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Syntheses of 2-Amino and 2-Halothiazole Derivatives as High-Affinity Metabotropic Glutamate Receptor Subtype 5 Ligands and Potential Radioligands for in Vivo Imaging

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The structure of the potent selective $mGlu_5$ ligand, SP203 (**1**, 3-fluoro-5-[[2-(fluoromethyl)thiazol-4-yl]ethynyl]benzonitrile), was modified by replacing the 2-fluoromethyl substituent with an amino or halo substituent and by variation of substituents in the distal aromatic ring to provide a series of new high-affinity $mGlu_5$ ligands. In this series, among the most potent ligands obtained, the 2-chlorothiazoles **7a** and **7b** and the 2-fluorothiazole **10b** showed subnanomolar $mGlu_5$ affinity. **10b** also displayed >10000-fold selectivity over all other metabotropic receptor subtypes plus a wide range of other receptors and binding sites. The 2-fluorothiazoles **10a** and **10b** were labeled using [^{18}F]fluoride ion ($t_{1/2}$ = 109.7 min) in moderately high radiochemical yield to provide potential radioligands that may resist troublesome radiodefluorination during the imaging of brain $mGlu_5$ with position emission tomography. The iodo compound **9b** has nanomolar affinity for $mGlu_5$ and may also serve as a lead to a potential ^{123}I-labeled ligand for imaging brain $mGlu_5$ with single photon emission computed tomography.

Introduction

Glutamate, the predominant excitatory neurotransmitter in the central nervous system, promotes fast-synaptic transmission and synaptic plasticity by activating any one of three ion channel ionotropic glutamate receptors, namely NMDA,[a] AMPA, or kainate receptors.[1] Glutamate also has a modulatory influence on neuronal excitability by activating metabotropic glutamate receptors (mGluRs), which are members of the G protein-coupled seven-membrane-domain class of receptors.[2] Eight mGluR subtypes have been identified and classified according to their sequence homology, signal transduction, and pharmacology.[3] Among these subtypes, the metabotropic glutamate receptor subtype 5 ($mGlu_5$) plays key roles in a variety of normal brain functions and is also putatively involved in several neuropsychiatric disorders. Activation of $mGlu_5$ stimulates phospholipase C, and this results in phosphoinositide hydrolysis and an increase in intracellular Ca^{2+} levels.[3,4]

Modulation of $mGlu_5$ receptors has potential for the treatment of schizophrenia,[5] fragile X syndrome,[6] and Alzheimer's disease.[7] Further evidence supports the use of antagonists or modulators of $mGlu_5$ in the treatment of anxiety,[8] depression,[9] and pain.[10] $mGlu_5$ may also play an important role in drug-related behaviors, particularly drug abuse,[11] drug addiction,[12] and alcohol withdrawal.[13] Hence, $mGlu_5$ antagonists may turn out to be useful therapeutics for a variety of central nervous system disorders.

We previously reported the discovery of a very potent and highly selective ligand for $mGlu_5$, which we dubbed SP203 (**1**, 3-fluoro-5-[[2-(fluoromethyl)thiazol-4-yl]ethynyl] benzonitrile; Chart 1).[14] [^{18}F]**1**, which has a fluorine-18 ($t_{1/2}$ = 109.7 min) label in the 2-fluoromethyl position, is an effective radioligand for imaging brain $mGlu_5$ receptors in human subjects in vivo without major complications arising from radiometabolites.[15] Only a low amount of radioactivity appears in the skeleton and that radioactivity is associated with marrow rather than bone, thereby showing this radioactivity is not present as [^{18}F]fluoride ion and that metabolic radiodefluorination is virtually absent.[16] [^{18}F]**1** is significantly easier to prepare than previous ^{18}F-labeled $mGlu_5$ radioligands, such as the structurally related [^{18}F]3-fluoro-5-[(2-methyl-1,3-thiazole-4-yl)ethynyl]-benzonitrile ([^{18}F]F-MTEB,[17] [^{18}F]**2**; Chart 1), and has broad potential utility, ranging from receptor occupancy studies preceding drug clinical trials to studies of $mGlu_5$ receptor expression in neuropsychiatric patients.

In rat and in monkey, [^{18}F]**1** also shows acceptable brain entry and a sizable receptor-specific signal.[14] However, unlike in human subjects, radiodefluorination occurs,[18] leading to steady accumulation of fluorine-18 in bones and skull. This radioactivity confounds measurement of rat or monkey brain $mGlu_5$ receptors with this radioligand and positron emission tomography (PET).

Although metabolic defluorination often occurs from an aliphatic carbon,[19] this is relatively rare from an aryl carbon. The thiazole moiety is strongly aromatic. We therefore considered that a 2-fluoro-thiazole moiety might resist defluorination

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[a] Abbreviations: AMPA, α-amino-3-hydroxyl-5-methyl-4-isoxazolepropionate; DCM, dichloromethane; F-PEB, 3-fluoro-5-[2-methyl-1,3-thiazol-4-yl)ethynyl]benzonitrile; mGlu, metabotropic glutamate; mGluR, metabotropic glutamate receptor; M-MTEB, 3-methyl-5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]benzonitrile; MPEP, 2-methyl-6-(phenylethynyl)pyridine; NCA, decay-corrected radiochemical yield; NMDA, *N*-methyl-D-aspartate; PET, positron emission tomography; RCY, decay-corrected radiochemical yields; SPECT, single photon emission computed tomography.

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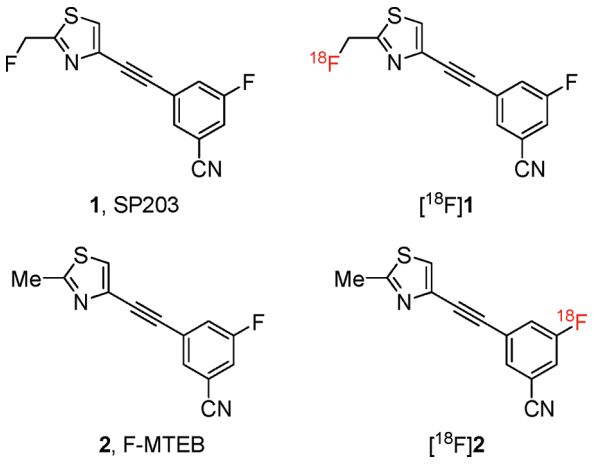
in vivo, unlike the 2-fluoromethylthiazole moiety of **1** when in monkey or rat. One report suggests that fluorination on a thiazole ring might increase stability toward ring metabolism.[20]

Here we report the synthesis of a series of compounds related to **1** in which the 2-fluoromethylthiazole moiety in **1** was replaced with a halogen, including fluorine, or with an amino group. The substitution pattern in the distal phenyl ring was also varied. We report the affinities of these new ligands toward $mGlu_5$ receptors. Finally, we describe the labeling of some of the novel 2-fluorothiazoles to produce candidate ^{18}F-labeled PET $mGlu_5$ radioligands.

