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[^{11}C]GSK2126458 and [^{18}F]GSK2126458, the first radiosynthesis of new potential PET agents for imaging of PI3K and mTOR in cancers

Min Wang [a], Mingzhang Gao [a], Kathy D. Miller [b], George W. Sledge [b], Qi-Huang Zheng [a,*]

[a] Department of Radiology and Imaging Sciences, Indiana University School of Medicine, 1345 West 16th Street, Room 202, Indianapolis, IN 46202, USA
[b] Department of Medicine, Indiana University School of Medicine, Indianapolis, IN 46202, USA

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ABSTRACT

GSK2126458 is a highly potent inhibitor of phosphoinositide 3-kinase (PI3K) and mammalian target of rapamycin (mTOR) with low picomolar to subnanomolar activity. [^{11}C]GSK2126458 and [^{18}F]GSK212 6458, new potential PET agents for imaging of PI3K and mTOR in cancer, were first designed and synthesized in 40–50% and 20–30% decay corrected radiochemical yield, and 370–740 and 37–222 GBq/μmol specific activity at end of bombardment (EOB), respectively.

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The phosphoinositide 3-kinase (PI3K) is a critical regulator of cell growth and transformation.[1] The mammalian target of rapamycin (mTOR) is a key component of PI3K pathway and is also a central regulator of cell growth.[2] Protein kinase B (PKB), also known as Akt, is a serine/threonine protein kinase.[3] The PI3K/Akt/mTOR pathway is an intracellular signaling pathway that is involved in several cell functions including growth, proliferation, apoptosis and autophagy, and is among the most commonly activated pathways in human cancers.[4,5] PI3K has emerged as an attractive target for cancer therapeutics, and several PI3K inhibitors are currently under evaluation in human clinical trials, such as GSK2126458 (GlaxoSmithKline), BEZ235 (Novartis), GDC-0941 (Genentech), PX-866 (ProlX), and XL765 (Exelixis).[1] Among these PI3K inhibitors, GSK2126458(2,4-difluoro-*N*-(2-methoxy-5-(4-(pyridazin-4-yl)quinolin-6-yl)pyridin-3-yl)benzenesulfonamide) is a highly potent inhibitor of the PI3K/Akt/mTOR signaling pathway with low picomolar to subnanomolar biological activity against PI3K, mTOR and Akt, K_i values: 0.019 nM (PI3Kα), 0.13 nM (PI3Kβ), 0.024 nM (PI3Kδ), 0.06 nM (PI3Kγ), 0.18 nM (mTORC1) and 0.3 nM (mTORC2); and IC_{50} values: 0.04 nM (PI3Kα), 0.41 nM (pAkt-S473/T47D) and 0.18 nM (pAkt-S473/BT474), originally developed and recently reported by GlaxoSmithKline.[1] GSK2126458 acting on more than one target has resulted in a better biological response and in enhanced therapeutic potential, and this multiple-target inhibitor results of great interest as potential antitumor agent.[5] PI3K/Akt/mTOR signaling pathway has become an attractive target for cancer imaging, however, no specific imaging agents have been developed so far.[6,7] Carbon-11 and fluorine-18 labeled GSK2126458 compounds may serve as new probes for the biomedical imaging technique positron emission tomography (PET), and enable non-invasive monitoring of PI3K/Akt/mTOR signaling pathway in cancers, since most PET imaging agents currently used for evaluation of oncologic drug treatment are 2-[^{18}F]fluoro-2-deoxyglucose ([^{18}F]FDG), 3′-[^{18}F]fluoro-L-thymidine ([^{18}F]FLT), and [^{18}F]fluoromisonidazole ([^{18}F]FMISO).[8] To radiolabel therapeutic agents as diagnostic agents for imaging of PI3K/Akt/mTOR signaling pathway and monitoring of therapeutic efficacy of PI3K/Akt/mTOR inhibitors, we have designed and synthesized [^{11}C]GSK2126458 {2,4-difluoro-*N*-(2-[^{11}C]methoxy-5-(4-(pyridazin-4-yl)quinolin-6-yl)pyridin-3-yl)benzenesulfonamide} and [^{18}F]GSK2126458 {2-[^{18}F]fluoro-4-fluoro-*N*-(2-methoxy-5-(4-(pyridazin-4-yl)quinolin-6-yl)pyridin-3-yl)benzenesulfonamide and 2-fluoro-4-[^{18}F]fluoro-*N*-(2-methoxy-5-(4-(pyridazin-4-yl)quinolin-6-yl)pyridin-3-yl)benzenesulfonamide} as new potential PET agents, for the first time. Due to the important role of PI3K/Akt/mTOR signaling pathway in cancer progression, many pharmaceutical companies and academic laboratories are actively developing its inhibitors and many of these such as LY294002, wortmannin, or rapamycin analogues are already used in later clinical trials (II/III) through mono-targeted therapy or in combination with other therapy for cancer treatment. Although GSK2126458 is a relatively new developed PI3K/Akt/mTOR inhibitor and being evaluated in phase I clinical trial through multiple-targeted

* Corresponding author. Tel.: +1 317 278 4671.
E-mail address: qzheng@iupui.edu (Q.-H. Zheng).

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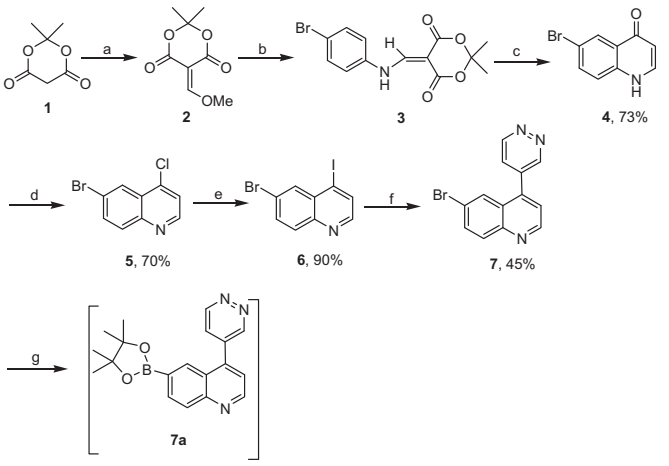
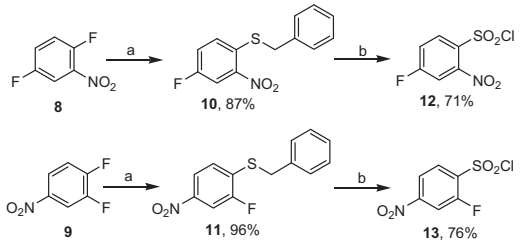
therapy, it displays superior PI3K/Akt/mTOR biological activities to other more established or matured development inhibitors.[1] Therefore, we selected GSK2126458 as based model compound for labeling, without changing the GSK2126458 structure. These radiolabeled GSK2126458 compounds as potential PET probes will provide great help to accelerate GSK2126458 clinical development and will monitor the PI3K/Akt/mTOR pathway and understanding the pharmacology of GSK2126458 in vivo. On the other hand, these PET probes will be ease getting approval as IND (Investigational New Drug) from FDA (Food and Drug Administration), and will help to select right patient for PI3K/Akt/mTOR targeted therapy if GSK2126458 continues success in clinical trial in the near future.

