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Organomediated cleavage of benzoyl group enables an efficient synthesis of 1-(6-nitropyridin-2-yl)thiourea and its application for developing ^{18}F-labeled PET tracers

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Abstract

A novel organomediated cleavage of benzoyl group using ethane-1,2-diamine and acetic acid under neutral condition enables an efficient synthesis of 1-(6-nitropyridin-2-yl)thiourea, which previously has been challenging to prepare by conventional methods. The successful synthesis of 1-(6-nitropyridin-2-yl)thiourea as a synthon permits development of a variety of ^{18}F labeled heterocycles as PET imaging ligands such as N-(pyridin-2-yl)thiazol-2-amine derivatives. The utility of this synthon is demonstrated with the synthesis of a ^{18}F-labeled PET tracer for studying prion disease. *In vitro* autoradiography using this PET tracer on sagittal rat brain slices showed highest accumulation of radioactivity in the hippocampus, cortex, and striatum, in accordance with reported immunostaining of PrP^c in rat brain.

Keywords

Cleavage reaction; Heterocycles; Organomediated reaction; *ortho*-Fluoropyridines; Positron emission tomography

1. Introduction

1-(Pyridin-2-yl)thioureas are versatile building blocks for synthesizing *N*-(pyridin-2-yl)thiazol-2-amine derivatives, which are used to construct a variety of heterocycles and

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

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bioactive compounds. These heterocycle compounds include anti-prion compound **1** [1–3], metabotropic glutamate receptor 4 (mGluR4) positive allosteric modulator (PAM) **2** [4], anti-diabetic glucokinase activator **3** [5,6], anti-tubercular agent **4** [7], nerve growth factor TrKA inhibitor **5** [8], and antileishmanial agent **6** et al. (Fig. 1) [9].

Positron emission tomography (PET) is a technology currently available for *in vivo* assessment and quantification of specific biological and pharmacological processes in man and animal [10]. The application of PET relies on development of radiolabeled tracers possessing selectivity for targets of interest. Fluorine-18 (^{18}F) has been predominately used for PET tracers in both clinic and research due to its favorable physical and nuclear characteristics, as well as its relatively long half-life compared to other positron emitting radioelements such as ^{11}C, ^{13}N, and ^{15}O, allowing transportation of ^{18}F-labeled compounds to off-site facilities.

Furthermore, fluorine is considered a classical bioisostere for replacement of univalent atoms and groups such as H, –CH_3, and as a substitute for lone pairs of electrons in medicinal chemistry. Since fluorine and hydrogen share similar van der Waal's radii, steric perturbations are of minimal concern, thus F-for-H substitutions are often well tolerated and useful in development of small molecule drugs and PET tracers [11]. Moreover, fluorine atom substitution increases metabolic stability [12]. An ^{18}F may be introduced to the *ortho* position of the pyridine in structures **1**–**6** (Fig. 1) to generate PET tracers for studying these targets.

Pyridine derivatives are one of the most commonly studied heterocycles for incorporation of [^{18}F]fluoride by S_NAr reaction and thus the resultant *ortho*-[^{18}F]fluoropyridines have emerged as a widely used functionality in PET tracers [13–15]. Pyridine has lower LUMO energy at *ortho* and *para* position than benzene, which allows the direct ^{18}F-substitution by using either Br, I, Cl, NO_2 or N^+Me_3 as a leaving group at *ortho* and *para* positions. It is reported that when 2-nitropyridine is subjected to [^{18}F]KF/K_{222} in DMSO at 120 °C for 10 min 2-[^{18}F]-fluoropyridine is obtained in 76% RCY, while using the trimethylammonium triflate precursor gives an 81% RCY at 120 °C for 5 min [16]. The ^{18}F-substitution using Br, I, or Cl as leaving groups at *ortho* and *para* positions of pyridine requires elevated temperatures (150–180 °C). Although trimethylammonium triflate is a superior leaving group compared to the nitro group, there are some issues to limit its application in more complicated heterocycles and biomolecules: 1) The corresponding starting material is not commercially available which requires multistep syntheses; 2) It displays divergent reactivities under certain reaction conditions such as C-, O- & heteroatom arylation; O- & C-H methylation and a range of metal-catalyzed cross-coupling methodologies [17], which is preferably to introduce the trimethylammonium triflate at the late stage of the synthesis to avoid these conditions; 3) The *ortho*$N^+Me_3^-$OTf pyridine analogues are prepared from the *ortho*-NMe_2 pyridine analogues by using methyl triflate [18]. Since methyl triflate is a powerful methylating agent, it may react with many functional groups including very poor nucleophiles such as aldehydes, amides, and nitriles and some *N*-heterocycles. On the other hand, methyl triflate is also extremely hazardous. Therefore, due to the difficulty in preparation of the trimethylammonium triflate analogues we selected NO_2 as the leaving group at *ortho*-pyridine position for the ^{18}F-substitution in current approach. Because

the ^{18}F-substitution is preferably carried out at the last stage in a synthetic pathway, *ortho*-nitropyridine derivatives may offer better stability to different chemical reactions and transformations.

The *ortho*-nitropyridine derivative, 1-(6-nitropyridin-2-yl)thiourea **8**, potentially can be a useful synthon for synthesizing precursor **9**, thereby promoting development of ^{18}F labeled heterocycles [^{18}F]**10** as PET tracers for numerous targets and applications (Scheme 1). To the best of our knowledge, there is no reported effective synthesis of **8.** We disclose here an organomediated cleavage of benzoyl (Bz) group using ethane-1,2-diamine and acetic acid under neutral conditions enabling an efficient synthesis of **8a**, which could be used to synthesize ^{18}F-labeled heterocycles for PET. As an example of this application, **8a** was used to prepare the PET radioligand [^{18}F]**10a** for studying prion disease [1,3].