Results and Discussion

Our primary goal was to produce high-affinity $mGlu_5$ ligands that would be suitable for development as ^{18}F-labeled ligands for imaging brain $mGlu_5$ in animals without being susceptible to troublesome radiodefluorination. We considered that this aim might be achieved by modifying [^{18}F]**1** so that the fluorine-18 atom was directly bound to the thiazole ring at the 2-position. Computation indicated that this modification, the replacement of a fluoromethyl group with a single fluorine atom, would not greatly alter lipophilicity. For example, the cLogD value of the 2-fluoro compound **10b** is 3.58 and similar to that of the 2-fluoromethyl analogue **1** (cLogD = 3.31). These values are within the range usually considered desirable for a prospective brain imaging agent.[21] In accord with this guideline, [^{18}F]**1**, in rodents and primates, shows good penetration of the blood−brain barrier, has high peak uptake in brain, and shows relatively low nonspecific binding.[14]

Chart 1. Structures of Some $mGlu_5$ Ligands and Derived PET Radioligands



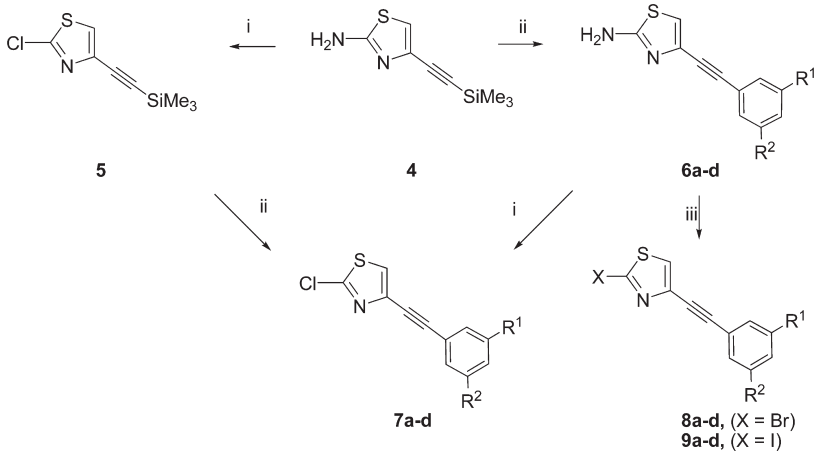
Chemistry

The 2-amino compounds (**6a**−**d**, Scheme 1) were prepared by Sonogashira cross-coupling of the aminothiazole **4** with the appropriate haloarenes. Yields were low from bromoarenes (< 30%) but moderate to high from iodoarenes (60 to ∼90%). Therefore, iodoarenes were used in all coupling reactions. The amines **6a**−**d** were then halogenated regioselectively[22] with CuX (X = Cl, Br, I) in the presence of *n*-butyl nitrite to give the 2-chloro (**7a**−**d**), 2-bromo (**8a**−**d**), and 2-iodo derivatives (**9a**−**d**) (Table 1). Yields increased with halogen size. Thus, yields for chlorination were low and typically in the range 15−25%. Yields for bromination and iodination were usually over 50% (Table 1).

Because the 2-chloro derivatives **7a**−**d** could only be obtained in small amounts and their purifications were tedious, we decided to explore an alternative synthesis to improve their yields. We considered that the use of the 2-chlorothiazole synthon **5** (Scheme 1) in a Sonogashira cross-coupling reaction might lead to higher yields. Synthon **5** was prepared by reaction of the easily accessible compound **4** with CuCl and *n*-butyl nitrite and submitted to Sonogoshira cross-coupling. Yields of the 2-chloro compounds **7a**−**d** from cross-coupling reactions with **5** were greatly improved (48−67%). The purifications of the 2-chloro products were also easier than those for the amino compounds **6a**−**d**. Noticeably, during the cross-coupling reactions, no coupling was observed at position 2 of the 2-chloro-thiazole acetylene **5**.

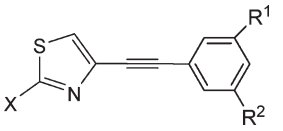
With the 2-chloro, 2-bromo, and 2-iodo compounds available, we aimed to prepare the corresponding 2-fluorothiazoles. The use of electrophilic reagents, either Accufluor[23] or Selectfluor,[24] gave almost negligible yields (1−5%) of the desired fluorinated products. Therefore, we next investigated direct nucleophilic substitution in the halo precursors with potassium fluoride. We recently reported a procedure for the rapid fluorination of 2-chloro and 2-bromothiazole derivatives under microwave irradiation,[25] and we looked to apply

Scheme 1[a]



[a] Reagents and conditions: (i) CuCl, *n*-$BuNO_2$; 30−67%; (ii) $PdPPh_4$, ArI, Et_3N, TBA, DME, 62−89%; (iii) CuX, *n*-$BuNO_2$ (X = Br or I), 32−83%. See Table 1 for identity of R^1 and R^2.

Table 1. Ligand Yields, Lipophilicities, and $mGlu_5$ Affinities



entry	X	R^1	R^2	yield (%)	cLogD[a]	K_i (nM)[b]
1	FCH_2	F	CN	NA	3.66 (2.18)[14]	0.036[14]
2	Me	F	CN	NA	3.42	0.08 ± 0.02[17]
6a	NH_2	H	CN	71	2.52	0.90 ± 0.19
6b	NH_2	F	CN	62	3.06	0.25 ± 0.04
6c	NH_2	H	CH_2CN	86	2.49	5.90 ± 0.95
6d	NH_2	H	OMe	89	2.72	18.6 ± 0.38
7a	Cl	H	CN	56[c]	2.88	0.27 ± 0.04
7b	Cl	F	CN	64[c]	3.41	0.40 ± 0.09
7c	Cl	H	CH_2CN	67[c]	2.99	3.10 ± 0.46
7d	Cl	H	OMe	48[c]	3.44	8.10 ± 1.36
8a	Br	H	CN	32[d]	3.38	3.70 ± 0.25
8b	Br	F	CN	48	3.95	0.95 ± 0.10
8c	Br	H	CH_2CN	61	3.48	3.30 ± 0.53
8d	Br	H	OMe	59	3.86	22.3 ± 0.50
9a	I	H	CN	83	3.56	4.20 ± 0.50
9b	I	F	CN	71	4.21	1.30 ± 0.23
9c	I	H	CH_2CN	62	3.63	23.3 ± 3.53
9d	I	H	OMe	50	3.96	132.9 ± 2.54
10a	F	H	CN	24, 75[e]	3.12	1.60 ± 0.11*
10b	F	F	CN	35, 72[e]	3.58	0.28 ± 0.05*
10c	F	H	CH_2CN	43, 78 [e]	3.18	3.90 ± 0.56
10d	F	H	OMe	33, 65[e]	3.56	22.7 ± 0.28
10e	F	H	H	46, 78[f]	3.38	122 ± 3.3

[a] cLogD values were calculated with Pallas 3.7.1.1 software (CompuDrug Chemistry Ltd), except for the value in parentheses which is a measured value. [b] Values were determined in triplicate from rat brain homogenates, except those marked * (n = 6). [c] Obtained by coupling from compound **5**. [d] Value reported in ref 22. [e] From the 2-bromo and 2-chloro-thiazoles, respectively (each treated with KF in DMSO at 130 °C). [f] From the 2-bromo- and 2-chloro-thiazoles, respectively.[25]

this method to obtain the target 2-fluoro ligands. By treating bromides **8a**−**d** with a potassium fluoride-Kryptofix 2.2.2 (K 2.2.2) complex in DMSO under microwave irradiation (30 W, 130 °C, 8−15 min), the respective 2-fluoro compounds **10a**−**d** were obtained in useful 24−43% yields (Table 1).