Procedures used by Knight et al. for the synthesis of GSK2126458 (**22**)[1] were adapted to synthesize its nitro precursors 2-nitro-GSK2126458 (**23**) and 4-nitro-GSK2126458 (**24**) for fluorine-18 labeling, and desmethyl-GSK2126458 (**25**) for carbon-11 labeling. The synthetic strategy included an in situ borylation and standard palladium-catalyzed cross-coupling reaction.[1] In particular, the use of 6-bromo-4-(pyridazin-4-yl)quinoline (**7**) as the precursor for the corresponding pinacol boronic ester **7a** via coupling with bis(pinacolato)diboron was pursued, as the pinacol boronic ester **7a** would be suitably poised to be coupled with aryl and heteroaryl halides. Thus, the key intermediate **7** was synthesized according to the procedures outlined in Scheme 1. Methoxymethylene Meldrum's acid (**2**) in situ was formed by treatment Meldrum's acid (**1**) with trimethyl orthoformate, which was condensed with 4-bromoaniline to afford enamine intermediate **3**. Thermal cyclization of **3** in Ph_2O was accomplished by spontaneous elimination of CO_2 and propanone to give quinoline-4-one derivative **4** in overall 73% yield.[9–12] Compound **4** was converted to 6-bromo-4-chloroquinoline (**5**) by treatment with $POCl_3$ using DMF as catalyst in 70% yield. The 4-chloro group of **5** was substituted by iodo via the formation of the hydrochloride salt of **5**, followed by treatment with NaI in propionitrile to afford 6-bromo-4-iodoquinoline (**6**) in 90% yield.[13] Palladium-catalyzed cross-coupling reaction between **6** and 4-(tributylstannyl)pyridazine in dioxane furnished the desired compound **7** in 45% yield.

Syntheses of synthons fluoronitrobenzenesulfonyl chlorides **12** and **13** were carried out in Scheme 2. Selective nucleophilic displacement of the fluorine at *ortho*- and *para*-position activated by the nitro group in difluoronitrobenzenes **8** and **9** was achieved via an equimolar amount of phenylmethanethiol in the presence of



Scheme 1. Synthesis of key intermediate **7**. Reagents and conditions: (a) trimethyl orthoformate, reflux; (b) 4-bromoaniline, trimethyl orthoformate, reflux; (c) Ph_2O, 250 °C; (d) $POCl_3$, DMF (cat.), reflux; (e) 2 M HCl in Et_2O, THF, room temperature (rt); NaI, propiontrile, reflux; (f) 4-(tributylstannanyl)pyridazine, $PdCl_2(dppf)_2$-CH_2Cl_2, dioxane, reflux; (g) bis(pinacolato)diboron, $PdCl_2(dppf)_2$-CH_2Cl_2, KOAc, dioxane, reflux.



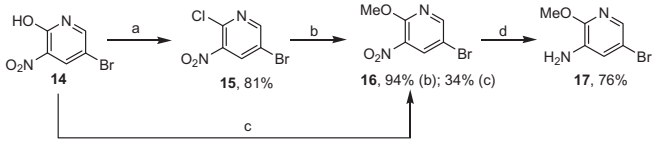
Scheme 2. Synthesis of synthons **12** and **13**. Reagents and conditions: (a) phenylmethanethiol, K_2CO_3, DMF, 0 °C to rt; (b) 1,3-dichloro-5,5-dimethylhydantoin, CH_3CN–HOAc–H_2O, 0 °C.

K_2CO_3 in DMF to form fluoronitrophenylbenzylthioethers **10** and **11** in 87% and 96% yield, respectively.[14] Based on a recent report in which a simple and highly effective oxidative chlorination protocol for the preparation of arenesulfonyl chlorides was described,[15] 1,3-dichloro-5,5-dimethylhydantoin as oxidative chlorination agent was used to convert **10** and **11** to their corresponding sulfonyl chlorides **12** and **13** in 71% and 76% yield, respectively.

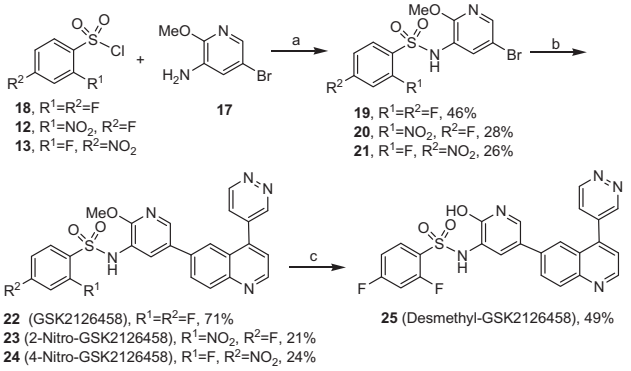
Scheme 3 describes the synthesis of another synthon 5-bromo-2-methoxy-3-pyridinamine (**17**). 5-Bromo-2-methoxy-3-nitropyridine (**16**) from 5-bromo-2-hydroxy-3-nitropyridine (**14**) was accomplished by two synthetic routes. Treatment of **14** with $POCl_3$ using DMF as catalyst gave 5-bromo-2-chloro-3-nitropyridine **15** in 81% yield, and subsequent reaction with NaOMe in MeOH afforded **16** in 94% yield. Compound **16** could also be achieved by direct methylation of **14** with CH_3I in the presence of Ag_2CO_3 in CH_3Cl in 34% yield.[16] The reduction of **16** was carried out with $SnCl_2{\cdot}2H_2O$ in EtOAc to give **17** in 76% yield.

Synthesis of GSK2126458, 2-nitro-GSK2126458, 4-nitro-GSK2126458 and desmethyl-GSK2126458 is shown in Scheme 4. Coupling benzenesulfonyl chlorides **18**, **12** and **13** with **17** in pyridine provided the corresponding aryl bromides derivatives **19**, **20** and **21** in 46%, 28% and 26% yield, respectively. The palladium-catalyzed cross-coupling reaction of bis(pinacolato)diboron with aryl bromide **7** gave arylboronic ester **7a** in situ. The reaction was catalyzed by $PdCl_2(dppf)$-CH_2Cl_2 in the presence of KOAc in dioxane. Arylboronic ester **7a** was coupled with aryl bromides derivatives **19**, **20** and **21** to yield the desired standard **22**, nitro precursors **23** and **24** in 71%, 21% and 24% yield, respectively. Direct demethylation was performed by treatment of GSK2126458 **22** with trimethylsilyl iodide in CH_3CN to afford the desmethylated precursor **25** in 49% yield.

