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5-Thienyltryptamine Derivatives as Serotonin 5-$HT_{1B/1D}$ Receptor Agonists: Potential Treatments for Migraine

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Abstract—A series of 5-(2- or 3-thienyl)tryptamine derivatives (**9**) has been synthesized and shown to be potent and selective 5-HT_{1D} versus 5-HT_{1B} receptor agonists and, therefore, potential treatments for migraine.

Migraine is a common, highly distressing disorder affecting normal daily life and economic productivity.[1] The introduction of sumatriptan (**1**)[2] (Fig. 1) into clinical practice has revolutionized migraine drug discovery and spurred further research for better treatments.[3] Several related compounds such as zolmitriptan (**2**) and naratriptan (**3**) have recently emerged on the market. These drugs are all serotonin receptor agonists and are collectively known as 'triptans'. The triptan class of antimigraine drugs bind to the 5-HT_{1D} (5-$HT_{1D\alpha}$ previously), 5-HT_{1B} (5-$TH_{1D\beta}$ previously) and 5-HT_{1F} receptors with high affinities.[3] Although the exact pathophysiology of migraine is unclear: direct vasoconstrictor effect on the cranial blood vessels[4] and/or inhibition of neurogenic inflammation in the dura mater,[5] it is generally accepted that one or more of the three receptors to which the triptans bind is involved in migraine. While all three receptors (5-HT_{1D}, 5-HT_{1B} and 5-HT_{1F}) have been found in human trigeminal ganglia, only 5-HT_{1B} and 5-HT_{1F} receptors are clearly present in cerebral blood vessels.[6] The vasoconstrictor effect could be mediated by the 5-HT_{1B} or 5-HT_{1F} receptors while the neurogenic effect by any of the three.

It has been proposed that selective agonists of the 5-HT_{1D} site alone might be effective in ameliorating migraine symptoms.[7] However, sumatriptan has shown no effect in the neurogenic model of knockout mice lacking the 5-HT_{1B} receptor.[8] In addition, the 5-HT_{1F} receptor is also a potential target for migraine. LY-334370 is a 5-HT_{1F} receptor specific ligand.[9] It has shown satisfactory phase II results, but was abandoned for safety reasons.

It has been shown that adverse cardiovascular effects associated with sumatriptian can be attributed to its 5-HT_{1B} receptor[10] which is present in human coronary arteries.[11] Other members of the triptan class also bind to the 5-HT_{1B} receptor and will likely cause the same cardiovascular side effects as sumatriptan. Thus, the search for the next generation of antimigraine drugs has focussed on achieving 5-HT_{1D}/5-HT_{1B} selectivity. To this end over 300-fold selectivity has been achieved in the indole series[12] and over 6000-fold selectivity in a non-indole series.[13] Since it is not certain whether the 5-HT_{1D} receptor alone is involved in the pathogenesis and/or treatment of migraine, it will be very interesting and important to see if these highly selective compounds show efficacy in humans.

In this Letter, we report the synthesis and biological evaluation of a series of 5-thienyltryptamine derivatives (**9**) as potential treatments for migraine. These compounds were synthesized by a cross-coupling reaction between the thiophene and the indole segments. As shown in Scheme 1, commercially available 5-bromoindole **4** was acylated by treatment with oxalyl chloride in diethylether at 0 °C and then refluxed overnight to afford intermediate **5**. It was further reacted with an excess amount of a variety of amines to give compounds **6**, which were coupled with thiopheneboronic acids under the Suzuki conditions[14] to give the targeted 5-thienyltryptamine

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derivatives **9**. Alternatively, bromides **6** were converted to their tin derivatives **8** by reaction with dibutylditin and catalytic Pd(0) in toluene at reflux, and then cross-coupled with a bromothiophene under the Stille conditions.[15] This manipulation is useful when the corresponding thiophenboronic acid is not commercially available. The reduction of the dicarbonyl intermediate with four equivalents of lithium aluminum hydride in refluxing tetrahydrofuran gave 5-thienyltryptamine derivatives **9** as final product suitable for biological evaluation.

