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FPL 64176: THE EFFECT OF THE CHAIN LENGTH SEPARATING THE TWO ARYL GROUPS ON CALCIUM AGONIST ACTIVITY

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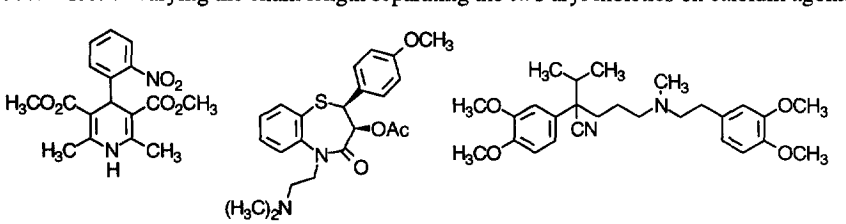
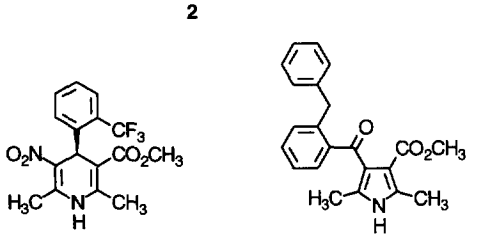
Abstract: Analogs of the L-type calcium channel agonist FPL 64176 (**5**) were prepared in which the chain length separating the two aryl moieties was varied between zero and four. FPL 64176 (**5**) and phenethyl derivative **19** were the most potent compounds tested, displaying EC_{50} values for enhancing calcium influx into GH_3 cells of $1\text{-}2x10^{-7}$ M.

Voltage-dependent L-type calcium channels play an important role in controlling calcium entry into a number of excitable tissues. A variety of compounds have been shown to modulate the activity of these channels. A majority of these substances block the entry of calcium through the L-type channel.[1,2] These calcium antagonists comprise a diverse group of structures which include 1,4-dihydropyridines such as nifedipine (**1**), benzothiazepines such as diltiazem (**2**), and phenylalkylamines such as verapamil (**3**). In contrast, relatively few compounds are known to promote calcium influx through the L-channel.[3,4] Most of these compounds are 1,4-dihydropyridine derivatives such as (S)-BAY K 8644 (**4**).[5] Recently, a novel benzoylpyrrole, FPL 64176 (**5**), was described as a potent activator of L-type calcium channels.[6-8] Three dimensional QSAR analysis of compounds which were close analogs of **5** using the GRID force field predicted that benzyl substituents and their isosteres should be preferred for calcium agonist activity.[9-11] In an effort to investigate this prediction further, we now report the effect of varying the chain length separating the two aryl moieties on calcium agonist activity.

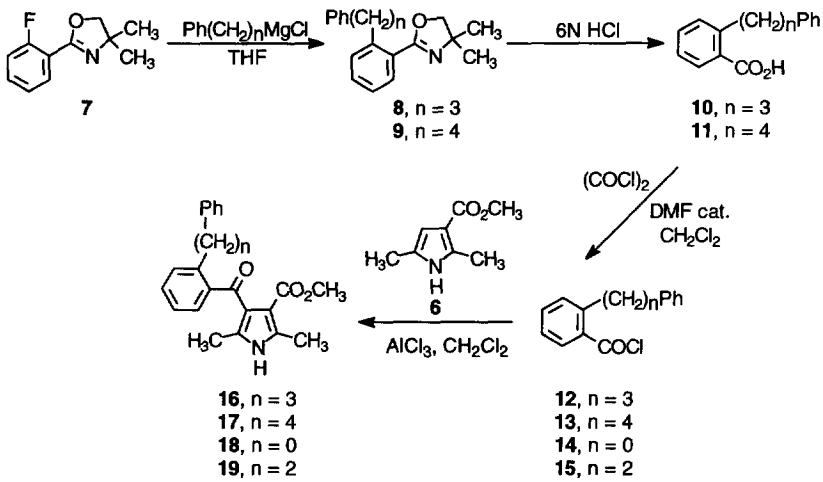


1 **2** **3**



4 **5**

With the exception of FPL 64176 (**5**), the benzoylpyrroles examined in this study were prepared by the Friedel-Crafts reaction of the appropriate acid chloride and methyl 2,5-dimethylpyrrole-3-carboxylate (**6**).[12] To elaborate, nucleophilic aromatic substitution of the fluorine in 4,4-dimethyl-2-(2-fluorophenyl)oxazoline (**7**)[13] by the Grignard reagents derived from both 1-chloro-3-phenylpropane[14] and 1-chloro-4-phenylbutane[15] afforded oxazolines **8**[16] and **9** in 78 and 91% yield. Hydrolysis of the oxazoline moiety[17] using 6N HCl gave the corresponding acids **10**[18] and **11**[19] in 75 and 70% yield. Reaction of **10**, **11**, 2-phenylbenzoic acid[14], and 2-phenethylbenzoic acid[14] with oxalyl chloride and a catalytic amount of DMF gave essentially quantitative yields of the acid chlorides **12-15** which were used without purification. Friedel-Crafts acylation of **6** using the acid chlorides **12-15** completed the synthesis of the desired benzoylpyrroles **16-19** in 30-62% yield. The synthesis of FPL 64176 (**5**) could not be accomplished by this method due to exclusive formation of anthrone. The synthesis of **5** was therefore accomplished by our previously reported tandem Friedel-Crafts method.[20]



