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N-(4-Cyanotetrahydro-2*H*-pyran-4-yl) and *N*-(1-Cyanocyclohexyl) Derivatives of 1,5-Diarylpyrazole-3-carboxamides Showing High Affinity for 18 kDa Translocator Protein and/or Cannabinoid Receptors

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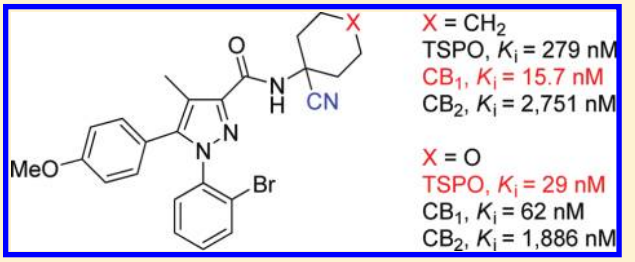
ABSTRACT: In order to develop improved radioligands for imaging brain CB_1 receptors with positron emission tomography (PET) based on rimonabant (5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-*N*-(piperidin-1-yl)-1*H*-pyrazole-3-carboxamide, **1**), we synthesized compounds **9a**−**s** in which the *N*-piperidinyl ring was replaced with a 4-(4-cyanotetrahydro-2*H*-pyranyl) or 1-cyanocyclohexyl ring. Such changes were expected to be almost isosteric with **1**, confer greater metabolic resistance, and in the case of the 4-(4-cyanotetrahydro-2*H*-pyranyl) compounds, substantially reduce lipophilicity. One derivative, 1-(2-bromophenyl)-*N*-(1-cyanocyclohexyl)-5-(4-methoxyphenyl)-4-methylpyrazole-3-carboxamide (**9n**), showed high affinity (K_i = 15.7 nM) and selectivity for binding to CB_1 receptors. The corresponding 4-(4-cyanotetrahydro-2*H*-pyranyl) derivative (**9m**) also showed quite high affinity for CB_1 receptors (K_i = 62 nM) but was found to have even higher affinity (K_i = 29 nM) for the structurally unrelated 18 kDa translocator protein (TSPO). Some other minor structural changes among **9a**−**s** were also found to switch binding selectivity from CB_1 receptors to TSPO or vice versa. These unexpected findings and their implications for the development of selective ligands or PET radioligands for CB_1 receptors or TSPO are discussed in relation to current pharmacophore models of CB_1 receptor and TSPO binding sites.



INTRODUCTION

Marijuana (*Cannabis sativa*) is one of the oldest known plant-derived substances used medicinally or as a drug of abuse.[1] Marijuana's principle psychoactive phytocannabinoid, Δ^9-tetrahydrocannabinol (Δ^9-THC),[2] binds with high affinity to two known receptor subtypes, cannabinoid type-1 (CB_1)[3] and cannabinoid type-2 (CB_2).[4] Both the CB_1 and CB_2 receptor subtypes are G-protein-coupled receptors (GPCRs) with seven-transmembrane domains. They have 48% protein sequence homology.[5] CB_1 receptors have high density in brain and are also located in some peripheral tissues, whereas CB_2 receptors are mostly located in peripheral tissues.[5] Brain CB_1 receptors are believed to play a role in the regulation of neurotransmitter (e.g., glutamate and γ-aminobutyric acid (GABA)) release through retrograde endocannabinoid-mediated depolarization-induced suppression of inhibition.[6] Alterations in brain CB_1 receptor densities and function have been implicated in several psychiatric disorders, such as drug dependence,[7] obesity,[8] depression,[9] and schizophrenia.[10] Therefore, there is keen interest to study brain CB_1 receptors in relation to such disorders in living human subjects with molecular imaging techniques, such as positron emission tomography (PET), and suitably selective radioligands.[11]

In 1994 Sanofi Recherche, presently Sanofi-Aventis, introduced the first high-affinity and selective CB_1 receptor "antagonist", rimonabant (5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-*N*-(piperidin-1-yl)-1*H*-pyrazole-3-carboxamide, SR141716A **1**, Chart 1).[12] This ligand is now considered to be an inverse agonist. The key 1,5- diarylpyrazole pharmacophore of **1** has been modified extensively to evaluate substituent effects on receptor affinity, selectivity, and physiochemical properties.[13] Additionally, **1** has been modified to allow labeling with a short-lived imaging radionuclide (e.g., carbon-11 or fluorine-18) in the development of PET radioligands.[11] Compound **1** is highly lipophilic with a computed cLogD value of 6.32 (Table 1), and hence, many candidate PET radioligands derived from **1** retain high lipophilicity.[11] This is usually detrimental to the success of a PET radioligand[14−18] because high lipophilicity generally promotes low and poorly measurable free radioligand fraction in plasma, low radioligand penetration from blood to brain, and high nonspecific binding to brain tissue. Therefore, success in the development of PET radioligands from **1** has been quite limited.

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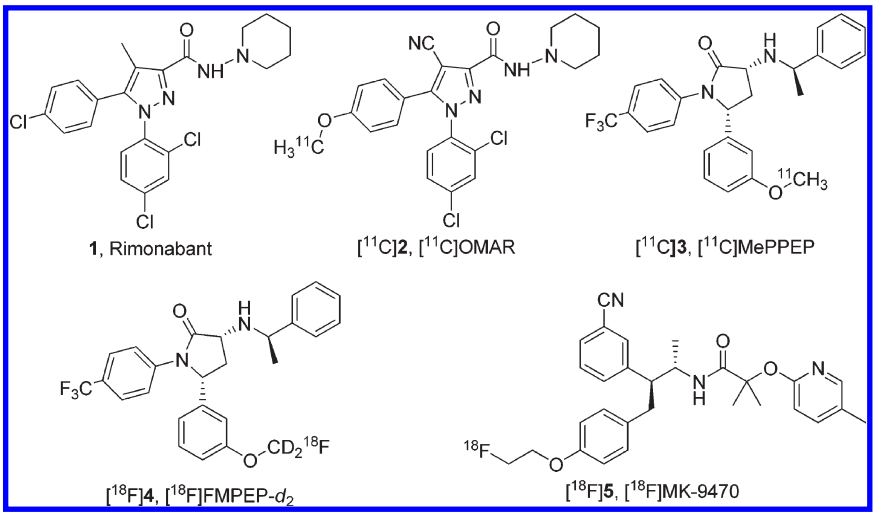
Chart 1. Structures of 1 and Some PET CB_1 Receptor Radioligands in Human Use



PET CB_1 receptor radioligands developed from other structural platforms also tend to be quite lipophilic, although some are gaining application in human subjects.[11] Examples are [^{11}C]OMAR[19] [^{11}C]**2**, [^{11}C]MePPEP[20,21] [^{11}C]**3**, [^{18}F]FMPEP-d_2[22] [^{18}F]**4**, and [^{18}F]MK-9470[23] [^{18}F]**5** (Chart 1).

The possible efficacious roles of the nitrile group in pharmacophore development have recently been highlighted[24] and include its ability to act as a carbonyl or halogen isostere, to act as a hydroxyl or carboxyl surrogate, and to reduce lipophilicity without adverse steric effect. In our search for leads to improved PET radioligands for CB_1 receptors, we considered that the replacement of the *N*-piperidinyl ring in **1** with a 1-cyanocyclohexyl or 4-(4-cyanotetrahydro-2*H*-pyranyl) ring (Scheme 1) would be a minor steric perturbation and would confer lower lipophilicity. Moreover, these rings, because of their nitrile substitution, may show greater resistance to metabolism than the replaced piperidinyl ring, which has been shown to be the exclusive region of metabolism of **1** in vitro[25] and in vivo.[25,26] We therefore set out to synthesize a set of compounds with replaced *N*-piperidinyl rings and to evaluate their structure−activity relationships at CB_1 receptors. Selective high-affinity CB_1 ligands were discovered and also very unexpectedly selective high-affinity ligands for a structurally and functionally distinct site, the 18 kDa translocator protein, previously known as the peripheral benzodiazepine receptor (PBR) and now known as TSPO.[27] These findings and their implications for ligand and PET radioligand development are discussed and rationalized in the context of an identified level of congruence between previously proposed pharmacophore models of the CB_1 receptor and TSPO.

RESULTS AND DISCUSSION

Chemistry. *N*-(4-Cyanotetrahydro-2*H*-pyran-4-yl) and *N*-(1-cyanocyclohexyl) derivatives of 1,5-diarylpyrazole 3-carboxamides constituted the two core scaffolds of all newly synthesized compounds. Substituents in the 2-, 3-, and 4-positions of the pyrazole-N^1 and -C^5 aryl rings and at the pyrazole-3-carboxamide and 4-positions of the core scaffolds were also varied. Because of our strong interest in developing radioligands for imaging with PET, nearly all of the new ligands were designed to be amenable to labeling with cyclotron-produced carbon-11 ($t_{1/2}$ = 20.4 min) by commonly used procedures such as C-^{11}C-methylation (**9b−f**, **9h−o**, **9r**, and **9s**), O-^{11}C-methylation (**9l−q**), N-^{11}C-methylation (**9d**), or ^{11}C-cyanation (**9g** and **9p**).[28]

Compounds were synthesized as shown in Scheme 2. Substituted anilines were first converted into diazonium salts and then treated with ethyl 2-chloroacetoacetate under basic conditions to give **6a−g** in good yields. A series of aryl ketones (**7a−f**) were converted into enamines with morpholine, $TiCl_4$, and DIPEA (diisopropylethylamine) in toluene solution using a modified general procedure.[29] Compounds **6a−g** were then treated with the morpholine enamines under basic conditions to give the 1,5-diarylpyrazoles **8a−k**, **8m**, and **8n** in low but useful yields by a regioselective 1,3-dipolar cycloaddition reaction.[30] Treatment of the acylacetonitrile **7h** with **6c** gave the diarylpyrazole **8p** in low yield. Diarylpyrazole **8l** was prepared in high yield by bromination of **8k** with NBS (*N*-bromosuccinimide) using acetonitrile as a polar solvent to favor the formation of bromine. Each of the diarylpyrazoles **8a−q** were hydrolyzed to the acids, converted into acyl chlorides, and treated with either 4-aminotetrahydro-2*H*-pyran-4-carbonitrile or 1-aminocyclohexanecarbonitrile HCl to give the desired carboxamides (**9a−c** and **9e−s**). Treatment of **9c** with NaH and MeI gave the tertiary amide **9d** in high yield.

