the most potent and selective ET_A receptor antagonist with an IC_{50} value of 0.8 nM and an ET_A-selectivity of 1004. Target compounds with ethoxy, *n*-propoxy, *n*-butoxy, *i*-butoxy substituents in both series were found to have similar or better activity than the positive control BQ-123. These results suggest that short chain saturated alkoxy groups at position 6 of the 4-oxo-1,4-dihydro-quinoline-2-carboxylic acid impart good ET_A receptor antagonism and selectivity over ET_B receptor. Tetrazole **54** exhibits similar or better ET_A receptor antagonist activity as compared to the clinically approved endothelin receptor antagonists for PAH (Figure 1) with ET_A-selectivity profile similar to that of the most recently approved drug, macitentan.

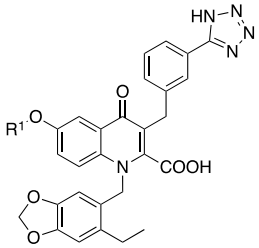
Acknowledgments

The authors thank Dr. Vladimir Poltoratsky and Zhihui Xiao for their help with the *in vitro* FRET assay. Support for this research was provided by Saint John's University.

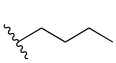
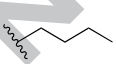
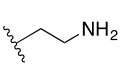
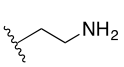
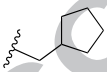
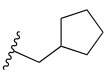
Table 1. Endothelin receptor antagonist activities of compounds **41-62** using *in vitro* GeneBLAzer® FRET assay.



General Structure for Target Compounds **41, 43-52**



General Structure for Target Compounds **42, 53-62**

Compound	R^1	IC_{50} (nM)†		ET_A-selectivity	Compound	R^1	IC_{50} (nM)†		ET_A-selectivity
		ET_A	ET_B				ET_A	ET_B	
41^	-H	37.01 ± 2.1	15602.3 ±158.7	421	**42**	-H	29.2 ± 3.4	16203.5 ± 182.7	558
43^		6.6 ± 1.1	3119 ± 54.3	472	**53**		7.1 ± 2.1	4072.1 ± 54.3	581
44^		4.2 ± .88	2868.4 ± 12.5	683	**54**		0.8 ± .05	803.2 ± 17.1	1004
45^		1.88 ± 0.6	548.2 ± 14.5	291	**55**		1.2 ± .3	617.5 ± 14.7	514
46^		9.9 ± 2.1	713 ± 11.6	72	**56**		6.2 ± .7	698 ± 5.6	112.5
47^		38.1 ± 3.6	1131.2 ± 23.6	29	**57**		48.2 ± 2.4	1003.7 ± 13.8	21
48^		24.4 ± 2.9	1030.2 ± 17.2	43	**58**		17.1 ± 2.8	972 ± 56.3	57
49		364.5 ± 3.5	1353 ± 63.7	3.7	**59**		373 ± 17.3	562 ± 31.7	1.5
50^		121.3 ± 32.5	856 ± 73	7	**60**		78.4 ± 5.4	758.3 ± 53.7	9.7
51		342 ± 12.5	935 ± 7.5	2.7	**61**		279.1 ± 9.5	1435 ± 23.5	5
52		1024 ± 23.3	2156 ± 45.7	2.1	**62**		873 ± 13.1	1983 ± 35.2	2
BQ-123		7.3 ± .56	N.D.††		**BQ-788**		N.D.††	1.2 ± .06	

Assay procedure performed in triplicate.

^Compounds previously published by Patel et al.[21] and were evaluated using FRET assay for comparison.

†Given IC_{50} values are Mean ± SD.

††N.D. = Not determined.

References and notes

1. Davenport, A. P.; Hyndman, K. A.; Dhaun, N.; Southan, C.; Kohan, D. E.; Pollock, J. S.; Pollock, D. M.; Webb, D. J.; Maguire, J. J. *Pharmacol. Rev.* **2016**, *68*, 357–418.
2. Aubert, J.-D.; Juillerat-Jeanneret, L. *J. Med. Chem.* **2016**, *59*, 8168–8188.
3. Maguire, J. J.; Davenport, A. P. *Br. J. Pharmacol.* **2014**, *171*, 5555–5572.
4. Masaki, T. *Trends Pharmacol. Sci.* **2004**, *25*, 219–224.
5. Keating, G. M. *Am. J. Cardiovasc. Drugs* **2016**, *16*, 453.
6. Hong, I. S.; Coe, H. V; Catanzaro, L. M. *Ann. Pharmacother.* **2014**, *48*, 538–547.
7. Bagnato, A.; Spinella, F.; Rosano, L. *Endocr. Relat. Cancer* **2005**, *12*, 761–772.
8. Aubert, J.-D.; Juillerat-Jeanneret, L. *Expert Opin. Ther. Targets* **2009**, *13*, 1069–1084.
9. Nelson, J.; Bagnato, A.; Battistini, B.; Nisen, P. *Nat. Rev.* **2003**, *3*, 110–116.
10. Rosano, L.; Spinella, F.; Bagnato, A. *Nat. Rev.* **2013**, *13*, 637–651.
11. Kitada, K.; Ohkita, M.; Matsumura, Y. *Cardiol. Res. Pract.* **2012**, *2012*, 1–7.
12. Boss, C.; Bolli, M. H.; Gatfield, J. *Bioorganic Med. Chem. Lett.* **2016**, *26*, 3381–3394.
13. Battistini, B.; Berthiaume, N.; Kelland, N. F.; Webb, D. J.; Kohan, D. E. *Exp. Biol. Med.* **2006**, *231*, 653–695.

