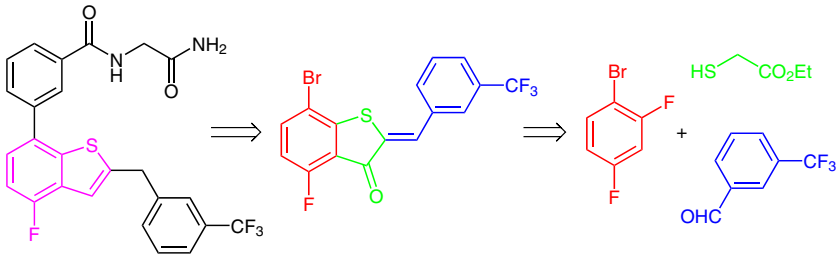
Synthesis N. Fukuda, T. Ikemoto Paper

Scalable and Straightforward Synthesis of a 2-Alkyl-7-Arylbenzothiophene as a GPR52 Agonist via a Hemithioindigo Derivative

Naohiro Fukuda*
Tomomi Ikemoto

Chemical Development Laboratories, Takeda Pharmaceutical Company Limited, Yodogawa-ku, Osaka 532-8686, Japan
naohiro.fukuda@takeda.com

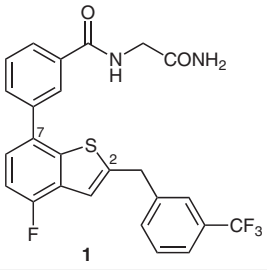


Received: 01.06.2015
Accepted after revision: 29.06.2015
Published online: 11.08.2015
DOI: 10.1055/s-0034-1378746; Art ID: ss-2015-f0349-op

Abstract A simple and efficient procedure has been developed for the synthesis of the GPR52 agonist *N*-(2-amino-2-oxoethyl)-3-[4-fluoro-2-[3-(trifluoromethyl)benzyl]-1-benzothien-7-yl]benzamide. The benzothiophene unit was directly constructed by reduction of a hemithioindigo derivative prepared by an intramolecular Friedel–Crafts cyclization of (phenylsulfanyl)acetic acid, followed by dehydrative benzylidene formation.

Key words benzothiophenes, Friedel–Crafts reactions, cyclizations, scalable syntheses, medicinal chemistry

Activation of G protein-coupled receptor 52 (GPR52) might inhibit D_2 receptor signaling as well as activating the dopamine/*N*-methyl-D-aspartate (D_1/NMDA) function through accumulation of intracellular cyclic adenosine monophosphate (cAMP).[1,2] GPR52 agonist **1** (Figure 1) was discovered by our colleagues,[2] and is expected to give rise to a novel class of antipsychotics.



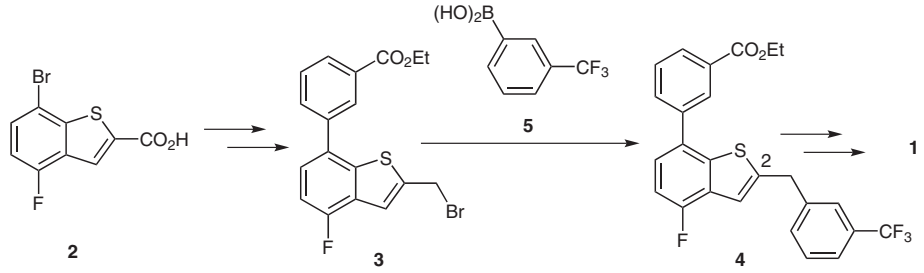
1

Figure 1

The structure of GPR52 agonist **1** is characterized by a 2-benzyl-7-arylbenzothiophene core. Benzothiophenes exist in the core structure of many biologically and pharmaceutically active compounds and they are also widespread in material chemistry.[3,4] Several methods are known for the synthesis of the benzothiophene ring system,[5] including classical Bischler-type cyclizations of aryl thioketones to give 2-substituted benzothiophenes[6] or the annulation of 1-halo-2-ethynylbenzenes with sodium sulfide.[7] Also, intramolecular cyclizations of *o*-alkynyl thioethers by using iodine[8] or transition metals such as palladium, copper, manganese, or gold have been recently reported.[9–12] However, there are few methods for syntheses of benzothiophenes compared with those available for benzofurans and indoles, probably due to deactivation of the catalysts by the sulfur atom in the precursor.[13,14] Although methods for the synthesis 2-benzylbenzothiophenes, including arylation of 2-methylbenzothiophenes and direct benzylation of benzothiophenes, have been reported, they are often not suitable for scaling up, because they involve cryogenic or harsh conditions or require laborious workups.[15] In its medicinal chemistry synthesis, GPR52 agonist **1** was constructed by a strategy involving the Suzuki–Miyaura arylation of the 2-(bromomethyl)benzothiophene **3** (obtained from carboxylic acid **2**) with the arylboronic acid **5** (Scheme 1).[2] Several steps in this synthesis involved chromatographic purifications, which decreased its scalability and productivity.[16]

Therefore, a practical synthesis of 2-benzylbenzothiophenes would be attractive, not only to medicinal chemists, but also to process chemists. Here, we describe the development of a scalable synthesis of GPR52 inhibitor **1**.