A synthesis starting from serotonin was also pursued. As shown in Scheme 2, the primary amine of serotonin

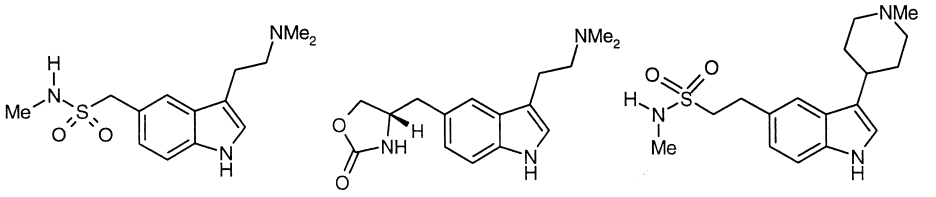
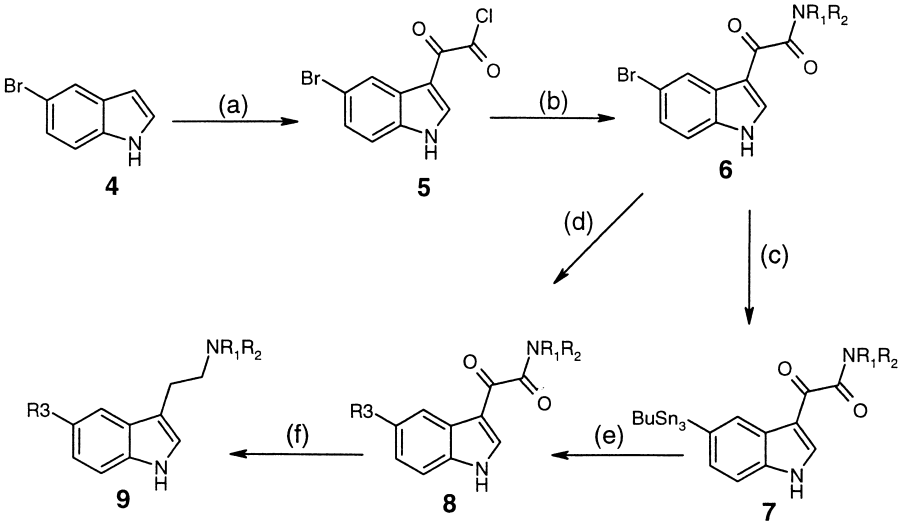
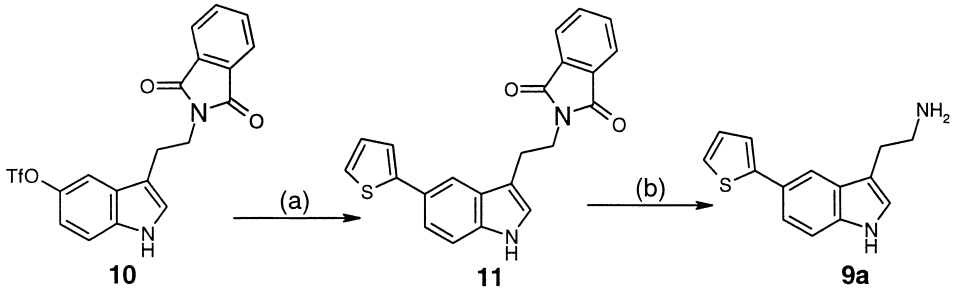


Figure 1.



9b; $NR_1R_2 = NMe_2$, R_3 = 2-thienyl
9c; $NR_1R_2 = NMe_2$, R_3 = 3-thienyl
9d; $NR_1R_2 = NMe_2$, R_3 = 5-methyl-(2-thienyl
9e; $NR_1R_2 = NMe_2$, R_3 = 5-chloro-(2-thienyl)
9f; NR_1R_2 = pyrrolidine, R_3 = 2-thienyl
9g; NR_1R_2 = pyrrolidine, R_3 = 5-chloro-(2-thienyl)
9h; NR_1R_2 = 2,5-di-methylpyrrolidine, R_3 = 2-thienyl
9i; NR_1R_2 = (S)-(+)-2-pyrrolidinemethanol, R_3 = 2-thienyl
9j; NR_1R_2 = (S)-(+)-2-(methoxymethyl)pyrrolidine, R_3 = 2-thienyl
9k; NR_1R_2 = 3-pyrroline, R_3 = 2-thienyl

