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A New Synthesis of FPL 64176 and Analogues: The Discovery of Benzoylpyrrole Calcium Channel Activators with Low Nanomolar Potency[1]

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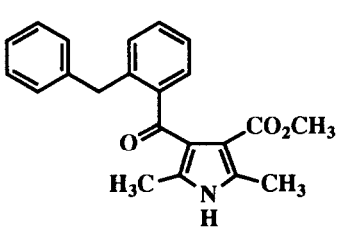
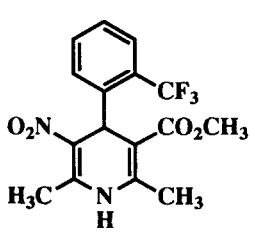
Abstract: Heavy metal assisted halogen displacement on 2-halobenzoylpyrroles (**2** and **3**) leads to a simple synthesis of FPL 64176 (**1**) and a variety of analogues (**4-10**). The difluoro derivative (**4**), EC_{50} 1nM, and the amino linked analogue (**7**), EC_{50} 2.7nM, are presently the most potent calcium channel activators known.

Methyl 2,5-dimethyl-4-(2-(phenylmethyl)benzoyl)-1H-pyrrole-3-carboxylate (**1**, FPL 64176) is the first of a new class of calcium channel activators, the benzoylpyrroles. A recent publication from our own laboratories[2] has detailed the medicinal chemistry background and first synthesis of FPL 64176, while we[3] and other groups[4-7] have presented detailed accounts of the biochemical, pharmacological and electrophysiological properties of this interesting compound. The data in these publications support the view that this class of compounds do not interact at the same site/receptor as the well known dihydropyridine calcium channel activator Bay K8644.



