Discovery and Synthesis of Methyl 2,5-Dimethyl-4-[2-(phenylmethyl)benzoyl]-1*H*-pyrrole-3-carboxylate (FPL 64176) and Analogues: The First Examples of a New Class of Calcium Channel Activator[1]

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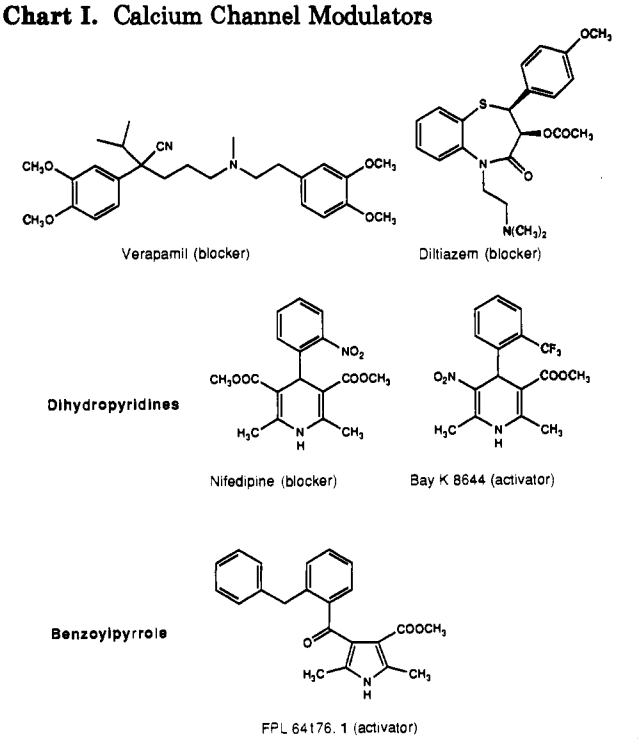
Methyl 2,5-dimethyl-4-[2-(phenylmethyl)benzoyl]-1*H*-pyrrole-3-carboxylate, FPL 64176 (1), is the first example of a new class of calcium channel activator (CCA) that does not act on any of the well-defined calcium channel modulator receptor sites, as typified by verapamil, diltiazem, and the dihydropyridines. The potent activity of 1, having the 2-(phenylmethyl)benzoyl substituent, was predicted using QSAR on an initial set of less potent benzoylpyrroles. When compared to the CCA Bay K 8644, 1 has simialr potency on calcium uptake into GH3 cells (both have $EC_{50} \sim 0.015$ μM) but is appreciably more potent functionally at increasing contractility in a guinea pig atria preparation (1 has $EC_{50} = 0.049$ μM vs Bay K 8644 $EC_{50} = 1.95$ μM). 1 is an achiral, pharmacologically clean agonist with no demonstrable partial agonist properties and possesses appreciably higher efficacy than Bay K 8644. It should therefore become a useful biochemical and pharmacological tool for the study of calcium channels in many cell types.

The modulation of transmembrane calcium movement is an important area of current pharmaceutical research with applications in many therapeutic areas and disease states.[2] Three distinct classes of clean, potent agents that act on the L-type voltage operated channel are recognized.[3] These are typified by verapamil (blocker), diltiazem (blocker), and the dihydropyridines nifedipine (blocker) and Bay K 8644 (activator). Recent publications from our own[4] and other laboratories[5-8] have demonstrated that methyl 2,5-dimethyl-4-[2-(phenylmethyl)benzoyl]-1*H*-pyrrole-3-carboxylate (1, FPL 64176) activates calcium channels in cardiac and vascular tissues with a novel mechanism and site of action. Chart I shows the structures of these various ligands. In this paper we disclose the background and QSAR leading to the discovery of 1 along with its single crystal X-ray structure. The synthesis of 1 and related compounds is also presented[9] together with the relevant biological data on calcium channel activation in GH3 cells and cardiac contractility in guinea pig atria.

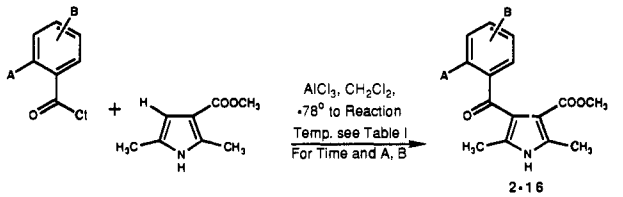
Chart I. Calcium Channel Modulators



Chemistry

Our initial lead compound was the (2-chlorobenzoyl)-pyrrole 2. Its synthesis was carried out by Friedel–Crafts benzoylation of methyl 2,5-dimethyl-1*H*-pyrrole-3-carboxylate using aluminum trichloride as Lewis acid (Scheme I). A variety of substituted benzoylpyrroles (compounds 3–16) were also prepared using this route (Table I). We were not able to isolate the 2′-hydroxy compound when these standard conditions were used with 2-hydroxybenzoyl chloride. However we were able to characterize a number of more complicated products, the simplest of which was [2-[(2-hydroxybenzoyl)oxy]benzoyl]pyrrole 13. QSAR based on this initial set of compounds (see below) predicted that the 2′-(phenylmethyl) substituent would be particularly advantageous. Unfortunately, when we tried to prepare this compound by the standard route, cyclization of 2-(phenylmethyl)benzoyl chloride (17) to anthrone occurred. Observing that this acid chloride was stable in the absence of aluminium trichloride, we were

