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A new high-yield synthetic route to PET CB1 radioligands [^{11}C]OMAR and its analogs

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ABSTRACT

OMAR analogs reference standards and their corresponding desmethylated precursors were synthesized from substituted anilines either in 4 and 5 steps with 27–32% and 24–31% yield, or in 3 and 4 steps with 21–30% and 19–28% yield, respectively. [^{11}C]OMAR and its analog radioligands were prepared from their desmethylated precursors with [^{11}C]CH_3OTf through O-[^{11}C]methylation and isolated by HPLC combined with solid-phase extraction (SPE) in 50–65% radiochemical yields based on [^{11}C]CO_2 and decay corrected to end of bombardment (EOB), with 370–740 GBq/μmol specific activity at EOB.

The endogenous cannabinoid system consists of cannabinoid receptors, cannabinoid receptor 1 (CB1) and cannabinoid receptor 2 (CB2), and they are G protein-coupled receptors.[1] CB1 is found predominantly in the brain, CB2 is expressed mainly on immune tissues and cancer cells, and thus cannabinoid receptors are associated with various brain, cardiovascular and cancer diseases.[2,3] Cannabinoid receptors provide an attractive target for the development of therapeutic agents, and many CB1 antagonists and CB2 agonists have been developed and described in the literature.[4] Cannabinoid receptors also provide a particularly attractive target for the development of imaging agents, and numerous papers have reported the synthesis and evaluation of radioligands for imaging of CB1 and CB2 receptors using the biomedical imaging technique positron emission tomography (PET).[5,6] In our previous work, we have developed a series of PET radioligands for imaging CB2 receptor in cancer.[7] In this ongoing study, we turn our effort to the development of CB1 PET radioligands. CB1 is predominantly expressed in the central nervous system, and involved in a variety of brain functions and disorders such as schizophrenia and depression, obesity, drug addiction and alcoholism, and traumatic brain injury.[8] Many CB1 PET radioligands have been developed, and latest promising candidates progressing to human PET studies are [^{11}C]OMAR ([^{11}C]JHU75528) and [^{18}F]FMPEP-d_2,[5,9–11] as indicated in Figure 1.

[^{11}C]OMAR is originally developed and characterized at the John Hopkins University.[12,13] The importance of this compound as a PET brain imaging agent is great, and broader research investigation to fully explore and validate the utility of [^{11}C]OMAR-PET is important. However, the limited commercial availability, complicated synthetic procedure, and high costs of starting materials and precursor can present an obstacle to more widespread evaluation of this intriguing agent. Wishing to study this compound in our PET center, we decided to make our own material by following the literature methods.[12–16] Although several papers[12–16] dealing with the synthesis of [^{11}C]OMAR have appeared, there are gaps in synthetic detail among them, and certain key steps gave poor yields or were difficult to repeat in our hands. Consequently, we investigated alternate approaches and modifications that eventually resulted in a new high-yield synthesis of [^{11}C]OMAR and its analog radioligands starting from very beginning materials substituted anilines that was superior to previous works or addressed more synthetic details to reveal and explain technical tricks. In this Letter we provide complete experiment procedures, yields, analytical details and new findings for this new high-yield synthetic route, as well as OMAR analogs reference standards and desmethyled precursors, and present a fully automated radiosynthesis of [^{11}C]OMAR and its analog radioligands with [^{11}C]methyl triflate ([^{11}C]CH_3OTf) including a new radioligand, 1-(2-bromophenyl)-4-cyano-5-(4-[^{11}C]methoxyphenyl)-*N*-(pyrrolidin-1-yl)-1*H*-pyrazole-3-carboxamide ([^{11}C]**5d**).

As outlined in Scheme 1, OMAR analogs including 4-cyano-1-(2,4-dichlorophenyl)-5-(4-methoxyphenyl)-*N*-(piperidin-1-yl)-1*H*-pyrazole-3-carboxamide (OMAR, **5a**), 4-cyano-1-(2,4-dichloro-

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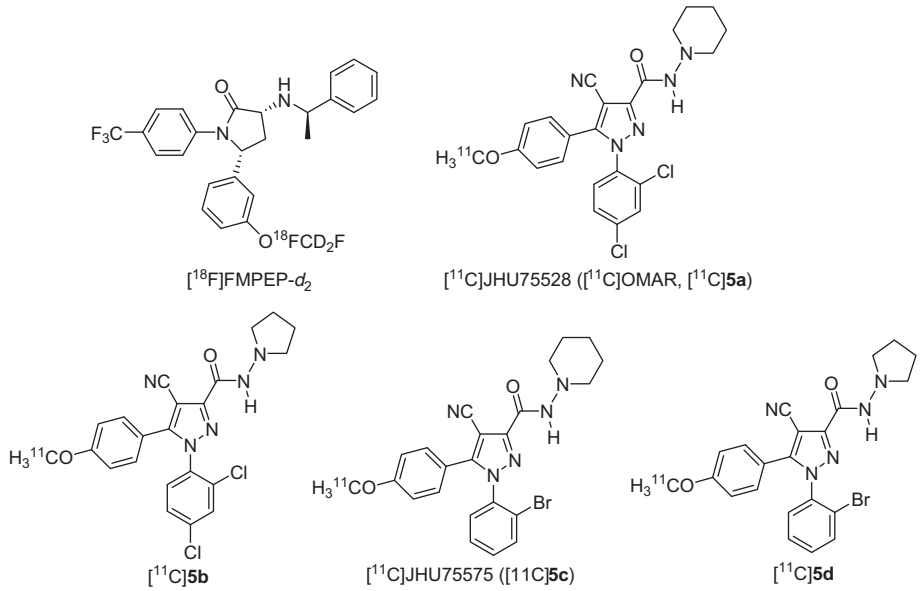
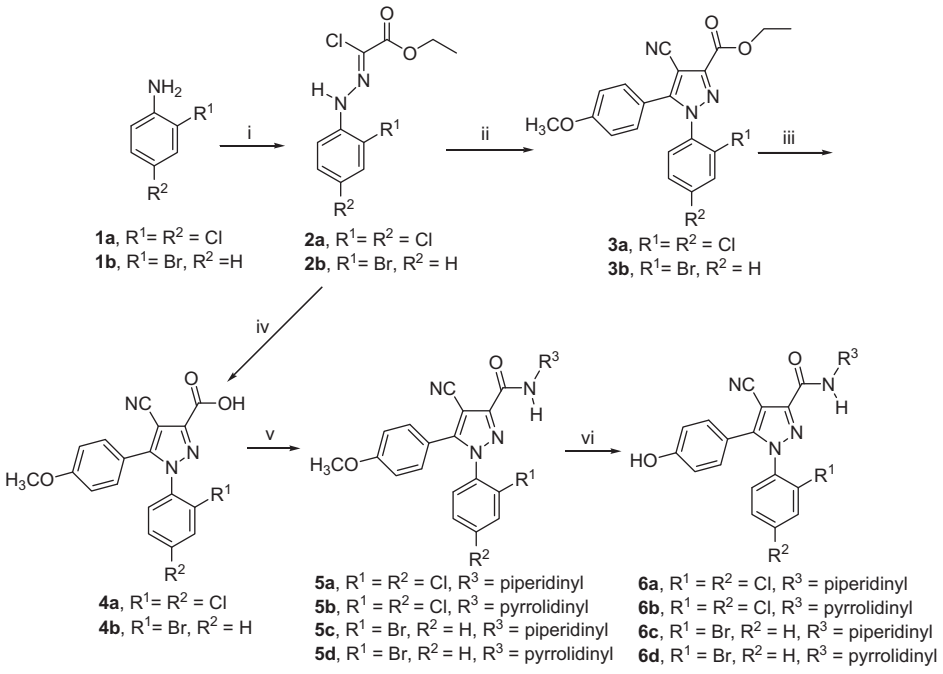