7

8, n = 3
9, n = 4

10, n = 3
11, n = 4

6

16, n = 3
17, n = 4
18, n = 0
19, n = 2

12, n = 3
13, n = 4
14, n = 0
15, n = 2

We assessed the ability of FPL 64176 (**5**) and compounds **16-19** to enhance L-channel activity by examining their effects on K^+ stimulated $^{45}Ca^{2+}$ influx in GH_3 cells.[21] Nonlinear least squares fit of the data in Figure 1 yield an EC_{50} value for **5** of 1.4×10^{-7} M and a maximal stimulation of $^{45}Ca^{2+}$ uptake of 298% (279-317%, 95% C.L.). Phenethyl derivative **19** was similarly potent displaying an EC_{50} value of 2.07×10^{-7} M. Interestingly, the maximal stimulation produced by **19** was significantly greater than that produced by FPL 64176 (**5**) measuring 420% (336-504%, 95% C.L.). The EC_{50} for phenpropyl derivative **16** measured 6.14×10^{-7} with a peak $^{45}Ca^{2+}$ influx measuring 265% (217-314%, 95% C.L.). Both the phenbutyl derivative **17** and the biphenyl derivative **18** were much less potent. No significant increase in $^{45}Ca^{2+}$ uptake was observed with **18** up to 10^{-5} M. Phenbutyl derivative **17**, on the other hand, increased $^{45}Ca^{2+}$ influx by 84±16% at 10^{-6} M. At higher concentrations, $^{45}Ca^{2+}$ influx decreased, perhaps due to nonselective inhibition of the channel by this highly hydrophobic molecule.

Figure 1

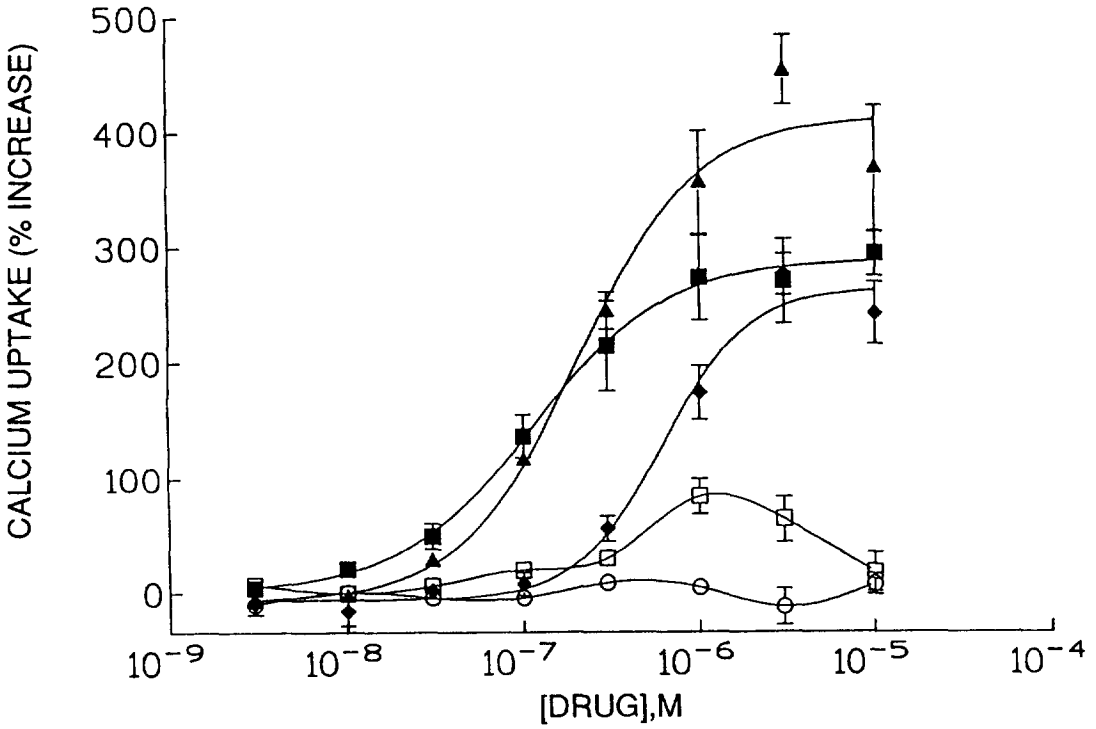


Figure 1. Effects of benzoylpyrroles on K^+ stimulated Ca^{2+} influx in GH_3 cells. Data is expressed as the percent increase in Ca^{2+} influx over control conditions. Dose-response relationships for structures **5** (■), **16** (◆), **17** (□), **18** (○), and **19** (▲). Bars represent SEM (n = 3-4).

In summary, we have described the effects of varying the chain length separating the two aryl groups in the benzoylpyrrole series of L-channel activators. We find that a chain length of 1 or 2 gives optimum potency with EC_{50} values for stimulating $^{45}Ca^{2+}$ influx in GH_3 cells measuring approximately 100-200 nM. Furthermore, a chain length of 2 resulted in the highest efficacy of all the compounds tested as measured by the maximal increase in this $^{45}Ca^{2+}$ influx. Benzoylpyrroles such as FPL 64176 (**5**) display higher efficacy as L-channel activators relative to the 1,4-dihydropyridine agonists such as (S)-BAY K 8644 (**4**).[7] This property appears to be further enhanced in phenethyl derivative **19**, making it one of the most effective activators of L-type Ca^{2+} channels described to date.

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