2. Results and discussion

Initially, syntheses of the pyridyl thiourea derivatives **8a** and **12** were attempted using the reactions of pyridin-2-amines **7a** and **11** with a thiocyanate that has often been applied to the synthesis of arylthioureas (Scheme 2) [19–24]. However, neither method A nor B gave the desired product **8a** or **12**. When the reactions were carried out by using method A, no products **8a** or **12** were detected and both starting materials **7a** and **11** remained in the reaction mixture (ESI, Table S1, entries 1 and 2). When acidic method B was used, no reaction occurred with **11** and NH_4SCN (ESI, Table S1, entry 3). While more than 50% of **7a** was consumed by using method B, no desired product **8a** was detected and several unidentified by-products were observed in this reaction. Makam et al. also disclosed that the synthesis of pyridyl thioureas was not successful by using thiocyanate under con. HCl condition [25]. The failure for synthesizing thioureas from *ortho*-NO_2 or *ortho*-F aminopyridine **7a** and **11** might be due to the decreased nucleophilicity of the amino group on the electron deficient pyridine ring and the reactive nature of the *ortho*-nitro group.

An alternative 2-step reaction for the synthesis of pyridyl thioureas consists of formation of the *N*-(arylcarbamothioyl)benzamide derivative **15** *via* the reaction of pyridylamine **13** with benzoyl isothiocyanate **14**, followed by cleavage of Bz group to give the pyridyl thiourea **16** (Scheme 3) [1,3,6,26]. We studied the synthesis of the *ortho*-NO_2 and *ortho*-F pyridyl thiourea by using the 2-step reaction.

The reaction of 4-chloroaniline **17** with benzoyl isothiocyanate **14** was accomplished within 5 min, giving the corresponding thiourea **18** in 99% yield (Table 1, entry 1). The reaction of 6-fluoropyridin-2-amine **11** with **14** was completed in 30 min to offer **19** in 98% yield (Table 1, entry 2), which indicates the lower reactivity of **11** compared to aniline **17**. The reaction of **7a** with **14** was much slower, and unreacted **7a** could still be detected after 4 h under reflux in THF, (Table 1, entry 3). By extending the reaction time to 8 h, compound **20** was obtained in 97% yield. This further suggests that the strong electron-withdrawing nitro group significantly reduces the nucleophilicity of the amino group. Alternatively, compound **20** could be obtained in 95% yield within 10 min by refluxing **7a** with **14** in toluene (Table 1, entry 5). Compound **20** precipitated out from the reaction mixture as light brown needle crystals when cooling down to room temperature (rt).

With intermediates **19** and **20**, the cleavage of the Bz group was subsequently carried out under conventional basic conditions [3,8,25]. When **19** was treated in EtOH containing 5% aqueous sodium hydroxide solution (1.0 M), >95% of compound **12** (Table 2, entry 1) was obtained in 20 min. However, when **20** was treated in a similar condition, no desired product **8a** was detected (Table 2, entry 2), and a large amount of red solid precipitated out of the solution in a few seconds. The collected solid showed very low solubility in DMSO and was later identified as oligomerization products by LC-MS analysis (ESI, Figure S1). Furthermore, when the reaction of **20** was carried out by using a weaker base such as K_2CO_3 or the organic base TEA (Table 2, entries 4 and 5), it also resulted in complicated reaction mixtures with red precipitate.

The benzoyl group has been applied to protection of hydroxyl and amino groups in organic synthesis and is removed by bases, acids such as HCl or HBr-AcOH [27], and hydrazine [28,29]. Since the *ortho*-nitro group on pyridine is reactive and is not stable under the basic conditions, we studied other reported deprotection methods. Results showed that although **20** was relatively stable under acid conditions, no reaction was observed by using HBr-AcOH mixture (37% HBr in HOAC) at RT for 10 h (Table 2 entry 6). When **20** was heated to reflux in either HBr-HOAc or HCl (32 wt% in H_2O), it led to complicated reaction mixtures (Table 2 entries 7 and 8), in which substitution of nitro group by Br or Cl was detected by LC-MS, respectively (ESI, Figures S2 and S3). By using the hydrazine method, **20** was completely consumed, however, no trace amount of product **8a** could be detected (Table 2 entry 9 and Figures S4 and S5).

Inspired by our previous experience with organocatalyzed activation (primary amine-acid system) of carbonyl groups with low reactivity including alkyl and aryl ketones [30–32], α,β-unsaturated ketones [33,34], glycosides [32], and esters (furanones) [31,33], the organomediated cleavage of Bz group on the thiourea was investigated with different amine-acid systems (Table 2, entries 8–13). As the results showed, both the primary amine-acid **A** and the secondary amine-acid **B** with only one amino group did not promote this reaction at rt (Table 2, entries 10 and 11), although the starting material **20** was stable and was recovered under these neutral conditions. We then turned to ethane-1,2-diamine and acetic acid combination **C**, which had been successfully used for organocatalyzed domino reaction as well as Michael addition reaction [30,31]. Interestingly, the reaction of **20** with one equiv of **C** in MeOH at rt gave the desired product **8a** in 17% yield with no by-product found (Table 2, entry 12). When the reaction was refluxed in methanol (65 °C) for 30 min, compound **8a** was obtained in 55% yield (Table 2, entry 13). Finally, the cleavage of Bz group from **20** could be accomplished in 97% yield with 5 equiv of **C** by refluxing in methanol for 20 min (Table 2, entry 14). Product **8a** crystalized from the reaction mixture as a light-yellow solid when cooling down. In a similar condition, the cleavage of Bz group from **19** gave **12** in 98% yield (Table 2, entry 15). These results demonstrate that the organomediated cleavage of Bz group from thioureas under neutral condition is a mild and general deprotection method specifically useful for basesensitive compounds.