When the 2-chloro-precursors **7a**−**d** were treated similarly (KF-K 2.2.2, DMSO, MW, 130 °C, 10−15 min), the fluorination yields were dramatically improved, reaching 78% in the case of **10c**. By contrast, only negligible product was detected when the iodo precursor **9a** was submitted to nucleophilic fluorination (yield, < 5%). These results accord with our previous observations on leaving group ability in the nucelophilic fluorination of simpler 2-halo-thiazoles.[25]

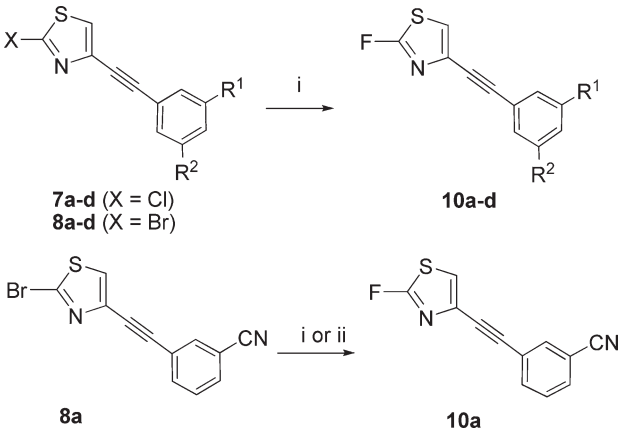
For the synthesis of **10a**, we also experimented with the use of a KF-AgF with the bromo precursor **8a** under microwave irradiation (Scheme 2). After 8 min of irradiation, the yield of **10a** reached 62%, as measured with HPLC. However, this fluorination method was less reproducible and we also observed the reduction of DMSO into the irritant and volatile dimethyl sulfide.

The 2-chloro and 2-bromo-(4-phenylacetylene)thiazoles **7e** and **8e** were also subjected to fluorination with KF in DMSO, as reported previously, to give the fluoro derivative **10e** in 78 and 46% yields, respectively.[25]

Pharmacology

The affinity of each new ligand for rat brain tissue $mGlu_5$ was determined in a binding assay with [^{3}H]MPEP

Scheme 2[a]



[a] Reagents and conditions: (i) KF, K 2.2.2 DMSO or MeCN, MW 130 °C, 10 min, 24−78%; (ii) KF-AgF, DMSO, MW, 130 °C, 8 min, 62%. See Table 1 for identities of R^1 and R^2.

([^{3}H]2-methyl-6-phenylethynyl)pyridine as reference radioligand. The majority of the prepared 2-halo-thiazoles exhibited high affinity, with K_i values in the nanomolar range. In general, the 2-iodo compounds had lower affinity than their bromo, chloro, or fluoro analogues. Unexpectedly, the amino compound intermediates **6a**−**d** also exhibited high to very high affinity for $mGlu_5$. The substituent pattern in the distal aryl group strongly influenced affinity for $mGlu_5$. Thus, the combination of fluoro and nitrile substituents in meta position to the alkynyl group, as also exists in **1**, generally gave the highest affinity among each subset of 2-substituted thiazoles. Removal of the *meta*-fluoro substituent generally had little effect. A single meta cyanomethyl or methoxy group reduced affinity appreciably, especially a methoxy group.

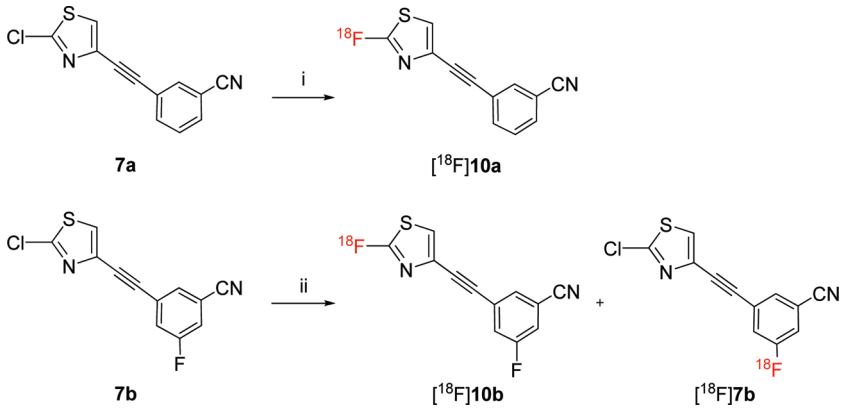
The high-affinity 2-fluoro ligand **10b** was screened for affinity at other mGluR subtypes ($mGlu_1$, $mGlu_2$, $mGlu_4$, $mGlu_6$, $mGlu_7$, and $mGlu_8$) and a panel of other brain receptors, binding sites, and ion channels as listed under the Experimental Section. In all cases, the affinity of **10b** was found to be > 10000 nM. Therefore, replacement of the 2-fluoromethyl group in **1** with a fluoro substituent retained excellent $mGlu_5$ selectivity. Such excellent selectivity is highly desirable in a prospective PET radioligand.

Currently, no effective radioligand exists for imaging brain $mGlu_5$ with single photon emission computed tomography (SPECT). Interestingly, the iodo compounds **9a** and **9b** show $mGlu_5$ affinity in the nanomolar range and are possibly suitable for labeling with iodine-123 to provide candidate radioligands for imaging brain $mGlu_5$ with single photon emission computed tomography (SPECT). The highest affinity iodinated ligand **9b** has affinity that almost matches that of PET radioligands, such as [^{11}C]M-MTEB ([^{11}C]3-methyl-5-[(2-methyl-1,3-thiazol-4-yl)ethynyl] benzonitrile) and [^{18}F]F-PEB ([^{18}F]3-fluoro-5-[2-methyl-1,3-thiazol-4-yl)ethynyl] benzonitrile), that have been shown to give strong receptor-specific signals in monkeys.[17] The computed lipophilicity of **9b** appears quite high for a prospective SPECT radioligand. However, this computed value, and also those for the other ligands, may be considerably overestimated because the true value for ligand **1** is much lower than that for its computed value (Table 1).