Computed Ligand Lipophilicities. The most common structural change made to the scaffold of **1**, namely, replacement of the *N*-(piperidin-1-yl)-4*H*-pyrazole-3-carboxamide moiety with an *N*-(4-cyanotetrahydro-2*H*-pyran-4-yl)-4*H*-pyrazole-3-carboxamide moiety, was computed to reduce lipophilicity by about 0.65 cLogD units. Consequently, the majority of the prepared ligands have much lower cLogD values than **1** (Table 1). These cLogD values approach values in the range that is generally preferred for PET radioligands (∼1.5−3.5).[14−18] Replacement of the 4-(4-cyanotetrahydro-2*H*-pyranyl) group with a 1-cyanocyclohexyl group increases the computed lipophilicity substantially (Table 1). Nevertheless, the prepared examples still have substantially lower lipophilicity than **1**.

Structure−Affinity Relationships. The sequence homologies and structures of TSPO and CB_1 and CB_2 receptors are each

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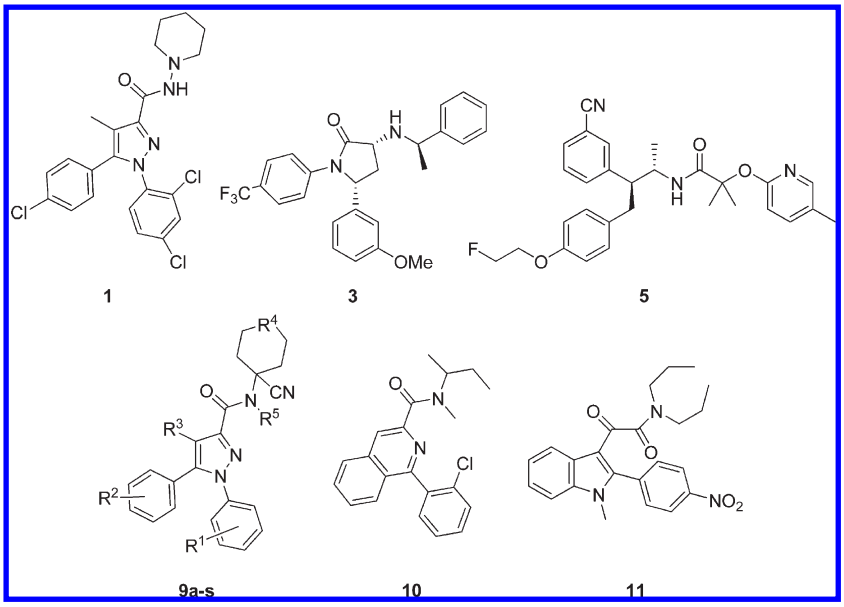
Table 1. cLogD and K_i at CB_1 and CB_2 Receptors and at TSPO for Known CB_1 Receptor Ligands 1, 3, 5, New Ligands 9a−s, and Known TSPO Ligands 10 and 11



							K_i (nM)[b]		
ligand	R^1	R^2	R^3	R^4	R^5	cLogD[a]	CB_1	CB_2	TSPO
1						6.32	1.4 ± 0.2	927 ± 66	NA
3						4.76	0.472[c]	>1980[c]	NA
5						4.98	0.70[d]	44[d]	NA
9a	2-Br	H	H	O	H	3.61	297 ± 31	>10000	3110 ± 572
9b	2-F	H	Me	O	H	3.55	>10000	2180 ± 224	394 ± 62.4
9c	2-Cl	H	Me	O	H	3.80	>10000	>10000	436 ± 40.5
9d	2-Cl	H	Me	O	Me	3.77	>10000	>10000	880 ± 36.2
9e	2-Br	H	Me	O	H	3.81	>10000	>10000	576 ± 27.3
9f	2-Br	H	Me	CH_2	H	5.85	>10000	>10000	75.2 ± 2.51
9g	2-Br	H	CN	O	H	3.22	437 ± 44	>10000	3690 ± 519
9h	3-Br	H	Me	O	H	3.81	>10000	226 ± 9.5	115 ± 4.9
9i	4-Br	H	Me	O	H	3.81	259 ± 26	655 ± 36.5	420 ± 20.5
9j	2-I	H	Me	O	H	3.92	>10000	>10000	762 ± 51.0
9k	2-Ph	H	Me	O	H	4.63	500 ± 58	>10000	2800 ± 116
9l	2-F	4-MeO	Me	O	H	3.66	115 ± 11	2460 ± 214	132 ± 4.91
9m	2-Br	4-MeO	Me	O	H	3.94	62.2 ± 12.8	1890 ± 350	29.0 ± 3.0
9n	2-Br	4-MeO	Me	CH_2	H	5.87	15.7 ± 2.3	2750 ± 183	279 ± 52.3
9o	3-Br	4-MeO	Me	O	H	3.94	680 ± 108	234 ± 13.8	61.8 ± 2.2
9p	2-I	4-MeO	CN	O	H	3.86	>10000	2370 ± 168	1920 ± 116
9q	3-Br	4-MeO	Br	O	H	4.00	356 ± 40	175 ± 10.4	155 ± 6.7
9r	2-Br	4-F	Me	O	H	4.08	55 ± 6	>10000	492 ± 28.2
9s	2-Br	3-F	Me	O	H	4.08	>10000	>10000	693 ± 28.1
10						4.89	NA	NA	1.0 ± 0.0
11						4.29	NA	NA	5.70[e]

[a] Computed with Pallas 3.70 software (Compudrug, South San Francisco, CA) for distribution of compound between *n*-octanol and pH 7.4 buffer. [b] Values represent the mean ± SD of three determinations. NA = not available. [c] K_b value from ref 20. [d] IC_{50} value from ref 23. [e] From ref 36.

highly conserved between species.[5,27] Therefore, the binding affinities of ligands determined for each of these sites in tissue from one species in vitro are expected to be quite representative of those in other animal species. Prompted by the serendipitous and unexpected discovery of the high affinity of **9m** for TSPO in a broad receptor screen of this compound (see later), each new ligand was assayed at TSPO, CB_1, CB_2, and $GABA_A$-Bz sites (Table 1). All compounds exhibited low affinity (K_i > 10 μM, n = 4)

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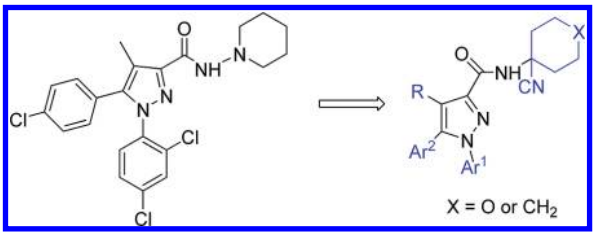
for the $GABA_A$-Bz site. Across the synthesized series of compounds, the K_i values for CB_1 and CB_2 receptors and TSPO ranged widely, namely, from 15.7 to >10000 nM, from 175 to >10000 nM, and from 29.0 to >10000 nM, respectively.