This interesting 1,2-ethanediamine-AcOH mediated Bz-deprotection method prompted us to examine the reaction mechanism (Scheme 4). Since the mono primary amine did not promote the reaction, we propose that both amino groups of 1,2-ethanediamine

synergistically participate in this reaction. Upon forming the iminium intermediate **I** by the reaction with an amino group, another amino group attacks the carbon of the iminium to form a 5-membered cyclic intermediate **II** and then the nucleophilic substitution by oxygen of water leads to the formation of the thiourea **8a** and the intermediate **III** that releases the Bz group as the diamine adduct **IV**. The Bz-diamine adduct **IV** was isolated from the reaction mixture and confirmed by LC-MS (ESI Figure S6).

The stability of 1-(6-nitropyridin-2-yl)thiourea **8a** under basic conditions was then studied by *in situ* ^{1}H NMR and LC-MS. In the ^{1}H NMR study, **8a** disappeared after addition of NaOH to the solution (Figure S7), wherein the soluble portion of the oligomerization products were revealed by the LC-MS analysis (ESI, Figure S1). This result clearly explains why compound **8a** could not be prepared under the conventional conditions because the *ortho*-nitro group does not tolerate basic conditions.

As discussed previously, **8a** is a useful synthon for synthesizing *N*-(6-nitropyridin-2-yl)thiazol-2-amine derivatives which can serve as precursors for direct ^{18}F-radiolabeling to generate PET tracers. To demonstrate the feasibility, the reactions of **8a** with 2-bromo-4′-phenylacetophenone **21** was carried out by refluxing in acetonitrile to give **9a** in near quantitative yield (Scheme 5). In a similar reaction, ^{18}F labeled compound **10a**, which may have therapeutical effect for prion disease, was prepared [1,3]. The radioligand [^{18}F]**10a** could serve as a useful tool for both disease imaging and drug development.

The radio-synthesis of [^{18}F]**10a** was initially attempted *via* the direct ^{18}F-fluorination of **9a** (Scheme 6), however, the reaction resulted in only trace amount of [^{18}F]**10a** and several unidentified by-products (Figure S8). Since the free amino group could interfere with the reaction, it should be protected to avoid side reactions. The Boc-protection of the amino group in **9a** was achieved by using di-*tert*-butyl dicarbonate and NaI-DMAP co-catalyst in THF at rt to give **22** in >95% yield as a white solid.

Finally, the radiosynthesis of [^{18}F]**23** from **22** was accomplished by using either [^{18}F]/K_2CO_3/K_{222} or [^{18}F]TEAF in acetonitrile (Scheme 7), which gave [^{18}F]**23** in >85% yield along with 5–10% of [^{18}F]**10a** in both reactions. The reaction mixture was treated with trifluoroacetic acid (TFA) at 25 °C and then purified by HPLC to obtain [^{18}F]**10a** in 52% radiochemical yield (RCY) at the end of synthesis (decay corrected) with high purity (>95%). The radiolabeled compound [^{18}F]**10a** was co-injected with the cold compound **10a** to confirm the identity of the radiolabeled product (ESI Figure S9).

In vitro autoradiography experiments of [^{18}F]**10a** (93 kBq/mL, 1.0–2.0 nM) were performed on sagittal rat brain slices (20 μm). Fig. 2 depicts a heterogeneous distribution of radioactivity in rat brain sections at the baseline with highest accumulation of radioactivity in the hippocampus, neocortex, striatum and thalamus, the regions known to express high levels of PrPc, in accordance with the reported immunostaining of rat brain.[35,36] The rat brain slices that were coincubated with [^{18}F]**10a** and 10 μM of cold compound **10a** displayed a substantially reduced and homogeneous accumulation of radioactivity (Fig. 2, self-blocking). These results suggested that ligand [^{18}F]**10a** had excellent *in vitro* binding specificity and further *in vitro* and *in vivo* evaluation of the compound is underway.

3. Conclusion

Compound **8a** and its derivatives could be used to construct a series of bioactive heterocycles such as *N*-(pyridin-2-yl)thiazol-2-amine derivatives, which could be utilized for PET tracer development toward different imaging targets. However, synthesis of **8a** from 6-nitropyridin-2-amines **7a** was challenging due to the reactive nature of the *ortho*-nitro group and significantly reduced nucleophilicity of the amino group. Our study found that the cleavage of Bz group from thiourea **20** was not achievable by conventional methods since the *ortho*-nitropyridine was not stable under basic conditions. Therefore, a novel organomediated method was developed using an ethane-1,2-diamine and acetic acid system to remove the Bz group under neutral condition. By using this method, **8a** was efficiently synthesized in high yield under mild conditions. To further demonstrate the feasibility for its application on PET tracer development, the coupling of **8a** with 2-bromo-4′-phenylacetophenone **21** was carried out to afford **9a** (>98%). Synthesis of the radioligand [^{18}F]**10a** was successfully accomplished and was further applied to the *in vitro* autoradiography on sagittal rat brain slices, which showed highest accumulation of radioactivity in the hippocampus, cortex, and striatum in agreement with the reported immunostaining of PrP^{c} in rat brain.