Scheme I



able to effect benzoylation by generation of a 4-lithiopyrrole (Scheme II). Thus bromination of methyl 2,5-dimethyl-1*H*-pyrrole-3-carboxylate followed by N-protection using the [2-(trimethylsilyl)ethoxy]methyl (SEM) group[10] gave the 4-bromopyrrole 18. Metal–halogen exchange was readily accomplished with *n*-BuLi at −78 °C and the

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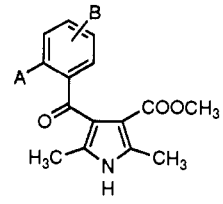
Table I. Physical Constants and Friedel–Crafts Reaction Conditions for Benzoylpyrroles

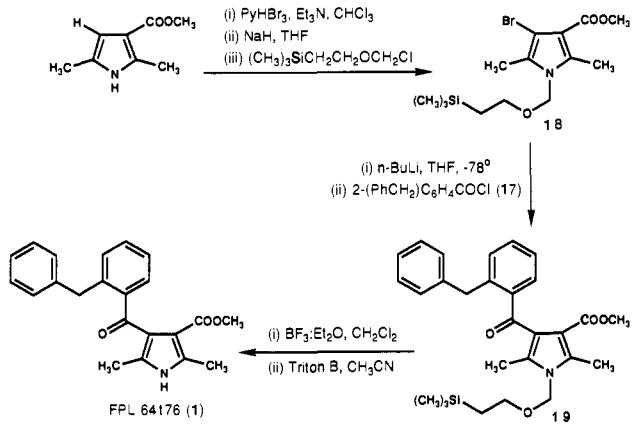


2-16

compd	A, B subst	reaction temp, °C and time	% yield	mp, °C	mol formula	anal.
2	2-Cl	20, 24 h	74	127–8	$C_{15}H_{14}ClNO_3$	C H N Cl
3	2-Cl, 3-Cl	20, 2 h	32	133–4	$C_{15}H_{13}Cl_2NO_3$	C H N
4	2-Cl, 4-Cl	20, 4 h	41	130–1	$C_{15}H_{13}Cl_2NO_3$	C H N Cl
5	2-Cl, 5-Cl	20, 2 h	37	169–70	$C_{15}H_{13}Cl_2NO_3$	C*a*H N Cl
6	2-Cl, 6-Cl	20, 2 days	66	190–1	$C_{15}H_{13}Cl_2NO_3$	C H N Cl
7	2-F	20, 24 h	22	131–2	$C_{15}H_{14}FNO_3$	C H N F
8	2-H	20, 24 h	69	114–5	$C_{15}H_{15}NO_3$	C H N
9	2-CH_3	20, 24 h	84	112–3	$C_{16}H_{17}NO_3$	C H N
10	2-Br	20, 3 h	61	113–5	$C_{15}H_{14}BrNO_3$	C H N Br
11	2-I	20, 5 h	46	125–6	$C_{15}H_{14}INO_3$	C H N I
12	2-CF_3	−10, 40 mins	30	166–7	$C_{16}H_{14}F_3NO_3$	C H N
13	2-OCO(2-HOC_6H_4)[b]	−30, 10 min	9[b]	172–3	$C_{22}H_{19}NO_6$	C H N
14	2-NO_2	−60, 5 min	15	121–2	$C_{15}H_{14}N_2O_5$	C H N
15	1-OCH_3	0, 30 min	73	117–8	$C_{16}H_{17}NO_4$	C H N
16	2-$COOCH_3$	20, 2 h	70	131–2	$C_{17}H_{17}NO_5$	C H N

[a] C: calcd, 55.23; found, 55.65. [b] From 2-hydroxybenzoyl chloride.

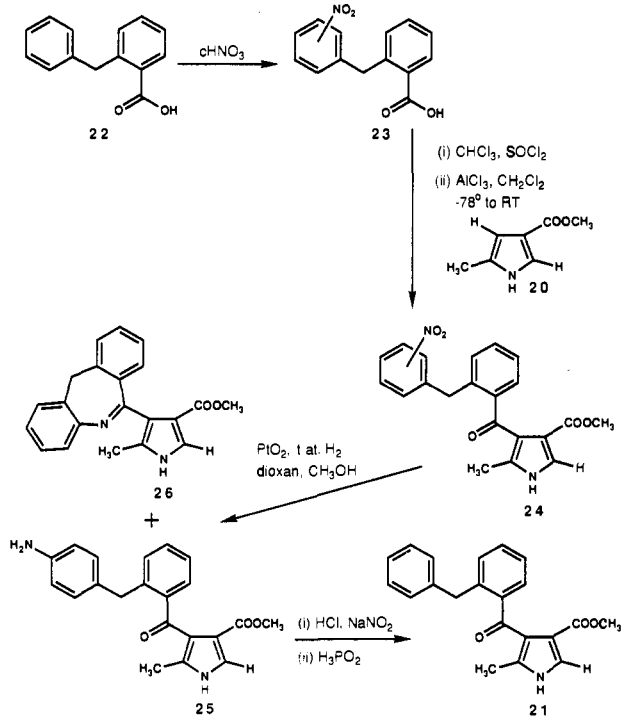
Scheme II



resulting anion was quenched with the acid chloride **17** to give the protected pyrrole **19**. Deprotection using boron trifluoride etherate followed by Triton B[10] gave the [2-(phenylmethyl)benzoyl]pyrrole **1**.