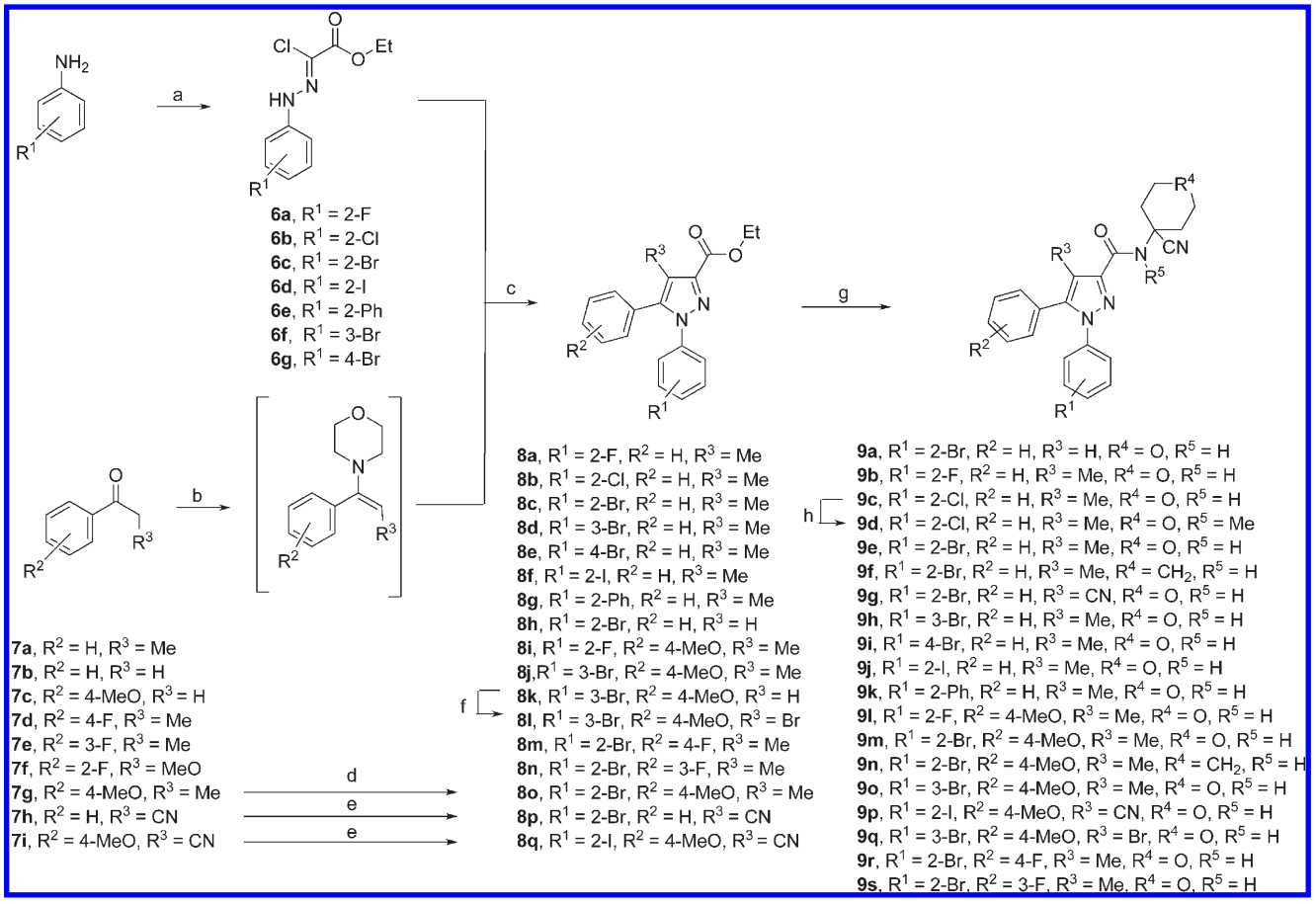
The substituent in the N^1-aryl ring (R^1, Table 1) was mainly varied with respect to halogen (F, Cl, Br, and I) and position. In compounds having a pyrazole-C^5 phenyl substituent (R^2, Table 1) (**9b**−**f**, **9h**−**k**), such variations failed to generate compounds with affinity for CB_1 or CB_2 receptors in the K_i < 100 nM range. All these compounds had measurable affinity for TSPO, with the majority of 4-(4-cyanotetrahydro-2*H*-pyranyl) compounds showing less than micromolar affinity. One compound, the relatively lipophilic 1-cyanocyclohexyl compound **9f**, showed relatively higher TSPO affinity (K_i = 75 nM). Remarkably, this compound was wholly selective for TSPO versus CB_1 or CB_2 receptors. Generally, high-affinity TSPO ligands are tertiary amides and their secondary amide counterparts have lower affinity.[31,32] However, methylation of the amido nitrogen in the ligand **9c** led to compound **9d** with a marked 2-fold reduction in TSPO receptor affinity (to K_i = 880 nM) but with retained selectivity versus CB_1 or CB_2 receptors. Introduction of the large phenyl substituent into the 2-position of the N^1-aryl ring in place of halogen (Cl, Br, or I), as in **9k**, switched the selectivity from TSPO to CB_1 receptors. A 4-bromo substituent, as in **9i**, also induced selectivity for CB_1 receptors. In this group of compounds, replacement of the 4-methyl group (R^3, Table 1) on the pyrazole ring with hydrogen (**9a**) or nitrile (**9g**) conferred CB_1 selectivity.

Introduction of a substituent into the C^5-aryl ring (R^2, Table 1) had a major influence on receptor affinity and selectivity. Compounds with a 4-methoxy substituent in the C^5-aryl ring plus a 2-fluoro or 2-bromo substituent on the N^1-aryl ring (**9l**−**n**) showed quite high affinity for both CB_1 receptors and TSPO, with very low affinity for CB_2 receptors. Remarkably, the 4-(4-cyanotetrahydro-2*H*-pyranyl) compound (**9m**) with a 2-bromo substituent in the C^5-aryl ring showed high affinity

Scheme 1. Main Structural Changes Made to 1 in the Newly Synthesized Set of Ligands



Scheme 2. Syntheses of 9a−s[a]



[a] Reagents, conditions, and yields: (a) HCl (aq), $NaNO_2$, AcONa, ethyl 2-chloroacetoacetate, 52-83%; (b) for **7a**−**f**, morpholine, DIPEA, $TiCl_4$, toluene, $MgSO_4$; (c) DIPEA, MeCN or EtOH, 18−26%; (d) ref 35;)e) DIPEA, *t*-BuOH or MeCN, reflux, 16 h, 6−8%, ref 36; (f) NBS, MeCN, 91%; (g) (1) LiOH (aq)−THF; (2) oxalyl chloride, DMF (cat.), DCM; (3) 4-aminotetrahydro-2*H*-pyran-4-carbonitrile or 1-aminocyclohexanecarbonitrile HCl, DIPEA, DCM, 34−71% (for **9a**−**e**, **9g**−**n**, and **9p**−**s**), 36−68% for **9f** and **9o**; (h) NaH (60% dispersion in oil), DMF, MeI, 64%.

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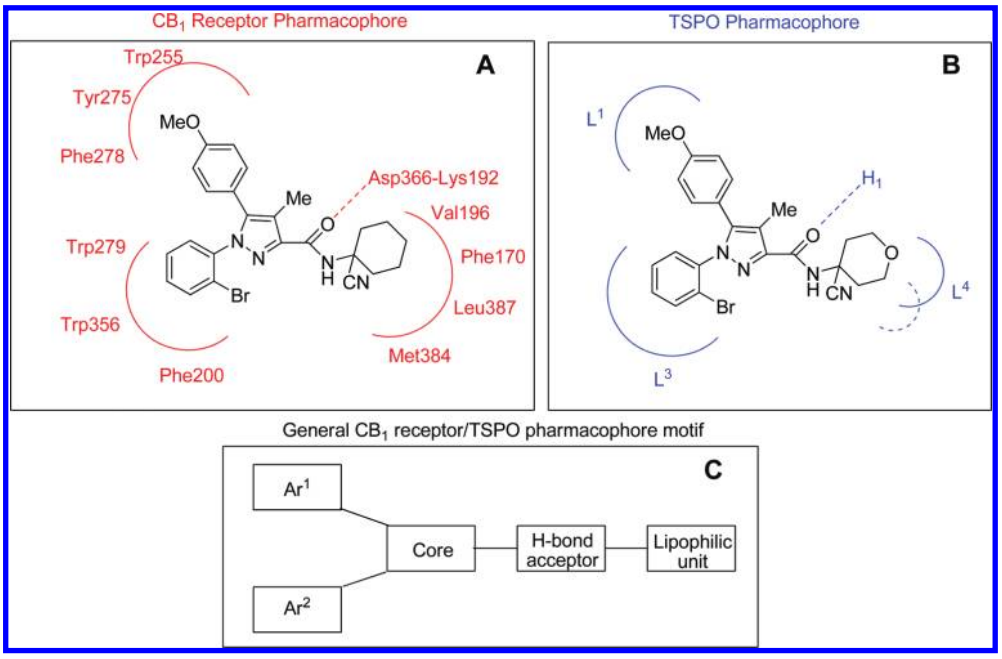
Scheme 3. Compatibility of Some New Ligands with Previously Proposed Pharmacophore Models[a]



[a] (A) Compatibility of **9n** with a proposed[13] CB_1 receptor pharmacophore model. (B) Compatibility of **9m** with a proposed[31−33] TSPO receptor pharmacophore model. (C) Common general features of proposed CB_1 receptor and TSPO pharmacophore models. Known CB_1-selective ligands such as **1**−**5** (Chart 1) and known TSPO-selective ligands **10** and **11** (Table 1) are examples of compounds from different structural classes that are compatible with the pharmacophore motif shown in panel C.

(K_i = 29 nM) for binding to TSPO with 2-fold preference over binding to CB_1 receptors. Even more remarkably, replacement of the tetrahydro-2*H*-pyranyl ring oxygen atom with a methylene group, as in the 1-cyanocyclohexyl analogue (**9n**), caused selectivity to be reversed and affinity for CB_1 receptors to be enhanced (K_i = 15.7 nM). In the whole group of pyrazole-C^5 4-methoxyphenyl compounds (**9l**−**q**), binding site affinity and selectivity were sensitive to position and type of substituent in the pyrazole-C^5 aryl ring. Thus, a compound with a 3-bromo substituent (**9o**) showed quite a high affinity (K_i = 62 nM) and selectivity for binding to TSPO versus CB_1 receptors. This compound also showed very low affinity for CB_2 receptors, as did the other N^1-3-bromophenyl compounds (**9h**, **9q**). A 2-iodo substituent in the N^1-aryl ring and a 4-nitrile group in the pyrazole ring (**9p**) led to very low affinity at CB_1 and CB_2 receptors and at TSPO. Introduction of a 4-fluoro substituent into the C^5-aryl ring, as in **9r**, in place of a 4-methoxy substituent enhanced selectivity of binding to CB_1 receptors versus TSPO. However, a shift of this substituent to the 3-position, as in **9s**, abolished high-affinity CB_1 receptor binding.

Receptor and Binding Site Screening of 9m and 9n. Ligands **9m** and **9n** at 10 μM showed <50% inhibition (n = 4) for radioligand binding to the following receptors and binding sites: 5-$HT_{1A,E}$, 5-HT_{1D} (CycMEP), 5-HT_{2A-C}, 5-HT_3, 5-HT_{5A}, 5-HT_6, 5-HT_7, $\alpha_{1A,B}$, α_{2A-C}, $\beta_{1,3}$, D_{1-4}, DAT, DOR, H_{1-4}, M_{1-5}, MOR, NET, SERT, $\sigma_{1,2}$, and $V_{1A,1B,2}$. The K_i values (n = 3) of **9m** at 5-HT_{1A}, 5-HT_{1D}, D_5, and KOR were 6280 ± 1100, >10000, >10000, and 798 ± 84 nM, respectively. The corresponding K_i values for **9n** were 1130 ± 96, >10000, >10000, and 597 ± 67 nM. Thus, **9m** is highly selective for TSPO and CB_1 receptors versus other tested binding sites and **9n** is highly selective for CB_1 receptors versus all other tested binding sites and receptors.