Radiochemistry

We previously reported reaction conditions for the preparation of [^{18}F]2-fluorothiazole derivatives with cyclotron-produced

Scheme 3[a]



[a] Reagents and conditions: (i) [^{18}F]FK, K 2.2.2., DMSO or MeCN, MW, 130 °C, 10 min, 26% RCY; (ii) [^{18}F]FK, K 2.2.2., MeCN, MW, 110 °C, 10 min, 26−48% RCY.

no-carrier-added (NCA) [^{18}F]fluoride ion under thermal and microwave heating conditions.[25] We established that simple 2-chlorothiazole structures label efficiently with [^{18}F]fluoride ion in the presence of K^+-K 2.2.2 in DMSO or MeCN. The radiochemical yield was slightly higher for 2-chlorothiazoles than for 2-bromothiazoles. These conditions were applied successfully for the radiosynthesis of [^{18}F]**10a** from the chloro compound **7a**. Thus, at 130 °C in DMSO under inert atmosphere and with brief microwave heating (90 W, 150 °C, 10 min), [^{18}F]**10a** was obtained in 36% decay-corrected radiochemical yields (RCY) and with a measured specific activity of 2.1 Ci/μmol at the end of synthesis.

Because of its high affinity, we then selected **10b** as the major target for labeling with fluorine-18. The chloro compound **7b** was selected as precursor for radiofluorination. The conversion of **7b** into [^{18}F]**10b** was initially attempted using the reaction conditions mentioned above. Reaction for 10 min at 130 °C gave decay-corrected RCYs of 26% (Scheme 3). Unexpectedly, under these conditions, some exchange of the aryl fluoro group with [^{18}F]fluoride ion was also observed and [^{18}F]**7b** was detected as a byproduct of radiofluorination. Typically, with the use of anhydrous DMSO at 130 °C, the ratio of [^{18}F]**10b** to [^{18}F]**7b** was 45:55. The use of anhydrous acetonitrile under similar conditions (K 2.2.2-K_2CO_3; MW, 130 °C) switched the major labeled product to [^{18}F]**10b** ([^{18}F]**10b**:[^{18}F]**7b**; 82:18). In acetonitrile, when the temperature of reaction was lowered to 110 °C and the incorporation of [^{18}F]fluoride ion was up to 48%, with the ratio of [^{18}F]**10b** to [^{18}F]**7b** being 92:8.

The radioligands were easily purified by HPLC in high chemical purity (>95%) and high radiochemical purity (>99%). The specific activity of the target compound [^{18}F]**10b**, was 0.5 Ci/μmol at the end of synthesis (about 150 min from the end of radionuclide production) and somewhat lower than for [^{18}F]**10a**, probably because of the ^{18}F for F exchange occurring in precursor **7b**. Nonetheless, this new radioligand now merits further evaluation with PET in animals to assess its resistance to radiodefluorination and efficacy for imaging brain $mGlu_5$.

Conclusions

Several new 2-amino and 2-halo-thiazole-4-(alkynylbenzenes) were synthesized, and they showed moderate to high affinity as ligands at $mGlu_5$ in rat brain tissue. The labeling of some of the 2-fluorothiazole derivatives with [^{18}F]fluoride ion was shown to be feasible to provide new candidate radioligands, [^{18}F]**10a** and [^{18}F]**10b**, for $mGlu_5$ imaging with PET. A candidate, **9b**, for development as a SPECT radioligand for imaging brain $mGlu_5$, was also identified.

Experimental Section

Materials and General Methods. 5-Amino-3-fluorobenzonitrile was obtained from Oakwood Products, Inc. All other reagents and solvents were obtained from Sigma-Aldrich in the highest purity available (≥98%) and were used as purchased. All reactions were performed under argon atmosphere unless otherwise indicated. 4-((Trimethylsilyl)ethynyl)thiazol-2-amine (**4**),[26] 3-((2-fluorothiazol-4-yl)ethynyl) benzonitrile (**10b**),[25] and 2-fluoro-4-(phenylethynyl)thiazole (**10e**)[25] were prepared as described previously. Thin layer chromatography (TLC) was performed with silica gel layers (type 60 F254; 400−630 mesh) with compounds visualized under UV light (λ = 254 nm). Column chromatography was performed on silica gel with hexane−EtOAc mixtures as eluents. Constituent proportions in chromatographic mobile phases are expressed by volume. Separation of compounds with HPLC was performed on a Luna column (10 μm, 250 mm × 10 mm, Phenomenex, Torrance, CA) eluted with H_2O-MeCN. The purities of all new compounds were determined by HPLC on a Luna C18 column (5 μm, 250 mm × 4.6 mm, Phenomenex) eluted isocratically with H_2O−MeCN and were greater than 95%. All HPLC eluates were monitored for absorbance at 254 nm. Yields were recorded for chromatographically pure materials (≥98%).

The ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra of all compounds were acquired in $CDCl_3$ using the chemical shift of residual deuterated solvent as internal standard; chemical shifts (δ) for the proton and carbon resonance are reported in parts per million (ppm) downfield from TMS (δ = 0). The following abbreviations were used to describe peak splitting patterns when appropriate: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = double of doublet. ^{19}F-NMR (376.5 MHz) spectra were acquired in $CDCl_3$ in the presence of $CFCl_3$ as internal standard (δ = 0). Mass spectra were acquired with either a GC-MS instrument equipped with a capillary RTX-5 ms column (30 m × 0.25 mm; flow rate, 1 mL/min; carrier gas, He) or by LC-MS. LC-MS analyses were performed on a LCQ Deca MS instrument interfaced with a Surveyor HPLC pump and autosampler (Thermo Fisher Scientific, Waltham, MA). High-resolution mass spectra were acquired with ESI.

3-Fluoro-5-iodobenzonitrile (3). 3-Amino-5-fluorobenzonitrile (2.72 g, 20 mmol) was treated with *n*-butyl nitrite (3.09 g, 35.6 mmol) and CuI (5.71 g, 30 mmol) in MeCN (30 mL) at 80 °C. The mixture was refluxed for 20 min, and allowed to cool

to rt. Then the solvent was evaporated off. The residue was suspended in water (20 mL) and extracted twice with DCM (2 × 25 mL). The organic layers were combined, washed with brine (15 mL), dried over $MgSO_4$, and evaporated to dryness under vacuum. Chromatography of the residue on silica gel (hexane−EtOAc; 90:10, v/v) gave **3** as yellow crystals (2.32 g; yield, 47%); mp 29−30 °C. ^{1}H NMR: δ 7.80 (s, 1H) 7.71 (m, 1H), 7.36 (m, 1H). ^{13}C NMR: δ 161.6 (d, J = 256.03 Hz), 136.7 (d, J = 3.8 Hz), 129.1 (d, J = 23.20 Hz), 118.7 (d, J = 24.34 Hz), 115.9 (d, J = 3.23 Hz), 115.3 (d, J = 9.59 Hz), 93.9 (d, J = 8.23 Hz). ^{19}F-NMR: δ −107.54 (s, 1F). GC-MS m/z: 247.94 $[M + H]^+$.