4. Experimental section

4.1. General methods

All reagents and starting materials were obtained from the commercial sources including Sigma-Aldrich (St. Louis, MO), Thermo Fisher Scientific, Oakwood Products, Inc., Matrix Scientific and used as received. The reactions were monitored by TLC using a UV lamp monitored at 254 nm. If necessary, the reactions were also checked by LC − MS using the Agilent 1200 Series HPLC system coupled with a multiwavelength UV detector and a model 6310 ion trap mass spectrometer (Santa Clara, CA) equipped with a Luna C18 column (Phenomenex, 100 × 2 mm, 5 μm, 100 Å). The RP-HPLC was carried out by using a 7 min gradient method (LC-MS Method): the mobile phase A was water with 0.1% Formic acid (FA) added; mobile phase B was acetonitrile with 0.1% FA added; gradient: 5% B to 95% B from 0 to 3 min, 95% B from 3 to 4.5 min, 95% to 5% B from 4.5 to 5 min, 5% B from 5 to 7 min; flow rate at 0.7 mL/min. The silica gel used in flash column chromatography was from Aldrich (Cat. 60737, pore size 60 Å, 230–400 mesh). The products were identified by ^{1}H NMR and ^{13}C NMR using a Varian 500 MHz spectrometer. Chemical shifts were expressed as ppm and calculated downfield or upfield from the NMR signal of the reference standard. *J* was expressed as Hz, and its splitting patterns were reported as s, d, t, q, or m. Unless otherwise specified, the purity of all new compounds was over 95% determined by HPLC.

4.2. Radiochemistry procedure

[^{18}F]Fluoride was generated by a GE PETtrace 16.5 Mev cyclotron (GE Healthcare, Waukesha, WI, USA) using ^{18}O enriched water (Isoflex Isotope, San Francisco, CA) with proton bombardment. Fluorine-18 labeling of [^{18}F]**10a** was accomplished in one pot *via* two steps. First, [^{18}F]fluoride in ^{18}O-enriched water was passed through a QMA Sep-Pak

cartridge (Waters, Milford, MA) to trap [^{18}F]fluoride ions, which was washed off by a mixture of acetonitrile (0.9 mL) and water (0.1 mL) solution containing 5.0 mg of tetraethylammonium bicarbonate. And the solvents were evaporated at 115 °C in a stream of nitrogen. To remove water completely, 1.0 mL of acetonitrile was added and evaporated in a stream of nitrogen three more times. To the residue containing [^{18}F]fluoride was added **22** (2.0 mg) in 0.7 mL of acetonitrile. The resulting solution was heated to 85 °C for 10 min and then cooled to room temperature, and the solvent was removed by a stream of nitrogen (2 mins). Then 0.5 mL of TFA was added to the reactor for 5 mins at room temperature. The resulting mixture was diluted with water and neutralized by NaOH then purified by a semipreparative HPLC (Waters 4000 system equipped with an Xbridge BEH C18 OBD column: 130 Å, 5 μm, 10 × 250 mm) by eluting with a solution of water and acetonitrile (20:80) at a flow rate of 4 mL/min to give the fractions containing [^{18}F]**10a**. The combined fraction was diluted with water to 40 mL and loaded on a C18 Sep-Pak column to give the final formulation of [^{18}F]**10a** in saline containing 10% ethanol. The purity of [^{18}F]**10a** was over 99% that was analyzed by an analytical HPLC (Waters 2487 series equipped with a UV detector and a BIOSCAN radioactivity detector and an ACE 5 C18-AR column: 250 × 10 mm, 5 μm). The identity of [^{18}F]**10a** was confirmed by co-injection of the cold compound **10a** in HPLC analysis.

4.3. In vitro autoradiography

Rat brains were cut into sections 20 μm-thick in a cryostat, mounted on Histobond adhesion slides and used for [^{18}F]**10a** phosphor screen autoradiography. Brain slices were pre-incubated with Tris-HCl buffer (50 mM), $MgCl_2$ (1.2 mM) and $CaCl_2$ (2 mM) solution for 10 min at ambient temperature, followed by incubation in 10% neutral buffered formalin for another 10 min. The brain slices were then washed with Tris-HCl buffer followed by incubation with [^{18}F]10a (93 kBq/mL, 1–2 nM) for another 45 mins. For the blocking studies, the rat brain slices were incubated with [^{18}F]**10a** containing cold compound **10a** (10 μM) to determine the specificity of radioligand binding. After incubation, brain slices were rinsed with ice-cold buffer three times for 2 min and then were dipped in cold distilled water for 10 s. The brain sections were allowed to air dry before transfer of the slides to a storage phosphor screen (BAS-MS2025, GE Healthcare, NJ, USA) that had been photobleached immediately prior by exposure on a white light box for a minimum of 15 min. Autoradiograms were obtained by a GE Typhoon FLA 9000 Imager and regions of interest (ROIs) were carefully drawn.

4.4. General synthetic procedures

General procedure A for the synthesis of *N*-(arylcarbamothioyl) benzamides. To a solution of the corresponding pyridin-2-amine (3.0 mmol) in THF (5.0 mL) was added benzoyl isothiocyanate (1.2 equiv). The reaction mixture was refluxed until pyridin-2-amine was consumed. After cooling to rt, the reaction mixture was subjected to silica gel column chromatography directly using ethyl acetate and hexanes as eluents to give pure products

General procedure B for the synthesis of **20**. To a solution of 6-nitropyridin-2-amine (3.0 mmol) in toluene (5.0 mL) was added benzoyl isothiocyanate (1.2 equiv). The reaction mixture was refluxed for 10 min. After cooling, needle crystals were collected by filtration.