Relationship of Ligand Structures to Previously Proposed CB_1 Receptor and TSPO Pharmacophore Models. CB_1 receptors and TSPO are structurally distinct proteins. The CB_1 receptor belongs to the family of GPCRs having seven-transmembrane domains, and considerable information has been obtained on the likely topography and makeup of the binding site for ligands structurally resembling **1**. This information has been summarized and a pharmacophore model proposed.[13] The model proposes (i) a hydrogen bond interaction between the amide oxygen of the ligand and the Asp366-Lys192 salt bridge in the receptor, (ii) a pocket formed by Val 196, Phe 170, Leu 387, and Met 384 that can accommodate a lipophilic alicyclic group, and (iii) two distal pockets, one formed by Trp255, Tyr 275, and Phe 278 and the other by Trp279, Trp356, and Phe 200 which can each accept a substituted phenyl ring, as depicted in panel A, Scheme 3. It may be hypothesized that the highest affinity and most CB_1-selective ligand found in this study, **9n**, fits into the proposed pharmacophore in the same manner as the prototypical selective CB_1 receptor ligand **1** (panel A, Scheme 3). TSPO protein is not a GPCR but a tryptophan-rich 18 kDa protein that is a component of a trimeric complex with the 32 kDa voltage-dependent anion channel and the 30 kDa adenine nucleotide translocase to constitute the mitochodrial permeability transition pore.[27] Relatively less is known about the amino acids composing the binding site for high-affinity TSPO ligands from a plethora of structural classes. Nevertheless, a pharmacophore model has been proposed that comprises three lipophilic pockets (dubbed L1, L3, and L4) and an H-bond donor group (panel B, Scheme 3).[33−35] This pharmacophore model accommodates classical TSPO ligands such as the isoquinoline-3-carboxamide **10** (see Table 1 for structure) and TSPO ligands from some other structural classes, including the recently described N^1-methyl-2-phenylindol-3-ylglyoxylamides, of which **11** (Table 1)

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is a recent example.[36] The model also accommodates the highest affinity TSPO ligand found in this study, namely, **9m** (panel B, Scheme 3).

We observe that the previously described pharmacophore models for CB_1 receptors and TSPO are strikingly similar in the arrangement of key domains of binding site−ligand interaction; that is, the pharmacophores appear quite congruent at this macro level of description. Ligands with the general structural motif shown in panel C (Scheme 3) therefore have potential to bind to either or both pharmacophores. This provides a rational basis for our unexpected findings on binding selectivity. Clearly, our CB_1 and TSPO ligand binding data also reveal marked sensitivities to subtle differences in ligand structure, as exemplified by **9m** and **9n** (Table 1). At a deeper level of description the pharmacophores would be expected to be noticeably different, and this would account for the severe alterations or even reversals of ligand selectivity with minor structural changes.

Implications for PET Radioligand Development. As for CB_1 receptors, the development of PET radioligands for imaging brain and peripheral TSPO currently attracts immense effort.[32] This effort on TSPO radioligands is driven by their potential to become important biomarkers of inflammation in a variety of neuropsychiatric and peripheral conditions. Most of the radioligands being developed for CB_1 receptors or TSPO share the general structural motif depicted in panel C (Scheme 3). PET radioligands are required to bind selectively to their target proteins. Therefore, a message from this study is to screen candidate PET radioligands for CB_1 receptors for high affinity binding at TSPO and vice versa in order to confirm adequate target selectivity. Screens against CB_2 receptors are also advised.

The ligand **9m** possesses too low affinity and selectivity to be developed as a PET radioligand for TSPO but could be a lead to better candidates. [^{11}C]**2** (Chart 1) has been developed as a promising PET radioligand for brain CB_1 receptors and is now in use in human subjects. This radioligand is selective with moderately high affinity (K_b = 30 nM) and a cLogD of 5.3. By comparison, ligand **9n** also shows excellent selectivity for CB_1 receptors, high affinity (K_i = 16 nM), and only somewhat higher cLogD (5.87, Table 1). The labeling of **9n** with carbon-11, which is feasible in its 4-methoxy group, for evaluation in vivo may therefore be warranted.

CONCLUSION

Modification of the prototypical CB_1 receptor ligand **1**, primarily by replacing the *N*-piperidinyl ring with a 4-(4-cyanotetrahydro-2*H*-pyranyl) or 1-cyanocyclohexyl ring, led respectively to one high-affinity CB_1 selective ligand (**9n**) and also surprisingly to a ligand with a preference to bind with high affinity to TSPO (**9m**). Many of the prepared ligands showed quite high affinity for both CB_1 and TSPO. These unexpected findings may be rationalized on the basis of the observed congruence between previously proposed phamacophore models for CB_1 receptors and TSPO.

EXPERIMENTAL SECTION

Materials. All reagents and solvents (ACS or HPLC grade) were purchased from commercial sources and used as supplied. 1-(2-Chlorophenyl)-*N*-methyl-*N*-*sec*-butylisoquinoline-3-carboxamide (PK 11195, **10**) was purchased from Tocris Biosciences. Chloro[-(phenyl)hydrazono]ethyl acetates **6a**−**d** were synthesized according to a previously described procedure.[30,37] The 1,5-diarylpyrazoles **8o** and **8q** were prepared as previously described.[38,39]

General Methods. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded at room temperature on a Varian-400 spectrometer (Varian, Walnut Creek, CA) or Avance-400 spectrometer (Bruker; Billerica, MA). Chemical shifts are reported in δ units (ppm) downfield relative to the chemical shift of tetramethylsilane. Signals are quoted as s (singlet), d (doublet), dd (double doublet), dt (double triplet), t (triplet), q (quartet), or m (multiplet). High-resolution mass spectra (HRMS) were determined at the University of Illinois at Urbana (Champaign, IL, U.S.) or Notre Dame Mass Spectrometry Facility (Notre Dame, IN, U.S.). Melting points were determined using a Mel-Temp II (Laboratory Devices, Holliston, MA, U.S.) or Mel-Temp apparatus (Electrothermal, Fisher Scientific, U.S.) and are uncorrected. Flash column chromatography was performed on silica gel (230−400 mesh, 60 Å) (Sigma-Aldrich). Elemental analyses were acquired from Midwest Microlab, LLC (Indianapolis, IN, U.S.).

Chemistry. Chloro[(2-phenylphenyl)hydrazono]ethyl Acetate (6e). A solution of 2-aminobiphenyl (7.6 g, 45 mmol) in concentrated HCl (12 M, 5.4 mL) plus H_2O (200 mL) was stirred in a 1 L round-bottomed flask for 30 min. The reaction mixture was cooled to about 5 °C in an ice−water bath. A solution of sodium nitrite (3.2 g, 46 mmol) in H_2O (10 mL) was slowly added to the reaction mixture so that the reaction temperature remained below 15 °C. The reaction mixture was then stirred for another 30 min. A separate solution of sodium acetate (3.5 g, 43 mmol) and ethyl 2-chloroacetoacetate (6.2 mL, 45 mmol) in EtOH−H_2O (400 mL, 4:1 v/v) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred overnight (16 h). The precipitate was filtered off, washed with water, and dried to give **6e** (11.3 g, 83%) as a light yellow solid. Mp 82−84 °C; ^{1}H NMR δ 8.60 (s, 1H), 7.69 (d, J = 8.4 Hz, 1H), 7.51−7.36 (m, 6H), 7.26−7.22 (m, 1H), 7.12 (t, J = 6.8 Hz, 1H), 4.40 (q, J = 7.2 Hz, 2H), 1.41 (t, J = 6.8 Hz, 3H).

Chloro[(3-bromophenyl)hydrazono]ethyl Acetate (6f). The procedure described for the synthesis of **5e** was applied to 3-bromoaniline to give **6f** (52%) as a light brown solid. Mp 84−86 °C; ^{1}H NMR δ 8.60 (s, 1H), 7.69 (d, J = 8.4 Hz, 1H), 7.53 (t, J = 6.8, 2H), 7.45−7.36 (m, 4H), 7.26 (t, J = 6.8 Hz, 1H), 7.12 (t, J = 7.6 Hz, 1H), 4.40 (q, J = 7.2 Hz, 2H), 1.41 (t, J = 6.8 Hz, 3H).

Chloro[(4-bromophenyl)hydrazono]ethyl Acetate (6g). The procedure described for the synthesis of **5e** was applied to 4-bromoaniline to give **6g** (78%) as a pale white solid. Mp 84−86 °C; ^{1}H NMR δ 8.30 (s, 1H), 7.44 (t, J = 1.6, 1H), 7.21−7.11 (m, 3H), 4.43 (q, J = 7.2 Hz, 2H), 1.43 (t, J = 6.8 Hz, 3H).

Ethyl 1-(2-Fluorophenyl)-4-methyl-5-phenyl-1*H*-pyrazole-3-carboxylate (8a). Morpholine (33 mL, 358 mmol) was added to a suspension of $MgSO_4$ (4 g) in toluene 60 mL) and was stirred at room temperature. $TiCl_4$ (47 mL, 1 M in toluene) was slowly added to give a dark green suspension. Propiophenone (**7a**, 8.0 g, 60 mmol) and DIPEA (52 mL, 298 mmol) were dissolved separately in toluene (20 mL). This mixture was slowly added to the solution containing $TiCl_4$ and morpholine. The mixture was heated to 60 °C for 16 h, cooled to room temperature, and then filtered. The cake was washed with toluene, which was then added to the filtrate. The combined filtrate was concentrated in vacuo to give the crude morpholine enamine (8.2 g, 68%) as a pale yellow oil.