2-Chloro-4-((trimethylsilyl)ethynyl)thiazole (5). 4-(Trimethylsilyl)ethynyl)thiazol-2-amine (**4**; 2.25 g, 11.48 mmol) and CuCl (2.85 g, 28.78 mmol) were dissolved in MeCN (25 mL) at rt. *n*-Butyl nitrite (1.6 mL, 13.7 mmol) was added with stirring, and the solution was heated to 75 °C. TLC showed the reaction to be complete after 45 min. The reaction mixture was then evaporated to dryness under vacuum. The residue was dissolved in ethyl acetate (20 mL) and washed with ammonia solution (0.1M; 2 × 50 mL). The organic layer was dried over $MgSO_4$ and evaporated to dryness under vacuum. Chromatography of the residue on silica gel (hexane−EtOAc; 95:5, v/v) gave **5** as a white powder (750 mg; yield, 30%); mp 67−68 °C. ^{1}H NMR: δ 7.34 (s, 1H), 0.25 (s, 9H). ^{13}C NMR: δ 151.1, 136.7, 125.2, 97.4, 96.3, 0.0. HRMS (ESI+): calcd for $C_8H_{11}NClSSi$ 207.0070, found 207.0067. HPLC purity: 98.45%.

3-[(2-Aminothiazol)-4-ethynyl]benzonitrile (6a). Compound **4** (375 mg, 1.91 mmol), 3-iodobenzonitrile (650 mg, 2.85 mmol), CuI (25 mg, 0.12 mmol), $Pd(PPh_3)_4$ (74 mg, 0.7 mmol), and Et_3N(1.2 mL) were added to dimethylethylene glycol (10 mL) under argon. Argon was bubbled into the resulting dark solution while it was heated to 80 °C. A solution of TBAF (1.0 M) in THF (2.5 mL) was then added via syringe over 25 min. The reaction mixture was heated at 80 °C until TLC showed no starting material present (15 min) and then cooled to rt and evaporated to dryness. The residue was dissolved in EtOAc (25 mL) and then washed with water (2 × 40 mL) and brine (1 × 40 mL). The combined organic fractions were dried over $MgSO_4$ and evaporated to dryness in vacuo. Chromatography of the residue on silica gel (hexane−EtOAc, 70:30, v/v) gave **6a** (230 mg; yield, 54%) as a brown solid; mp 154−155 °C. ^{1}H NMR: δ 7.52 (m, 2H), 7.33 (m, 2H), 6.78 (s, 1H). ^{13}C NMR: δ 166.6, 133.1, 131.7, 128.5, 128.3, 122.6, 113.15, 88.1, 83.9. HRMS (ESI+): calcd for $C_{11}H_9N_2S$ 201.0486, found 201.0485. HPLC purity: 99.75%.

3-[(2-Aminothiazol)-4-ethynyl]-5-fluorobenzonitrile (6b). This compound was prepared from **4** and 3-fluoro-5-iodobenzonitrile with the method and chromatography described for **6a** and gave **6b** as a brown powder (288 mg; yield, 62%); mp 209−210 °C. ^{1}H NMR: δ 7.64 (m, 1H), 7.59 (s, 1H), 7.55 (m, 1H), 7.44 (m, 1H). ^{13}C NMR: δ 166.5 (d, J = 256.10 Hz), 160.7, 152.3, 135.1, 131.2 (d, J = 3.56 Hz), 125.9, 123.1 (d, J = 22.86 Hz), 118.9 (d, J = 24.76 Hz), 116.7, 115.3 (d, J = 10.10 Hz), 85.9, 84.6. ^{19}F-NMR: δ −109.18 (s, 1F). HRMS (ESI+): calcd for $C_{11}H_9N_2S$ 244.0345, found 244.0334. HPLC purity: 97.32%.

2-(3-((2-Aminothiazol-4-yl)ethynyl)acetonitrile (6c). This compound was prepared from **4** and 2-(3-iodophenyl)acetonitrile with the method and chromatography described for **6a** and gave **6c** as a brown powder (395 mg; yield, 86%); mp 154−156 °C. ^{1}H NMR: δ 7.47 (m, 2H), 7.30 (t, J = 7.80 Hz, 1H), 7.31 (t, J = 7.8 Hz, 1H), 6.82 (s, 1H), 3.75 (s, 2H). ^{13}C NMR: δ 166.7, 159.5, 133.3 (2 C), 129.6, 124.4, 123.8, 116.5, 115.5, 113.5, 88.3, 83.9, 22.4. HRMS (ESI+): calcd for $C_{12}H_7FN_3S$ 240.0591, found 240.0595. HPLC purity: 96.40%.

4-(3-Methoxyphenyl)ethynyl(thiazol)-2-amine (6d). This compound was prepared from **4** and 1-iodo-3-methoxybenzene with the method and chromatography described for **6a** and gave **6d** as a yellow powder (392 mg; yield, 89%); mp 94−95 °C. ^{1}H NMR: δ 7.24 (t, J = 7.64 Hz, 1H), 7.12 (d, J = 7.60 Hz, 1H), 7.05 (s, 1H), 6.89 (m, 1H), 6.78 (s, 1H), 3.80 (s, 3H). ^{13}C NMR: δ 166.8, 159.5, 133.3, 129.6, 124.4, 123.8, 116.5, 115.5, 113.5, 88.3, 83.9, 55.5. HRMS (ESI+): calcd for $C_{12}H_{11}N_2OS$ 231.0585, found 231.0592. HPLC purity: 97.22%.

3-((2-Chlorothiazol)-4-yl)ethynyl)benzonitrile (7a). Compound **5** (431 mg, 2.0 mmol), 3-iodobenzonitrile (650 mg, 2.85 mmol), CuI (25 mg, 0.12 mmol), $Pd(PPh_3)_4$ (74 mg, 0.7 mmol), and Et_3N (1.2 mL) were added to dimethylethylene glycol (10 mL) under argon. Argon was bubbled into the resulting dark solution while it was heated to 80 °C. A solution of TBAF (1.0 M) in THF (2.5 mL) was added via syringe over 25 min. The reaction mixture was stirred at 80 °C. After 15 min, TLC showed no starting material present. The reaction mixture was then cooled to rt and evaporated to dryness. The residue was dissolved in EtOAc (25 mL) and then washed with water (2 × 40 mL) and brine (1 × 40 mL). The combined organic fractions were dried over $MgSO_4$ and evaporated to dryness in vacuo. Chromatography of the residue on silica gel (hexane−EtOAc, 85:15, v/v) gave **7a** as a brown solid (274 mg; 56%); mp 118−120 °C. ^{1}H NMR: δ 7.81 (t, J = 1.4 Hz, 1H), 7.75 (dt, J_1 = 7.88 Hz, J_2 = 1.34 Hz, 1H), 7.65 (dt, J_1 = 7.84 Hz, J_2 = 1.33 Hz, 1H), 7.58 (s, 1H), 7.49 (t, J = 7.86 Hz, 1H). ^{13}C NMR: δ 138.1, 136.6, 135.2, 133.2, 132.7, 129.9, 126.1, 123.7, 117.1, 114.4, 87.5, 84.8. HRMS (ESI+): calcd for $C_{12}H_6{}^{79}BrN_2S$ 244.9936, found 244.9940. HPLC purity: 99.11%.