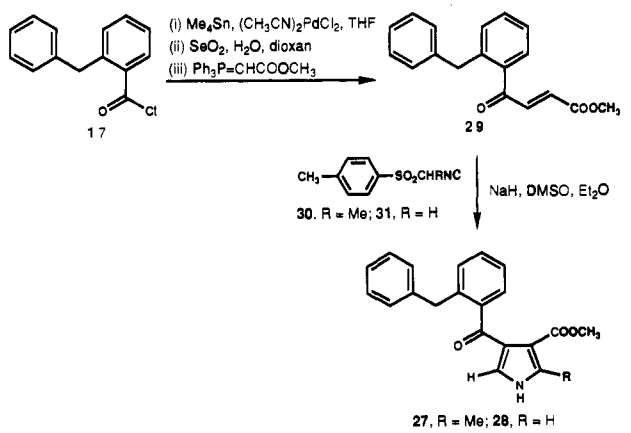
We next wished to explore the effects of removal of one or both of the pyrrole ring methyl substituents since the X-ray crystal structure (see Figure 1) indicated that these substituents could be implicated in causing the 3- and 4-substituent carbonyls to be twisted out of the plane of the pyrrole. The lithiation strategy used for the synthesis of **1** was not used for these analogues since selective bromination in the 4-position is not possible when 2- and/or 5-positions are unsubstituted.[11] We had previously found that aluminium trichloride catalyzed benzoylation of methyl 5-methyl-1*H*-pyrrole-3-carboxylate (**20**) exclusively gave the 4-benzoylpyrrole.[12] This unusual regiochemical outcome is thought to be due to complexation of the catalyst with the ester since uncatalyzed electrophilic substitution (bromination, Vielsmier formylation) occurs in the more usual 2-position. Similar regiochemical control of electrophilic substitution has been reported for 2-substituted pyrroles.[13] In order to utilize this route for the preparation of the required 2-protiopyrrole **21**, it was necessary to find an alternative way of preventing the

Scheme III



cyclization of 2-(phenylmethyl)benzoyl chloride (**17**). This was achieved by nitrating the pendant phenyl ring, thereby protecting it from electrophilic reactions. Thus nitration of the acid **22** gave a mixture of the 2′- and 4′-nitro acids **23** (Scheme III). These were not readily separable and so were converted via the acid chlorides into a mixture of the (2″- and 4″-nitrophenyl)pyrroles **24** using the standard Friedel–Crafts conditions. Again separation at this stage was found to be difficult and so the mixture was catalytically hydrogenated. Chromatography gave pure (4″-aminophenyl)pyrrole **25**; the (2″-aminophenyl)pyrrole cyclized to give the dibenzazepine **26**. Diazotization of **25** followed by hypophosphorous acid treatment gave the 5-methylpyrrole **21**.

Scheme IV



A completely different route was needed to prepare pyrroles **27** and **28**. We decided to use the van Leusen method,[14,15] which involves ring formation with tosylalkyl isocyanides (Scheme IV). The required benzoylacrylate **29** was prepared from the acid chloride **17** by methylation, oxidation to the glyoxal, and subsequent Wittig reaction with a stabilized phosphorane. Reaction with the anion of the isocyanides **30** and **31** with acrylate **29** directly gave the pyrroles **27** and **28**, respectively. Chemical shifts of the 2- and 5-protons in these compounds is indicative of the substitution pattern: 2-H at δ 7.1–7.3 and 5-H at δ 6.5–6.9.

Biological Evaluation

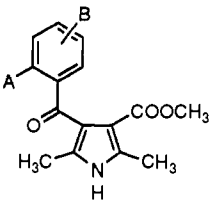
The compounds were examined for calcium channel activation and for increases in cardiac contractility using procedures previously described for the dihydropyridine activator Bay K 8644. The increase in $^{45}Ca^{2+}$ uptake into rat pituitary GH3 cells depolarized with 50 mM K^+ was used to determine channel activation;[16] "Ca^{2+} uptake EC_{50}" is the concentration of test compound which produced 50% of the maximal Ca^{2+} uptake produced by Bay K 8644. Inotropic activity was measured using guinea pig atria paced at 1 Hz;[17] "force EC_{50}" is quoted as the concentration value required to increase developed tension to 50% of the isoprenaline maximum. Bay K 8644, the standard CCA, was used as a comparison.

Structure–Activity Relationships

The (2-chlorobenzoyl)pyrrole **2** was our initial lead compound having a Ca^{2+} uptake EC_{50} = 3.3 μM and a force EC_{50} = 14 μM. For comparison the standard CCA Bay K 8644 has a Ca^{2+} uptake EC_{50} = 0.015 μM and a force EC_{50} = 1.95 μM. Taking **2** as our starting point, we sought to increase potency by means of structural variation.