DIPEA (7.2 mL, 41.4 mmol) was added to a stirred solution of **6a** (3.3 g, 13.7 mmol) and the morpholine enamine (2.8 g, 13.7 mmol) in EtOH (100 mL). The mixture was stirred at room temperature for 16 h and then concentrated in vacuo. The resulting crude product was purified by column chromatography on silica gel (20% EtOAc in hexanes) to give **8a** (1.1 g, 25%) as a white solid. Mp 66−68 °C; ^{1}H NMR δ 7.47 (td, J = 1.6 and 7.6 Hz, 1H), 7.32−7.29 (m, 4H), 7.18−7.15 (m, 3H), 7.02 (td, J = 1.6 and 7.6 Hz), 4.49 (q, J = 7.2 Hz, 2H), 2.35 (s, 3H), 1.43 (t, J = 6.8 Hz, 3H).

Ethyl 1-(2-Chlorophenyl)-4-methyl-5-phenyl-1*H*-pyrazole-3-carboxylate (8b). The procedure described for the synthesis of **8a**

was applied to **6b** and **7a** to yield **8b** (21%) as a solid. Mp 116−118 °C; ^{1}H NMR δ 7.42 (dd, J = 1.6 and 7.2 Hz, 1H), 7.36−7.26 (m, 6H), 7.17−7.14 (m, 2H), 4.49 (q, J = 7.2 Hz, 2H), 2.36 (s, 3H), 1.45 (t, 6.8 Hz, 3H).

Ethyl 1-(2-Bromophenyl)-4-methyl-5-phenyl-1*H*-pyrazole-3-carboxylate (8c). The procedure described for the synthesis of **8a** was applied to **6c** and **7a** to yield **8c** (23%) as a solid. Mp 116−118 °C; ^{1}H NMR δ 7.54 (dd, J = 1.6 and 7.2 Hz, 1H), 7.39 (dd, J = 1.6 and 7.2 Hz, 1H), 7.33−7.16 (m, 7H), 4.49 (q, J = 7.2 Hz, 2H), 2.37 (s, 3H), 1.45 (t, J = 6.8, 3H).

Ethyl 1-(3-Bromophenyl)-4-methyl-5-phenyl-1*H*-pyrazole-3-carboxylate (8d). The procedure described for the synthesis of **8a** was applied to **6f** and **7a** to yield **8d** (15%) as a semisolid. ^{1}H NMR δ 7.56 (t, J = 2.0 Hz, 1H), 7.45−7.39 (m, 4H), 7.17−7.00 (m, 4H), 4.49 (q, J = 7.2 Hz, 2H), 2.39 (s, 3H), 1.43 (t, J = 6.8, 3H).

Ethyl 1-(4-Bromophenyl)-4-methyl-5-phenyl-1*H*-pyrazole-3-carboxylate (8e). The procedure described for the synthesis of **8a** was applied to **6g** and **7a** to yield **8e** (25%) as a solid. Mp 76−78 °C; ^{1}H NMR δ 7.42−7.37 (m, 5H), 7.16−7.17 (m, 4H), 4.49 (q, J = 7.2 Hz, 2H), 2.39 (s, 3H), 1.43 (t, J = 6.8, 3H).

Ethyl 1-(2-Iodophenyl)-4-methyl-5-phenyl-1*H*-pyrazole-3-carboxylate (8f). The procedure described for the synthesis of **8a** was applied to **6d** and **7a** to yield **8f** (22%) as a solid. Mp 122−124 °C; ^{1}H NMR δ 7.80 (d, J = 8.0 Hz, 1H), 7.34−7.27 (m, 5H), 7.20−7.18 (m, 2H), 7.08−7.04 (m, 1H), 4.49 (q, J = 7.2 Hz, 2H), 2.37 (s, 3H), 1.45 (t, J = 6.8 Hz, 3H).

Ethyl 1-(2-Phenylphenyl)-4-methyl-5-phenyl-1*H*-pyrazole-3-carboxylate (8g). The procedure described for the synthesis of **8a** was applied to **6e** and **7a** to yield **8g** (17%) as a semisolid. ^{1}H NMR δ 7.73 (d, J = 7.2 Hz, 1H), 7.21 (dd, J = 1.6 and 8.0 Hz, 1H), 7.17−7.12 (m, 2H), 7.08 (p, J = 8.4 Hz, 4H), 6.51 (d, J = 7.6 Hz, 2H), 6.42 (d, J = 7.6 Hz, 2H), 4.45 (q, J = 7.2 Hz, 2H), 2.17 (s, 3H), 1.48 (t, J = 7.2 Hz).

Ethyl 1-(2-Bromophenyl)-5-phenyl-1*H*-pyrazole-3-carboxylate (8h). The procedure described for the synthesis of **8a** was applied to **6c** and **7b** to yield **8h** (24%) as a solid. Mp 90−92 °C; ^{1}H NMR δ 7.62 (d, J = 8.4 Hz, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.49 (t, J = 7.6 Hz, 1H), 7.34−7.20 (m, 6H), 7.10 (s, 1H), 4.49 (q, J = 7.2 Hz, 2 Hz), 1.45 (t, J = 6.8 Hz).

Ethyl 1-(2-Fluorophenyl)-5-(4-methoxyphenyl)-4-methyl-1*H*-pyrazole-3-carboxylate (8i). The procedure described for the synthesis of **8a** was applied to **6a** and **7c** to yield **8i** (19%) as a white solid. Mp 86−88 °C; ^{1}H NMR δ 7.46 (td, J = 1.6 and 7.6 Hz, 1H), 7.35−7.29 (m, 1H), 7.18 (t, J = 7.6 Hz, 1H), 7.09 (d, J = 11.2 Hz, 2H), 7.04 (t, J = 9.2 Hz), 6.85 (d, J = 11.2 Hz, 2H), 4.48 (q, J = 7.2 Hz, 2H), 3.79 (s, 3H), 2.33 (s, 3H), 1.45 (t, J = 6.8 Hz, 3H).

Ethyl 1-(3-Bromophenyl)-5-(4-methoxyphenyl)-4-methyl-pyrazole-3-carboxylate (8j). The procedure described for the synthesis of **8a** was applied to **6f** and **7g** to yield **8j** (12%) as a semisolid. ^{1}H NMR δ 7.57 (t, J = 1.9 Hz, 1H) 7.46−7.44 (m, 1H), 7.22−7.11 (m, 3H), 7.06−7.04 (m, 2H), 6.93 (d, J = 8.8), 4.47 (q, J = 7.2 Hz, 2H), 3.84 (s, 3H), 2.29 (s, 3H), 1.45 (t, J = 6.8 Hz, 3H).

Ethyl 1-(3-Bromophenyl)-5-(4-methoxyphenyl)-1*H*-pyrazole-3-carboxylate (8k). The procedure described for the synthesis of **8a** was applied to **6f** and **7c** to yield **8k** (26%) as a solid. Mp 64−68 °C; ^{1}H NMR δ 7.61 (d, J = 8.4 Hz, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.42 (t, J = 7.6 Hz, 1H), 7.33 (t, J = 7.6 Hz, 1H), 7.14 (d, J = 8.0 Hz, 2H), 7.03 (s, 1H), 6.80 (d, J = 7.2 Hz, 2H), 4.49 (q, J = 7.2 Hz, 2H), 3.78 (s, 3H), 1.45 (t, J = 6.8 Hz, 3H).

Ethyl 4-Bromo-1-(3-bromophenyl)-5-(4-methoxyphenyl)-1*H*-pyrazole-3-carboxylate (8l). NBS (334 mg, 1.9 mmol) was added to a stirred solution of **8k** (500 mg, 1.2 mmol) in MeCN (25 mL). The reaction mixture was heated to reflux for 8 h and then concentrated in vacuo. The crude was purified with flash chromatography (hexanes−EtOAc, 8:2 v/v) to give **8l** (543 mg, 91%). Mp 118−120 °C; ^{1}H NMR δ 7.61 (t, J = 2.0 Hz, 1H), 7.46 (dd, J = 6.8 Hz, 1H), 7.21 (d, J = 9.3 Hz, 2H), 7.16 (t, J = 8.4 Hz, 1H), 7.06 (d, J = 7.6 Hz, 1H), 6.93 (d, J = 8.4 Hz, 2H), 4.50 (q, J = 7.2 Hz, 2H), 3.84 (s, 3H), 1.47 (t, J = 6.8 Hz, 3H).

Ethyl 1-(2-Bromophenyl)-5-(4-fluorophenyl)-4-methyl-1*H*-pyrazole-3-carboxylate (8m). The procedure described for the synthesis of **8a** was applied to **6c** and **7d** to yield **8m** (20%) as a white solid. Mp 109−110 °C; ^{1}H NMR δ 7.56 (d, J = 7.6 Hz, 1H), 7.39−7.32 (m, 2H), 7.25−7.23 (m, 1H), 7.17 (dd, J = 5.6 and 3.2 Hz, 2H), 7.01 (t, J = 8.4 Hz, 2H), 4.49 (q, J = 7.2 Hz, 2H), 2.34 (s, 3H), 1.45 (t, J = 6.8 Hz, 3H).