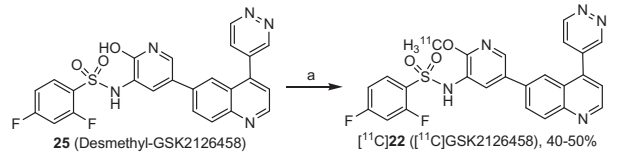
Synthesis of the target tracer [^{11}C]GSK2126458 ([^{11}C]**22**) is indicated in Scheme 5. Desmethyl-GSK2126458 precursor **25** was labeled by [^{11}C]methyl triflate ([^{11}C]CH_3OTf)[17,18] through O-[^{11}C]methylation[19] at 80 °C under basic condition (2 N NaOH) and isolated by a semi-preparative high performance liquid chromatography (HPLC) method (C-18 column) and a solid-phase extraction (SPE) method (C-18 Plus Sep-Pak cartridge) (a second purification or isolation process)[20] to produce the corresponding pure radiolabeled compound [^{11}C]**22** in 40–50% radiochemical yield, decay corrected to end of bombardment (EOB), based on



Scheme 3. Synthesis of synthon **17**. Reagents and conditions: (a) $POCl_3$, DMF (cat.), reflux; (b) NaOMe, MeOH, 0 °C to rt; (c) MeI, Ag_2CO_3, CH_3Cl; (d) $SnCl_2{\cdot}2H_2O$, EtOAc, reflux.



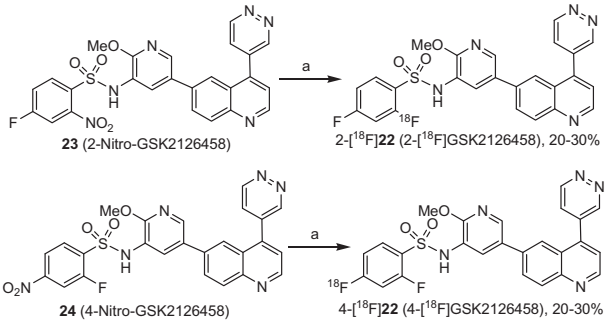
Scheme 4. Synthesis of standard GSK2126458 **22** and precursors 2-nitro-GSK2126458 **23**, 4-nitro-GSK2126458 **24**, and desmethyl-GSK2126458 **25**. Reagents and conditions: (a) pyridine, 0 °C to rt; (b) **7**, bis(pinacolato)diboron, $PdCl_2(dppf)_2$-CH_2Cl_2, KOAc, dioxane, reflux; $PdCl_2(dppf)_2$-CH_2Cl_2, 2 M Na_2CO_3, reflux; (c) iodotrimethylsilane, CH_3CN, reflux.



Scheme 5. Synthesis of [^{11}C]GSK2126458. Reagents and conditions: (a) [^{11}C]CH_3OTf, 2 N NaOH, CH_3CN, 80 °C.

[^{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),[21] and thus, the radiochemical yield of [^{11}C]GSK2126458 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]**22** from its heteroaryl hydroxyl precursor.[20,22] The radiosynthesis was performed in a home-built automated multi-purpose [^{11}C]-radiosynthesis module, allowing measurement of specific radioactivity during synthesis.[23,24] The overall synthesis, purification and formulation time was 30–40 min from EOB. The specific radioactivity was in a range of 370–740 GBq/μmol at EOB. Chemical purity and radiochemical purity were determined by analytical HPLC.[25] The chemical purity of the precursor desmethyl-GSK2126458 and reference standard GSK2126458 was >96%. The radiochemical purity of the target tracer [^{11}C]GSK2126458 was >99% determined by radio-HPLC through γ-ray (PIN diode) flow detector, and the chemical purity of [^{11}C]GSK2126458 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. Initial HPLC purification was employed to separate the labeled product from its un-reacted excess precursor and other labeled by-products. The second SPE purification with Sep-Pak[20,25] was employed, instead of rotary evaporator, to remove potential impurities from the HPLC co-elution with the precursor and from the residual solvents including HPLC mobile phase solvents and module set-up cleaning solvents. Rotary evaporation was unable to perform in this regard. Moreover, it could result in the decomposition of the labeled product such as desmethylation during the heating. The chemical purity of the [^{11}C]GSK2126458 tracer solution with Sep-Pak purification was increased higher 10–20% than that without Sep-Pak purification.[20,26]

Synthesis of the target tracers 2-[^{18}F]GSK2126458 (2-[^{18}F]**22**) and 4-[^{18}F]GSK2126458 (4-[^{18}F]**22**) is outlined in Scheme 6. 2-Nitro-GSK2126458 (**23**) or 4-nitro-GSK2126458 (**24**) precursor was



Scheme 6. Synthesis of [^{18}F]GSK2126458. Reagents and conditions: (a) K[^{18}F]F/Kryptofix 2.2.2, DMSO, 140 °C.

