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Discovery of a Series of (4,5-Dihydroimidazol-2-yl)-biphenylamine 5-HT$_7$ Agonists

Vinod Parikh,* Willard M. Welch* and Anne W. Schmidt

Pfizer Global Research and Development, Eastern Point Road, Groton, CT 06340, USA

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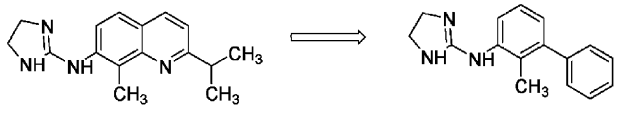
Abstract—A novel (4,5-dihydroimidazol-2-yl)-biphenylamine series of 5-HT$_7$ agonist compounds was developed from a structurally related lead compound **1**. The newly discovered series is exemplified by compound **2** that possesses high affinity for 5-HT$_7$ receptors and shows intrinsic agonist activity in functional assays. This new series has significant α_1 and α_2 activities perhaps due to the presence of the 2-aminoimidazoline moiety.

The neurotransmitter serotonin (5-hydroxytryptamine, 5-HT) has been implicated in a variety of physiological and pathophysiological processes such as cardiovascular regulation, memory, thermoregulation, sleep, feeding, depression, anxiety, drug abuse and migraine. Fourteen subtypes of 5-HT receptors organized into seven distinct receptor classes, 5-HT$_1$–5-HT$_7$, are now recognized.[1] The 5HT$_7$ receptor has cloned from several species including rat, guinea pig, human and shows a high degree of homology (~95%). The 5-HT$_7$ receptor is well represented in a diversity of neuronal and non-neuronal tissue where, in at least some tissues, its activation has been shown to elevate intracellular cAMP.[2]

Functionally, the 5-HT$_7$ receptor has been implicated in regulation of circadian rhythms in mammals.[2] In the CNS, cells containing this receptor are found in the superchiasmatic nucleus[3] (SCN), a region long associated with circadian rhythm regulation. For a number of years, disruption of circadian rhythms has been implicated in a variety of CNS disorders including depression, seasonal affective disorder, shift worker syndrome and jet lag among others. We reasoned that compounds that regulated the circadian cycle in humans might be useful in alleviating these conditions.

Stimulation of this receptor by standard agents such as 8-hydroxy-2-(*N*,*N*-dipropylamino)-1,2,3,4-tetrahydronaphthalene (8-OH-DPAT), a 5-HT$_7$ agonist,[4] has been reported to cause a phase advance in peak circadian cell firing rates in SCN cells in slices[5] taken from rats constrained to a 12/12 light–dark cycle prior to test. We sought compounds that would be selective and potent agonists of this receptor.

Compounds capable of binding to the 5-HT$_7$ receptor were identified by their ability to block binding of ^{3}H-5-carboxamidotryptamine (^{3}H-5-CT), a potent 5-HT$_7$ agonist, to 5-HT$_7$ receptors. High-Throughput screening of the Pfizer compound library identified compound **1**, which binds potently to the 5-HT$_7$ receptor and which was characterized as a full agonist at this receptor, compound **1** at 10 uM increasing adenylate cyclase activity to the same extent as 10 uM 5-HT.[6] The subject series of (4,5-dihydroimidazol-2-yl)-biphenylamine derivatives was derived from compound **1** by elimination of the pyridyl ring while adding a lipophilic aromatic ring at the 6-position. Through overlap of these two molecules, we reasoned that *meta*-substitution in this second aromatic ring, as suggested by the presence of the isopropyl group in compound **1**, might be favored for agonist activity at the 5-HT$_7$ receptor.



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*Corresponding author. Fax: +1-860-686-0013; e-mail: vinod_d_parikh@groton.pfizer.com

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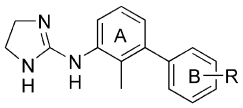
Table 1.



Compd[a]	R	Rat 5HT$_7$ pK_i±SEM	Rat α_1 pK_i±SEM	Rat α_2 pK_i±SEM
2	H	7.79±0.08	6.68[c]	7.71[c]
3	3-CH_3	7.67±0.05	6.78±0.09	7.75±0.11
4	3-F	7.55±0.07	6.56±0.15	7.58±0.20
5	3-OCH_3	7.45[c]	7.36[d]	8.00[d]
6	3-CF_3	7.34±0.05	6.59±0.10	7.10±0.08
7	3-Cl	7.58±0.09	6.88±0.09	7.62±0.16
8[b]	3-CN	6.77±0.04	7.04±0.16	7.66±0.18
9[b]	3-$COCH_3$	6.81±0.04	7.05±0.01	7.49±0.03
10	3-$CH(CH_3)_2$	6.74±0.09	5.92[c]	6.96±0.01
11	4-OCH_3	7.56±0.11	6.58±0.04	7.59±0.03
12	2,4-$(OCH_3)_2$	7.39±0.08	6.68±0.04	7.13±0.16

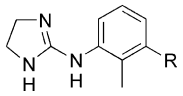
[a]All compounds were characterized by ^{1}H NMR, MS, and IR.
[b]Tested as hydrochloride salt.
[c]$n=2$.
[d]$n=1$.