Figure 1. Chemical structure of [^{18}F]FMPEP-d_2, [^{11}C]OMAR and its analog radioligands.



Scheme 1. Synthesis of OMAR analogs and their corresponding desmethylated precursors. Reagents and yields: (i) HCl, $NaNO_2$; ethyl 2-chloroacetoacetate, NaOAc, EtOH–H_2O, 90–92%; (ii) 4-methoxybenzoylacetonitrile, Et_3N, *t*-BuOH, 60–63%; (iii) KOH, MeOH, 95–96%; (iv) 4-methoxybenzoylacetonitrile, MeONa/MeOH, 49–56%; (v) oxalyl chloride, DMF (cat.), 1-aminopiperidine or 1-aminopyrrolidine, DIEPA, CH_2Cl_2, 53–68%; (vi) LiBr, DMF, reflux, 87–95%.

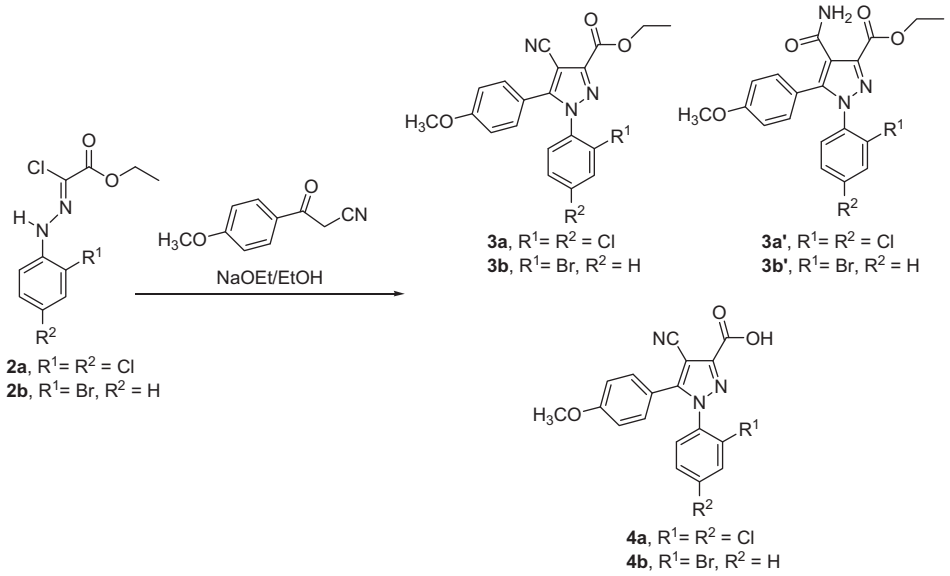
phenyl)-5-(4-methoxyphenyl)-*N*-(pyrrolidin-1-yl)-1*H*-pyrazole-3-carboxamide (**5b**), 1-(2-bromophenyl)-4-cyano-5-(4-methoxyphenyl)-*N*-(piperidin-1-yl)-1*H*-pyrazole-3-carboxamide (**5c**), and 1-(2-bromophenyl)-4-cyano-5-(4-methoxyphenyl)-*N*-(pyrrolidin-1-yl)-1*H*-pyrazole-3-carboxamide (**5d**); and their corresponding desmethylated precursors 4-cyano-1-(2,4-dichlorophenyl)-5-(4-hydroxyphenyl)-*N*-(piperidin-1-yl)-1*H*-pyrazole-3-carboxamide (**6a**), 4-cyano-1-(2,4-dichlorophenyl)-5-(4-hydroxyphenyl)-*N*-(pyrrolidin-1-yl)-1*H*-pyrazole-3-carboxamide (**6b**), 1-(2-bromophenyl)-4-cyano-5-(4-hydroxyphenyl)-*N*-(piperidin-1-yl)-1*H*-pyrazole-3-carboxamide (**6c**), and 1-(2-bromophenyl)-4-cyano-5-(4-hydroxyphenyl)-*N*-(pyrrolidin-1-yl)-1*H*-pyrazole-3-carboxamide (**6d**) were synthesized from substituted anilines either in 4 and 5 steps with 27–32% and 24–31% yield, or in 3 and 4 steps with 21–30% and 19–28% yield, respectively. Ethyl 2-chloro-2-(2-(2,4-dichlorophenyl)hydrazono)acetate (**2a**) and ethyl 2-(2-(2-bromophenyl)hydrazono)-2-chloroacetate (**2b**) were obtained in a two-step reaction by conversion of commercially available anilines (**1a**,**b**) into arenediazonium salts followed by reaction with ethyl 2-chloro-acetoacetate in 90–92% yields. According to the published method,[12–14] the key intermediates **3a**,**b** were firstly prepared through cycloaddition of 4-methoxybenzoylacetonitrile and compounds **2a**,**b** in presence of NaOEt at reflux in low yields (13–19%), because under this reaction condition, the 4-cyano