labeled with K[^{18}F]F/Kryptofix 2.2.2 through nucleophilic substitution and isolated by a semi-preparative HPLC method with C-18 column and a SPE method with a C-18 Plus Sep-Pak cartridge (a second purification or isolation process)[20,26] to produce the corresponding pure radiolabeled compound 2-[^{18}F]**22** or 4-[^{18}F]**22** in 20–30% radiochemical yield, decay-corrected to EOB, based on H[^{18}F]F. Likewise, 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 labeled product 2-[^{18}F]GSK2126458 or 4-[^{18}F]GSK2126458 from its corresponding 2-nitro or 4-nitro precursor.[20,22] The radiosynthesis was performed using a self-designed automated multi-purpose [^{18}F]-radiosynthesis module.[20,26] The overall synthesis, purification and formulation time was 50–60 min from EOB. The specific radioactivity was 37–222 GBq/μmol at EOB. No-carrier-added [^{18}F]fluoride ion in [^{18}O]water was trapped without a QMA cartridge. This way[20,26,27] significantly increased the specific activity of the prepared F-18 labeled product. As indicated in the literature,[27] when the cyclotron-produced [^{18}F]fluoride ion was dried without the use of a cartridge, but through cycles of evaporation with added acetonitrile, the specific radioactivity of the prepared 2-[^{18}F]GSK2126458 and 4-[^{18}F]GSK2126458 was substantially higher, and was similar to that we achieved in the radiosynthesis of [^{18}F]fallypride and [^{18}F]PBR06.[20,26] The reason was that there was a low-level contamination of QMA anionic resins with fluoride ion.[27] The amounts of 2-nitro or 4-nitro precursor used were ~1 mg. A large amount of precursor would increase the radiochemical yield of 2-[^{18}F]GSK2126458 or 4-[^{18}F]GSK2126458, but decrease the chemical purity of the 2-[^{18}F]**22** or 4-[^{18}F]**22** tracer solution due to precursor contamination. To our F-18 labeling experiences on [^{18}F]fallypride and [^{18}F]PBR06,[20,26] although the HPLC systems we employed have shown good separation from precursor and products, there always was a co-elution of the F-18 labeled product with its corresponding precursor from the HPLC column. 2-[^{18}F]GSK-2126458 and 4-[^{18}F]GSK2126458 were also in the same case. In addition, a large amount of precursor would also decrease the specific activity of final labeled product due to potential F-18/F-19 exchange during the radiolabeling. The reaction solvent and temperature were either CH_3CN/120 °C or DMSO/140 °C. Radiolabeling procedure with DMSO at 140 °C resulted in higher radiochemical yield.[20,26,28] Chemical purity and radiochemical purity were determined by analytical HPLC.[25] The chemical purity of 2-nitro-GSK2126458 (**23**) and 4-nitro-GSK2126458 precursors and reference standard GSK2126458 was >96%. The radiochemical purity of the target tracers 2-[^{18}F]GSK2126458 and 4-[^{18}F]GSK2126458 was >99%, and the chemical purity of 2-[^{18}F]GSK2126458 and 4-[^{18}F]GSK2126458 was >90% determined by HPLC methods. Most impurity of 2-[^{18}F]GSK2126458 and 4-[^{18}F]GSK2126458 was their corresponding precursor contamination from the HPLC co-elution. Likewise, a C-18 Plus Sep-Pak cartridge was used to significantly improve the chemical purity of the tracer solution as aforemen-

tioned.[20,26] The chemical purity of the 2-[^{18}F]GSK2126458 or 4-[^{18}F]GSK2126458 tracer solution with Sep-Pak purification was increased higher 10–20% than that without Sep-Pak purification. GSK2126458 was ^{18}F-labeled at 2- and 4-positions to be 2-[^{18}F]GSK2126458 and 4-[^{18}F]GSK2126458. No significantly different results were identified. This could be that both *ortho*-nitro precursor and *para*-nitro precursor have similar reactivity for F-18 labeling.

The synthetic information of GSK2126458 was limited in the literature.[1] Thus, the experimental details and characterization data for compounds **4–7**, **10–13**, **15–17**, and **19–25**, and for the tracers [^{11}C]**22**, 2-[^{18}F]**22** and 4-[^{18}F]**22** are given.[29]

In summary, [^{11}C]GSK2126458 and [^{18}F]GSK2126458 were first designed and synthesized as new potential PET agents for imaging of PI3K and mTOR in cancers. New desmethyl-GSK2126458 precursor (for C-11 labeling) and 2-nitro-GSK2126458 and 4-nitro-GSK2126458 precursors (for F-18 labeling) have been designed and synthesized for the first time. Desmethyl-GSK2126458 was labeled with [^{11}C]CH_3OTf, and isolated by semi-preparative HPLC combined with SPE purification to provide [^{11}C]GSK2126458, a carbon-11 labeled form of GSK2126458, in high radiochemical yield with excellent specific activity and shorter reaction times. 2-Nitro-GSK2126458 and 4-nitro-GSK2126458 were labeled with K[^{18}F]F/Kryptofix 2.2.2 through nucleophilic substitution, and isolated by semi-preparative HPLC combined with SPE purification to produce 2-[^{18}F]GSK2126458 and 4-[^{18}F]GSK2126458, fluorine-18 labeled forms of GSK2126458, in moderate radiochemical yield, high chemical purity and specific activity. Automated self-designed multi-purpose [^{11}C]- and [^{18}F]-radiosynthesis modules for the synthesis of [^{11}C]GSK2126458 and [^{18}F]GSK2126458 have been built, featuring the measurement of specific activity by the on-the-fly technique. New and improved results in the synthetic methodology, radiolabeling, preparative separation and analytical details for GSK2126458, desmethyl-GSK2126458, 2-nitro-GSK2126458 and 4-nitro-GSK2126458, [^{11}C]GSK2126458 and [^{18}F]GSK2126458 have been presented. These methods are efficient and convenient. It is anticipated that the approaches for the design, synthesis and automation of new tracer and radiolabeling precursors, and improvements to increase radiochemical yield, chemical purity and specific activity of the tracers described here can be applied with advantage to the synthesis of other ^{11}C- and ^{18}F-radiotracers for PET imaging. These chemistry results warrant future preclinical and clinical PET studies of [^{11}C]GSK2126458 and [^{18}F]GSK2126458 in animals and humans to image cancer. This work will provide useful information for other investigators who will perform in vitro and in vivo biological evaluations of these [^{11}C] and [^{18}F] tracers and develop new PET tracers for imaging the PI3K and mTOR in vivo.

Acknowledgments

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29. (a) 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.[18] Melting points were determined on a MEL-TEMP II capillary tube apparatus and were uncorrected. ^{1}H NMR spectra were recorded on Bruker Avance II 500 MHz NMR spectrometers 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). The high resolution mass spectra (HRMS) were obtained using a Thermo Electron Corporation MAT 95XP-Trap 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. Preparative TLC was run using Analtech silica gel UV 254 plates (20×20 cm^2). 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/or 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; 3:1:3 CH_3CN/MeOH/20 mM, pH 6.7 phosphate (buffer solution) mobile phase; 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, 10×250 mm C-18 column; 3:1:3 CH_3CN/MeOH/20 mM, pH 6.7 phosphate (buffer solution) mobile phase; 5.0 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) 6-Bromoquinolin-4(1*H*)-one (**4**). A solution of Meldrum's acid (**1**) (32.4 g, 225.0 mmol) in trimethyl orthoformate (250 mL) was stirred and heated at reflux for 3 h under N_2 to give **2**. The solution was allowed to cool to ~50 °C, and 4-bromoaniline (25.8 g, 150.0 mmol) in trimethyl orthoformate (80 mL) was added dropwise. The reaction mixture was heated at reflux for 2 h. After removal of the solvent in vacuo, the residue was diluted with hexanes, filtered, and the solid was washed with hexanes and dried to give Meldrum's acid derivative **3** as a yellow solid. Compound **3** was added slowly in small portions (~1.0 g each) to preheated (245 °C) Ph_2O (500 mL). **Caution not to perform this addition too rapidly must be taken as gas violently evolves!** The reaction mixture was stirred and heated at 250 °C for 15 min, then allowed to cool to room temperature (rt) and diluted with hexanes, filtered. The solid was washed with hexanes, then 30% Et_2O/hexanes. The crude product was purified

by silica gel column chromatography (16:1–10:1 CH_2Cl_2/MeOH) to afford **4** (24.6 g, 73%) as a pale brown solid, mp 282–284 °C (lit[30] 282–284 °C). ^{1}H NMR (DMSO-d_6) δ 11.93 (br s, 1H, NH), 8.17 (d, J = 2.0 Hz, 1H, Ar-H), 7.96 (dd, J = 7.5, 6.0 Hz, 1H), 7.79 (dd, J = 9.0, 2.5 Hz, 1H, Ar-H), 7.53 (d, J = 8.5 Hz, 1H), 6.08 (d, J = 2.5 Hz, 1H, Ar-H).