1, FPL 64176



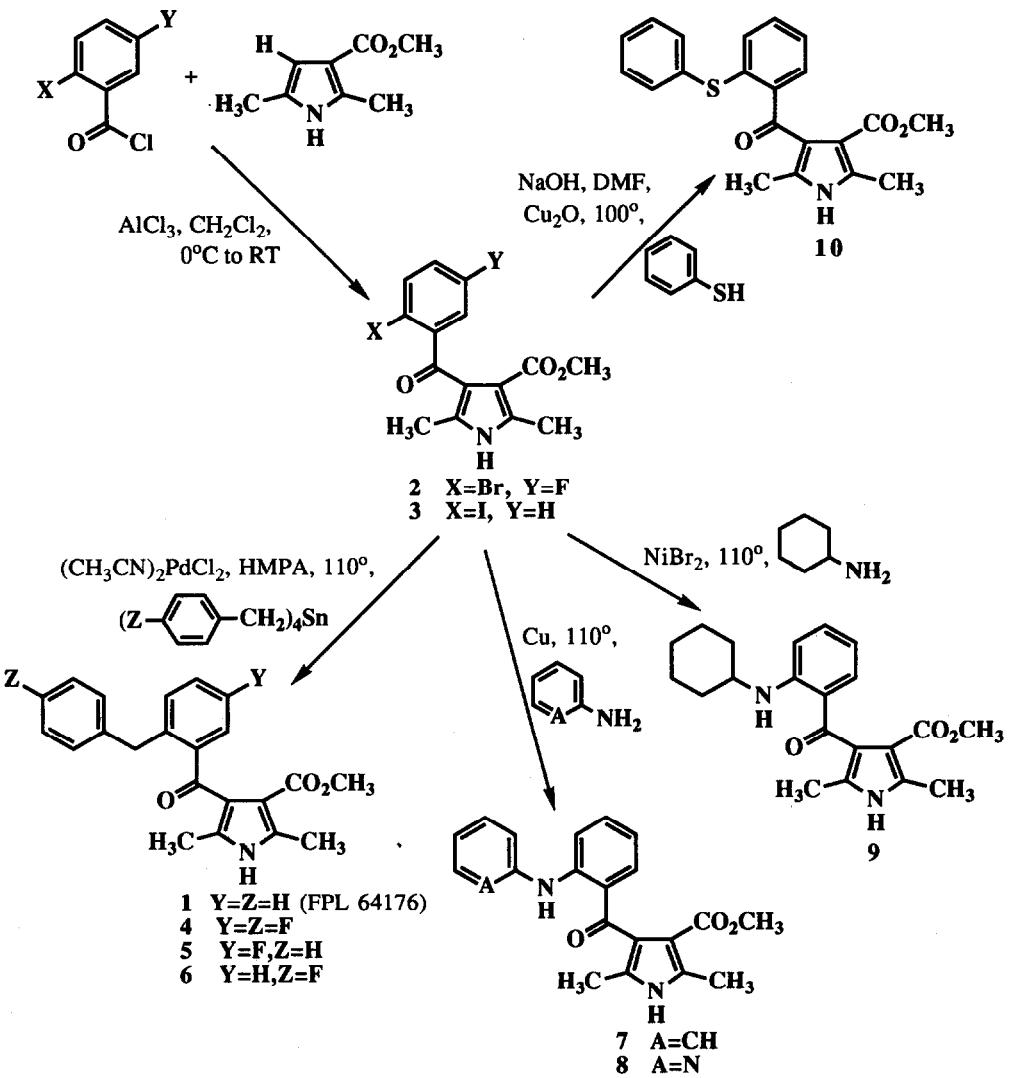
Bay K8644

Following on from the initial publications in this area, Dalton et al.[8] have published an alternative, short route to FPL 64176 and compounds with a substituted pendant phenyl ring. As part of our medicinal chemical programme exploring the SAR of this series, we wanted to prepare analogues in which the important benzylbenzoyl substituent on **1** was varied. We chose to use the stable 2-halobenzoylpyrroles (**2** and **3**, Scheme I) and to investigate heavy metal assisted (Ullman type and Heck) halogen displacements. It was hoped that this would enable us to prepare a range of compounds which had the pendant ring specifically substituted, saturated or heterocyclic and with it joined to the parent benzoylpyrrole with linkers other than methylene. This short paper details these studies together with initial biological evaluation of these analogues as calcium channel activators. Certain of these compounds, especially **4** and **7**, are the most potent calcium channel activators yet described being active in the low nanomolar range. To allow other investigators ready access to these valuable biochemical and pharmacological tools, full experimental details are also given.

The required halobenzoylpyrroles (**2** and **3**) were prepared (Scheme 1) using standard Friedel Crafts conditions.[2] Palladium(0) catalysed[9] tetrabenzyltin displacement in HMPA cleanly gave **1**. This route was extended to allow the synthesis of various fluoro analogues (**4-6**). The preparation of the amino linked compounds (**7** and **8**) was conviently carried out using copper bronze and the amine as reactant and solvent. This procedure did not work for cyclohexylamine and so alternative conditions using nickel(II) bromide[10] were successfully employed for the synthesis of **9**. Copper(I) oxide assisted thiolate displacement[11] cleanly gave the sulphur linked analogue **10**.

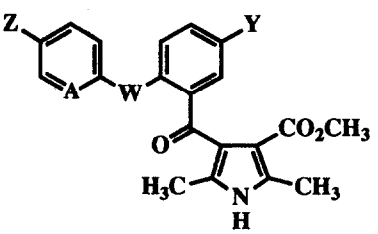
The compounds were examined for calcium channel activation properties (Table 1) using a procedure previously described for the dihydropyridine activator Bay K 8644, the standard compound in this area.[12] The increase in [$^{45}Ca^{2+}$] uptake into rat pituitary GH3 cells depolarised with 50mM K^+ was used to determine channel activation, 'Ca^{2+} uptake' is quoted as the EC_{50} value vs. Bay K 8644=100%.