group can easily undergo a side reaction carbamoylation yielding the corresponding 4-carbamoylpyrazoles **3a′**,**b′** as major by-products described elsewhere;[13] furthermore, we discovered that the 3-carboxylate group can also easily undergo the hydrolysis to yield 3-carboxylic acids **4a**,**b** as other by-products, as shown in Scheme 2. These side reactions resulted in the poor yields of the key step cycloaddition reaction. Then other reported methods {*N*,*N*-diisopropylethylamine (DIPEA) as base}[15,16] were tested, it was still to produce by-product of 4-carbamoylpyrazole easily and low yields (6–26%) of **3a**,**b**. We realized that high reaction temperature is not suitable for this reaction because the cyano group is easy to convert into carbamoyl group under strong base condition especially at high reaction temperature, and lower temperature should be better for this reaction. Subsequently other reaction conditions including several solvents such as MeOH, EtOH, *i*-PrOH, *t*-BuOH, DMF, MeCN, THF, and 1,4-dioxane; and bases such as Et_3N, DIPEA, NaOH, NaOMe, NaOEt, and NaO^{i}Pr were also optimized. We found the optimized reaction conditions were Et_3N as base and *t*-BuOH as solvent at room temperature (RT), and key intermediates **3a**,**b** were obtained in higher yields (60–63%), as shown in Table 1. Et_3N/*t*-BuOH instead of EtONa/EtOH or DIPEA was used in cycloaddition reaction to avoid side reactions carbamoylation and hydrolysis and to significantly improve the yield. The ethyl esters **3a**,**b** were saponified with KOH at RT to give the carboxylic acids **4a**,**b** in near quantitative yields (95–96%). The alternative method for preparation of compounds **4a**,**b** was directly from the reaction of compounds **2a**,**b** with 4-methoxybenzoylacetonitrile in NaOMe/MeOH at RT in reasonable yields(49–56%). The idea was derived from the investigation of the cycloaddition reaction to prepare compounds **3a**,**b**. This method (NaOMe/MeOH instead of NaOEt/EtOH) combined two steps cycloaddition and hydrolysis as a single step to shorten the synthetic steps and to increase the yield as well. It is a two-step reaction, firstly producing **3a**,**b** through cycloaddition and secondly affording **4a**,**b** by hydrolysis. The carboxylic acids **4a**,**b** were converted to the carbonyl chloride intermediates with oxalyl chloride and tiny amount (two drops) of DMF as the catalyst followed by coupling with 1-aminopiperidine or 1-aminopyrrolidine to afford reference standard **5a**–**d** in 53–68% yields. Oxalyl chloride/DMF/CH_2Cl_2 instead of $SOCl_2$/toluene was used in coupling reaction to rise up the yield. Desmethylated precursors **6a**–**d** were successfully obtained in high yields (87–95%) through direct demethylation of compounds **5a**–**d** using LiBr as demethylation agent in DMF.[17,18] Attempts to prepare desmethylated precursors for radiolabeling either via demethylation or by a direct synthesis were failed, and a similar and parallel synthetic route (multiple-step protective group approach) to firstly prepare intermediates containing protective group followed by removal of protective group was employed in the literature.[12–14]

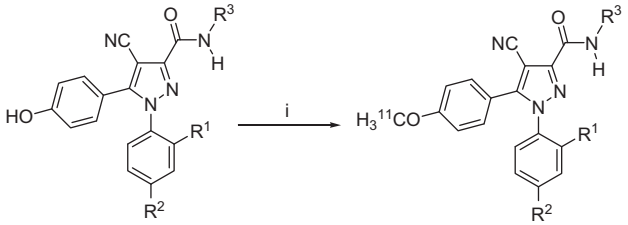
Table 1
The representative optimized reaction conditions to produce compounds **3a**,**b**

Reaction conditions	Yield (%)	References and notes
NaOEt/EtOH, reflux	13–19	[12–14]
DIPEA, CH_3CN, EtOH or *t*-BuOH, reflux	6–26	[15,16]
Et_3N, *t*-BuOH, RT	60–63	[36]

Synthesis of the target tracer [^{11}C]OMAR and its analog radioligands [^{11}C]**5a**–**d** is indicated in Scheme 3. The precursors **6a**–**d** were labeled by [^{11}C]methyl triflate ([^{11}C]CH_3OTf)[19,20] through *O*-[^{11}C]methylation[21,22] at 80 °C under basic condition (2 N NaOH) and isolated by a semi-preparative high performance liquid chromatography (HPLC) with a C-18 column and a solid-phase extraction (SPE) with a disposable C-18 Plus Sep-Pak cartridge (a second purification or isolation process)[23–25] to produce the corresponding pure radiolabeled compound [^{11}C]**5a**–**d** in 50–65% radiochemical yield, decay corrected to end of bombardment (EOB), based on [^{11}C]CO_2. [^{11}C]CH_3OTf is a proven methylation reagent with greater reactivity than commonly used [^{11}C]methyl iodide ([^{11}C]CH_3I),[26] and thus, the radiochemical yield of [^{11}C]**5** was relatively high. Addition of $NaHCO_3$ to quench the radiolabeling reaction and to dilute the radiolabeling mixture prior to the injection onto the semi-preparative HPLC column for purification gave better separation of [^{11}C]**5** from its phenol hydroxyl precursor **6**.[23–25,27] The radiosynthesis was performed in a home-built automated multi-purpose ^{11}C-radiosynthesis module, allowing measurement of specific radioactivity during synthesis.[28,29] This ^{11}C-radiosynthesis module includes the overall design of the reaction, purification and reformulation capabilities of the prototype system. In addition, ^{11}C-tracer specific activity (GBq/mol at EOB) can be automatically determined prior to product delivery for compounds purified by the HPLC-portion of the system. Briefly, analysis of the chromatographic data utilized PeakSimple software (SRI Instruments, Las Vegas, NV). Immediately following elution of the product peak, the chromatographic data are exported to PeakSimple readable



Scheme 2. Cycloaddition reaction and subsequent side reactions carbamoylation and hydrolysis in NaOEt/EtOH at reflux.