(c) 6-Bromo-4-chloroquinoline (**5**). A mixture of **4** (17.0 g, 131.5 mmol), $POCl_3$ (180 mL) and anhydrous DMF (18 mL) was stirred and heated at reflux for 2 h. After removal of $POCl_3$, the residue was poured into ice water and extracted with EtOAc. The combined organic layers were washed with saturated aqueous $NaHCO_3$, brine, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by silica gel column chromatography (4:1 hexanes/EtOAc) to afford **5** (12.8 g, 70%) as a white solid, mp 111–112 °C (lit[31] 111–112 °C). ^{1}H NMR ($CDCl_3$) δ 8.79 (d, J = 5.0 Hz, 1H, Ar-H), 8.40 (d, J = 2.5 Hz, 1H, Ar-H), 8.00 (d, J = 9.0 Hz, 1H, Ar-H), 7.84 (dd, J = 9.0, 2.0 Hz, 1H, Ar-H), 7.52 (d, J = 5.0 Hz, 1H, Ar-H).

(d) 6-Bromo-4-iodoquinoline (**6**). To a solution of **5** (11.0 g, 45.6 mmol) in anhydrous THF (150 mL) was added 2 M HCl in Et_2O (29 mL, 58.0 mmol) dropwise. After stirring at rt for 30 min, the solvent was removed in vacuo and the solid was dried to afford 6-bromo-4-chloroquinoline hydrochloride as an off-white solid. The hydrochloride salt and anhydrous NaI (34.2 g, 228.3 mmol) were suspended in propionitrile (300 mL). After the reaction mixture was stirred and heated at reflux for 96 h, it was cooled to rt. 10% aqueous K_2CO_3 (200 mL) was added, followed by 5% aqueous Na_2SO_3 (80 mL), and the mixture was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by silica gel column chromatography (100:10:1–100:20:1 hexanes/EtOAc/Et_3N) to afford **6** (13.7 g, 90%) as a white solid, mp 140–142 °C. ^{1}H NMR ($CDCl_3$) δ 8.45 (d, J = 4.5 Hz, 1H, Ar-H), 8.21 (d, J = 2.0 Hz, 1H, Ar-H), 8.01 (d, J = 4.5 Hz, 1H, Ar-H), 7.93 (d, J = 9.0 Hz, 1H, Ar-H), 7.81 (dd, J = 9.0, 2.5 Hz, 1H, Ar-H).

(e) 6-Bromo-4-(pyridazin-4-yl)quinoline (**7**). A suspension of **6** (3.61 g, 10.8 mmol), 4-(tributylstannyl)pyridazine (4.0 g, 10.8 mmol) and $PdCl_2$(dppf)-CH_2Cl_2 (632.0 mg, 0.8 mmol) in anhydrous 1,4-dioxane (50 mL) was stirred and heated at reflux for overnight. After cooling to rt, the reaction mixture was filtered through a pad of Celite, washed with abundant CH_2Cl_2, and concentrated in vacuo. The crude product was purified by silica gel column chromatography (50:1–20:1 EtOAc/MeOH) to afford **7** (1.38 g, 45%) as a pale brown solid, mp 176 °C (dec.). ^{1}H NMR ($CDCl_3$) δ 9.46 (d, J = 5.0 Hz, 1H, Ar-H), 9.39 (s, 1H, Ar-H), 9.06 (d, J = 3.0 Hz, 1H, Ar-H), 8.16 (d, J = 8.5 Hz, 1H, Ar-H), 7.90 (dd, J = 9.0, 2.0 Hz, 1H, Ar-H), 7.88 (d, J = 1.5 Hz, 1H, Ar-H), 7.67 (d, J = 3.0 Hz, 1H, Ar-H), 7.43 (d, J = 3.5 Hz, 1H, Ar-H).

(f) 1-(Benzylsulfanyl)-4-fluoro-2-nitrobenzene (**10**). To a suspension of 2,5-diflouronitrobenzene (**8**) (15.0 g, 94.3 mmol), anhydrous K_2CO_3 (26.1 g, 138.2 mmol) in anhydrous DMF (100 mL) was added phenylmethanethiol (11.7 g, 94.3 mmol) dropwise at 0 °C. After the reaction mixture was allowed to warm to rt and stirred for 2 h, it was poured into ice-water. The precipitate was filtered off, washed with water and dried. The crude product was purified by silica gel column chromatography (2:1 hexanes/$CHCl_3$) to afford **10** (21.6 g, 87%) as a yellow solid; mp 98–99 °C (lit[15] 104 °C). ^{1}H NMR ($CDCl_3$) δ 7.91 (dd, J = 8.5, 3.0 Hz, 1H, Ar-H), 7.43–7.40 (m, 3H, Ar-H), 7.35–7.32 (m, 2H, Ar-H), 7.30–7.25 (m, 2H, Ar-H), 4.39 (s, 2H, Ph-CH_2).

(g) 1-(Benzylsulfanyl)-2-fluoro-4-nitrobenzene (**11**). To a suspension of 3, 4-diflouronitrobenzene (**9**) (15.0 g, 94.3 mmol), anhydrous K_2CO_3 (26.1 g, 138.2 mmol) in anhydrous DMF (100 mL) was added phenylmethanethiol (11.7 g, 94.3 mmol) dropwise at 0 °C. After the reaction mixture was allowed to warm to rt and stirred for 2 h, it was poured into ice-water. The precipitate was filtered off, washed with water and dried to afford **11** (23.7 g, 96%) as a yellow solid, mp 122–123 °C (lit[15] 126 °C). ^{1}H NMR ($CDCl_3$) δ 7.94–7.91 (m, 1H, Ar-H), 7.88 (dd, J = 9.5, 2.5 Hz, 1H, Ar-H), 7.38–7.26 (m, 6H, Ar-H), 4.24 (s, 2H, Ph-CH_2).