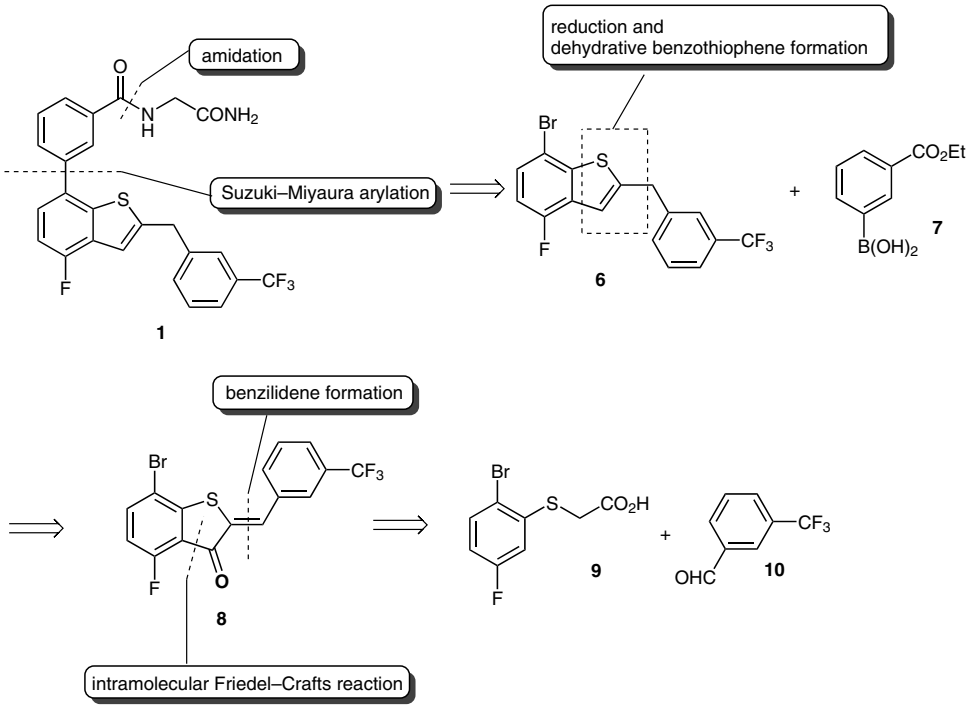
In our retrosynthetic analysis, compound **6** appeared to be an appropriate precursor of the target compound **1**, which could then be obtained by a Suzuki–Miyaura arylation with [3-(ethoxycarbonyl)phenyl]boronic acid (**7**), followed by hydrolysis and subsequent amide formation with 2-aminoacetamide (Scheme 2). We surmised that the benzothiophene skeleton in **6** might be directly obtainable by reduction of both the double bond and ketone group of



Scheme 1 Medicinal chemistry synthesis of GPR52 agonist **1**

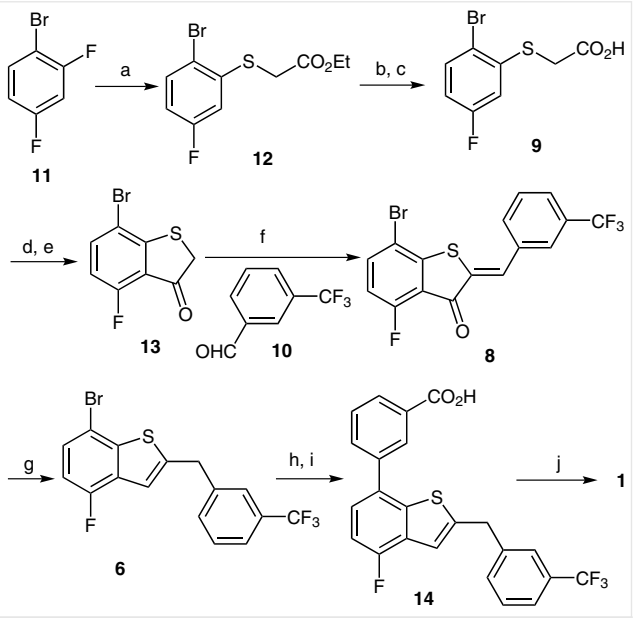
hemithioindigo **8**, followed by dehydration. There had been little previous investigation[17] on such reductions compared with similar reductions of aurones and hemiindigos into benzofurans[18] and indoles,[19] respectively. The reported conditions for reductions of hemithioindigo using triethylsilane and trifluoroacetic acid gave the corresponding benzothiophene in low yield, along with an unexpected rearranged product (a thioflavonol) and other unidentified byproducts.[17] Therefore, alternative effective reaction conditions were required to give the corresponding benzothiophene skeleton. The key intermediate **8** was thought to be obtainable by intramolecular Friedel–Crafts cyclization of carboxylic acid **9**, followed by a Knoevenagel-type condensation with benzaldehyde **10**.