6a, $R^1 = R^2 = Cl$, R^3 = piperidinyl
6b, $R^1 = R^2 = Cl$, R^3 = pyrrolidinyl
6c, $R^1 = Br$, $R^2 = H$, R^3 = piperidinyl
6d, $R^1 = Br$, $R^2 = H$, R^3 = pyrrolidinyl

[^{11}C]**5a**, $R^1 = R^2 = Cl$, R^3 = piperidinyl
[^{11}C]**5b**, $R^1 = R^2 = Cl$, R^3 = pyrrolidinyl
[^{11}C]**5c**, $R^1 = Br$, $R^2 = H$, R^3 = piperidinyl
[^{11}C]**5d**, $R^1 = Br$, $R^2 = H$, R^3 = pyrrolidinyl

Scheme 3. Synthesis of [^{11}C]OMAR and its analog radioligands. Reagents, conditions and yields: (i) [^{11}C]CH_3OTf, CH_3CN, 2 N NaOH, 80 °C, 3 min, 50–65%.

files, and the area of the radioactivity peak is converted to mCi at EOB by comparison to a reference calibration curve previously constructed using the same detector, loop and flow rate. The mass peak from the UV chromatogram (without decay correction) is similarly compared to a standard curve made at the same UV wavelength, mobile phase and flow rate. Simple division of the total EOB radioactivity peak (in mCi) by the total mass peak (in nmoles) gives specific activity at EOB in Ci/μmol. The overall synthesis, purification and reformulation time was 30–40 min from EOB. The specific radioactivity was in a range of 370–740 GBq/mol at EOB. Chemical purity and radiochemical purity were determined by analytical HPLC.[30] The chemical purity of the precursor **6a–d** and reference standard **5a–d** was >96%. The radiochemical purity of the target tracer [^{11}C]**5a–d** was >99% determined by radio-HPLC through γ-ray (PIN diode) flow detector, and the chemical purity of [^{11}C]**5a–d** was >93% determined by reverse-phase HPLC through UV flow detector. A C-18 Plus Sep-Pak cartridge was used to significantly improve the chemical purity of the tracer solution.[23–25,30] The chemical purity of the [^{11}C]**5a–d** tracer solution with Sep-Pak purification was increased higher 10–20% than that without Sep-Pak purification.[23–25]

The target compounds **5a–c** are known compound,[12,13] and the target compound **5d** is a new compound. In view of the structure-activity relationship (SAR) data reported in the literature,[13] as summarized in Table 2, compound **5b** (pyrrolidinyl) has better binding affinity than compound **5a** (piperidinyl), and compound **5c** (Br) has better binding affinity than compound **5a** (Cl). Therefore we can predict/hypothesize new compound **5d** will exhibit the best binding affinity in this series of compounds **5a–d**. Further SAR study of the substituent effect is currently under way to confirm this hypothesis. The measured HPLC lipophilicity coefficient (octanol-water partition coefficient, Log*P*) is an important parameter in selecting PET brain radioligand candidates (small organic molecules) for further evaluations.[31–34] The ability of a brain radioligand to penetrate the blood brain barrier (BBB) could be due, at least in part, to its lipophilicity, and thus we were interested in identifying an analog that was significantly lipophilic brain tracer. We calculated Log*P* values of [^{11}C]**5a–d** based on their retention times that were measured by C-18 HPLC method.[31–34] Briefly, the chromatographic capacity factors (k′) were measured by reversed-phase HPLC. $k' = (t_R - t_{R0})/t_{R0}$, where t_R is the compound's retention time, and t_{R0} is retention of an unretained substance determined by injection of an aqueous solution of potassium nitrite (t_{R0} = 1.84 min). Log*P* measurement is based on the linear relationship, which has been established between the Log k′ values of most compounds and their Log*P* values. Four compounds, benzyl alcohol (Log*P* 1.16), acetophenone (Log*P* 1.66), toluene (Log*P* 2.74) and naphthalene (Log*P* 3.37), were chosen as a 'standard' calibration mixture for the evaluation of the Log*P*'s of unknowns. Log*P*exp = partition coefficient calculated from k′ value and calibration curve established by these four compounds. Calibration equation: Log*P* = 2.222 Log k′ + 1.915. Retention times in the analytical HPLC system for [^{11}C]**5a–d** were 5.11, 4.17, 4.56 and 3.92 min, respectively. The calculation results showed the Log*P* values for [^{11}C]**5a–d** were 2.47, 2.14, 2.29 and 2.03, respectively. The results indicate [^{11}C]OMAR ([^{11}C]**5a**) is more lipophilic than [^{11}C]**5b**, [^{11}C]**5c**, or [^{11}C]**5d**; and new compound [^{11}C]**5d** is less lipophilic than [^{11}C]**5a**, [^{11}C]**5b**, or [^{11}C]**5c**. The calculated Log*P* values from ChemDraw Ultra 9.0 (ChemOffice 2005) for [^{11}C]**5a–d** are 5.14, 4.72, 4.85 and 4.43, respectively. Obviously, the measured Log*P* data sequence of [^{11}C]**5a–d** is consistent with the calculated Log*P* data sequence of [^{11}C]**5a–d**. In general, the Log*P* values (C18 HPLC) for the compounds expected to enter the brain readily are in a range of 1–3.[35] The data suggest all compounds [^{11}C]**5a–d** have suitable lipophilicity. Therefore, we assume the new tracer [^{11}C]**5d** has suitable ability to pass the BBB, and is a promising candidate as potential brain imaging agent.

Table 2
The binding affinity (*Ki*, nM) and lipophilicity (Log*P*). nd: not determined

Compound	*Ki* (nM)[a]	Log*P* calculated from ChemOffice	Log*P* measured by HPLC
5a	11 ± 7	5.14	2.47
5b	2.0, 3.7	4.72	2.14
5c	4.7	4.85	2.29
5d	nd	4.43	2.03

[a] Data cited from the literature.[13]

The experimental details and characterization data for compounds **2a**,**b–6a–d** and for the tracers [^{11}C]**5a–d** are given.[36]

In summary, a new high-yield synthetic route to PET CB1 radioligands [^{11}C]OMAR and its analogs has been developed. This new synthetic approach provided OMAR analogs and their corresponding desmethylated precursors in high overall chemical yields. An automated self-designed multi-purpose [^{11}C]-radiosynthesis module for the synthesis of [^{11}C]OMAR and its analogs has been built, featuring the measurement of specific activity by the on-the-fly technique. The radiosynthesis employed *O*-[^{11}C]methylation radiolabeling on oxygen position of the precursor. Radiolabeling procedures incorporated efficiently with the most commonly used [^{11}C]methylating agent, [^{11}C]CH_3OTf, produced by gas-phase production of [^{11}C]methyl bromide ([^{11}C]CH_3Br) from our laboratory. The target tracers were isolated and purified by a semi-preparative HPLC combined with SPE procedure in high radiochemical yields, short overall synthesis time, and high specific activity. These results facilitate the potential preclinical and clinical PET studies of [^{11}C]OMAR and its analog radioligands as brain CB1 imaging agents in animals and humans.