(h) 4-Fluoro-2-nitrobenzene-1-sulfonyl chloride (**12**). To a cooled solution of **10** (10.5 g, 40.0 mmol) in CH_3CN–HOAc–H_2O (400 mL, 5 mL, 10 mL) was added 1,3-dichloro-5,5-dimethylhydantoin (15.8 g, 80.0 mmol) portionwise at 0 °C. After stirring at 0 °C for 3 h, the reaction mixture was concentrated to near dryness in vacuo. The crude product was diluted with CH_2Cl_2 (500 mL), and the solution was cooled down to ~0 °C. 5% aqueous $NaHCO_3$ (550 mL) was added slowly at <10 °C, the mixture was stirred at 0 °C for 15 min, The separated organic layer was washed with cooled brine, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. This liquid product was used without further purification. Small amount of the analytical pure sample was obtained by preparative TLC plate (9:1 hexanes/EtOAc) to afford **12** (71% yield) as a pale yellow solid, mp 44–45 °C (lit[15] 45–47 °C). ^{1}H NMR ($CDCl_3$) δ 8.32 (dd, J = 9.0, 5.0 Hz, 1H, Ar-H), 7.64 (dd, J = 7.5, 2.5 Hz, 1H, Ar-H), 7.61–7.57 (m, 1H, Ar-H).

(i) 2-Fluoro-4-nitrobenzene-1-sulfonyl chloride (**13**). A similar procedure for **12** was used to prepare **13** from **11** in 76% yield as a pale yellow solid, mp 69–70 °C (lit[15] 70 °C). ^{1}H NMR ($CDCl_3$) δ 8.34 (dd, J = 9.5, 2.0 Hz, 1H, Ar-H), 8.31–8.27 (m, 2H, Ar-H).

(j) 5-Bromo-2-chloro-3-nitropyridine (**15**). A mixture of 5-bromo-2-hydroxy-3-nitropyridine (**14**) (28.8 g, 131.5 mmol), $POCl_3$ (288 mL) and anhydrous DMF (30 mL) was stirred and heated at reflux for 3 h. After removal of $POCl_3$, the residue was poured into ice water and extracted with EtOAc. The combined organic layers were washed with saturated aqueous $NaHCO_3$, brine, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by silica gel column chromatography (4:1 hexanes/EtOAc) to afford **15** (25.4 g, 81%) as a pale yellow solid, mp 66–67 °C (lit[32] 68 °C). ^{1}H NMR ($CDCl_3$) δ 8.70 (d, J = 2.0 Hz, 1H, Ar-H), 8.37 (d, J = 2.5 Hz, 1H, Ar-H).

(k) 5-Bromo-2-methoxy-3-nitropyridine (**16**). Method A: to a cooled suspension of **15** (15.0 g, 63.2 mmol) in anhydrous MeOH (60 mL) was added 20% NaOMe in MeOH (15 mL, 66.4 mmol) dropwise at 0 °C. After the reaction mixture was allowed to warm to rt and stirred overnight, the pale yellow precipitate was filtered off to give the crude product. The crude product was diluted with water and stirred for 1 h. The solid was collected by filtration, washed with water and dried to afford **16** (9.22 g, 62%) as a pale yellow solid. The original filtrate was concentrated in vacuo and diluted with water. Saturated aqueous NH_4Cl was added and the mixture was stirred for 1 h. The solid was collected by filtration, washed with water and dried in a vacuum oven (40 °C) to give the second crop of **16** (4.74 g, 32%) as a pale yellow solid, mp 88–90 °C. ^{1}H NMR ($CDCl_3$) δ 8.45 (d, J = 2.5 Hz, 1H, Ar-H), 8.39 (d, J = 2.0 Hz, 1H, Ar-H), 4.11 (s, 3H, OCH_3). Method B: to a suspension of **14** (5.0 g, 22.8 mmol) in anhydrous CH_3Cl (50 mL) under N_2 in the dark (wrapped in aluminum foil) was added Ag_2CO_3 (7.55 g, 28.0 mmol), followed by CH_3I (14.2 mL, 230.0 mmol). After stirring at rt for 48 h, the reaction mixture was filtered through a pad of Celite, washed with abundant CH_2Cl_2, and concentrated in vacuo. The crude product was purified by silica gel column chromatography (10:1 hexanes/EtOAc) to afford **16** (1.86 g, 34%) as a pale yellow solid. The analytical data were same as aforementioned.

(l) 5-Bromo-2-methoxy-3-pyridinamine (**17**). To a solution of **16** (12.0 g, 51.7 mmol) in EtOAc (200 mL) was added $SnCl_2{\cdot}2H_2O$ (50.0 g, 221.6 mmol). The reaction mixture was stirred and heated at reflux for 4 h. After removal of the solvent, the residue was treated with 2 N aqueous NaOH and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by silica gel column chromatography (9:1 hexanes/EtOAc) to afford **17** (8.0 g, 76%) as a pale yellow solid, mp 58–60 CH_3. ^{1}H NMR ($CDCl_3$) δ 7.58 (d, J = 2.0 Hz, 1H, Ar-H), 6.98 (d, J = 2.0 Hz, 1H, Ar-H), 3.96 (s, 3H, OCH_3).

(m) *N*-(5-Bromo-2-methoxypyridin-3-yl)-2,4-difluorobenzenesulfonamide (**19**). To a cooled solution of **17** (4.0 g, 19.8 mmol) in pyridine (40 mL) was added 2,4-difluorobenzenesulfonyl chloride (**18**) (3.2 mL, 23.8 mmol) dropwise at 0 °C. After the reaction mixture was allowed to warm to rt and stirred overnight, it was diluted with cold water. The precipitate was collected by filtration, washed with water, dried to afford **19** (3.42 g, 46%) as a pale pink solid, mp 154–156 °C. ^{1}H NMR ($CDCl_3$) δ 7.91–7.88 (m+d, J = 2.0 Hz, 2H, Ar-H), 7.82 (d, J = 2.0 Hz, 1H, Ar-H), 7.22 (br s, 1H, NH), 7.00–6.92 (m, 2H, Ar-H), 3.90 (s, 3H, OCH_3).

(n) *N*-(5-Bromo-2-methoxypyridin-3-yl)-4-fluoro-2-nitrobenzenesulfonamide (**20**). To a cooled solution of **17** (1.0 g, 5.0 mmol) in pyridine (6 mL) was added a solution of **12** (1.19, 5.0 mmol) in pyridine (2 mL) dropwise at 0 °C. After the reaction mixture was allowed to warm to rt and stirred overnight, it was poured into ice water and extracted with EtOAC. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by silica gel column chromatography (3:1 hexanes/EtOAc) to afford **20** (561 mg, 28%) as a yellow solid, mp 140–142 °C. ^{1}H NMR ($CDCl_3$) δ 8.03 (dd, J = 9.0, 5.5 Hz, 1H, Ar-H), 8.01 (d, J = 2.0 Hz, 1H, Ar-H), 7.96 (d, J = 2.0 Hz, 1H, Ar-H), 7.83 (br s, 1H, NH), 7.68 (dd, J = 7.5, 2.5 Hz, 1H, Ar-H), 7.41–7.36 (m, 1H, Ar-H), 3.83 (s, 3H, OCH_3). HRMS (ESI, m/z): calcd for $C_{12}H_{10}N_3O_5FSBr$ ($[M+H]^+$) 405.9503, found 405.9504.