We first explored the effect of introducing extra substituents onto the phenyl ring. We prepared the four (dichlorobenzoyl)pyrroles (compounds **3–6**). Of these only the 2′,5′-dichloropyrrole **5** had any CCA activity (Table II), being 4–5 times more potent than the 2′-chloropyrrole **2**. The specificity exhibited by these two compounds (**2** and **5**) in binding to and activating the receptor is indicated by the almost total abolition of Ca^{2+} uptake activity for the other three disubstituted compounds (compounds **3**, **4**, and **6**). We next investigated variation of the 2-position substituent on the benzoyl ring. Our initial series of compounds (compounds **7–16**) was prepared and evaluated. A range of potencies for Ca^{2+} uptake and particularly force (EC_{50} values in the range 4–70 μM and inactive)

Table II. Biological Data for Benzoylpyrroles



1-16

compd	A, B subst	EC_{50}, μM: Ca^{2+} uptake	EC_{50}, μM: force
2	2-Cl	3.3	14
3	2-Cl, 3-Cl	0% @ 10 μM	18% @ 30 μM
4	2-Cl, 4-Cl	0% @ 10 μM	40% @ 10 μM
5	2-Cl, 5-Cl	0.6	3.98
6	2-Cl, 6-Cl	0% @ 10 μM	0% @ 100 μM
7	2-F	1.3	70
8	2-H	5.4	21.9
9	2-CH_3	3.6	9.47
10	2-Br	2.4	8.95
11	2-I	3.4	5.9
12	2-CF_3	4.3	4.84
13	2-OCO(2-HOC_6H_4)	0.5	3.8
14	2-NO_2	0% @ 10 μM	17% @ 100 μM
15	2-OCH_3	0% @ 10 μM	44% @ 100 μM
16	2-$COOCH_3$	0% @ 10 μM	16% @ 100 μM
1	2-CH_2Ph	0.018	0.047

were obtained. QSAR analysis[18] was undertaken on the set of active compounds (**2**, **7–13**). No good correlations were obtained for Ca^{2+} uptake, however, single and then multiple regression analysis of force EC_{50} values led to eq 1:

$$\log[1/\text{force}] = 0.42(\pm 0.15)\pi + 0.33(\pm 0.19)B_x - 1.97 \quad (1)$$

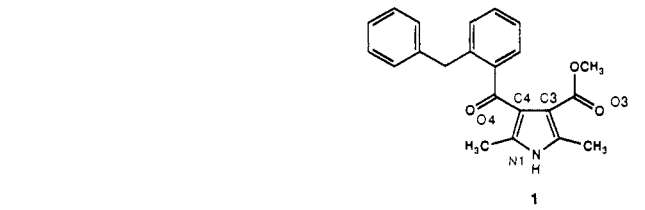
$$n = 8, r^2 = 0.79, F = 9.3, p = 0.02, \text{sd} = 0.22$$

where [force] is the force EC_{50} in μM, π is the substituent lipophilicity, and B_x is the Verloop STERIMOL width opposite to the minimum width B_1.[19] The B_x for the (2-HOC_6H_4)CO_2 substituent (compound **13**) was assumed to be identical with $PhCO_2$ since the hydroxyl group should not alter B_x. Thus increased force potency is to be expected for substituents that are lipophilic (large π) and wide (large B_x). A receptor possessing a large lipophilic pocket into which the 2′-substituent fits would be consistent with this data. This analysis also helped in explaining the weak activity shown by compounds **14–16**, as these are examples of hydrophilic substituents. We next sought to identify substituents that would be predicted to give increased potency. Of simple substituents, the benzyl group was particularly attractive, having large π (2.01) and B_x (6.02). Substituting these values into eq 1 gave the following:

$$\log[1/\text{force}] = (0.42 \times 2.01) + (0.33 \times 6.02) - 1.97 = 0.86$$

and so predicted force EC_{50} = 0.14 μM.

This was an extrapolation which predicted a compound with about 30-fold increased potency over the most potent compound in the original series (compound **13**, force EC_{50} = 3.8 μM). On the basis of this analysis of simple compounds, we therefore prepared the 2′-benzyl analogue (compound **1**) and were very gratified to observe an even greater increase in force potency than predicted. Methyl 2,5-dimethyl-4-[2-(phenylmethyl)benzoyl]-1*H*-pyrrole-3-carboxylate (**1**) has a Ca^{2+} uptake EC_{50} = 0.016 μM and



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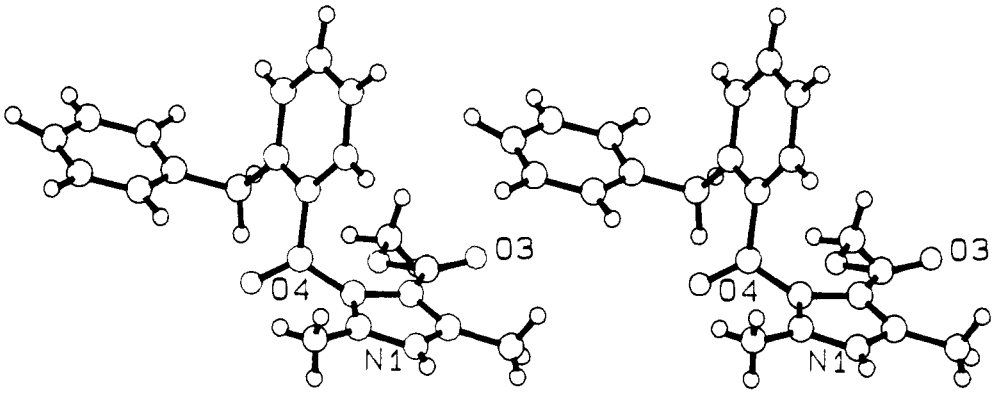
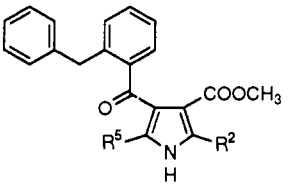


Figure 1. Stereoview of FPL 64176 (1) from X-ray Crystal Structure.