Acknowledgments

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36. (a) General. All commercial reagents and solvents were purchased from Sigma–Aldrich and Fisher Scientific, and used without further purification. [^{11}C]CH_3OTf was prepared according to a literature procedure.20 Melting points were determined on a MEL-TEMP II capillary tube apparatus and were uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded at 500 and 125 MHz, respectively, on a Bruker Avance II 500 MHz NMR spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shift data for the proton resonances were reported in parts per million (ppm, δ scale) relative to internal standard TMS (δ 0.0), and coupling constants (J) were reported in hertz (Hz). Liquid chromatography-mass spectra (LC–MS) analysis was performed on an Agilent system, consisting of an 1100 series HPLC connected to a diode array detector and a 1946D mass spectrometer configured for positive-ion/negative-ion electrospray ionization. The high resolution mass spectra (HRMS) were obtained using a Waters/Micromass LCT Classic spectrometer. Chromatographic solvent proportions are indicated as volume: volume ratio. Thin-layer chromatography (TLC) was run using Analtech silica gel GF uniplates (5×10 cm^2). Plates were visualized under UV light. Normal phase flash column chromatography was carried out on EM Science silica gel 60 (230–400 mesh) with a forced flow of the indicated solvent system in the proportions described below. All moisture- and air-sensitive reactions were performed under a positive pressure of nitrogen maintained by a direct line from a nitrogen source. Analytical HPLC was performed using a Prodigy (Phenomenex) 5 μm C-18 column, 4.6×250 mm; mobile phase 3:1:1 CH_3CN/MeOH/20 mM, pH 6.7 phosphate (buffer solution); flow rate 1.5 mL/min; and UV (254 nm) and γ-ray (PIN diode) flow detectors. Semi-preparative HPLC was performed using a Prodigy (Phenomenex) 5 μm C-18 column, 12 nm, 10×250 mm; 3:1:1 CH_3CN/MeOH/20 mM, pH 6.7 phosphate (buffer solution) mobile phase; 4.0 mL/min flow rate; UV (254 nm) and γ-ray (PIN diode) flow detectors. C18 Plus Sep-Pak cartridges were obtained from Waters Corporation (Milford, MA). Sterile Millex-FG 0.2 μm filter units were obtained from Millipore Corporation (Bedford, MA).; (b) Ethyl 2-chloro-2-(2-(2,4-dichlorophenyl)hydrazono)acetate (**2a**). A mixture of 2,4-dichloroaniline (**1a**) (7.29 g, 45 mmol) in 24% HCl (75 mL, 0.52 mol) and water (180 mL) was stirred for 1.5 h at RT. A solution of sodium nitrite (3.26 g, 47 mmol) in water (30 mL) was added dropwise to the reaction mixture at 0 °C, and the reaction was stirred for 45 min at 0 °C. Then the resulting solution was treated with NaOAc (3.69 g, 45 mmol) and subsequently with ethyl 2-chloro-acetoacetate (7.41 g, 45 mmol) in ethanol (450 mL) at 0 °C. The reaction temperature was keep at 0 °C for 1.5 h and RT for 1.5 h. The resulting precipitate was filtered, washed with cold water and dried to give **2a** (12.3 g, 92%), as a white solid, mp 88–90 °C. ^{1}H NMR ($CDCl_3$) : 1.41 (t, J = 7.0 Hz, 3H, CH_3), 4.39 (q, J = 7.0 Hz, 2H, CH_2), 7.25 (ddd, J = 0.5, 2.0, 7.5 Hz, 1H, Ph-H), 7.35 (d, J = 2.0 Hz, 1H, Ph-H), 7.55 (d, J = 8.5 Hz, 1H, Ph-H), 8.73 (s, 1H, NH). MS (ESI): 295 ([M+H]$^+$, 100%).; (c) Ethyl 2-(2-(2-bromophenyl)hydrazono)-2-chloroacetate (**2b**). Compound **2b** was prepared from 2-bromoaniline (**1b**) and ethyl 2-chloro-acetoacetate with the same procedure described for **2a** in 90% yield. White solid, mp 100–102 °C. ^{1}H NMR ($CDCl_3$) : 1.41 (t, J = 7.0 Hz, 3H, CH_3), 4.39 (q, J = 7.0 Hz, 2H, CH_2), 6.90–6.91 (m, 1H, Ph-H), 7.31–7.34 (m, 1H, Ph-H), 7.49 (dd, J = 1.5, 8.0 Hz, 1H, Ph-H), 7.60 (dd, J = 1.5, 8.0 