3-((2-Chlorothiazol)-4-yl)ethynyl)-5-fluorobenzonitrile (7b). This compound was prepared from **5** and 3-fluoro-5-iodobenzonitrile with the method and chromatography described for **7a** and gave **7b** as a yellow powder (335 mg; yield, 64%); mp 120−121 °C. ^{1}H NMR: δ 7.62 (s, 1H), 7.49 (s, 1H), 7.46 (m, 1H), 7.36 (m, 1H). ^{13}C NMR: δ 161.9 (d, J = 251.85 Hz), 152.3, 135.1, 131.2 (d, J = 3.56 Hz), 125.9, 123.2 (d, J = 23.07 Hz), 119.5 (d, J = 24.80 Hz), 116.7, 114.4 (d, J = 10.22 Hz), 85.9, 84.6. ^{19}F-NMR: δ −109.12 (s, 1F). HRMS (ESI+): calcd for $C_{12}H_5ClFN_2S$ 262.9841, found 262.9844. HPLC purity: 98.75%.

2-(3-((2-Chlorothiazol)-4-yl)ethynyl)-phenyl)acetonitrile (7c). This compound was prepared from **5** and 2-(3-iodophenyl)-acetonitrile with the method and chromatography described for **7a** and gave **7c** as a beige powder (346 mg; yield, 67%); mp 108−110 °C. ^{1}H NMR: δ 7.52 (m, 1H), 7.50 (m, 1H), 7.43 (s, 1H), 7.36 (m, 2H), 3.75 (s, 2H). ^{13}C NMR: δ 150.7, 135.0, 130.4, 130.1, 129.3, 128.3, 127.4, 123.5, 122.0, 116.3, 87.6, 82.2, 22.4. HRMS (ESI+): calcd for $C_{13}H_8ClN_2S$ 259.0097, found 259.0098. HPLC purity: 98.62%.

2-Chloro-4-((3-methoxyphenyl)ethynyl)thiazole (7d). This compound was prepared from **5** and 1-iodo-3-methoxybenzene with the method and chromatography described for **7a** and gave **7d** as a light-yellow powder (238 mg; yield, 48%); mp 88 °C. ^{1}H NMR: δ 7.39 (s, 1H), 7.26 (t, J = 7.96 Hz, 1H), 7.15 (m, 1H), 7.07 (m, 1H), 6.93 (m, 1H), 3.81 (s, 3H). ^{13}C NMR: δ 159.3, 151.6, 136.4, 129.5, 124.4, 124.1, 122.9, 116.5, 115.9, 89.7, 82.1, 55.3. HRMS (ESI+): calcd for $C_{12}H_9ClNOS$ 250.0093, found 250.0097. HPLC purity: 99.08%.

3-((2-Bromothiazol)-4-ethynyl)-5-fluorobenzonitrile (8b). The 2-aminothiazole derivative **6b** (0.245 g, 1 mmol) and CuBr (0.2 g, 1.39 mmol) were dissolved in MeCN (8 mL) at rt. *n*-Butyl nitrite (162 μL, 1.39 mmol) was added with stirring, and the solution was heated to 60 °C. The reaction was complete after 15 min, as monitored by TLC. The reaction mixture was then evaporated to dryness in vacuo. The residue was dissolved in EtOAc (20 mL) and washed with ammonia solution (0.1 M; 2 × 50 mL). The organic layer was dried over $MgSO_4$ and evaporated to dryness in vacuo. Chromatography of the residue on silica gel (hexane−EtOAc; 97:3, v/v) gave **8b** (150 mg; yield, 48%); mp 139−140 °C. ^{1}H NMR: δ 7.62 (t, J_1 = 1.28 Hz, 1H), 7.54 (s, 1H), 7.47 (ddd, J_1 = 8.72 Hz, J_2 = 1.36 Hz, J_2 = 1.12 Hz, 1H), 7.36 (ddd, J_1 = 7.82 Hz, J_2 = 1.40 Hz, J_2 = 1.12 Hz, 1H). ^{13}C NMR: δ 161.9 (d, J = 251.71 Hz),136.6, 136.3 (d, J = 32.20 Hz), 131.2 (d, J = 3.56 Hz), 127.6, 125.7 (d, J = 10.08 Hz), 123.2 (d, J = 23.50 Hz), 119.5 (d, J = 24.57 Hz), 116.7, 114.4 (d, J = 10.20 Hz), 86.2 (J = 3.45 Hz), 85.3. ^{19}F-NMR: δ −108.7 (s, 1F).

HRMS (ESI+) calcd for $C_{12}H_5BrFN_2S$ 306.9335, found 306.9338. HPLC purity: 98.45%.

2-(3-((2-Bromothiazol-4-yl)ethynyl)phenyl)acetonitrile (8c). This compound was prepared from the 2-aminothiazole derivative **6c** with the method described for **8b**. Chromatography (hexane−EtOAc, 95:5, v/v) gave **8c** as a white powder (185 mg; yield, 61%); mp 110−111 °C. ^{1}H NMR δ 7.51 (m, 2H), 7.47 (s, 1H), 7.37 (m, 2H), 3.76 (s, 2H). ^{13}C NMR δ 137.9, 136.1, 131.7, 131.4, 130.5, 129.5, 128.7, 126.4, 123.3, 117.5, 89.2, 83.2, 23.6. HRMS (ESI+): calcd for $C_{13}H_8BrN_2S$ 302.9592, found 302.9587. HPLC purity: 98.08%.

2-Bromo-4-((3-methoxyphenyl)ethynyl)thiazole (8d). This compound was prepared from the amino-thiazole derivative **6d** with the method and chromatography described for **8c** and gave **8d** as a white powder (175 mg; yield, 59%); mp 98 °C. ^{1}H NMR: δ 7.44 (s, 1H), 7.25 (t, J = 8.01 Hz, 1H), 7.14 (m, 1H), 7.08 (m, 1H), 6.92 (m, 1H), 3.81 (s, 3H). ^{13}C NMR: δ 159.5, 138.2, 135.9, 129.7, 126.0, 124.5, 123.1, 116.7, 116.1, 90.2, 82.0, 55.5. HRMS (ESI+): calcd for $C_{12}H_9BrNOS$ 293.9588, found 293.9594. HPLC purity: 97.91%.