Table III. Biological Data Showing Effect of Removal of 2- and 5-Methyls from 1



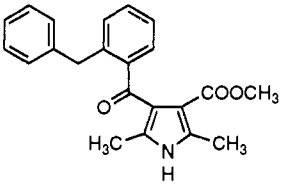
1, 21, 27, 28

compd	R^2	R^5	Ca^{2+} uptake EC_{50} μM	force EC_{50} μM
1	CH_3	CH_3	0.016	0.049
21	H	CH_3	0.089	0.144
27	CH_3	H	0.42	0.46
28	H	H	6.2	2.1

a force EC_{50} = 0.049 μM (Table II). Thus the experimentally found force potency is 80 times that of the most potent compound in the original series and the Ca^{2+} uptake potency represents a 30-fold increase.

Having prepared 1 and observed its potent CCA properties, we sought further confirmation of structure by single-crystal X-ray analysis (Figure 1). This also provided information on the three-dimensional arrangement of substituents on the sterically crowded tetrasubstituted pyrrole ring. It reveals that the two carbonyls attached at C3 and C4 (O3 and O4 in Figure 1) are twisted out of the plane of the pyrrole ring with torsional angles of 17° and 43°, respectively. This appears to result from interactions between the bulky C3 and C4 substituents, further exacerbated by interactions with the C2 and C5 methyls. If this is the case, then replacement of one or both of these methyls with a smaller group, e.g. hydrogen, would be expected to relieve steric crowding, resulting in a change in carbonyl–pyrrole torsional angles. These changes in shape might be expected to give rise to corresponding changes in biological activity. Table III shows the results of the biological evaluation of the desmethyl analogues (21, 27 and 28) of 1. While some potency reduction is observed for the 2-desmethyl compound 21, much larger reductions are obtained in compounds lacking the 5-methyl (27 and 28 vs 1 and 21). These results perhaps indicate the importance of the flanking 3- and 5-substituents in twisting the 4-substituent out of the plane of the pyrrole ring.

Table IV. Comparison of 1 with Bay K 8644



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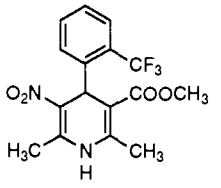

Bay K 8644

		1	Bay K 8644
$^{45}Ca^{2+}$ uptake in rat pituitary GH3 cells (n = 6)	EC_{50} mM	0.016 ± 0.002	0.015 ± 0.004
(Bay K8644 = 100%)	% max	383% @ 10 μM	100% @ 1 μM
force increases in guinea pig atria (n = 7)	EC_{50} μM	0.049 ± 0.006	1.95 ± 1.5
(isoprenaline = 100%)	% max	105% @ 0.3 μM	61% @ 10 μM

Discussion and Conclusions

Methyl 2,5-dimethyl-4-[2-(phenylmethyl)benzoyl]-1*H*-pyrrole-3-carboxylate (1) represents the first of a new class of CCAs that acts on a binding site distinct from other calcium channel modulators. QSAR led from a weakly active set of compounds (2-13) to the much more potent CCA, 1. The single-crystal X-ray structure of 1 shows that, while being a reasonably simple achiral tetrasubstituted pyrrole, the steric crowding present leads to an interesting three-dimensional structure. Relief of some of this crowding led to the expected reductions in potency.

Comparison of 1 with the standard CCA, Bay K 8644, is shown in Table IV. While having similar potency to Bay K 8644 on Ca^{2+} uptake in GH3 cells, 1 is significantly more potent as a positive inotrope in the more complex functional guinea pig atria assay. At the receptor level 1 has been shown not bind to the same site as Bay K 8644.[5] It is also an achiral, pharmacologically clean agonist with no demonstrable partial agonist properties and possesses appreciably higher efficacy than Bay K 8644. A number of other differences have also been described including

those at the electrophysiological level[5,8] and concerned with its possible extracellular receptor site[6] (vs intracellular sites for DHPs and verapamil type compounds). Methyl 2,5-dimethyl-4-[2-(phenylmethyl)benzoyl]-1*H*-pyrrole-3-carboxylate (1) should therefore become a useful biochemical and pharmacological tool for the study of calcium channels in many cell types.

Experimental Section

Melting points were determined in open capillary tubes with a Büchi melting point apparatus and are uncorrected. The structures of all compounds are consistent with spectroscopic data (IR, ^{1}H NMR, and MS), and satisfactory elemental analyses were obtained where stated. NMR spectra were recorded on a Bruker AM360 360-MHz spectrometer using TMS as standard. The chemical shifts are in ppm (δ), in the solvents indicated. Mass spectra were recorded on a VG 70-250SEQ machine. Flash chromatography was performed with thick-walled glass columns on silica gel (silica 60, 35–70 μm, Matrex, Merck, or Sorbsol). In the text petroleum ether refers to the fraction boiling in the range 60–80 °C.

Procedure for Friedel–Crafts Benzoylation of Methyl 2,5-Dimethyl-1*H*-pyrrole-3-carboxylate. Methyl 2,5-dimethyl-1*H*-pyrrole-3-carboxylate (2.5 g, 16 mmol) in dichloromethane (20 mL) was added to a stirred suspension at −78 °C of aluminium trichloride (7.6 g, 57 mmol) in dichloromethane (150 mL). The reaction mixture was allowed to warm to room temperature and was then recooled to −78 °C. The benzoyl chloride (18 mmol) in dichloromethane (20 mL) was then added and the mixture was allowed to warm to the temperature indicated in Table I and stirred for the indicated time. The progress of individual reactions was followed by TLC and visual inspection (extensive decomposition was sometimes observed on warming). Water was added to quench the reaction and the organic layer was separated, washed with sodium hydrogen carbonate solution, and dried ($MgSO_4$). The solvent was evaporated and the residue was chromatographed on silica eluting with ethyl acetate/petroleum ether mixtures to give the ketones **2–16**.