Hz, 1H, Ph-H), 8.85 (s, 1H, NH). MS (ESI): 305 ([M+H]$^+$, 85%), 307 ([M+3H]$^+$, 100%).; (d) Ethyl 4-cyano-1-(2,4-dichlorophenyl)-5-(4-methoxyphenyl)-1*H*-pyrazole-3-carboxylate (**3a**). A mixture of 4-methoxybenzoylacetonitrile (1.75 g, 10.0 mmol), compound **2a** (3.31 g, 11.2 mmol), Et_3N (4.04 g, 40.0 mmol) in *t*-BuOH (120 mL) was stirred at RT for 22 h. The resulting precipitate was filtered, washed with solvent *t*-BuOH, dried in air, then washed with some water, and dried to give white solid product **3a** (2.13 g). The filtrate was evaporated and residue was extracted with EtOAc (3×60 mL), washed with brine, dried over Na_2SO_4, and concentrated. The crude product was purified by column chromatography on silica gel with eluent (1:9 EtOAc/hexanes) to afford white solid compound **3a** (0.49 g). Combined two parts of product gave **3a** (2.62 g, 63%) as a white solid, R_f = 0.30 (1:3 EtOAc/hexanes), mp 157–159 °C. ^{1}H NMR ($CDCl_3$) : 1.46 (t, J = 7.0 Hz, 3H, CH_3), 3.81 (s, 3H, OCH_3), 4.51 (q, J = 7.0 Hz, 2H, CH_2), 6.87 (dt, J = 2.0, 9.0 Hz, 2H, Ph-H), 7.24 (dt, J = 2.0, 9.0 Hz, 2H, Ph-H), 7.35–7.42 (m, 2H, Ph-H), 7.45 (d, J = 2.0 Hz, 1H, Ph-H). MS (ESI): 416 ([M+H]$^+$, 100%).; (e) Ethyl 1-(2-bromophenyl)-4-cyano-5-(4-methoxyphenyl)-1*H*-pyrazole-3-carboxylate (**3b**). Compound **3b** was prepared from compound **2b** and 4-methoxybenzoylacetonitrile with the same procedure described for **3a**, except the reaction time was 45 h, in 60% yield. White solid, R_f = 0.30 (1:3 EtOAc/hexanes), mp 165–167 °C. ^{1}H NMR ($CDCl_3$) : 1.46 (t, J = 7.0 Hz, 3H, CH_3), 3.79 (s, 3H, OCH_3), 4.51 (q, J = 7.0 Hz, 2H, CH_2), 6.85 (dt, J = 2.0, 9.0 Hz, 2H, Ph-H), 7.26 (dt, J = 2.0, 9.0 Hz, 2H, Ph-H), 7.34–7.37 (m, 1H, Ph-H), 7.41–7.45 (m, 2H, Ph-H), 7.61 (dd, J = 1.0, 8.0 Hz, 1H, Ph-H). MS (ESI): 426 ([M+H]$^+$, 100%).; (f) 4-Cyano-1-(2,4-dichlorophenyl)-5-(4-methoxyphenyl)-1*H*-pyrazole-3-carboxylic acid (**4a**). Method A (from **3a**): A mixture of compound **3a** (0.83 g, 2.0 mmol) and KOH (0.90 g) in methanol (60 mL) was stirred at RT for 24 h, and TLC was used to monitor the reaction. After the solvent was removed *in vacuo*, the residue was added a little bit of water, and residual aqueous solution was adjusted to pH 6 with HCl (1 N). The resulting precipitate was filtered, washed with cold water, and dried to obtain **4a** (0.74 g, 96%) as a white solid, R_f = 0.66 (1:3 MeOH/CH_2Cl_2), mp 280–282 °C. ^{1}H NMR (acetone-d_6) : 3.83 (s, 3H, OCH_3), 7.00 (dt, J = 2.5, 9.0 Hz, 2H, Ph-H), 7.37 (dt, J = 2.5, 9.0 Hz, 2H, Ph-H), 7.62 (dd, J = 2.5, 8.5 Hz, 1H, Ph-H), 7.69 (d, J = 2.5 Hz, 1H, Ph-H), 7.85 (d, J = 8.5 Hz, 1H, Ph-H). MS (ESI): 386 ([M−H]$^-$, 10%), 342 (100%); 388 ([M+H]$^+$, 80%). Method B (from **2a**): 25% NaOMe solution (21.6 g, 100 mmol) was added slowly to a mixture of 4-methoxybenzoylacetonitrile (1.40 g, 8.0 mmol), compound **2a** (2.65 g, 8.96 mmol) in methanol (100 mL) at RT, and the reaction mixture was stirred for 16 h. Additional 25% NaOMe (2.16 g, 10 mmol) was added to the reaction mixture. Then the reaction mixture was stirred at RT for another 16 h. After the solvent methanol was evaporated under reduced pressure, the residue was added a little bit of water, and residual aqueous solution was adjusted to pH 6 with HCl (1 N), extracted with EtOAc (3×80 mL), washed with brine, dried over $MgSO_4$, and concentrated. The crude product was purified by column chromatography on silica gel with eluent (1:15 MeOH/CH_2Cl_2) to afford **4a** (1.52 g, 49%) as a white solid. The analytical data were same with the data from Method A.; (g) 1-(2-Bromophenyl)-4-cyano-5-(4-methoxyphenyl)-1*H*-pyrazole-3-carboxylic acid (**4b**). Method A (from **3b**):