In accordance with this strategy, we attempted to convert 2-bromo-5-fluoroaniline into carboxylic acid **9**. However, the reaction of the diazonium salt of 2-bromo-5-fluoroaniline with potassium ethylxanthate was sluggish and gel-like materials were obtained in the reaction mixture. Next, we attempted the sulfenylation of trihalide **11** with ethyl sulfanylacetate (**15**) in the presence of tripotassium phosphate in *N*,*N*-dimethylacetamide. The reaction proceeded regioselectively at the 2-position (approximately 10:1)[20] to give ester **12**, which was hydrolyzed to give carboxylic acid **9** in 51% yield from **11** after recrystallization (Scheme 3). To avoid the use of halogenated solvents such as dichloromethane or chloroform, which cause significant adverse environmental impacts, we attempted an intramolecular Friedel–Crafts cyclization of the acid chloride obtained from acid **9** with aluminum(III) chloride or zirconi-



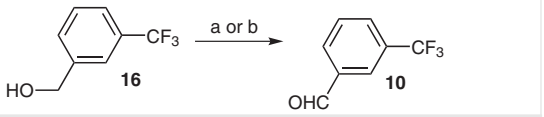
Scheme 2 Retrosynthetic analysis of **1**

um(IV) chloride in chlorobenzene, but this gave many byproducts. It was thought that the chlorobenzene solvent reacted predominantly with the acid chloride of **9** through an intermolecular Friedel–Crafts acylation rather than by intramolecular cyclization to produce **13**; the presence of two halogen atoms (F and Br) on the aromatic ring of **9** might retard the desired reaction. Although the reaction in less reactive 1,2-dichlorobenzene as solvent gave thioindoxyl **13** without considerable amounts of byproducts, it was difficult to distill off the 1,2-dichlorobenzene in a large-scale preparation. Fortunately, it was found that **13** could be enolized with aqueous sodium hydroxide solution to afford its sodium salt, which could then be readily extracted into aqueous solution; **13** was then obtained by re-extraction into the organic layer after neutralization. In general, thioindoxyl derivatives are readily oxidized to thioindigos under aerobic conditions.[21] Therefore, freshly prepared **13** was used in the next step. The hemithioindigo **8** was obtained in 72% yield from **9** by the reaction of thioindoxyl **13** with 3-(trifluoromethyl)benzaldehyde (**10**) in the presence of a catalytic amount of piperidine.



Scheme 3 *Reagents and conditions*: (a) $HSCH_2CO_2Et$ (**15**), K_3PO_4, *N*,*N*-dimethylacetamide, 25 °C; (b) 2 M aq NaOH, EtOH, 25 °C; (c) recrystallization from EtOAc–heptane, 51% from **11**; (d) $SOCl_2$, DMF (cat.), 1,2-dichlorobenzene, 60 °C; (e) $AlCl_3$, 1,2-dichlorobenzene, 0–10 °C; (f) **10**, piperidine (5 mol%), toluene, 72% from **9**; (g) $NaBH_4$, THF, EtOH, 60 °C, then H_2SO_4, 89%; (h) 3-$EtO_2CC_6H_4B(OH)_2$ **7**, $Pd(OAc)_2$ (4 mol%), (*o*-Tol)$_3$P (16 mol%), Na_2CO_3, DME, reflux; (i) aq NaOH, EtOH, r.t., 87% from **8**; (j) HCl·$NH_2CH_2CONH_2$, EDC·HCl, HOBt·H_2O, DIPEA, *N*,*N*-dimethylacetamide, 25 °C, then recrystallization from aq EtOH, 97%.