In this short paper we have presented full details for the synthesis of novel calcium channel activators with increased potency over the standard compounds FPL 64176 and Bay K8644 together with a simple method of preparing FPL 64176 itself. Details of structure-activity relationships will be presented in a full paper. These compounds should be useful tools for the study of calcium channel currents in cell types that are associated with many disease states.[13]

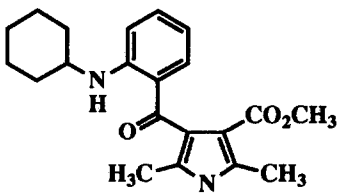


Scheme 1. Synthetic Route to FPL 64176 (**1**) and Analogues

Compound	A	W	Y	Z	Ca^{2+} Uptake EC_{50} nM
1	CH	CH_2	H	H	18.0
4	CH	CH_2	F	F	1.0
5	CH	CH_2	F	H	1.6
6	CH	CH_2	H	F	3.9
7	CH	NH	H	H	2.7
8	N	NH	H	H	12.0
9					11.0
10	CH	S	H	H	79.0
Bay K8644					22.0



1, 4-8, 10



9

Table 1. Calcium Channel Activation Potencies for FPL 64176 (1) and Analogues vs. Bay K8644

EXPERIMENTAL

Melting points were determined in open capillary tubes with a Buchi melting point apparatus and are uncorrected. The structures of all compounds are consistent with spectroscopic data (IR, ^1H NMR and MS) and satisfactory elemental analyses were obtained where stated. NMR spectra were recorded in $CDCl_3$ solution on a Bruker AM360 360-MHz spectrometer using TMS as standard. The chemical shifts are in ppm (δ). Mass spectra were recorded on a VG 70-250SEQ machine. UV spectra were recorded in ethanol solution on a Philips PU8720 UV/Vis spectrophotometer. IR spectra were recorded on a Perkin Elmer 1720X FT-IR spectrometer using diffuse reflectance, samples were diluted with KBr. Flash chromatography was performed with thick-walled glass columns on silica gel (Silica 60, 35-70 mm, Matrex, Merck or Sorbsol). In the text petroleum ether refers to the fraction boiling in the range 60-80°. Temperatures are in °C.

Methyl 4-(2-bromo-4-fluorobenzoyl)-2,5-dimethyl-1H-pyrrole-3-carboxylate (2). Thionyl chloride (2.5 mL) and 2-bromo-4-fluorobenzoic acid (3.2g, 14.6 mmole) in toluene (50 mL) were heated at reflux for 3 hours. The solvent was evaporated and this oil was azeotroped with toluene. Dichloromethane (150 mL) was added followed by methyl 2,5-dimethyl-1H-pyrrole-3-carboxylate (4g, 26 mmole). The reaction mixture was cooled to 0°, and aluminium trichloride (12g) was added. After stirring for 16 hours at room temperature, the reaction mixture was poured onto ice. The organic layer was separated, dried

($MgSO_4$) and the solvent was evaporated. Chromatography on silica eluting with ethyl acetate/petroleum ether mixtures followed by recrystallisation from toluene gave **2** (4.2g, 81% yield): mp 125-6°; Found: C, 51.06; H, 3.84; N, 3.74%. $C_{15}H_{13}BrFNO_3$ requires C, 50.86; H, 3.70; N, 3.74%; δ_H 2.38 (3H, s), 2.43 (3H, s), 3.34 (3H, s), 6.94-7.00 (2H, m), 7.58 (1H, dd) and 8.45 (1H, br s); m/z 353/5 M^+.

Tetrakis((4-Fluorophenyl)methyl)stannane. 1-(Bromomethyl)-4-fluorobenzene (50g, 260 mmol) in THF (100 mL) was added dropwise with stirring to magnesium (20g) in refluxing THF (300mL) (CAUTION exotherm). After cooling to room temperature, tin(IV) chloride (10.4g, 40 mmole) in hexane (50 mL) was added slowly (CAUTION exotherm). After stirring for 4 hours, the mixture was poured onto aqueous ammonium chloride solution. The mixture was filtered, the solid obtained was washed with ether and the filtrates combined. The aqueous layer was saturated with sodium chloride and the organic layer was separated, dried ($MgSO_4$) and the solvent was evaporated. The stannane was obtained as a solid (28g), approx. 70% pure, and was used without further purification: δ_H 2.12 (2H, s), 6.61 (2H, dt) and 6.84 (2H, t).