Compound **4b** was prepared from **3b** with the same procedure described for **4a** in 95% yield. Yellowish solid, R_f = 0.66 (1:3 MeOH/CH_2Cl_2), mp 297–299 °C. ^{1}H NMR (DMSO-d_6) : 3.74 (s, 3H, OCH_3), 6.95 (dt, *J* = 2.5, 9.0 Hz, 2H, Ph-H), 7.24 (dt, *J* = 2.5, 9.0 Hz, 2H, Ph-H), 7.44 (td, *J* = 1.5, 7.5 Hz, 1H, Ph-H), 7.52 (td, *J* = 1.5, 7.5 Hz, 1H, Ph-H), 7.71 (dd, *J* = 1.5, 4.0 Hz, 1H, Ph-H), 7.73 (dd, *J* = 1.5, 4.0 Hz, 1H, Ph-H). MS (ESI): 398 ([M+H]$^+$, 100%). Method B (from **2b**): Compound **4b** was prepared from **2b** with the same procedure described for **4a** in 56% yield. The analytical data were same with the data from Method A.; (h) General procedure for preparation of OMAR and its analogs (**5a**–**d**). DMF (2 drops) and oxalyl chloride (2.5 mL) were added to a stirring solution of compound **4a** (512 mg, 1.32 mmol) (or 1.32 mmol **4b**) in CH_2Cl_2 (40 mL). After bubbling had ceased (about 1–2 h), the reaction mixture was concentrated *in vacuo*. A solution of 1-aminopiperidine (145 mg, 1.45 mmol) (or 1.45 mmol 1-aminopyrrolidine) and DIEPA (0.43 g, 3.3 mmol) in CH_2Cl_2 (10 mL) was added to above freshly prepared acid chloride solution in CH_2Cl_2 (20 mL) at 0 °C and then stirred at RT for 2.5 h. The volatile compounds were removed *in vacuo* and residue was extracted with CH_2Cl_2 (3 × 60 mL), washed with brine, dried over Na_2SO_4, and concentrated. The crude residue was purified by column chromatography on silica gel with eluent (1:4 EtOAc/hexanes) to give **5** as a white solid in 53–68% yield. 4-Cyano-1-(2,4-dichlorophenyl)-5-(4-methoxyphenyl)-*N*-(piperidin-1-yl)-1*H*-pyrazole-3-carboxamide (**5a**). R_f = 0.30 (1:1 EtOAc/hexanes), mp 168–170 °C. ^{1}H NMR ($CDCl_3$) : 1.43 (br s, 2H, piperidine-H), 1.68–1.77 (m, 4H, piperidine-H), 2.90 (br s, 4H, piperidine-H), 3.80 (s, 3H, OCH_3), 6.86 (dt, *J* = 2.5, 9.0 Hz, 2H, Ph-H), 7.22 (dt, *J* = 2.5, 9.0 Hz, 2H, Ph-H), 7.36–7.40 (m, 2H, Ph-H), 7.49 (d, *J* = 1.5 Hz, 1H, Ph-H), 7.53 (s, 1H, CONH). MS (ESI): 468 ([M−H]$^-$, 100%). 4-Cyano-1-(2,4-dichlorophenyl)-5-(4-methoxyphenyl)-*N*-(pyrrolidin-1-yl)-1*H*-pyrazole-3-carboxamide (**5b**). R_f = 0.25 (1:1 EtOAc/hexanes), mp 125–127 °C. ^{1}H NMR ($CDCl_3$) : 1.89–1.92 (m, 4H, pyrrolidine-H), 3.05 (br s, 4H, pyrrolidine-H), 3.80 (s, 3H, OCH_3), 6.86 (dt, *J* = 2.5, 9.0 Hz, 2H, Ph-H), 7.22 (dt, *J* = 2.5, 9.0 Hz, 2H, Ph-H), 7.36–7.40 (m, 2H, Ph-H), 7.48 (dd, *J* = 0.5, 2.0 Hz, 1H, Ph-H), 7.54 (br s, 1H, CONH). MS (ESI): 456 ([M+H]$^+$, 60%). 1-(2-Bromophenyl)-4-cyano-5-(4-methoxyphenyl)-*N*-(piperidin-1-yl)-1*H*-pyrazole-3-carboxamide (**5c**). R_f = 0.29 (1:1 EtOAc/Hexanes), mp 254–256 °C. ^{1}H NMR ($CDCl_3$) : 1.43 (br s, 2H, piperidine-H), 1.73-1.77 (m, 4H, piperidine-H), 2.90 (br s, 4H, piperidine-H), 3.79 (s, 3H, OCH_3), 6.83 (dt, *J* = 2.5, 9.0 Hz, 2H, Ph-H), 7.24 (dt, *J* = 2.5, 9.0 Hz, 2H, Ph-H), 7.36–7.44 (m, 3H, Ph-H), 7.57 (br s, 1H, CONH), 7.65 (dd, *J* = 1.5, 8.0 Hz, 1H, Ph-H). MS (ESI): 480 ([M+H]$^+$, 80%), 482 ([M+3H]$^+$, 100%); 478 ([M−H]$^-$, 100%). 1-(2-Bromophenyl)-4-cyano-5-(4-methoxyphenyl)-*N*-(pyrrolidin-1-yl)-1*H*-pyrazole-3-carboxamide (**5d**). R_f = 0.23 (1:1 EtOAc/hexanes), mp 229–231 °C. ^{1}H NMR (DMSO-d_6) : 1.72 (br s, 4H, pyrrolidine-H), 2.89 (br s, 4H, pyrrolidine-H), 3.73 (s, 3H, OCH_3), 6.97 (dd, *J* = 2.0, 7.0 Hz, 2H, Ph-H), 7.28 (dd, *J* = 2.0, 7.0 Hz, 2H, Ph-H), 7.46 (td, *J* = 1.5, 8.0 Hz, 1H, Ph-H), 7.54 (td, *J* = 1.5, 8.0 Hz, 1H, Ph-H), 7.73 (dd, *J* = 1.5, 8.0 Hz, 1H, Ph-H), 7.84 (dd, *J* = 1.5, 8.0 Hz, 1H, Ph-H), 9.63 (s, 1H, CONH). ^{13}C NMR (DMSO-d_6) : 21.91, 53.34, 55.30, 92.11, 113.18, 114.40, 117.37, 121.22, 128.83, 130.50, 130.88, 132.44, 133.22, 137.09, 147.34, 151.35, 157.02, 160.75. MS (ESI): 466 ([M+H]$^+$, 62%). HRMS (ESI) calcd for $C_{22}H_{21}N_5O_2Br$ 466.0879 ([M+H]$^+$); found 466.0863.; (i) General procedure for preparation of the desmethylated precursors of OMAR and its analogs (**6a**–**d**). Lithium bromide (0.86 g, 10 mmol) was added to a solution of compound **5** (0.5 mmol) in DMF (10 mL) under nitrogen, then the reaction mixture was refluxed for 44 h. The reaction mixture was cooled down to RT, added some water, extracted with EtOAc (3 × 80 mL), washed with brine, and dried over $MgSO_4$. The organic layer was evaporated under reduced pressure to give crude product, which was purified by column chromatography on silica gel with eluent (2:98 MeOH/CH_2Cl_2) to obtain **6** as a white solid in 87–95% yield, R_f = 0.21–0.28 (4:96 MeOH/CH_2Cl_2). 