The aldehyde **10** was readily prepared from 3-(trifluoromethyl)benzyl alcohol (**16**) according to our previously reported practical oxidation procedure using sodium hypochlorite in 1,2-dimethoxyethane or by an imide and nitroxyl radical dual-catalyzed sodium hypochlorite oxidation (Scheme 4).[22]



Scheme 4 *Reagents and conditions*: (a) aq NaOCl, DME, r.t., 81%; (b) TEMPO (3 mol%), cyanuric acid (10 mol%), aq NaOCl, EtOAc, 98%.

Regarding the formation of the 2-benzylbenzothiophene, it was found that the reduction of **8** by triethylsilane in methanesulfonic acid proceeded smoothly to give **6** in 87% yield. However, the hexaethyldisiloxane byproduct required removal by chromatographic purification, which is unsuitable for a scaled-up synthesis. By further investigation, we found an alternative pathway involving the reduction of **8** by sodium borohydride and methanol, followed by dehydration with sulfuric acid; this procedure gave **6** in 89% yield and in a form that could be used in the next reaction without further purification. Whereas the Suzuki–Miyaura arylation of **6** purified by silica gel column chromatography with boronic acid **7** proceeded smoothly in the presence of 4 mol% of palladium(II) acetate and 16 mol% of triphenylphosphine, the corresponding reaction using crude **6** stalled, with recovery of **6**. Attempts to remove the unknown contaminant that deactivated the catalyst system by treatment of crude **6** by washing with aqueous sodium bicarbonate or by treatment with activated charcoal were ineffective. On the other hand, the reaction using 16 mol% of tri(*o*-tolyl)phosphine was readily completed and, when followed by hydrolysis, afforded the penultimate intermediate **14** in 87% yield over three steps. Finally, amidation of **14** with 2-aminoacetamide gave the target compound **1** in 97% yield.

In conclusion, we have established a scalable and simple synthesis of the GPR52 agonist, *N*-(2-amino-2-oxoethyl)-3-{4-fluoro-2-[3-(trifluoromethyl)benzyl]-1-benzothien-7-yl}benzamide (**1**), starting from 1-bromo-2,4-difluorobenzene (**11**). Key features were the development of a regioselective sulfenylation of **11** with ethyl sulfanylacetate (**15**), and direct benzothiophene formation from hemithioindigo **8** by reduction with sodium borohydride followed by dehydration with sulfuric acid. The overall yield was dramatically improved to 33% from the 2% obtained in the previously reported synthesis. Because this synthesis proceeds in ten chemical transformations under mild reaction conditions with effective telescoping of operations and four isolations of synthetic intermediates, it should be easy to prepare **1** on a large scale.[16a,23] The processes described here might prove useful for similar organic transformations or for the efficient synthesis of related structures.

All reactions were performed under N_2. All chemicals were obtained from commercial suppliers and were used without further purification. Melting points were determined on a Büchi Melting Point B-540 or a Stanford Research Systems OptiMelt MPA 100 apparatus, and are uncorrected unless otherwise noted. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 600 (^{1}H: 600 MHz, ^{13}C: 151 MHz) in $CDCl_3$ with TMS as an internal standard. HPLC analysis of the compounds and reaction monitoring was carried out on a Shimadzu LC-2010CHT chromatograph. High-resolution mass spectra were recorded on a Shimadzu Prominence UFLC system with a Thermo Fisher LTQ Orbitrap Discovery. Elemental analyses were recorded on an Elementar vario MICRO cube. IR spectra were recorded on a Thermo Electron FT-IR Nicolet 4700 spectrophotometer in the ATR mode.

[(2-Bromo-5-fluorophenyl)sulfanyl]acetic Acid (9)

K_3PO_4 (88.20 g, 415.73 mmol, 1.2 equiv) was added to a mixture of 1-bromo-2,4-difluorobenzene (**11**; 66.90 g, 346.44 mmol) and $HSCH_2CO_2Et$ (**15**; 50.00 g, 415.73 mmol, 1.2 equiv) in *N*,*N*-dimethylacetamide (335 mL) at 20–25 °C, and the mixture was stirred for 18 h. 1 M aq NaOH (693 mL, 693 mmol, 2.0 equiv) was added, and the mixture was stirred for 1.5 h. The pH of the mixture was adjusted to 2.5–3.0 with 6 M aq HCl (310 mL), and the mixture was extracted with toluene (669 mL). The aqueous layer was then extracted with toluene (2 × 200 mL). The organic layers were combined and extracted with 1 M aq NaOH (669 mL). The aqueous layer was adjusted to pH 3.5 with 6 M aq HCl (110 mL), a seed of **9** (33 mg, 0.05 wt%) was added to the mixture, and the slurry was stirred for 1 h at r.t. The solids were collected by filtration to give wet **9**. A mixture of the wet **9** and EtOAc (100 mL) was warmed to 50 °C then cooled to r.t. Heptane (300 mL) was added dropwise to the mixture, and the resulting slurry was stirred for 1 h. The solids were collected by filtration and washed with 1:4 EtOAc–heptane (134 mL). The wet solids were dried at 50 °C under reduced pressure to give a white solid; yield: 46.7 g (51% over 2 steps from **11**); mp 132.6–133.5 °C.