General procedure C for the synthesis of *N*-(pyridin-2-ylcarbamothioyl)benzamides. To a solution of *N*-(arylcarbamothioyl) benzamide (2.0 mmol) in MeOH (5.0 mL) was added ethane-1,2-diamine (10.0 mmol) and acetic acid (20.0 mmol). The reaction mixture was refluxed and monitored by HPLC until *N*-(arylcar-bamothioyl)benzamide was consumed. After cooling to room temperature, the products were collected by filtration. The filtrates were further subjected to silica gel column chromatography directly using ethyl acetate and hexanes as eluent to give pure products.

General procedure D for the synthesis of *N*-(pyridin-2-yl)thiazol-2-amine derivatives. To a solution of *N*-(pyridin-2-ylcarbamothioyl) benzamides (0.7 mmol) in acetonitrile (5.0 mL) was added 2-bromo-4′-phenylacetophenone (0.7 mmol). The reaction mixture was refluxed and a large amount of solid precipitated out within 2 min. The solid was collected by simple filtration as pure products.

General procedure E for the Boc protection. To a solution of **9a** or **10a** (0.5 mmol) in THF (5 mL) was added Di-*tert*-butyl dicarbonate (2.5 mmol), DMAP (2.5 mmol) and NaI (0.5 mmol). The reaction mixture was stirred at room temperature for 30 s and was subjected to silica gel column chromatography using ethyl acetate and hexanes as eluents to give pure product.

4.5. Synthesis

Compound **18** was prepared according to the general procedure A in 99% yield as white solid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 9.10 (s, 1H), 7.97–7.80 (m, 2H), 7.77–7.60 (m, 3H), 7.54 (t, J = 7.8 Hz, 2H), 7.48–7.31 (m, 2H).

Compound **19** was prepared according to the general procedure A in 98% yield as white solid. 1H NMR (500 MHz, Chloroform-*d*) δ 9.06 (s, 1H), 8.78 (dd, J = 7.9, 2.1 Hz, 1H), 7.93–7.88 (m, 2H), 7.86 (q, J = 8.0 Hz, 1H), 7.75–7.61 (m, 1H), 7.59–7.45 (m, 2H), 6.79 (dd, J = 8.0, 2.7 Hz, 1H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 177.3, 166.5, 162.0 (d, J = 242.6 Hz), 149.5 (d, J = 14.3 Hz), 142.7 (d, J = 7.5 Hz), 134.0, 131.5, 129.4, 127.7, 112.5 (d, J = 4.4 Hz), 106.6 (d, J = 35.2 Hz).

Compound **20** was prepared according to the general procedure A in 90% yield as light yellow solid. 1H NMR (500 MHz, Chloroform-*d*) δ 9.24 (d, J = 6.9 Hz, 1H), 9.15 (s, 1H), 8.23–8.01 (m, 2H), 7.91 (d, J = 7.6 Hz, 2H), 7.67 (t, J = 7.4 Hz, 1H), 7.56 (t, J = 7.7 Hz, 2H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 178.2, 166.6, 155.1, 150.5, 141.4, 134.2, 131.3, 129.4, 127.7, 121.5, 115.0.

Compound **12** was prepared according to the general procedure C in 98% yield as white solid. 1H NMR (500 MHz, Chloroform-*d*) δ 10.20 (s, 1H), 9.46 (s, 1H), 7.74 (q, J = 8.0 Hz, 1H), 7.14 (s, 1H), 6.81 (d, J = 7.8 Hz, 1H), 6.60 (dd, J = 8.0, 2.0 Hz, 1H). ^{19}F NMR (470 MHz, Chloroform-*d*) δ −68.5. ^{13}C NMR (126 MHz, Chloroform-*d*) δ 181.0, 161.4 (d, J = 244.5 Hz), 151.0 (d, J = 14.0 Hz), 143.4 (d, J = 8.4 Hz), 108.8 (d, J = 4.8 Hz), 103.0 (d, J = 34.1 Hz).

Compound **8a** was prepared according to the general procedure C in 97% yield as light brown solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.05 (s, 1H), 10.02 (d, J = 3.7 Hz, 1H), 9.24 (s, 1H), 8.12 (t, J = 8.0 Hz, 1H), 7.92 (d, J = 7.8 Hz, 1H), 7.56 (d, J = 8.2 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 181.2, 153.4, 152.23, 143.1, 119.4, 112.2. LC-MS (LC-MS Method): t_R = 2.97 min, m/z: $[M+H]^+$ Calcd for$C_6H_7N_4O_2S$ 199.0; Found 199.1.

Compound **9a** was prepared according to the general procedure D in 98% yield as light brown solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.07 (t, J = 8.0 Hz, 1H), 7.98 (d, J = 8.4 Hz, 2H), 7.82 (dd, J = 7.8, 2.7 Hz, 1H), 7.75–7.66 (m, 4H), 7.65 (d, J = 3.0 Hz, 1H), 7.51 (d, J = 8.3 Hz, 1H), 7.44 (t, J = 7.7 Hz, 2H), 7.34 (t, J = 7.3 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 159.5, 154.9, 151.7, 149.2, 141.9, 140.2, 139.7, 134.1, 129.5, 128.1, 127.5, 127.2, 127.0, 126.8, 117.8, 110.2, 108.1. LC-MS (LC-MS Method): t_R = 4.50 min, m/z: $[M+H]^+$ Calcd for $C_{20}H_{15}N_4O_2S$ 375.09; Found 375.1.