4-Cyano-1-(2,4-dichlorophenyl)-5-(4-hydroxyphenyl)-*N*-(piperidin-1-yl)-1*H*-pyrazole-3-carboxamide (**6a**). Mp 159–161 °C. ^{1}H NMR (acetone-d_6) : 1.42 (br s, 2H, piperidine-H), 1.64–1.68 (m, 4H, piperidine-H), 2.93–2.94 (m, 4H, piperidine-H), 6.89 (dd, *J* = 2.0, 8.0 Hz, 2H, Ph-H), 7.27 (dd, *J* = 2.0, 8.0 Hz, 2H, Ph-H), 7.63 (dd, *J* = 2.0, 8.5 Hz, 1H, Ph-H), 7.71 (d, *J* = 2.5Hz, 1H, Ph-H), 7.82 (d, *J* = 8.5 Hz, 1H, Ph-H), 8.59 (1H, OH), 9.08 (s, 1H, CONH). MS (ESI): 456 ([M+H]$^+$, 53%). 4-Cyano-1-(2,4-dichlorophenyl)-5-(4-hydroxyphenyl)-*N*-(pyrrolidin-1-yl)-1*H*-pyrazole-3-carboxamide (**6b**). Mp 279 °C (decomposed). ^{1}H NMR (DMSO-d_6) : 1.74 (br s, 4H, pyrrolidine-H), 2.90 (br s, 4H, pyrrolidine-H), 6.80 (dt, *J* = 2.5, 8.5 Hz, 2H, Ph-H), 7.16 (dt, *J* = 2.5, 8.5 Hz, 2H, Ph-H), 7.65 (dd, *J* = 2.0, 8.5 Hz, 1H, Ph-H), 7.85(d, *J* = 2.0 Hz, 1H, Ph-H), 7.88 (d, *J* = 8.5 Hz, 1H, Ph-H), 9.65 (s, 1H, OH), 10.12 (s, 1H, CONH). MS (ESI): 442 ([M+H]$^+$, 50%). 1-(2-Bromophenyl)-4-cyano-5-(4-hydroxyphenyl)-*N*-(piperidin-1-yl)-1*H*-pyrazole-3-carboxamide (**6c**). Mp 239-241 °C. ^{1}H NMR (acetone-d_6) : 1.41–1.43 (m, 2H, piperidine-H), 1.62–1.68 (m, 4H, piperidine-H), 2.92 (t, *J* = 5.5 Hz, 4H, piperidine-H), 6.87 (dt, *J* = 2.5, 9.0 Hz, 2H, Ph-H), 7.27 (dt, *J* = 2.5, 9.0 Hz, 2H, Ph-H), 7.52 (td, *J* = 1.5, 7.5 Hz, 1H, Ph-H), 7.60 (td, *J* = 1.5, 7.5 Hz, 1H, Ph-H), 7.76 (dd, *J* = 1.5, 3.5 Hz, 1H, Ph-H), 7.77 (dd, *J* = 1.5, 3.5 Hz, 1H, Ph-H), 8.60 (s, 1H, OH), 9.05 (br s, 1H, CONH). MS (ESI): 466 ([M+H]$^+$, 100%). 1-(2-Bromophenyl)-4-cyano-5-(4-hydroxyphenyl)-*N*-(pyrrolidin-1-yl)-1*H*-pyrazole-3-carboxamide (**6d**). Mp 161–163 °C. ^{1}H NMR (acetone-d_6) : 1.83–1.84 (m, 4H, pyrrolidine-H), 3.05 (br s, 4H, pyrrolidine-H), 6.87 (dd, *J* = 2.0, 7.0 Hz, 2H, Ph-H), 7.27 (dd, *J* = 2.0, 7.0 Hz, 2H, Ph-H), 7.53 (td, *J* = 1.5, 8.0 Hz, 1H, Ph-H), 7.61 (td, *J* = 1.5, 7.5 Hz, 1H, Ph-H), 7.76 (t, *J* = 1.5 Hz, 1H, Ph-H), 7.77 (t, *J* = 1.5 Hz, 1H, Ph-H), 8.59 (s, 1H, OH), 9.00 (s, 1H, CONH). ^{13}C NMR (DMSO-d_6) : 23.15, 54.52, 54.59, 93.40, 113.68, 116.61, 117.84, 122.34, 129.71, 131.56, 131.70, 133.00, 134.41, 138.92, 148.42, 152.84, 158.21. MS (ESI): 452 ([M+H]$^+$, 80%). HRMS (ESI) calcd for $C_{21}H_{19}N_5O_2Br$ 452.0722 ([M+H]$^+$); found 452.0724.; (j) General procedure for preparation of [^{11}C]OMAR and its analog radioligands ([^{11}C]**5a**–**d**). [^{11}C]CO_2 was produced by the ^{14}N(p,)^{11}C nuclear reaction in the small volume (9.5 cm^3) aluminum gas target provided with the Siemens RDS-111 Eclipse cyclotron. The target gas consisted of 1% oxygen in nitrogen purchased as a specialty gas from Praxair, Indianapolis, IN. Typical irradiations used for the development were 50 A beam current and 15 min on target. The production run produced approximately 25.9 GBq of [^{11}C]CO_2 at EOB. In a small reaction vial (5 mL), the precursor **6** (0.3–0.5 mg) was dissolved in CH_3CN (400 L). To this solution was added 2 N NaOH (2 μL). No carrier-added (high specific activity) [^{11}C]CH_3OTf that was produced by the gas-phase production method20 from [^{11}C]CO_2 through [^{11}C]CH_4 and [^{11}C]CH_3Br with silver triflate (AgOTf) column was passed into the reaction vial at RT, until radioactivity reached a maximum (~2 min), and then the reaction vial was isolated and heated at 80 °C for 3 min. The contents of the reaction vial were diluted with $NaHCO_3$ (0.1 M, 1 mL), and injected onto the semi-preparative HPLC column with 3 mL injection loop for purification. The product fraction was collected in a recovery vial containing 30 mL water. The diluted tracer solution was then passed through a C-18 Sep-Pak Plus cartridge, and washed with water (5 mL × 4). The cartridge was eluted with EtOH (1 mL × 2), followed by 10 mL saline, to release [^{11}C]**5**. The eluted product was then sterile-filtered through a Millex-FG 0.2 m membrane into a sterile vial. Total radioactivity was assayed and total volume was noted for tracer dose dispensing. Retention times in the semi-preparative HPLC system were: t_R **6a** = 6.53 min, t_R **5a** = 9.81 min, t_R [^{11}C]**5a** = 9.81 min; t_R **6b** = 5.78 min, t_R **5b** = 8.43 min, t_R [^{11}C]**5b** = 8.43 min; t_R **6c** = 6.02 min, t_R **5c** = 8.78 min, t_R [^{11}C]**5c** = 8.78 min; and t_R **6d** = 5.13 min, t_R **5d** = 7.83 min, t_R [^{11}C]**5d** = 7.83 min. Retention times in the analytical HPLC system were: t_R **6a** = 3.12 min, t_R **5a** = 5.11 min, t_R [^{11}C]**5a** = 5.11 min; t_R **6b** = 2.83 min, t_R **5b** = 4.17 min, t_R [^{11}C]**5b** = 4.17 min; t_R **6c** = 2.95 min, t_R **5c** = 4.56 min, t_R [^{11}C]**5c** = 4.56 min; and t_R **6d** = 2.45 min, t_R **5d** = 3.92 min, t_R [^{11}C]**5d** = 3.92 min. The decay corrected radiochemical yields of [^{11}C]**5a**–**d** from [^{11}C]CO_2 were 50–65%.