(o) *N*-(5-Bromo-2-methoxypyridin-3-yl)-2-fluoro-4-nitrobenzenesulfonamide (**21**). A similar procedure for **20** was used to prepare **21** from **13** and **17** in 26% yield as a yellow solid, mp 144–146 °C. ^{1}H NMR ($CDCl_3$) δ 8.14–8.06 (m, 3H, Ar-H), 7.93 (d, J = 2.5 Hz, 1H, Ar-H), 7.86 (d, J = 2.0 Hz, 1H, Ar-H), 7.30 (br s, 1H, NH), 3.89 (s, 3H, OCH_3). HRMS (CI, m/z): calcd for $C_{12}H_{10}N_3O_5FSBr$ ($[M+H]^+$) 405.9503, found 405.9497.

(p) 2,4-Difluoro-*N*-(2-methoxy-5-(4-(pyridazin-4-yl)quinolin-6-yl)pyridin-3-yl)benzenesulfonamide (GSK2126458, **22**). A suspension of **7** (570.0 mg, 2.0 mmol), bis(pinacolato)diboron (559.4 mg, 2.2 mmol), $PdCl_2$(dppf)-CH_2Cl_2 (82.0 mg, 0.1 mmol) and KOAc (392.7 mg, 4.0 mmol) in anhydrous 1,4-dioxane (20 mL) was stirred and heated at reflux for 3 h. The reaction mixture was treated with **19** (790.0 mg, 2.1 mmol), 2 M Na_2CO_3 (4 mL), and another portion of $PdCl_2$(dppf)-CH_2Cl_2 (82.0 mg, 0.2 mmol), then heated at reflux overnight. After the reaction mixture was allowed to cool to rt, it was filtered through a pad of Celite, washed with abundant CH_2Cl_2, and concentrated in vacuo. The crude product was purified by silica gel column (90:5:5 EtOAc/CH_2Cl_2/MeOH) to afford **22** (717.0 mg, 71%) as a pale brown solid, mp 183–184 °C (lit[1] 187–189 °C). ^{1}H NMR (DMSO-d_6) δ 10.3 (br s, 1H, NH), 9.57–9.56 (m, 1H, Ar-H), 9.47 (dd, J = 5.0, 1.0 Hz, 1H, Ar-H), 9.05 (d, J = 4.5 Hz, 1H, Ar-H), 8.42 (d, J = 4.5 Hz, 1H, Ar-H), 8.25 (d, J = 8.5 Hz, 1H, Ar-H), 8.12 (dd, J = 9.0, 2.0 Hz, 1H, Ar-H), 8.07 (dd, J = 5.0, 2.0 Hz, 1H, Ar-H), 7.94 (dd, J = 4.0, 2.0 Hz, 2H, Ar-H), 7.74–7.70 (m, 1H, Ar-H), 7.67 (d, J = 4.5 Hz, 1H, Ar-H), 7.58–7.53 (m, 1H, Ar-H), 7.19 (td, J = 8.5, 2.5 Hz, 1H, Ar-H), 3.64 (s, 3H, OCH_3). HRMS (ESI, m/z): calcd for $C_{25}H_{18}N_5O_3F_2S$ ($[M+H]^+$) 506.1098, found 506.1101.

(q) 4-Fluoro-*N*-(2-methoxy-5-(4-(pyridazin-4-yl)quinolin-6-yl)pyridin-3-yl)-2-nitrobenzenesulfonamide (2-nitro-GSK2126458, **23**). A suspension of **7** (285.0 mg, 1.0 mmol), bis(pinacolato)diboron (279.7 mg, 1.1 mmol), $PdCl_2$(dppf)-CH_2Cl_2 (41.0 mg, 0.05 mmol) and KOAc (196.3 mg, 2.0 mmol) in anhydrous 1,4-dioxane (10 mL) was stirred and heated at reflux for 3 h. The reaction mixture was treated with **20** (426.5 mg, 1.05 mmol), 2 M Na_2CO_3 (2 mL), and another portion of $PdCl_2$(dppf)-CH_2Cl_2 (41.0 mg, 0.1 mmol), then heated at reflux overnight. After the reaction mixture was allowed to cool to rt, it was filtered through a pad of Celite, washed with abundant CH_2Cl_2, and concentrated in vacuo. The crude product was purified by preparative TLC plate (90:5:5 EtOAc/CH_2Cl_2/MeOH) to afford **23** (110.0 mg, 21%) as a pale yellow solid, mp 119–120 °C. ^{1}H NMR (DMSO-d_6) δ 10.4 (br s, 1H, NH), 9.57–9.56 (m,

1H, Ar-H), 9.46 (dd, *J* = 5.0, 1.0 Hz, 1H, Ar-H), 9.06 (d, *J* = 4.5 Hz, 1H, Ar-H), 8.44 (d, *J* = 1.5 Hz, 1H, Ar-H), 8.26 (d, *J* = 8.5 Hz, 1H, Ar-H), 8.12 (dd, *J* = 9.0, 2.0 Hz, 1H, Ar-H), 8.07–8.04 (m, 3H, Ar-H), 7.96 (d, *J* = 1.5 Hz, 1H, Ar-H), 7.91 (d, *J* = 2.5 Hz, 1H, Ar-H), 7.77–7.73 (m, 1H, Ar-H), 7.68 (d, *J* = 4.0 Hz, 1H, Ar-H), 3.65 (s, 3H, OCH_3). HRMS (ESI, *m/z*): calcd for $C_{25}H_{18}N_6O_5FS$ ($[M+H]^+$) 533.1043, found 533.1019.