3-[(2-Iodothiazol)-4-ethynyl]-benzonitrile (9a). This compound was prepared from **6a** with the method described for **8b** but with CuI in place of CuBr. Chromatography (hexane−EtOAc, 95:5, v/v gave **9a** as a beige powder (280 mg; yield 83%); mp 118−120 °C. ^{1}H NMR: δ 7.81 (t, J = 1.4 Hz, 1H), 7.76 (dt, J_1 = 7.60 Hz, J_2 = 1.32 Hz, 1H), 7.65 (dt, J_1 = 7.64 Hz, J_2 = 1.32 Hz, 1H), 7.53 (s, 1H), 7.49 (t, J = 8.00 Hz, 1H). ^{13}C NMR: δ 138.1, 136.6, 135.2, 133.2, 132.7, 129.9, 126.1, 123.7, 117.1, 114.4, 87.5, 84.8. HRMS (ESI+): calcd for $C_{12}H_6IN_2S$ 336.9296, found 336.9307. HPLC purity: 98.25%.

3-((2-Iodothiazol)-4-ethynyl)-5-fluorobenzonitrile (9b). This compound was prepared from **6b** with the method described for **9a**. Chromatography (hexane−EtOAc, 90:10, v/v) gave **9b** as a light-yellow powder (250 mg; yield 71%); mp 158−160 °C. ^{1}H NMR: δ 7.62 (s, 1H), 7.56 (s, 1H), 7.47 (m, 1H), 7.36 (m, 1H). ^{13}C NMR: δ 161.9 (d, J = 251.76 Hz), 138.5, 131.2 (d, J = 3.51 Hz), 130.1, 125.8 (d, J = 10.01 Hz), 123.2 (d, J = 22.95 Hz), 119.4 (d, J = 24.76 Hz), 116.7 (d, J = 3.05 Hz), 114.4 (d, J = 10.18 Hz), 100.7, 86.5 (d, J = 3.31 Hz), 85.0. ^{19}F-NMR: δ −108.7 (s, 1F). HRMS (ESI+): calcd for $C_{12}H_5FIN_2S$ 354.9202, found 354.9192. HPLC purity: 99.05%.

2-(3-((2-Iodothiazol-4-yl)ethynyl)phenyl)acetonitrile (9c). This compound was prepared from **6c** with the method described for **9b**. Chromatography (hexane−EtOAc, 90:10, v/v) gave **9c** as a beige powder (215 mg; yield 62%); mp 120−122 °C. ^{1}H NMR: δ 7.52 (m, 2H), 7.50 (s, 1H), 7.37 (m, 2H), 3.76 (s, 2H). ^{13}C NMR: δ 139.7, 131.7, 131.4, 130.5, 129.5, 128.9, 128.6, 123.3, 117.5, 100.3, 89.5, 82.8, 23.6. HRMS (ESI+): calcd for $C_{13}H_8IN_2S$ 350.9453, found 350.9443. HPLC purity: 97.77%.

2-Iodo-4-((3-methoxyphenyl)ethynyl)thiazole (9d). This compound was prepared from **6d** with the method described for **9a**. Chromatography (hexane−EtOAc, 90:10, v/v) gave **9d** as a pale-yellow (170 mg; yield 50%); mp 106−108 °C. ^{1}H NMR: δ 7.46 (s, 1H), 7.26 (t, J = 7.95 Hz, 1H), 7.15 (dt, J_1 = 7.6 Hz, J_2 = 1.16 Hz,1H), 7.08 (m, 1H), 6.92 (m, 1H), 3.81 (s, 3H). ^{13}C NMR: δ 159.3, 139.9, 129.5, 128.2, 124.4, 123.0, 116.5, 115.8, 99.9, 90.3, 81.4, 55.3. HRMS (ESI+): calcd for $C_{12}H_9INOS$ 341.9450, found 341.9449. HPLC purity: 98.65%.

3-((2-Fluorothiazol-4-yl)ethynyl)benzonitrile (10a). 8a (105 mg, 0.36 mmol) was placed in a microwave vial with Kryptofix 2.2.2 (135 mg, 0.36 mmol), anhydrous KF (42 mg, 0.72 mmol), and DMSO (1 mL). The solution was irradiated with microwaves (30 W, 130 °C 10 min). Reaction was monitored with ^{1}H NMR until disappearance of the signal of the proton in C5 in the thiazole ring. The reaction mixture was then poured into water (10 mL) and extracted with EtOAc (3 × 25 mL). The combined organic phases were washed with water (3 × 10 mL) and then brine (10 mL). The organic fraction was dried over $MgSO_4$, evaporated to dryness under vacuum, and chromatographed on silica gel (DCM−hexane, 50:50, v/v) to give **10a** as an off-white powder (30 mg; yield, 24%); mp 113−114 °C. ^{1}H NMR: δ 7.81 (t, J = 1.4 Hz, 1H), 7.75 (dt, J_1 = 7.88 Hz, J_2 = 1.34 Hz, 1H), 7.65 (dt, J_1 = 7.84 Hz, J_2 = 1.33 Hz, 1H), 7.48 (t, J = 8.0 Hz, 1H) 7.18 (d, J_2 = 1.6 Hz, 1H). ^{13}C NMR: δ 169.1 (d, J = 285.7 Hz), 135.8, 135.0, 132.2, 130.0 (d, J = 19.2 Hz), 129.4, 123.6, 119.7 (d, J = 5.03 Hz), 117.8, 113.1, 86.6, 84.9. ^{19}F-NMR: δ −77.7 (s, 1F). HRMS (ESI+): calcd for $C_{12}H_6FN_2S$ 229.0231, found 229.0236. HPLC purity: 99.85%.

3-((2-Fluorothiazol-4-yl)ethynyl)-5-fluorobenzonitrile (10b). The method described for **10a** was applied to **7b** and gave **10b** as a white powder (65 mg; yield, 72%); mp 128−130 °C. ^{1}H NMR: δ 7.81 (t, J = 1.4 Hz, 1H), 7.75 (dt, J_1 = 7.88 Hz, J_2 = 1.34 Hz, 1H), 7.65 (dt, J_1 = 7.84 Hz, J_2 = 1.33 Hz, 1H), 7.48 (t, J = 8.0 Hz, 1H) 7.18 (d, J_2 = 1.6 Hz, 1H). ^{13}C NMR: δ 169.2 (d, J = 286.0 Hz), 161.9 (d, J = 251.7 Hz), 131.2 (d, J = 3.5 Hz), 129.6 (d, J = 19.1 Hz), 125.7 (d, J = 9.7 Hz), 123.2 (d, J = 22.8 Hz), 120.5 (d, J = 4.9 Hz), 119.5 (d, J = 24.8 Hz), 115.4, 114.4 (d, J = 10.2 Hz), 86.6, 84.9 (d, J = 3.6 Hz). ^{19}F-NMR: δ −109.02 (s, 1F), −77.2 (s, 1F). HRMS (ESI+): calcd for $C_{12}H_5F2N_2S$ 247.0142, found 247.0133. HPLC purity: 100.00%.