In this paper, we describe the synthesis of a series of (4,5-dihydroimidazol-2-yl)-biphenylamine derivatives and the 5-HT$_7$ binding activity of the series.

The synthesis of the biaryl moiety of the series of (4,5-dihydroimidazol-2-yl)-biphenylamine analogues shown in Table 1 was carried out using straightforward Suzuki coupling methodology. Thus, *meta* and *para* substituted phenylboronic acids 2-thiophene boronic acid and 3-pyridyl boronic acid reacted with commercially available 2-bromo-6-nitrotoluene in the presence of the Pd° catalyst Pd $(PPh_3)_4$ and CsF in dimethoxyethane to give the corresponding cross coupled intermediates in good yields. The nitro group could be reduced quantitatively to the desired aniline derivative with iron powder and hydrochloric acid.[7] The resulting aniline intermediate was then converted to the thiourea in two steps with carbon disulfide and the water-soluble carbodiimide DEC[8] followed by reaction with ethylenediamine. This intermediate thiourea was then readily cyclized to the 2-aminoimidazoline derivative by refluxing in ethanol in presence of mercury oxide (Scheme 1).[9]

Within the series of derivatives shown in Table 1, it will be noted that binding to the 5-HT$_7$ receptor was highly dependant upon substituent with the unsubstituted analogue **2** being most potent. Electron withdrawing or donating groups has as marginally effects in the binding affinity compare to the unsubstituted analogue. In the case of the heterocyclic analogues presented in Table 2, the 2-thiophene analogues **13** and **14** were active at the 5-HT$_7$ receptor but demonstrated significant α_2 binding activity using rat cortical membranes. The 3-pyridyl analogue **15** was much less active at 5-HT$_7$ and α_1 receptors but the potent α_2 binding activity was retained.

Table 2.

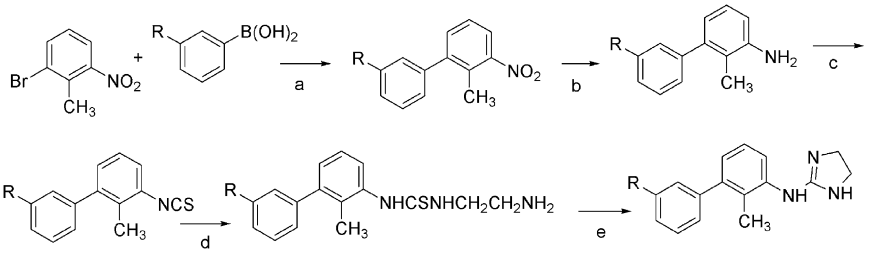


Compd[a]	R	Rat 5HT$_7$ pK_i±SEM	Rat α_1 pK_i±SEM	Rat α_2 pK_i±SEM
13	2-Thiophene	7.78±0.05	6.99±0.07	8.21±0.09
14	3-Thiophene	7.50[b]	7.16[c]	7.96[c]
15	3-Pyridyl	6.59±0.06	6.59±0.07	8.29±0.14

[a]All compounds were characterized by ^{1}H NMR, MS, and IR.
[b]$n=2$.
[c]$n=1$.

2-Anilinoimidazoline derivatives such as clonidine and brimonidine[10] have been shown to have clinical antihypertensive activity attributable to the α_2 activity inherent in the 2-aminoimidazoline moiety. Unfortunately, this antihypertensive property was also seen within compounds of the present series, the most potent 5- HT$_7$ binding derivative **2** causing pronounced hypertension in rats.

Compounds from a series of (4,5-dihydroimidazol-2-yl)-biphenylamine derivatives were shown to bind to 5-HT$_7$ receptors with moderate to good potencies. A representative compound from this series was shown to be a full agonist in a 5-HT$_7$ functional assay. Because of the association of blood pressure changes related to α_1 and α_2 activity, compound **2** was examined in a rat hypertension model. Profound blood pressure and heart rate changes were seen after iv Administration of compound **2**. These effects are likely due to the α_2 activity of compound **2**, a discovery that greatly decreased future interest in these analogues. As a result of this finding, we have since terminated synthetic efforts in this area.



Scheme 1. Reagents and yields (range): (a) DME, CsF, Pd, 100 °C, 4 h, 75–100%; (b) Fe powder, HCl, EtOH, 80 °C, 2 h, 82–100%; (c) CS_2, DEC, THF, rt, 24 h, 11–82%; (d) $NH_2(CH_2)_2NH_2$, CH_2Cl_2, rt, 24 h, 85–100%; (e) H_gO, EtOH, 80 °C, 2 h, 70–100%.

Acknowledgements

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References and Notes

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