(r) 2-Fluoro-*N*-(2-methoxy-5-(4-(pyridazin-4-yl)quinolin-6-yl)pyridin-3-yl)-4-nitrobenzenesulfonamide (4-nitro-GSK2126458, **24**). A similar procedure for **23** was used to prepare **24** from **7** and **21** in 24% yield as a yellow solid, mp 124–125 °C. ^{1}H NMR (DMSO-d_6) δ 10.7 (br s, 1H, NH), 9.57 (q, 1H, *J* = 1.0 Hz, Ar-H), 9.47 (dd, *J* = 5.0, 1.0 Hz, 1H, Ar-H), 9.06 (d, *J* = 4.5 Hz, 1H, Ar-H), 8.43 (d, *J* = 2.0 Hz, 1H, Ar-H), 8.38 (dd, *J* = 10.0, 2.0 Hz, 1H, Ar-H), 8.26 (d, *J* = 9.0 Hz, 1H, Ar-H), 8.16–8.14 (m, 2H, Ar-H), 8.07 (dd, *J* = 5.0, 2.0 Hz, 1H, Ar-H), 7.99 (d, *J* = 2.0 Hz, 1H, Ar-H), 7.96–7.93 (m, 2H, Ar-H), 7.68 (d, *J* = 4.5 Hz, 1H, Ar-H), 3.60 (s, 3H, OCH_3). HRMS (ESI, *m/z*): Calcd for $C_{25}H_{18}N_6O_5FS$ ($[M+H]^+$) 533.1043, found 533.1028.

(s) 2,4-Difluoro-*N*-(2-hydroxy-5-(4-(pyridazin-4-yl)quinolin-6-yl)pyridin-3-yl)benzenesulfonamide (desmethyl-GSK2126458, **25**). To a solution of GSK2126458 **22** (283.0 mg, 0.56 mmol) in anhydrous CH_3CN (5 mL) was added iodotrimethylsilane (152 μL, 1.12 mmol). After the reaction mixture was stirred and heated at reflux for 4 h, it was concentrated in vacuo and the residue was purified by preparative TLC plate (1:9 CH_2Cl_2/MeOH) to afford **25** (135.0 mg, 49%) as a yellow solid: mp 179 °C (dec.). ^{1}H NMR (DMSO-d_6) δ 12.3 (br s, 1H, OH), 9.87 (br s, 1H, NH), 9.56 (s, 1H, Ar-H), 9.48 (d, *J* = 5.0 Hz, 1H, Ar-H), 9.02 (d, *J* = 4.0 Hz, 1H, Ar-H), 8.20 (d, *J* = 9.0 Hz, 1H, Ar-H), 8.06 (dd, *J* = 5.0, 2.0 Hz, 1H, Ar-H), 8.03 (dd, *J* = 8.5, 1.5 Hz, 1H, Ar-H), 7.85 (q, *J* = 1.0 Hz, 1H, Ar-H), 7.78 (d, *J* = 1.5 Hz, 1H, Ar-H), 7.75 (d, *J* = 2.0 Hz, 1H, Ar-H), 7.71 (s, 1H, Ar-H), 7.65 (d, *J* = 4.5 Hz, 1H, Ar-H), 7.50 (td, *J* = 10.0, 2.0 Hz, 1H, Ar-H), 7.21 (td, *J* = 8.5, 2.0 Hz, 1H, Ar-H). HRMS (ESI, *m/z*): calcd for $C_{24}H_{16}N_5O_3F_2S$ ($[M+H]^+$) 492.0942, found 492.0928.

(t) 2,4-Difluoro-*N*-(2-[^{11}C]methoxy-5-(4-(pyridazin-4-yl)quinolin-6-yl)pyridin-3-yl)benzenesulfonamide ([^{11}C]GSK2126458, [^{11}C]**22**). [^{11}C]CO_2 was produced by the ^{14}N(p,α)^{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 μA 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 desmethyl-GSK2126458 precursor **25** (0.5–1.0 mg) was dissolved in CH_3CN (400 μL). 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 method[18] 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 0.1 M $NaHCO_3$ (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) to release [^{11}C]GSK2126458 ([^{11}C]**22**). The eluted product was then sterile-filtered through a Millex-FG 0.2 μm membrane into a sterile vial and formulated with 10 mL saline. Total radioactivity was assayed and total volume was noted for tracer dose dispensing. Retention times in the semi-preparative HPLC system were: t_R **25** = 4.07 min, t_R **22** = 10.81 min, t_R [^{11}C]**22** = 10.81 min. Retention times in the analytical HPLC system were: t_R **25** = 2.51 min, t_R **22** = 5.12 min, t_R [^{11}C]**22** = 5.12 min. The decay corrected radiochemical yields of [^{11}C]**22** from [^{11}C]CO_2 were 40–50%.

(u) 2-[^{18}F]Fluoro-4-fluoro-*N*-(2-methoxy-5-(4-(pyridazin-4-yl)quinolin-6-yl)pyridin-3-yl)benzenesulfonamide (2-[^{18}F]GSK2126458, 2-[^{18}F]**22**) and 2-fluoro-4-[^{18}F]fluoro-*N*-(2-methoxy-5-(4-(pyridazin-4-yl)quinolin-6-yl) pyridin-3-yl)benzenesulfonamide (4-[^{18}F]GSK2126458, 4-[^{18}F]**22**). No-carrier-added (NCA) aqueous H[^{18}F]F was produced by ^{18}O(p,n)^{18}F nuclear reaction using a Siemens Eclipse RDS-111 cyclotron by irradiation of $H_2{}^{18}O$ (2.5 mL). H[^{18}F]F (7.4–18.5 GBq) in [^{18}O]water plus 0.1 mL K_2CO_3 solution (1.7 mg) and Kryptofix 2.2.2 (10 mg) in 1.0 mL CH_3CN with additional 1 mL CH_3CN were placed in the fluorination reaction vial (10-mL V-vial) and repeated azeotropic distillation (17 min) was performed at 110 °C to remove water and to form the anhydrous K[^{18}F]F-Kryptofix 2.2.2 complex. The precursor 2-nitro-GSK2126458 (**23**) or 4-nitro-GSK2126458 (**24**) (1 mg) dissolved in DMSO (1.0 mL) was introduced to the reaction vessel and heated at 140 °C for 15 min to affect radiofluorination. After cooling to ~90 °C, the contents of the reaction vial were diluted with 0.1 M $NaHCO_3$ (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) to release 2-[^{18}F]GSK2126458 (2-[^{18}F]**22**) or 4-[^{18}F]GSK2126458 (4-[^{18}F]**22**). The eluted product was then sterile-filtered through a Millex-FG 0.2 μm membrane into a sterile vial and formulated with 10 mL saline. Total radioactivity was assayed and total volume was noted for tracer dose dispensing. Retention times in the semi-preparative HPLC system were: t_R **23** = 6.50 min, t_R **24** = 5.87 min, t_R **22** = 10.81 min, t_R 2-[^{18}F]**22** = 10.81 min, t_R 4-[^{18}F]**22** = 10.81 min. Retention times in the analytical HPLC system were: t_R **23** = 2.62 min, t_R **24** = 2.57 min, t_R **22** = 5.12 min, t_R 2-[^{18}F]**22** = 5.12 min, t_R 4-[^{18}F]**22** = 5.12 min. The decay corrected radiochemical yields of 2-[^{18}F]**22** and 4-[^{18}F]**22** from H[^{18}F]F were 20–30%.

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