Ethyl 1-(2-Bromophenyl)-5-(3-fluorophenyl)-4-methyl-1*H*-pyrazole-3-carboxylate (8n). The procedure described for the synthesis of **8a** was applied to **6c** and **7e** to yield **8n** (19%) as a white solid. Mp 106−108 °C; ^{1}H NMR δ 7.57 (d, J = 76. Hz, 1H), 7.40−7.32 (m, 2H), 7.29−7.24 (m, 2H), 7.02 (t, J = 6.4 Hz, 1H), 6.96 (d, J = 8.0 Hz, 1H), 6.90 (d, J = 9.6 Hz, 1H), 4.49 (q, J = 7.2 Hz, 2H), 2.34 (s, 3H), 1.45 (t, J = 6.8 Hz, 3H).

Ethyl 1-(2-Bromophenyl)-4-cyano-5-phenyl-1*H*-pyrazole-3-carboxylate (8p). A solution of **6c** (10.5 g, 34.4 mmol), benzoylacetonitrile (**7h**, 5.0 g, 34.4 mmol), and DIPEA (13.3 g, 103.2 mmol) was refluxed in MeCN (100 mL) for 16 h. The reaction mixture was then concentrated in vacuo and the crude product extracted with ether (3 × 100 mL). The ethereal extracts were combined and concentrated in vacuo. The crude was purified with flash chromatography (hexanes−EtOAc, 7:3 v/v) to give **8p** (1.1 g, 8%) as a pale white solid. Mp 106−108 °C; ^{1}H NMR δ 7.63 (d, J = 8.0 Hz, 1H), 7.46−7.35 (m, 8H), 4.56 (q, J = 7.2 Hz, 2H), 1.49 (t, J = 6.8 Hz, 3H).

1-(2-Bromophenyl)-*N*-(4-cyanotetrahydro-2*H*-pyran-4-yl)-5-phenyl-1*H*-pyrazole-3-carboxamide (9a). An aqueous solution (6 mL) of LiOH (819 mg, 34.2 mmol) was added to a stirred solution of **8c** (500 mg, 966 μmol) in THF (60 mL) and heated to reflux for 6 h. The mixture was cooled to room temperature, and volatile compounds were removed in vacuo. The residue was dissolved in water (50 mL) and neutralized with aqueous HCl. The resulting precipitate was filtered off and dried in vacuo, yielding crude acid (242 mg, 52%). DMF (1 drop) and oxalyl chloride (66 μL, 777 μmol) were added to a stirred solution of the acid (200 mg, 518 μmol) in dry dichloromethane (DCM, 10 mL). After bubbling had ceased, the mixture was concentrated in vacuo. A solution of 4-aminotetrahydro-2*H*-pyran-4-carbonitrile (101 mg, 673 μmol) and DIPEA (90 μL, 777 μmol) in DCM (10 mL) was added to the acid chloride and stirred at room temperature for 2 h. The volatile compounds were removed in vacuo and the crude residue was purified with silica gel chromatography (hexanes−EtOAc, 60:40 v/v) to yield **9a** (58% from acid) as a white solid. Mp 226−228 °C; ^{1}H NMR δ 7.68 (d, J = 8.0 Hz, 1H), 7.44−7.39 (m, 2H), 7.39−7.35 (m, 1H), 7.35−7.25 (m, 3H), 7.12 (s, 1H), 7.06 (s, 1H), 4.01 (dt, J = 3.2 and 12.8 Hz, 2H), 3.88 (td, J = 2.0 and 12.4 Hz, 2H), 2.57 (d, J = 12.8 Hz, 2H), 2.11 (td, J = 4.4 and 10.0 Hz); HRMS (tof) $[M + Na]^+$, calcd for $C_{22}H_{19}{}^{79}BrN_4NaO_2$, 473.0584; found, 473.0562; error, 4.5 ppm. Anal. Calcd for $C_{22}H_{19}BrN_4O_2$: C 58.5, H 4.2, N 12.4. Found: C 58.4, H 4.3, N 12.3.

***N*-(4-Cyanotetrahydro-2*H*-pyran-4-yl)-1-(2-fluorophenyl)-4-methyl-5-phenyl-1*H*-pyrazole-3-carboxamide (9b).** The procedure described for the synthesis of **9a** was applied to **8a** and 4-aminotetrahydro-2*H*-pyran-4-carbonitrile to yield **9b** (68% from acid) as a white solid. Mp 212−214 °C; ^{1}H NMR δ 7.40−7.32 (m, 5H), 7.21−7.05 (m, 5H), 4.00 (dt, J = 3.2 and 12.8 Hz, 2H), 3.87 (td, J = 2.0 and 12.4 Hz, 2H), 2.56 (d, J = 12.8 Hz, 2H), 2.40 (s, 3H), 2.07−2.04 (m, 2H); HRMS (tof) $[M + H]^+$, calcd for $C_{23}H_{22}FN_4O_2$, 405.1721; found, 405.1711; error, 2.5 ppm. Anal. Calcd for $C_{23}H_{21}FN_4O_2 \cdot 0.3\ H_2O$: C 67.4, H 5.3, N 13.7. Found: C 67.4, H 5.3, N 13.7.

1-(2-Chlorophenyl)-*N*-(4-cyanotetrahydro-2*H*-pyran-4-yl)-4-methyl-5-phenyl-1*H*-pyrazole-3-carboxamide (9c). The procedure described for the synthesis of **9a** was applied to **8b** and 4-aminotetrahydro-2*H*-pyran-4-carbonitrile to yield **9c** (56% from acid) as a white solid. Mp 208−210 °C; ^{1}H NMR δ 7.43−7.28 (m, 7H), 7.15−7.12 (m, 2H), 7.10 (s, 1H), 4.01 (dt, J = 3.2 and 12.8 Hz, 2H), 3.86 (td, J = 2.0 and 12.4 Hz, 2H), 2.55 (d, J = 12.8 Hz, 2H), 2.40 (s, 3H),

2.06−2.04 (m, 2H); HRMS (tof) $[M + Na]^+$, calcd for $C_{23}H_{21}ClN_4NaO_2$, 443.1245; found, 443.1231; error, 3.2 ppm. Anal. Calcd for $C_{23}H_{21}ClN_4O_2$: C 65.6, H 5.0, N 13.3. Found: C 65.7, H 5.0, N 13.0.

1-(2-Chlorophenyl)-*N*-(4-cyanotetrahydro-2*H*-pyran-4-yl)-*N*,4-dimethyl-5-phenyl-1*H*-pyrazole-3-carboxamide (9d). NaH (60% in dispersion) (17 mg, 428 μmol) was added to a stirred solution of **9c** (90 mg, 223 μmol) and methyl iodide (61 mg, 428 μmol) in DMF (5 mL). The mixture was stirred for 1 h and then concentrated in vacuo. The crude was purified with flash chromatography (hexanes−EtOAc, 8:2 v/v) to give **9d** (62 mg, 64%) as a pale white solid. Mp 182−184 °C; ^{1}H NMR δ 7.45 (d, *J* = 9.2 Hz, 1H), 7.35−7.20 (m, 6H), 7.18−7.14 (m, 2H), 4.09 (dd, *J* = 2.8 and 12.8 Hz, 2H), 3.45 (s, 3H), 2.58 (d, *J* = 2.8 Hz, 2H), 2.28 (s, 3H), 2.17 (td, *J* = 4.0 and 12.0 Hz, 2H); HRMS (tof) $[M + Na]^+$, calcd for $C_{24}H_{23}ClN_4NaO_2$, 457.1402; found, 457.1386; error, 3.4 ppm. Anal. Calcd for $C_{24}H_{23}ClN_4O_2$: C 66.3, H 5.3, N 12.9. Found: C 65.9, H 5.3, N 12.6.

1-(2-Bromophenyl)-*N*-(4-cyanotetrahydro-2*H*-pyran-4-yl)-4-methyl-5-phenyl-1*H*-pyrazole-3-carboxamide (9e). The procedure described for the synthesis of **9a** was applied to **8c** and 4-aminotetrahydro-2*H*-pyran-4-carbonitrile to yield **9e** (58% from acid) as a white solid. Mp 188−190 °C; ^{1}H NMR δ 7.62 (d, *J* = 8.0, 1H), 7.36−7.28 (m, 6H), 7.18−7.14 (m, 2H), 7.10 (s, 1H), 4.01 (td, *J* = 2.0 and 12.4 Hz, 2H), 3.87 (td, *J* = 2.0 and 12.4 Hz, 2H), 2.56 (d, *J* = 12.8 Hz, 2H), 2.41 (s, 3H), 2.07−2.04 (m, 2H); HRMS (tof) $[M + H]^+$, calcd for $C_{23}H_{22}{}^{79}BrN_4O_2$, 465.0921; found, 465.0908; error, 2.8 ppm. Anal. Calcd for $C_{23}H_{21}BrN_4O_2$: C 59.4, H 4.5, N 12.0. Found: C 59.5, H 4.6, N 11.7.

1-(2-Bromophenyl)-*N*-(1-cyanocyclohexyl)-4-methyl-5-phenyl-1*H*-pyrazole-3-carboxamide (9f). The procedure described for the synthesis of **9a** was applied to **8c** and 1-aminocyclohexanecarbonitrile HCl to yield **9f** (62% from acid) as a white solid. Mp 212−214 °C; ^{1}H NMR δ 7.61 (d, *J* = 8.0 Hz, 7.37−7.25 (m, 6H), 7.16−7.14 (m, 2H), 7.04 (s, 1H), 2.51 (bs, 2H), 2.41 (s, 3H), 1.78−1.69 (m, 7H), 1.32 (bs, 1H). HRMS (tof) $[M + H]^+$, calcd for $C_{24}H_{23}{}^{79}BrN_4NaO$, 485.0953; found, 485.0947; error, 3.8 ppm. Anal. Calcd for $C_{24}H_{23}BrN_4O$: C 62.2, H 5.0, N 12.1. Found: C 62.1, H 5.2, N 12.3.