14. Houde, M.; Labonte, J.; D'Orleans-Juste, P. *Curr. Pharm. Des.* **2011**, *17*, 2613–2625.
15. ClinicalTrials.gov Identifier: NCT00111085. *[https//clinicaltrials.gov/ct2/show/NCT00111085?term=clazosentan&rank=1]*. Date Accessed: Mar 4, 2017
16. ClinicalTrials.gov Identifier: NCT00181558. *[https//clinicaltrials.gov/ct2/show/NCT00181558?term=atrasentan&rank=2]*. Date Accessed: Mar 4, 2017.
17. ClinicalTrials.gov Identifier: NCT00525707. *[https//clinicaltrials.gov/ct2/show/NCT00525707?term=tezosentan&rank=1]*. Date Accessed: Mar 4, 2017.
18. ClinicalTrials.gov Identifier: NCT00738049. *[https//clinicaltrials.gov/ct2/show/NCT00738049?term=darusentan&rank=1]*. Date Accessed: Mar 4, 2017.
19. ClinicalTrials.gov Identifier: NCT01178073. *[https//clinicaltrials.gov/ct2/show/NCT01178073?term=tadalafil+and+ambrisentan&rank=2]*. Date Accessed: Mar 4, 2017.
20. Patel, H. St. John's University. *Thesis.* **2008**.
21. Patel, H. J.; Olgun, N.; Lengyel, I.; Reznik, S.; Stephani, R. A. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6840–6844.
22. Invitrogen GeneBLAzer® EDNRA HEK 293T DA Cell-based Assay. *In: thermofisher.com [https://tools.thermofisher.com/content/sfs/manuals/GB_EDNRA_HEK293T_man.pdf]*. Date Accessed: Mar 4, 2017.
23. Invitrogen GeneBLAzer® EDNRB HEK 293T DA Cell-based Assay. *In: thermofisher.com [https://tools.thermofisher.com/content/sfs/manuals/GB_EDNRB_HEK293T_man.pdf]*. Date Accessed: Mar 4, 2017.
24. Zhang, R.; Xie, X. *Acta Pharmacol. Sin.* **2012**.
25. Bold, G.; Frei, J.; Lang, M.; Traxler, P. WO1998014450A1. **1998**.
26. Klinke, P.; Gibian, H. *Chem. Ber.* **1961**, *94*, 26–38.
27. Nicolaou, K.; Hongming, L.; Nold, A.; Pappo, D.; Lenzen, A. *J. Am. Chem. Soc.* **2007**, *129*, 10356–10357.

Supplementary Material

Supporting information containing all experimental procedures (for both synthesis and biological assays) and full characterization of compounds is electronically available.

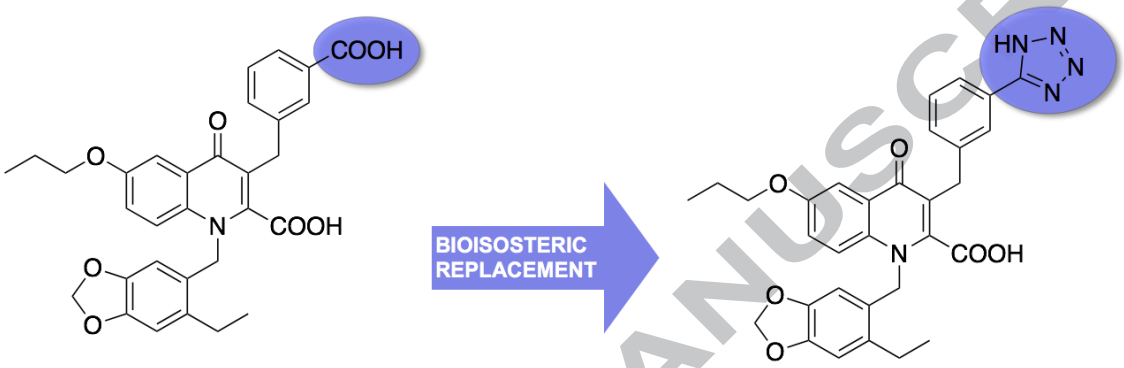
Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Design, synthesis and evaluation of 1,3,6-trisubstituted-4-oxo-1,4-dihydroquinoline-2-carboxylic acid derivatives as ET_A receptor selective antagonists using FRET assay

Nikhil Khadtare, Ralph Stephani and Vijaya Korlipara*

Leave this area blank for abstract info.



44
ET_A IC_{50} = 4.2 nM
ET_B IC_{50} = 2868.4 nM
ET_A-selectivity = 683

54
ET_A IC_{50} = 0.8 nM
ET_B IC_{50} = 803.2 nM
ET_A-selectivity = 1004