Compound **10a** was prepared according to the general procedure D in 99% yield as white solid. ^{1}H NMR (500 MHz, Chloroform-d) δ 7.87 (dd, J = 8.0, 5.6 Hz, 3H), 7.72 (d, J = 8.2 Hz, 2H), 7.63–7.54 (m, 2H), 7.44 (t, J = 7.6 Hz, 2H), 7.40–7.32 (m, 1H), 7.16 (d, J = 7.7 Hz, 1H), 7.00 (s, 1H), 6.73 (dd, J = 8.1, 2.0 Hz, 1H). ^{13}C NMR (126 MHz, Chloroform-d) δ 162.7, 161.9 (d, J = 246.9 Hz), 147.0 (d, J = 13.0 Hz), 143.8 (d, J = 8.2 Hz), 139.6, 139.6, 129.1, 128.3, 128.2, 127.1, 126.4, 125.7, 109.5 (d, J = 4.7 Hz), 104.4, 104.3 (d, J = 33.9 Hz). LC-MS (LC-MS Method, ESI): t_R = 4.01 min, m/z: $[M+H]^+$ Calcd for $C_{20}H_{15}FN_3S$ 348.1; Found 348.1.

Compound **22** was prepared according to the general procedure E in 99% yield as light yellow solid. ^{1}H NMR (500 MHz, Chloroform-d) δ 8.33 (d, J = 8.0 Hz, 1H), 8.21 (t, J = 7.9 Hz, 1H), 7.85 (d, J = 7.8 Hz, 1H), 7.65 (d, J = 8.2 Hz, 2H), 7.60–7.54 (m, 2H), 7.52 (d, J = 8.2 Hz, 2H), 7.41 (t, J = 7.6 Hz, 2H), 7.32 (t, J = 7.4 Hz, 1H), 7.24 (s, 1H), 1.47 (s, 10H). ^{13}C NMR (126 MHz, Chloroform-d) δ 160.4, 155.9, 151.5, 151.5, 149.9, 141.7, 140.8, 140.7, 133.1, 129.9, 128.9, 127.4, 127.3, 127.0, 126.4, 117.5, 108.95, 85.1, 28.1. LC-MS (LC-MS Method): t_R = 4.71 min, m/z: $[M+H]^+$ Calcd for $C_{25}H_{23}N_4O_4S$ 475.1; Found 475.0.

Compound **23** was prepared according to the general procedure E in 99% yield as white solid. ^{1}H NMR (500 MHz, Chloroform-d) δ 7.96 (q, J = 7.9 Hz, 1H), 7.74–7.66 (m, 2H), 7.60–7.55 (m, 2H), 7.55–7.50 (m, 2H), 7.41 (t, J = 7.6 Hz, 2H), 7.33 (dd, J = 7.9, 1.9 Hz, 2H), 7.21 (s, 1H), 7.02 (dd, J = 8.1, 2.8 Hz, 1H), 1.48 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-d) δ 162.8 (d, J = 244.1 Hz), 160.7, 151.9, 150.3 (d, J = 13.5 Hz), 149.9, 142.7 (d, J = 7.4 Hz), 140.84, 140.51, 133.6, 128.9, 127.4, 127.3, 127.0, 126.5, 121.1 (d, J = 4.9 Hz), 109.2, (d, J = 34.0 Hz), 108.6, 84.3, 28.1. LC-MS (LC-MS Method): t_R = 4.89 min, m/z: $[M+H]^+$ Calcd for $C_{25}H_{23}FN_3O_2S$ 448.1; Found 448.0.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Uncategorized References

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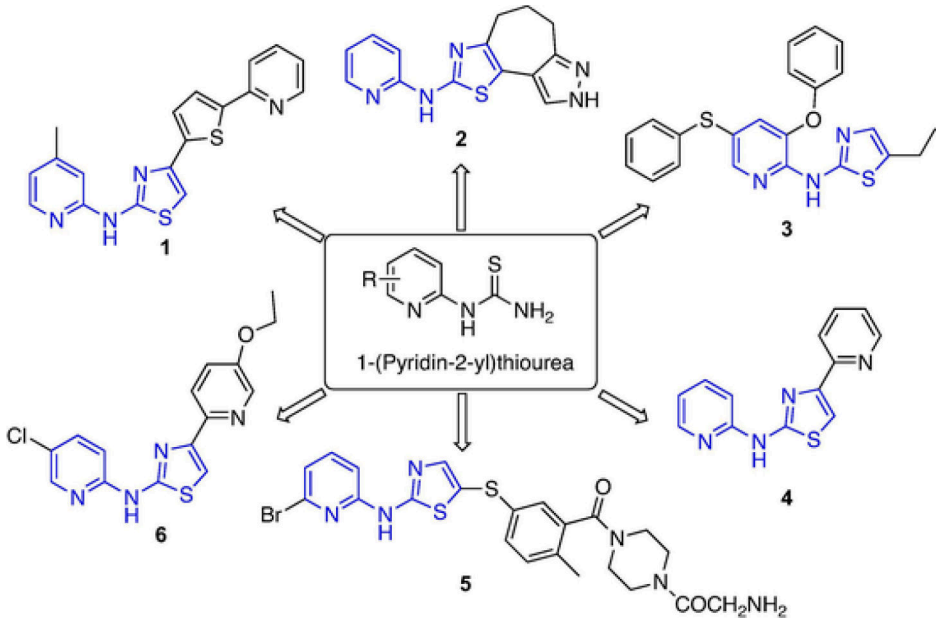


Fig. 1.
Examples of bioactive *N*-(pyridine-2-yl)thiazol-2-amine derivatives.