Methyl 4-(5-fluoro-2-((4-fluorophenyl)methyl)benzoyl)-2,5-dimethyl-1H-pyrrole-3-carboxylate (4). The bromide **2** (1.5g, 4.24 mmole), tetrakis((4-fluorophenyl)methyl)stannane (8g, 14.4 mmol) and bis(acetonitrile)palladium(II) chloride (catalytic) were heated at 110° in HMPA (30mL) for 16 hours. The cooled reaction mixture was diluted with dilute hydrochloric acid and ethyl acetate and filtered. The organic layer was separated and washed twice with dilute hydrochloric acid, dried ($MgSO_4$) and the solvent was evaporated. Chromatography on silica eluting with ethyl acetate/hexane mixtures followed by recrystallisation from ethyl acetate gave **4** (0.8g, 49% yield): mp 200-1°; Found: C, 68.81; H, 5.20; N, 3.42%. $C_{22}H_{19}F_2NO_3$ requires C, 68.92; H, 4.99; N, 3.65%; δ_H 2.20 (3H, s), 2.41 (3H, s), 3.25 (3H, s), 4.16 (2H, s), 6.92-7.30 (7H, m) and 10.53 (1H, br s); m/z 383 M^+; λ_{max} 204 (4.51), 240 (4.08), 297 (3.80) nm.

Also prepared by this method: **Methyl 4-(5-fluoro-2-(phenylmethyl)benzoyl)-2,5-dimethyl-1H-pyrrole-3-carboxylate (5).** 46% yield: mp 144-5°; Found: C, 71.36; H, 5.78; N, 3.27%. $C_{22}H_{20}FNO_3.(H_2O)_{0.33}$ requires C, 71.14; H, 5.61; N, 3.77%; δ_H 2.14 (3H, s), 2.40 (3H, s), 3.26 (3H, s), 4.13 (2H, s), 7.00-7.40 (8H, m) and 8.54 (1H, br s); m/z 366 $(M+1)^+$.

Methyl 2,5-dimethyl-4-(2-(phenylmethyl)benzoyl)-1H-pyrrole-3-carboxylate (1). From 2-(iodobenzoyl)pyrrole **3**[2] in 60% yield: identical with known sample.[2]

Methyl 4-(2-((4-fluorophenyl)methyl)benzoyl)-2,5-dimethyl-1H-pyrrole-3-carboxylate (6). From 2-(iodobenzoyl)pyrrole **3** in 54% yield: mp 190-1°; Found: C, 70.33; H, 5.49; N, 3.65%. $C_{22}H_{20}FNO_3.(H_2O)_{0.5}$ requires C, 70.57; H, 5.65; N, 3.74%; δ_H 2.20 (3H, s), 2.43 (3H, s), 3.18 (3H, s), 4.25 (2H, s), 6.94 (2H, t), 7.10-7.35 (6H, m) and 8.19 (1H, br s); m/z 366 $(M+1)^+$; λ_{max} 206 (4.51), 241 (4.09), 288 (3.75) nm.

Methyl 2,5-dimethyl-4-(2-(phenylamino)benzoyl)-1H-pyrrole-3-carboxylate (7). Methyl 2,5-dimethyl-4-(2-iodobenzoyl)-1H-pyrrole-3-carboxylate (**3**) (2.5g, 6.5 mmol), aniline (7.5 mL) and copper bronze (2.5g) were heated at 110° under nitrogen with stirring for 5 hours. The mixture was cooled, filtered and chromatographed on silica eluting with ether/hexane mixtures gave **7** (0.8g, 35% yield) as yellow crystals: mp 140-2°; Found: C, 72.47; H, 5.75; N, 7.97%. $C_{21}H_{20}N_2O_3$ requires C, 72.39; H, 5.79; N, 8.04%; δ_H 2.17 (3H, s), 2.48 (3H, s), 3.45 (3H, s), 6.63 (1H, dt), 7.07 (1H, t), 7.23-7.42 (6H, m), 7.48 (1H, dd), 8.47 (1H, br s) and 10.35 (1H, br s); m/z 348 M^+; λ_{max} 205 (4.52), 288 (4.09), 387 (3.92) nm; υ_{max} 3280, 1690, 1670 cm^{-1}.