Scheme 1. Reagents and conditions: (a) oxalylchloride, diethylether, 0 °C, then reflux overnight; (b) amines, triethylamine in tetrahydrofuran, RT/2 h; (c) $Bu_3SnSnBu_3$, $PdPh_3P_4$, toluene, reflux overnight; (d) thiopheneboronic acid, $PdPh_3P_4$, Na_2CO_3, DME, reflux/4 h; (e) thiophenebromide, $PdPh_3P_4$, Na_2CO_3, DMF, reflux/overnight; LAH, tetrahydrofuran, reflux/4 h.



Scheme 2. Reagent and conditions: (a) 2-thiopheneboronic acid, $PdPh_3P_4$, Na_2CO_3, DME, reflux/4 h; (b) NH_2NH_2, RT/overnight.

Table 1. Binding profile of 5-Thienyltryptamine derivatives **9** in comparison with sumatriptan at the cloned human 5-HT_{1D} and 5-HT_{1B} receptors

Compound	5-HT_{1D}, K_i, (nM)[a]	5-HT_{1B} (K_i, nM)[a]	5-HT_{1B}/5-HT_{1D}
Sumatriptan	11	36	3.2
9a	1.7	32	18.8
9b	0.7	23	32.8
9c	0.5	17	34
9d	3.2	133	41.5
9e	7.6	303	39.8
9f	19	714	37.5
9g	31	476	15.3
9h	2.5	70	28
9i	8.2	113	13.7
9j	1.8	9.9	5.5
9k	4.5	107	23.7

[a]K_i values are given as the mean of at least two independent determinations performed in duplicate.

was first protected as a phthalimide and the phenol group was converted to the triflate to give intermediate **10**.[16] Cross-coupling with 2-thiopheneboronic acid under Suzuki conditions afforded compound **11**. Finally, cleavage of phthalimide with hydrazine gave 5-thienyltryptamine **9a**.

As shown in Table 1, all compounds reported here exhibited high affinity for the 5-HT_{1D} receptor; most of them being more potent than or comparable to sumatriptan. In all cases, better 5-HT_{1D}/5-HT_{1B} selectivities were observed when compared to sumatriptan, some being over 10 times better. Both 2- and 3-thienyl analogues displayed very similar binding profiles at both 5-HT_{1B} receptors (compare **9b** with **9c**). Introduction of a substitution to the 5-position of the thieny1 ring in the *N*,*N*-dimethylamine series results in an at least 5-fold lower affinity for both the 5-HT_{1D} and 5-HT_{1B} receptors (compare **9b** and **9d** with **9e**), and slightly increased 5-HT_{1D}/5-HT_{1B} selectivity. The same trends are not observed in the pyrrolidine analogues (compare **9f** with **9g**). *N,N*-Dimethylamine derivative **9b**, showed an increased 5-HT_{1D}/5-HT_{1B} selectivity over the corresponding primary amine **9a**. The pyrrolidine derivative **9f** binds with almost 30-fold lower affinity than the *N,N* dimethylamine analogue **9b** at both 5-HT_{1D} and 5-HT_{1B} receptors. Introduction of mono- or di-substitutions to the pyrrolidine ring results in higher affinity, though not to the same extent at 5-HT_{1D} and 5-HT_{1B} receptors. In fact, the methoxymethyl derivative (**9j**) has the lowest 5-HT_{1D}/5-HT_{1B} selectivity. When a double bond is introduced into the pyrrolidine ring, potencies at both 5-HT_{1D} and 5-HT_{1B} receptors were gained, but the 5-HT_{1D}/5-HT_{1B} selectivity decreased (compare **9k** with **9f**).

In summary, we have discovered a series of 5-thieny1-tryptamine derivatives as potent, selective 5-$HT_{1D/1B}$ receptor agonists. Some of them are 10 times more potent at the 5-HT_{1D} receptor and 10 times more 5-HT_{1D}/5-HT_{1B} selective than sumatriptan. These compounds are currently under pharmacological evaluation which will be reported separately.

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