Yields, melting points and elemental analysis obtained are given in Table I.

Typical data for **Methyl 4-(2-chlorobenzoyl)-2,5-dimethyl-1H-pyrrole-3-carboxylate (2)**: ^{1}H NMR ($CDCl_3$) 2.37 (3H, s), 2.41 (3H, s), 3.27 (3H, s), 7.13–7.49 (4H, m) and 8.66 (1H, br s); mass spectrum *m/e* 291/293 M^+.

Methyl 4-[2-[(2-hydroxybenzoyl)oxy]benzoyl]-2,5-dimethyl-1*H*-pyrrole-3-carboxylate (13) was prepared by the method above using 2-hydroxybenzoyl chloride. No 2-hydroxybenzoyl compound was isolated, instead the title compound 13 was isolated in 9% yield: ^{1}H NMR ($CDCl_3$) 2.18 (3H, s), 2.23 (3H, s), 3.26 (3H, s), 6.84 (1H, dt), 6.99 (1H, dd), 7.00 (1H, dd), 7.40 (1H, dt), 7.43 (1H, dt), 7.53 (1H, dt), 7.50 (1H, br s), 7.50 (1H, dd), 7.79 (1H, dd), and 10.35 (1H, br s); mass spectrum *m/e* 393 M^+.

Methyl 2,5-Dimethyl-4-[2-(phenylmethyl)benzoyl]-1H-pyrrole-3-carboxylate (1). (i) Methyl 4-Bromo-2,5-dimethyl-1-[[2-(trimethylsilyl)ethoxy]methyl]-1*H*-pyrrole-3-carboxylate (18). Pyridinium hydrobromide perbromide (3.3 g, 10.9 mmol) was added portionwise to a stirred solution at 0 °C of methyl 2,5-dimethyl-1*H*-pyrrole-3-carboxylate (1.5 g, 9.8 mmol) and triethylamine (1.45 g, 1.4 mmol) in chloroform (60 mL). Evaporation of solvent and chromatography on silica eluting with ethyl acetate/petroleum ether gave methyl 4-bromo-2,5-dimethyl-1*H*-pyrrole-3-carboxylate. (1.38 g, 7.84 mmol, 80% yield): ^{1}H NMR ($CDCl_3$) 2.09 (3H, s), 2.36 (3H, s), and 3.68 (3H, s); mass spectrum *m/e* 231/233 M^+.

This bromide (2.0 g, 8.62 mmol) in THF (20 mL) was added dropwise to a stirred suspension at 0 °C of sodium hydride (0.6 g of 50% in oil, 12.5 mmol) in THF (60 mL). After 45 min at room temperature, [2-(trimethylsilyl)ethoxy]methyl chloride (1.6 g, 9.6 mmol) was added. After 2 h water was added and the THF evaporated. The residue was extracted with chloroform and the solution was dried ($MgSO_4$) and evaporated. Chromatography on silica eluting with ethyl acetate/petroleum ether mixtures gave the bromide 18 (2.67 g, 8.1 mmol, 94% yield): ^{1}H NMR ($CDCl_3$) 0.93 (2H, t), 2.26 (3H, s), 2.57 (3H, s), 3.58 (2H, t), 3.80 (3H, s), and 5.17 (2H, s), $(CH_3)_3Si$ obscured by TMS; mass spectrum *m/e* 363 M^+.

(ii) Methyl 4-[2-(Phenylmethyl)benzoyl]-2,5-dimethyl-1-[[2-(trimethylsilyl)ethoxy]methyl]-1*H*-pyrrole-3-carboxylate (19). *n*-Butyllithium (2.2 mL of 1.6 M in hexane, 3.56 mmol) was added to a stirred solution of 18 (1.3 g, 3.6 mmol) in THF (20 mL) at −78 °C. After 15 min 2-(phenylmethyl)benzoyl chloride (17) (1.0 g, 4.34 mmol) in THF (5 mL) was added and the mixture allowed to reach room temperature. Water was added and the THF evaporated. The residue was extracted with chloroform and the solution was dried ($MgSO_4$) and evaporated. Chromatography on silica eluting with ethyl acetate/petroleum ether mixtures gave the ketone 19 (0.93 g, 1.95 mmol, 54% yield): ^{1}H NMR ($CDCl_3$) 0.94 (2H, t), 2.26 (3H, s), 2.50 (3H, s), 3.15 (3H, s), 3.53 (2H, t), 4.30 (2H, s), 5.17 (2H, s) and 7.13–7.50 (9H, m), $(CH_3)_3Si$ obscured by TMS; mass spectrum *m/e* 477 (M^+).