Also prepared by this method: **Methyl 2,5-dimethyl-4-(2-(2-pyridinylamino)benzoyl)-1H-pyrrole-3-carboxylate (8).** Obtained as an oil in 55% yield: δ_H 2.18 (3H, s), 2.48 (3H, s), 3.40 (3H,

s), 6.80 (2H, m), 6.90 (1H, d), 7.44 (1H, dt), 7.55 (2H, m), 8.30 (1H, d), 8.37 (1H, br s), 8.73 (1H, d) and 11.16 (1H, br s). Converted to the maleate salt in 2-propanol/ether and isolated as the 1:1 salt with 1 mole of 2-propanol of crystallization: mp 113-5°; Found: C, 61.89; H, 6.05; N, 7.89%. $C_{20}H_{19}N_3O_3.C_4H_4O_4.C_3H_8O$ requires C, 61.70; H, 5.95; N, 8.00%; m/z 350 $(M+1)^+$; λ_{max} 252 (4.31), 360 (3.86) nm; υ_{max} 3230, 1695, 1660 cm^{-1}.

Methyl 4-(2-(cyclohexylamino)benzoyl)-2,5-dimethyl-1H-pyrrole-3-carboxylate (9). Methyl 2,5-dimethyl-4-(2-iodobenzoyl)-1H-pyrrole-3-carboxylate (**3**) (1.1g, 2.9 mmol), cyclohexylamine (10 mL) and nickel(II) bromide (0.1g) were heated at reflux with stirring for 3 hours. The excess cyclohexylamine was evaporated and the residue was chromatographed on silica eluting with petroleum ether/ethyl acetate. Recrystallization from dichloromethane/cyclohexane gave **9** (0.44g, 43% yield) as yellow crystals: mp 180-2°; Found: C, 70.76; H, 7.57; N, 7.69%. $C_{21}H_{26}N_2O_3$ requires C, 71.16; H, 7.39; N, 7.90%; δ_H 1.30-2.10 (10H, m), 2.12 (3H, s), 2.48 (3H, s), 3.43 (3H, s), 3.48 (1H, m), 6.40 (1H, t), 6.73 (1H, d), 7.26 (1H, t), 7.40 (1H, dd), 8.20 (1H, br s) and 8.79 (1H, d); m/z 354 M^+; λ_{max} 233 (4.41), 262 (4.01), 391 (3.88) nm; υ_{max} 3440, 1680, 1615 cm^{-1}.

Methyl 2,5-dimethyl-4-(2-(phenylthio)benzoyl)-1H-pyrrole-3-carboxylate (10). Sodium hydroxide (0.57g, 14 mmol) and benzenethiol (1.6g, 14 mmol) in DMF (20 mL) were stirred at room temperature under nitrogen for 2 hours. Methyl 2,5-dimethyl-4-(2-iodobenzoyl)-1H-pyrrole-3-carboxylate (**3**) (5g, 13 mmol) and copper(II) oxide (1g, 13.5 mmol) were added and the mixture heated at 100° for 16 hours. The cooled reaction mixture was poured onto 2M hydrochloric acid and ethyl acetate and then filtered. The solid was washed well with chloroform and the filtrates combined. The organic layer was separated, washed with 2M hydrochloric acid,water and saturated brine, dried (Na_2SO_4) and the solvent was evaporated. Chromatography on silica eluting with chloroform/ethyl acetate mixtures followed by recrystallization from ethyl acetate gave **10** (3.67g, 77% yield): mp 177-8°; Found: C, 68.82; H, 5.42; N, 3.87; S, 8.77%. $C_{21}H_{19}NO_3S$ requires C, 69.02; H, 5.24; N, 3.83; S, 8.77%; δ_H 2.32 (3H, s), 2.47 (3H, s), 3.30 (3H, s), 6.93 (1H, d), 7.04 (1H, dt), 7.17 (1H, dt), 7.38-7.46 (4H, m), 7.55-7.57 (2H, m) and 8.45 (1H, s); m/z 365 M^+; λ_{max} 238 (4.29), 324 (3.72) nm; υ_{max} 3300, 1685, 1670, 1640 cm^{-1}.

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(1) This work was presented in part at the 5th SCI-RSC Medicinal Chemistry Symposium, Cambridge, United Kingdom, September 1989; Abstract Number P.8.

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