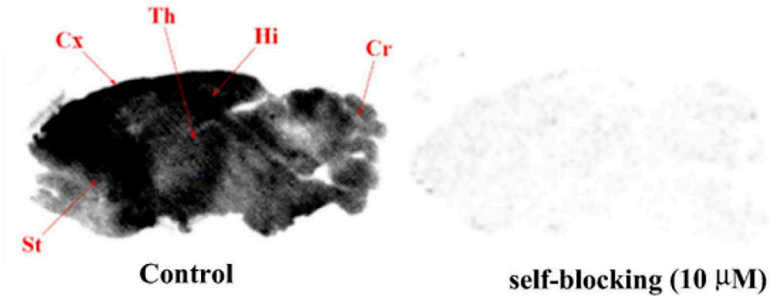
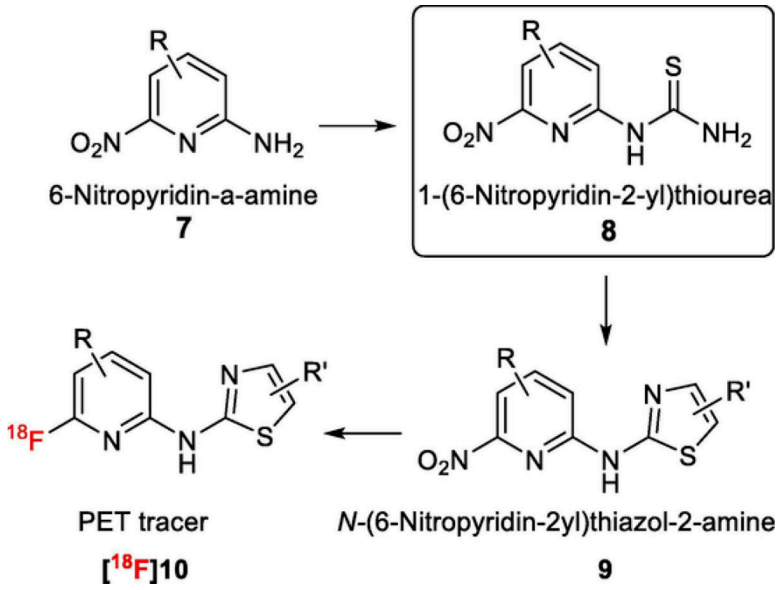


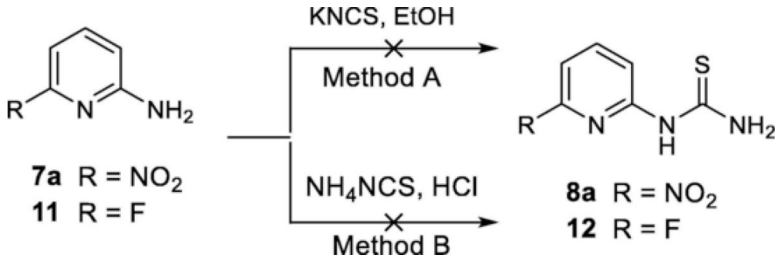
Fig. 2.

In vitro autoradiography of [^{18}F]**10a** on sagittal rat brain slices (20 μm). Anatomical regions are detailed in: St, Striatum; Cx, Cortex; Th, Thalamus; Hi, Hippocampus; Cr, Cerebellum.



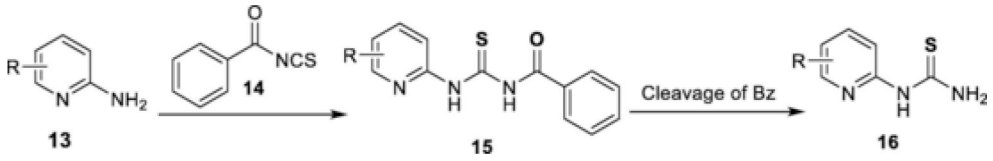
Scheme 1.

1-(6-Nitropyridin-2-yl)thioureas **8** could serve as a useful synthon for the development of ^{18}F labeled heterocycles [^{18}F]**10**.



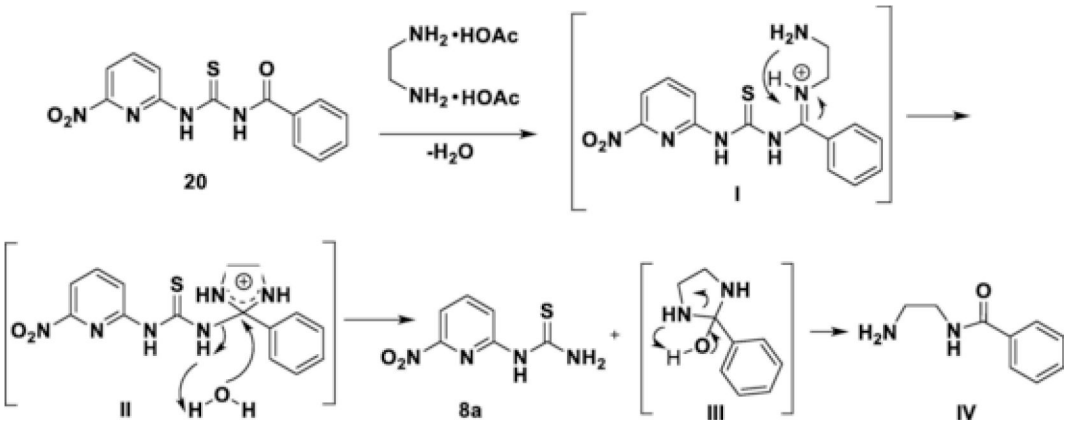
Scheme 2.