1-(2-Bromophenyl)-4-cyano-*N*-(4-cyanotetrahydro-2*H*-pyran-4-yl)-5-phenyl-1*H*-pyrazole-3-carboxamide (9g). The procedure described for the synthesis of **9a** was applied to **8p** and 4-aminotetrahydro-2*H*-pyran-4-carbonitrile to yield **9g** (71% from acid) as a solid. Mp 224−226 °C; ^{1}H NMR δ 7.69 (d, *J* = 8.4 Hz, 1H), 7.49−7.32 (m, 8H), 6.95 (s, 1H), 4.02 (dt, *J* = 3.2 and 12.8 Hz, 2H), 3.86 (td, *J* = 2.0 and 12.4 Hz, 2H), 2.58 (d, *J* = 12.8 Hz, 2H), 2.09−2.04 (m, 2H); HRMS (tof) $[M + H]^+$, calcd for $C_{23}H_{19}{}^{79}BrN_5O_2$, 476.0717; found, 476.0700; error, 3.6 ppm; Anal. for $C_{23}H_{18}BrN_5O_2$: C 58.0, H 3.8, N 14.7. Found: C 57.6, H 3.9, N 14.5.

1-(3-Bromophenyl)-*N*-(4-cyanotetrahydro-2*H*-pyran-4-yl)-4-methyl-5-phenyl-1*H*-pyrazole-3-carboxamide (9h). The procedure described for the synthesis of **9a** was applied to **8d** and 4-aminotetrahydro-2*H*-pyran-4-carbonitrile to yield **9h** (53% from acid) as a white solid. Mp 138−140 °C; ^{1}H NMR δ 7.56 (t, *J* = 2 Hz, 1H), 7.45 (m, 4H), 7.17−7.12 (m, 3H), 7.10 (s, 1H), 7.00 (d, *J* = 7.2 Hz, 1H), 4.02 (dt, *J* = 3.2 and 12.8 Hz, 2H), 3.88 (td, *J* = 2.0 and 12.4 Hz, 2H), 2.59 (d, *J* = 12.8 Hz, 2H), 2.36 (s, 3H), 2.10−2.04 (m, 2H); HRMS (tof) $[M + Na]^+$, calcd for $C_{23}H_{21}{}^{79}BrN_4NaO_2$, 487.0740; found, 487.0726; error, 2.8 ppm. Anal. Calcd for $C_{23}H_{21}BrN_4O_2$: C 59.4, H 4.5, N, 12.0. Found: C 59.3, H 4.5, N 12.0.

1-(4-Bromophenyl)-*N*-(4-cyanotetrahydro-2*H*-pyran-4-yl)-4-methyl-5-phenyl-1*H*-pyrazole-3-carboxamide (9i). The procedure described for the synthesis of **9a** was applied to **8e** and 4-aminotetrahydro-2*H*-pyran-4-carbonitrile to yield **9i** (34% from acid) as a solid. Mp 176−178 °C; ^{1}H NMR δ 7.46 (dt, *J* = 2.4 and 9.2 Hz, 2H), 7.41−7.38 (m, 3H), 7.16−7.13 (m,3H), 7.11 (dt, *J* = 2.4 and 9.2 Hz, 2H), 4.02 (dt, *J* = 3.2 and 12.8 Hz, 2H), 3.88 (td, *J* = 2.0 and 12.4 Hz, 2H), 2.57 (d, *J* = 12.8 Hz, 2H), 2.36 (s, 3H), 2.08−2.04 (m, 2H); HRMS (tof) $[M + Na]^+$, calcd for $C_{23}H_{21}{}^{79}BrN_4NaO_2$, 487.0740; found, 487.0721; error, 3.9 ppm. Anal. Calcd for $C_{23}H_{21}BrN_4O_2$: C 59.4, H 4.5, N 12.0. Found: C 59.2, H 4.6, N 11.9.

***N*-(4-Cyanotetrahydro-2*H*-pyran-4-yl)-1-(2-iodophenyl)-4-methyl-5-phenyl-1*H*-pyrazole-3-carboxamide (9j).** The procedure described for the synthesis of **9a** was applied to **8f** and 4-aminotetrahydro-2*H*-pyran-4-carbonitrile to yield **9j** (61% from acid) as a solid. Mp 200−202 °C; ^{1}H NMR δ 7.88 (dd, *J* = 1.2 and 7.6 Hz, 1H), 7.39 (td, *J* = 1.2 and 7.6 Hz, 1H), 7.31−7.29 (m, 3H), 7.27 (dd, *J* = 1.6 and 7.6, 1H), 7.18−7.16 (m, 2H), 7.14−7.09 (m, 2H), 4.01 (dt, *J* = 3.2 and 12.8 Hz, 2H), 3.87 (td, *J* = 2.0 and 12.4 Hz, 2H), 2.56 (d, *J* = 12.8 Hz, 2H), 2.41 (s, 3H), 2.08−2.04 (m, 2H); HRMS (tof) $[M + H]^+$, calcd for $C_{23}H_{22}IN_4O_2$, 513.0728; found, 513.0780; error, 0.5 ppm. Anal. Calcd for $C_{23}H_{21}IN_4O_2$: C 53.9, H 4.1, N 10.9. Found: C 54.0, H 4.1, N 10.8.

***N*-(4-Cyanotetrahydro-2*H*-pyran-4-yl)-1-(2-phenylphenyl)-4-methyl-5-phenyl-1*H*-pyrazole-3-carboxamide (9k).** The procedure described for the synthesis of **9a** was applied to **8g** and 4-aminotetrahydro-2*H*-pyran-4-carbonitrile to yield **9k** (44% from acid) as a white solid. Mp 98−100 °C; ^{1}H NMR δ 7.62 (d, *J* = 7.6, 1H), 7.51−7.47 (m, 2H), 7.29−7.02 (m, 8H), 6.51 (d, *J* = 7.6 Hz, 2H), 6.47 (d, *J* = 7.6 Hz, 2H), 4.01 (dt, *J* = 3.2 and 12.8 Hz, 2H), 3.87 (td, *J* = 2.0 and 12.4 Hz, 2H), 2.56 (d, *J* = 12.8 Hz, 2H), 2.41 (s, 3H), 2.08−2.04 (m, 2H); HRMS (tof) $[M + Na]^+$, calcd for $C_{29}H_{26}N_4NaO_2$, 463.2129; found, 463.2107; error, 4.7 ppm. Anal. Calcd for $C_{29}H_{26}N_4O_2$: C 75.3, H 5.7, N 12.1. Found: C 74.9, H 5.8, N 11.7.

***N*-(4-Cyanotetrahydro-2*H*-pyran-4-yl)-1-(2-fluorophenyl)-5-(4-methoxyphenyl)-4-methyl-1*H*-pyrazole-3-carboxamide (9l).** The procedure described for the synthesis of **9a** was applied to **8i** and 4-aminotetrahydro-2*H*-pyran-4-carbonitrile to yield **9l** (59% from acid) as a white solid. Mp 210−212 °C; ^{1}H NMR δ 7.41−7.34 (m, 2H), 7.22 (t, *J* = 7.2 Hz, 1H), 7.10−7.05 (m, 4H), 6.85 (d, *J* = 8.4 Hz, 2H), 4.01 (dt, *J* = 3.2 and 12.8 Hz, 2H), 3.88 (td, *J* = 2.0 and 12.4 Hz, 2H), 3.79 (s, 3H), 2.57 (d, *J* = 12.8 Hz, 2H), 2.35 (s, 3H), 2.11−2.04 (m, 2H); HRMS (tof) $[M + Na]^+$ calcd for $C_{24}H_{23}FN_4NaO_3$, 457.1646; found, 457.1831; error, 3.4 ppm. Anal. Calcd for $C_{24}H_{23}FN_4O_3 \cdot 0.3H_2O$: C 65.5, H 5.4, N 12.7. Found: C 65.5, H 5.4, N 12.7.

1-(2-Bromophenyl)-*N*-(4-cyanotetrahydro-2*H*-pyran-4-yl)-5-(4-methoxyphenyl)-4-methyl-1*H*-pyrazole-3-carboxamide (9m). The procedure described for the synthesis of **9a** was applied to **8o** and 4-aminotetrahydro-2*H*-pyran-4-carbonitrile to give **9m** (87 mg, 34% from acid) as a white solid. Mp 208−210 °C; ^{1}H NMR δ 7.62 (dd, *J* = 6.7 and 1.0 Hz, 1H), 7.37−7.23 (m, 3H), 7.09 (s, 1H), 7.08 (dt, *J* = 8.8 and 1.6 Hz, 2H), 6.82 (dt, *J* = 8.8 and 1.6 Hz, 2H), 3.99 (d, *J* = 8.1 Hz, 2H), 3.85 (t, *J* = 10.6 Hz, 2H), 3.77 (s, 3H), 2.54 (d, *J* = 13.4 Hz, 2H), 2.38 (s, 3H), 2.06 (t, *J* = 10.0 Hz, 3H); ^{13}C NMR δ 162.41, 159.70, 144.30, 143.16, 133.60, 131.07, 130.81, 130.02, 128.08, 122.10, 120.88, 119.03, 113.89, 63.81, 55.21, 49.15, 35.65, 9.48; HRMS (*m*/*z*) $[M + H]^+$, calcd for $C_{24}H_{24}{}^{79}Br\ N_4O_3$, 495.1032; found, 495.1029; error, −0.6 ppm. Anal. Calcd for $C_{24}H_{23}BrN_4O_3$: C 58.2, H 4.7, N 11.3. Found: C 58.2, N 4.8, H 11.2.