(iii) Methyl 2,5-Dimethyl-4-[2-(phenylmethyl)benzoyl]-1*H*-pyrrole-3-carboxylate (1). Boron trifluoride etherate (1.73 g, 12.2 mmol) was added dropwise to a stirred solution at 0 °C of 19 (0.58 g, 1.21 mmol) in dichloromethane (100 mL). After 2 h at room temperature, saturated sodium hydrogen carbonate (50 mL) was added. The organic layer was separated and dried ($MgSO_4$) and the solvent was evaporated. The residue was dissolved in acetonitrile (40 mL) and Triton B (2 mL of 40% in methanol) was added. Water and chloroform were added and the organic layer was separated, dried ($MgSO_4$), and evaporated. Chromatography on silica eluting with ethyl acetate/hexane mixtures gave the ketone 1 (0.31 g, 0.89 mmol, 74% yield) as a colorless solid: mp 143–4 °C; ^{1}H NMR ($CDCl_3$) 2.20 (3H, s), 2.43 (3H, s), 3.17 (3H, s), 4.29 (2H, s), 7.13–7.36 (9H, m), and 8.07 (1H, br s); mass spectrum *m/e* 347 M^+. Anal. ($C_{22}H_{21}NO_3$) C, H, N.

Methyl 5-Methyl-4-[2-(phenylmethyl)benzoyl]-1*H*-pyrrole-3-carboxylate (21). (i) Methyl 5-Methyl-4-[2-[(2-nitrophenyl)methyl]benzoyl]-1*H*-pyrrole-3-carboxylate and Methyl 5-Methyl-4-[2-[(4-nitrophenyl)methyl]benzoyl]-1*H*-pyrrole-3-carboxylate (24). 2-(Phenylmethyl)benzoic acid (22) (10 g, 47 mmol) was added with stirring to nitric acid (150 mL of d, 1.42). After 4 h, the mixture was poured onto ice/water with stirring. The solid was filtered off, washed with water, and then dissolved in ether. The ether solution was dried ($MgSO_4$) and the solvent was evaporated to give a mixture of [(2- and 4-nitrophenyl)methyl]benzoic acid (23). This solid was dissolved in chloroform (60 mL) and thionyl chloride (5 mL) was added. The solution was heated at reflux for 4 h and then the solvent was evaporated to give a mixture of [(2- and 4-nitrophenyl)-methyl]benzoyl chlorides. This oil was dissolved in dichloromethane (200 mL) along with methyl 5-methyl-1*H*-pyrrole-3-carboxylate (20) (6.5 g, 47 mmol). The solution was cooled to −78 °C and aluminum trichloride (8.0 g, 60 mmol) was added with stirring. After warming to room temperature, the reaction mixture was stirred for 16 h and then poured onto ice/water. The organic layer was separated, washed with water, sodium hydrogen carbonate solution, and brine, and dried ($MgSO_4$) and the solvent was evaporated. Prep HPLC (normal phase) eluting with ethyl acetate/petroleum ether mixtures gave a mixture of the 2- and 4-nitro esters 24 (7.9 g, 21 mmol, 44% yield) as an off-white solid: mass spectrum *m/e* 378 M^+; 2-nitro has ^{1}H NMR ($CDCl_3$) 2.24 (3H, s), 3.36 (3H, s), 4.55 (2H, s), 7.08 (1H, d), 7.22 (1H, d), 7.20–7.50 (6H, m), 7.93 (1H, d), and 8.77 (1H, br s) and 4-nitro has ^{1}H NMR ($CDCl_3$) 2.18 (3H, s), 3.39 (3H, s), 4.40 (2H, s), 7.23 (1H, d), 7.20–7.50 (6H, m), 8.12 (2H, d), and 8.72 (1H, br s).

(ii) Methyl 4-[2-[(4-Aminophenyl)methyl]benzoyl]-5-methyl-1*H*-pyrrole-3-carboxylate (25). The mixture of 2- and 4-nitro esters 24 (2.1 g, 5.6 mmol) was hydrogenated at 1 atm in dioxane (375 mL) and methanol (75 mL) over PtO_2 (0.09 g) for 16 h. The catalyst was filtered off and the solvent was evaporated. Chromatography on silica eluting with ethyl acetate/dichloromethane mixtures gave first **methyl 4-(11*H*-dibenz[*b,e*]azepin-6-yl)-5-methyl-1*H*-pyrrole-3-carboxylate (26)** (0.4 g, 1.2 mmol, 21% yield) which was recrystallized from ethyl acetate: mp 239–40 °C; ^{1}H NMR ($(CD_3)_2SO$) 2.43 (3H, s), 3.28 (3H, s), 3.73 (1H, d), 3.79 (1H, d), 6.91 (1H, d), 7.08–7.14 (2H, m), 7.20 (2H, d+m) and 7.30–7.36 (4H, m); mass spectrum *m/e* 330 M^+. Anal. Calcd for $C_{21}H_{18}N_2O_2 \cdot 0.2H_2O$: C, 75.52; H, 5.55; N, 8.39. Found: C, 75.55; H, 5.58; N, 8.40 and then methyl

4-[2-[(4-aminophenyl)methyl]benzoyl]-5-methyl-1*H*-pyrrole-3-carboxylate (25) (1.1 g, 3.2 mmol, 56% yield): ^{1}H NMR ($CDCl_3$) 2.13 (3H, s), 3.32 (3H, s), 3.56 (2H, br s), 4.16 (2H, s), 6.59 (2H, d), 7.00 (2H, d), 7.14 (1H, t), 7.18 (1H, d), 7.18 (1H, d), 7.30 (1H, t), 7.32 (1H, d), and 8.86 (1H, br s); mass spectrum *m/e* 348 M^+.