Reactions of **7a** and **11** with thiocyanates did not result in pyridyl thiourea **8a** or **12**.



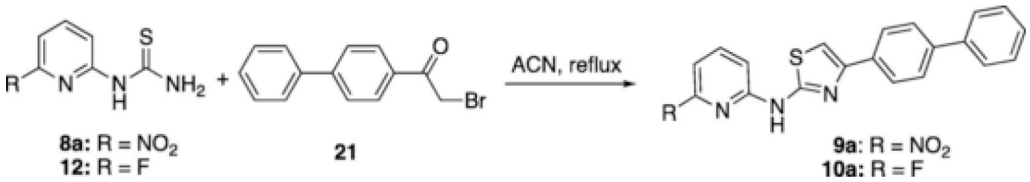
Scheme 3.

The 2-step reaction for the synthesis of the pyridyl thioureas.

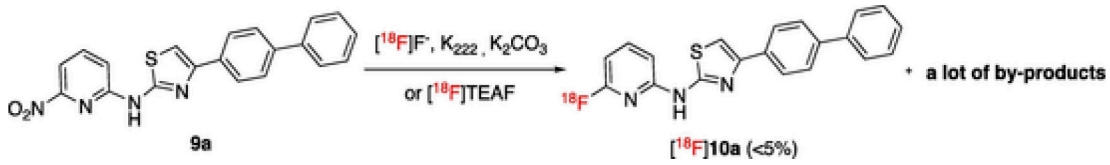


Scheme 4.

Proposed reaction mechanism for the deprotection of Bz from the thioureas **20**.

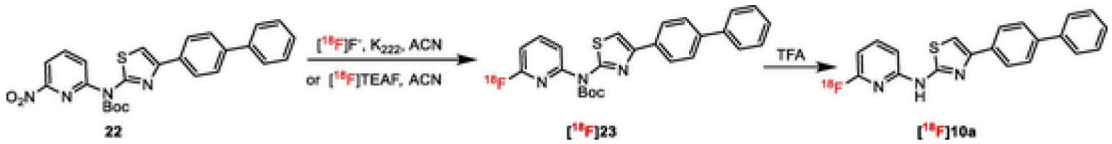


Scheme 5.
Synthesis of *N*-(pyridin-2-yl)thiazol-2-amine derivatives **9a** and **10a**



Scheme 6.

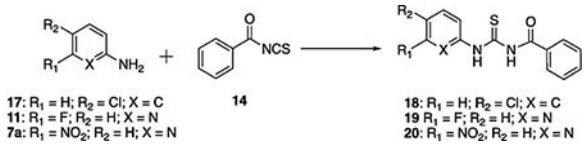
The direct ^{18}F-substitution of **9a** gave a complicated reaction mixture.



Scheme 7.
Radiosynthesis of **[^{18}F]10a** from precursor **22**.

Table 1

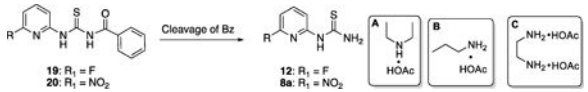
Synthesis of *N*-(arylcarbamothioyl)benzamide 18–20.



Entry	Solvent	Compound	Time (min)	Temperature	Product (Yield)
1	THF	17	<5	reflux	18 (99%)
2	THF	11	30	reflux	19 (98%)
3	THF	7a	240	reflux	20 (90%)
4	THF	7a	480	reflux	20 (97%)
5	Toluene	7a	10	reflux	20 (95%)

Table 2

Cleavage of Bz group from *N*-(pyridin-2-ylcarbamothioyl)benzamides **19** and **20**.



Entry	R	Reagents	solvent	T(°C)	Time (min)	Product (Yield)
1	F	NaOH	EtOH	reflux	20	**12** (99%)
2	NO_2	NaOH	EtOH	reflux	10	N.D[c]
3	NO_2	NaOH	EtOH	rt	10	N.D[c]
4	NO_2	K_2CO_3	EtOH	reflux	30	trace[c]
5	NO_2	TEA	EtOH	reflux	30	trace[c]
6	NO_2	HBr	HOAc	rt	600	N.D[d]
7	NO_2	HBr	HOAc	reflux	60	N.D[c]
8	NO_2	HCl	water	reflux	600	trace[c]
9	NO_2	NH_2NH_2	EtOH	reflux	60	N.D[c]
10[a]	NO_2	A	MeOH	rt	1200	N.D[d]
11[a]	NO_2	B	MeOH	rt	1200	N.D[d]
12[a]	NO_2	C	MeOH	rt	1200	**8a** (17%)
13[a]	NO_2	C	MeOH	reflux	30	**8a** (55%)
14[b]	NO_2	C	MeOH	reflux	20	**8a** (97%)
15[b]	F	C	MeOH	reflux	20	**12** (98%)

[a] One equiv of reagent was used.

[b] Five equiv of reagent were used.

[c] Complicated reaction mixtures.

[d] No clear reaction was observed and 20 remained intact in the medium