2-(3-((2-Fluorothiazol-4-yl)ethynyl)phenyl)acetonitrile (10c). The method described for **10a** was applied to **7c** and gave **10c** as a beige powder (68 mg; yield, 78%); mp 106−108 °C. ^{1}H NMR: δ 7.52 (m, 2H), 7.47 (s, 1H), 7.35 (m, 2H), 3.76 (s, 2H). ^{13}C NMR: δ 170.1 (d, J = 285.1 Hz), 137.9, 136.1, 131.5 (d, J = 30.1 Hz), 131.4, 130.5, 129.5, 128.7, 126.4, 123.3, 117.5, 89.2, 83.2, 23.6. ^{19}F-NMR: δ −78.05 (s, 1F). HRMS (ESI+): calcd for $C_{13}H_8FN_2S$ 243.0389, found 243.0383. HPLC purity: 98.85%.

2-Fluoro-4-((3-methoxyphenyl)ethynyl)thiazole (10d). The method described for **10a** was applied to **7d** and gave **10d** as a white crystals (70 mg; yield 65%); mp 64−66 °C. ^{1}H NMR: δ 7.26 (t, 1H, J = 7.94 Hz), 7.12 (dt, 1H, J = 7.96 Hz, J = 1.20 Hz), 7.10 (s, 1H), 7.06 (dd, 1H, J = 2.6 Hz, J = 1.40 Hz), 6.92 (ddd, 1H, J = 8.32 Hz, J = 2.60 Hz), 3.81 (s, 3H). ^{13}C NMR: δ 169.2 (d, J = 284.80 Hz), 159.5, 130.9 (d, J = 18.87 Hz), 129.7, 124.6, 123.1 (1C), 118.6 (d, J = 4.70 Hz), 116.7, 116.0, 89.4, 82.7, 55.5. ^{19}F-NMR: δ −78.23 (s, 1F). HRMS (ESI+): calcd for $C_{12}H_9FNOS$ 234.0389, found 234.0383. HPLC purity: 98.95%.

mGlu$_5$ Binding Assay and Pharmacological Screen. The prepared ligands were assayed for binding to rat brain mGlu$_5$ receptors by the National Institute of Mental Health (NIMH) Psychoactive Drug Screening Program (PDSP) in an assay using [^{3}H]MPEP (1.0 nM) as radioligand.

The high-affinity ligand **10b** was also screened by the PDSP for binding to a wide variety of receptor and binding sites (5-HT$_{1A}$, 5-HT$_{1B}$, 5-HT$_{1D}$, 5-HT$_{1E}$, 5-HT$_{2A}$, 5-HT$_{2B}$, 5-HT$_{2C}$, 5-HT$_3$, 5-HT$_{5A}$, 5-HT$_{6,7}$, α_{1A}, α_{1B}, α_{1D}, α_{2A}, α_{2B}, α_{2C}, β_{1-3}, BZP rat brain site, D$_{1-5}$, DAT, DOR, GABA$_A$, KOR, H$_{1-4}$, M$_{1-5}$, mGlu$_1$, mGlu$_2$, mGlu$_4$, mGlu$_6$, mGlu$_8$, MOR, NET, NMDA PCP site, SERT, σ1−2). Full details of the assays used by the PDSP may be found at their Web site (http://pdsp.med.unc.edu/indexR.html).

Radiochemistry. NCA [^{18}F]fluoride ion was obtained through the ^{18}O(p,n)^{18}F nuclear reaction by irradiating [^{18}O]water (95 atom %) for 90−120 min with a proton beam (17 MeV; 20 μA) produced with a PET trace cyclotron (GE Medical Systems, Milwaukee, MI). Radioactivity was measured with a calibrated ionization calibrator (Atomlab 300; Biodex Medical Systems, Shirley, NY) and corrected for background and physical decay. Radiochemistry was performed in a lead-shielded hot-cell for personnel safety with a Synthia MKII Lab System apparatus equipped with a microwave-heated reactor cavity.[27] The reactor cavity was linked via an RF coaxial cable to a controller of both irradiation time and power placed on the outside of the hot-cell. Reactions were performed in a V-vial (1 mL) equipped with a screw-on cap and septum (Tuf-Bond Teflon/silicone). The septum was pierced with a vent needle that was connected to a glass vial (20 mL) to collect any emitted solvents and also to a charcoal trap to retain any breakthrough of volatile radioactive species. Liquid handling was achieved with an Aspec autoinjector/dispenser which forms part of the Synthia apparatus. Other operations in the radiosyntheses and purification procedures were controlled by a Visual Chemistry-based recipe.

Cyclotron-produced [^{18}F]fluoride ion (50−100 mCi) in ^{18}O-enriched water (350−500 μL) was dried in the V-vial in the presence of Kryptofix 2.2.2 (13 μmol; 5 mg), K_2CO_3 (3.6 μmol, 0.5 mg) in MeCN-H_2O (9:1 v/v, 100 μL). Microwave heating (90 W in 3 pulses of 2 min) was applied under nitrogen gas flow (200 mL/min) to speed up the removal of MeCN-H_2O azeotrope. The acetonitrile (500 μL) addition and evaporation were repeated twice. Precursor for labeling (∼1.0−1.5 mg) in MeCN (100 μL) was then introduced into the sealed V-vial and heated at 130 °C (50−90 W in five pulses of 2 min). The reaction mixture was then diluted with water (0.75 mL) and injected onto a Luna C18 column (5 μm, 250 mm × 10 mm) eluted at 4 mL/min with MeCN−H_2O with MeCN at 45% (v/v) for 2 min and then 75% for 20 min and finally 25% for 30 min. The radioactive product was collected and measured for the calculation of decay-corrected radiochemical yield.

Measurement of Specific Radioactivity. The specific radioactivity of [^{18}F]**10b** was calculated by injecting a sample of known radioactivity content (0.1−0.4 mCi) into a mass-calibrated analytical HPLC system, comprising a Luna C18 column (5 μm, 4.6 mm × 250 mm; Phenomenex) eluted with MeCN−10 mM $HCOONH_4$ (60:40 v/v) at 2 mL/min with eluate monitored for absorbance at 254 nm. Specific radioactivity was calculated as the measured mass of **10b** divided by the activity of [^{18}F]**10b**, corrected for physical decay to the time of product isolation. The specific radioactivity of [^{18}F]**10a**, was measured similarly.

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