(iii) Methyl 5-Methyl-4-[2-(phenylmethyl)benzoyl]-1*H*-pyrrole-3-carboxylate (21). The 4-amino ester **25** (0.9 g, 2.6 mmol) was dissolved in methanol (30 mL) and concentrated hydrochloric acid (0.3 mL). Water (30 mL) was added, the methanol was evaporated, and then water (15 mL) and concentrated hydrochloric acid (0.9 mL) were added. The resulting solution was cooled to 5 °C and sodium nitrite (0.19 g, 2.8 mmol) in water (3 mL) was added. After 15 min at 5 °C, hypophosphorous acid (30 mL of 50%) was added. After warming to room temperature and stirring for 16 h, the solid was filtered off, washed with water, and dissolved in ethyl acetate. This organic solution was washed with brine and dried ($MgSO_4$), and the solvent was evaporated. Chromatography on silica eluting with ethyl acetate/petroleum ether mixtures gave the ester **21** (0.6 g, 1.8 mmol, 70% yield). Trituration with ether gave an analytically pure sample: mp 128–9 °C: ^{1}H NMR ($CDCl_3$) 2.14 (3H, s), 3.31 (3H, s), 4.29 (2H, s), 7.14–7.36 (10H, m), and 8.99 (1H, br s); mass spectrum *m/e* 333 M^+. Anal. ($C_{21}H_{19}NO_3$) C, H, N.

Methyl 2-Methyl-4-[2-(phenylmethyl)benzoyl]-1*H*-pyrrole-3-carboxylate (27). (i) Methyl 4-Oxo-4-[2-(phenylmethyl)benzoyl]-2-butenoate (29). Bis(acetonitrile)palladium(II) chloride (0.1 g) was added to a stirred solution of tetramethyltin (50 g, 280 mmol) and 2-(phenylmethyl)benzoyl chloride (**17**) (35 g, 152 mmol) in THF (200 mL). After 16 h at room temperature, the solvent was evaporated to dryness (80 °C, 12 mmHg) to give 1-[2-(phenylmethyl)phenyl]ethanone [^{1}H NMR ($CDCl_3$) 2.45 (3H, s), 4.28 (2H, s), 7.1–7.3 (5H, m), 7.4 (1H, t), and 7.65 (1H, d); mass spectrum *m/e* 210, M^+]. This ketone was dissolved in dioxane (300 mL), and selenium dioxide (20 g, 180 mmol) and water (5 mL) were added. The mixture was heated at reflux for 12 h and then cooled to room temperature. Methyl (triphenylphosphoranylidene)acetate (50 g, 150 mmol) was added and the stirring continued for 4 h. The solution was filtered and the solvent was evaporated. Chromatography on silica eluting with ether/petroleum ether mixtures gave the butenoate **29** (27 g, 96 mmol, 63% yield from acid chloride) as an oil: ^{1}H NMR ($CDCl_3$) 3.61 (3H, s), 4.14 (2H, s), 6.19 (1H, d), and 7.0–7.6 (10H, m); mass spectrum *m/e* 280, M^+.

(ii) Methyl 2-methyl-4-[2-(phenylmethyl)benzoyl]-1*H*-pyrrole-3-carboxylate (27). A solution of methyl 4-oxo-4-[2-(phenylmethyl)phenyl]-2-butenoate (**29**) (5.9 g, 21 mmol) and 1-[(1-isocyanoethyl)sulfonyl]-4-methylbenzene (**30**) (4.4 g, 21 mmol) in ether/dimethyl sulfoxide (100 mL of 2:1) was added dropwise to a stirred suspension of sodium hydride (1g of 80%, 33 mmol) in ether (100 mL). After 1 h, the reaction mixture was poured onto 2% sodium chloride solution (1 L). The aqueous layer was extracted four times with ether, the combined ethereal extracts were dried ($MgSO_4$), and the solvent was evaporated. Chromatography on silica eluting with ethyl acetate/dichloromethane mixtures followed by crystallization from toluene gave the ester **27** (3.2 g, 9.6 mmol, 46% yield) as a colorless solid: mp 98–9 °C; ^{1}H NMR ($CDCl_3$) 2.40 (3H, s), 3.44 (3H, s), 4.19 (2H, s), 6.73 (1H, d), 7.1–7.4 (9H, m), and 9.08 (1H, br s); mass spectrum *m/e* 334 $(M + 1)^+$. Anal. ($C_{21}H_{19}NO_3$) C, H, N.

Methyl 4-[2-(phenylmethyl)benzoyl]-1*H*-pyrrole-3-carboxylate (28) was prepared by the method for **27** using 1-[(isocyanomethyl)sulfonyl]-4-methylbenzene (**31**) and obtained as a colorless solid crystallized from toluene in 41% yield: mp 159–60 °C; ^{1}H NMR ($CDCl_3$) 3.55 (3H, s), 4.21 (2H, s), 6.92 (1H, t), 7.1–7.4 (10H, m), and 8.99 (1H, br s); mass spectrum *m/e* 320 $(M + 1)^+$. Anal. ($C_{20}H_{17}NO_3$) C, H, N.

Biological Assays. Standard assays for calcium channel activators were used.[16,17] Ca^{2+} uptake results for the QSAR training set were obtained from a full dose–response curve using duplicate measurements. Force results for the training set are $n = 5$. Statistical limits and number of determinations are given for 1 and Bay K8644.

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Supplementary Material Available: Full X-ray crystallographic data (crystal data, experimental, fractional coordinates, bond lengths and angles, anisotropic displacement parameters, and hydrogen atom coordinates and isotropic thermal parameters) (5 pages). Ordering information is given on any current masthead page.

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