1-(2-Bromophenyl)-*N*-(1-cyanocyclohexyl)-5-(4-methoxyphenyl)-4-methyl-1*H*-pyrazole-3-carboxamide (9n). The procedure described for the synthesis of **9a** was applied to **8o** to afford **9n** (36% from acid) as a white solid. Mp 220−222 °C; ^{1}H NMR δ 7.61 (dd, *J* = 6.7 and 1.0 Hz, 1H), 7.35−7.24 (m, 3H), 7.07 (dt, *J* = 8.8 and 1.6 Hz, 2H), 7.01 (s, 1H), 3.77 (s. 3H), 2.51 (bs, 2H), 2.39 (s, 3H), 1.77−1.71 (m, 8H), 1.15 (bs, 1H); ^{13}C NMR δ 162.22, 158.67, 144.12, 143.49, 138.98, 133.56, 132.84, 131.06, 130.70, 130.06, 128.05, 122.14, 119.90, 117.99,, 114.56, 68.74, 51.39, 35.64, 24.84, 22.15, 9.55; HRMS (*m*/*z*) $[M + H]^+$, calcd for $C_{25}H_{26}{}^{79}Br\ N_4O_2$, 493.1239; found, 493.1235; error, −0.8 ppm. Anal. Calcd for $C_{25}H_{25}BrN_4O_2$: C 60.9, H 5.1, N 11.4. Found: C 60.8, H 5.4, N 11.2.

1-(3-Bromophenyl)-*N*-(4-cyanotetrahydro-2*H*-pyran-4-yl)-5-(4-methoxyphenyl)-4-methyl-1*H*-pyrazole-3-carboxamide (9o). The procedure described for the synthesis of **9a** was applied to **8j** and 4-aminotetrahydro-2*H*-pyran-4-carbonitrile to yield **9o** (53% from acid) as a white solid. Mp 160−162 °C; ^{1}H NMR δ 7.58 (bs, 1H), 7.45 (d, J = 8.4 Hz, 1H), 7.15−7.11 (m, 2H), 7.09 (d, J = 8.8 Hz, 2H), 7.00 (d, J = 8.4 Hz, 1H), 6.92 (d, J = 8.4 Hz, 2H), 4.01 (dt, J = 3.2 and 12.8 Hz, 2H), 3.88−3.83 (m, 5H), 3.79 (s, 3H), 2.57 (d, J = 12.8 Hz, 2H), 2.35 (s, 3H), 2.10−2.04 (m, 2H); HRMS (tof) $[M + H]^+$, calcd for $C_{24}H_{24}{}^{79}BrN_4O_3$, 495.1028; found, 495.1020; error, 1.4 ppm. Anal. Calcd for $C_{24}H_{23}BrN_4O_3$: C 58.2, H 4.7, N 11.3. Found: C 58.2, H 4.8, N 11.2.

4-Cyano-*N*-(4-cyanotetrahydro-2*H*-pyran-4-yl)-1-(2-iodophenyl)-5-(4-methoxyphenyl)-1*H*-pyrazole-3-carboxamide (9p). The procedure described for the synthesis of **9a** was applied to **8q** and 4-aminotetrahydro-2*H*-pyran-4-carbonitrile to yield **9p** (68% from acid) as a white solid. Mp 232−214 °C; ^{1}H NMR δ 7.95 (dd, J = 1.2 and 8.0 Hz, 1H), 7.52 (td, J = 1.2 and 7.2 Hz, 1H), 7.38 (dd, J = 1.6 and 7.6 Hz, 1H), 7.29−7.22 (m, 3H), 6.95 (s, 1H), 6.88 (dt, J = 2.8 and 9.2 Hz), 4.02 (dt, J = 3.2 and 12.8 Hz, 2H), 3.86 (td, J = 2.0 and 12.4 Hz, 2H), 2.58 (d, J = 12.8 Hz, 2H), 2.09−2.04 (m, 2H); HRMS (tof) $[M + Na]^+$, calcd for $C_{24}H_{20}IN_5NaO_3$, 576.0503; found, 576.0483; error, 3.5 ppm. Anal. Calcd for $C_{24}H_{20}IN_5O_3$: C 52.1, H 3.6, N 12.7. Found: C 52.0, H 3.7, N 12.7.

4-Bromo-1-(3-bromophenyl)-*N*-(4-cyanotetrahydro-2*H*-pyran-4-yl)-5-(4-methoxyphenyl)-1*H*-pyrazole-3-carboxamide (9q). The procedure described for the synthesis of **9a** was applied to **8l** and 4-aminotetrahydro-2*H*-pyran-4-carbonitrile to yield **9q** (56% from acid) as a solid. Mp 182−184 °C; ^{1}H NMR δ 7.58 (t, J = 1.6 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.21−7.15 (m, 3H), 7.07 (s, 1H), 7.02 (d, J = 8.0 Hz, 1H), 6.94 (dt, J = 2.8 and 8.8 Hz, 2H), 4.01 (dt, J = 3.2 and 12.8 Hz, 2H), 3.88−3.83 (m, 5H), 3.79 (s, 3H), 2.57 (d, J = 12.8 Hz, 2H), 2.35 (s, 3H), 2.10−2.04 (m, 2H); HRMS (tof) $[M + Na]^+$, calcd for $C_{23}H_{20}{}^{79}Br_2N_4NaO_3$, 580.9794; found, 580.9774; error, 3.5 ppm. Anal. Calcd for $C_{23}H_{20}Br_2N_4O_3$: C 49.3, H 3.6, N 10.0. Found: C 49.2, H 3.6, N 9.8.

1-(2-Bromophenyl)-*N*-(4-cyanotetrahydro-2*H*-pyran-4-yl)-5-(4-fluorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide (9r). The procedure described for the synthesis of **9a** was applied to **8m** and 4-aminotetrahydro-2*H*-pyran-4-carbonitrile to yield **9r** (54%) as a solid. Mp 188−190 °C; ^{1}H NMR δ 7.62 (d, J = 6.4 Hz, 1H), 7.40−7.28 (m, 3H), 7.15−7.11 (m, 2H), 7.09 (s, 1H), 7.02 (t, J = 9.6 Hz, 2H), 4.01 (dt, J = 3.2 and 12.8 Hz, 2H), 3.88−3.83 (m, 5H), 3.79 (s, 3H), 2.56 (d, J = 12.8 Hz, 2H), 2.38 (s, 3H), 2.07−2.00 (m, 2H); HRMS (tof) $[M + H]^+$, calcd for $C_{23}H_{21}{}^{79}BrFN_4O_2$, 483.0826; found, 483.0821; error, 1.2 ppm. Anal. Calcd for $C_{23}H_{20}BrFN_4O_2$) C 57.2, H 4.2, N 11.6. Found: C 57.2, H 4.2, N 11.4.

1-(2-Bromophenyl)-*N*-(4-cyanotetrahydro-2*H*-pyran-4-yl)-5-(3-fluorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide (9s). The procedure described for the synthesis of **9a** was applied to **8n** and 4-aminotetrahydro-2*H*-pyran-4-carbonitrile to yield **9s** (62% from acid) as a solid. Mp 204−206 °C; ^{1}H NMR δ 7.64 (d, J = 8.0 Hz, 1H), 7.41−7.25 (m, 4H), 7.09 (s, 1H), 7.04 (td, J = 2.4 and 8.4 Hz, 1H), 6.95 (d, J = 8.0 Hz, 1H), 6.88 (dt, J = 2.0 and 9.6 Hz, 1H), 4.01 (dt, J = 3.2 and 12.8 Hz, 2H), 3.88−3.83 (m, 5H), 3.79 (s, 3H), 2.56 (d, J = 12.8 Hz, 2H), 2.38 (s, 3H), 2.07−2.00 (m, 2H); HRMS (tof) $[M + Na]^+$, calcd for $C_{23}H_{20}{}^{79}BrFNaN_4O_2$, 505.0646; found, 505.0623; error, 4.6 ppm. Anal. Calcd for $C_{23}H_{20}BrFN_4O_2$: C 57.2, H 4.2, N 11.6. Found: C 57.3, H 4.3, N 11.6.

Computation of cLogD. The lipophilicity of each synthesized ligand, expressed as the partition of the compound between *n*-octanol and buffer at pH 7.4 (cLogD), was computed with Pallas 3.70 software (CompuDrug, South San Francisco, CA).

Receptor Assays. Ligands **9a**−**s** were tested for affinity (K_i) at $GABA_A$-Bz site, TSPO, and CB_1 and CB_2 receptors by the National Institute of Mental Health Psychoactive Drug Screening Program. Detailed protocols are available online for all binding assays at NIMH-PDSP Web site (http://pdsp.med.unc.edu).

Receptor Screening. Ligands **9m** and **9n** were screened for binding to a wide range of receptors and transporters by National Institute of Mental Health Psychoactive Drug Screening Program. Detailed protocols are available online for all binding assays at NIMH-PDSP Web site (http://pdsp.med.unc.edu).

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ABBREVIATIONS USED

CB_1, cannabinoid type 1; CB_2, cannabinoid type 2; D, dopamine; DAT, dopamine transporter; DCM, dichloromethane; DIPEA, diisopropylethylamine; DMF, dimethylformamide; DOR, δ opiate receptor; $GABA_A$-Bz, γ-aminobutyric $acid_A$-benzodiazepine; GPCR, G-protein-coupled receptor; H, histamine; 5-HT, 5-hydroxytryptamine; KOR, κ opiate receptor; MeCN, acetonitrile; MOR, μ opiate receptor; NBS, *N*-bromosuccinimide; NCA, no carrier added; NET, noradrenaline transoporter; PET, positron emission tomography; PBR, peripheral benzodiazepine receptor; SERT, serotonin transporter; THF, tetrahydrofuran; Δ^9-THC, Δ^9-tetrahydrocannabinol; TSPO, 18 kDa translocator protein

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