IR (ATR): 433, 458, 485, 566, 578, 597, 679, 693, 803, 844, 881, 900, 932, 1021, 1093, 1142, 1213, 1259, 1293, 1388, 1417, 1352, 1571, 1591, 1697 cm^{-1}.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 3.99 (s, 2 H), 6.98 (td, *J* = 3.0, 8.5 Hz, 1 H), 7.18 (dd, *J* = 2.8, 10.0 Hz, 1 H), 7.64 (dd, *J* = 5.7, 8.7 Hz, 1 H), 13.03 (br s, 1 H).

^{13}C NMR (151 MHz, DMSO-d_6): δ = 34.1, 113.5 (d, *J* = 22.9 Hz), 113.7 (d, *J* = 26.7 Hz), 115.0, 134.0 (d, *J* = 8.7 Hz), 140.0 (d, *J* = 8.7 Hz), 161.7 (d, *J* = 245.8 Hz), 169.8.

HRMS (ESI): *m/z* [M – H]$^-$ calcd for $C_8H_5BrFO_2S$: 262.9183; found: 262.9180.

3-(Trifluoromethyl)benzaldehyde (10)[24]

[CAS Reg. No. 454–89–7]

Procedure A: Oxidation with NaOCl in DME

A mixture of (3-trifluoromethyl)benzyl alcohol (**16**; 500 mg, 2.84 mmol) in DME (10 mL) was stirred at 20–30 °C, and 12% (w/w) aq NaOCl (3.52 g, 5.68 mmol, 2.0 equiv) was gradually added to the mixture at 20–25 °C. The reaction was continued for 4 h while the temperature was maintained at 20–25 °C. When the reaction was complete, the mixture was extracted with EtOAc (20 mL). The organic layer was washed with 10% aq NaCl (10 mL) and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, EtOAc–hexane) to give a colorless oil; yield: 398 mg (81%).

Procedure B: Oxidation with NaOCl in the presence of catalytic amount of cyanuric acid and TEMPO

To a mixture of **16** (676 mg, 3.84 mmol), cyanuric acid (50 mg, 0.38 mmol, 0.1 equiv), and K_2CO_3 (1.06 g, 7.68 mmol, 2.0 equiv) in EtOAc (10 mL) were added TEMPO (18 mg, 0.12 mmol, 0.03 equiv) and 12% (w/w) aq NaOCl (2.86 g, 4.61 mmol, 1.2 equiv) at 0–10 °C, and the mixture was stirred for 5 h at 0–10 °C. The mixture was then extracted with EtOAc (20 mL). The organic layer was washed with 10% aq. NaCl (10 mL) then concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, EtOAc–hexane) to give a colorless oil; yield: 398 mg (98%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.70 (t, *J* = 7.7 Hz, 1 H), 7.90 (d, *J* = 7.9 Hz, 1 H), 8.09 (d, *J* = 7.6 Hz, 1 H), 8.15 (s, 1 H), 10.09 (s, 1 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 123.6 (q, *J* = 272.5 Hz), 126.5 (q, *J* = 3.8 Hz), 129.8, 130.8 (q, *J* = 3.3 Hz), 131.9 (q, *J* = 33.2 Hz), 132.7, 136.9, 190.7.

7-Bromo-4-fluoro-1-benzothiophen-3(2*H*)-one (13)

To a mixture of acid **9** (5.00 g, 18.85 mmol) and DMF (69 mg, 0.94 mmol, 0.05 equiv) in 1,2-dichlorobenzene (15 mL) was added $SOCl_2$ (2.47 g, 20.74 mmol, 1.1 equiv) at r.t. The resulting mixture was stirred at 60 °C for 1 h then cooled to r.t. The mixture was added dropwise to a mixture of $AlCl_3$ (5.03 g, 37.70 mmol, 1.5 equiv) and 1,2-dichlorobenzene (10 mL) at 0–10 °C, and the resulting mixture was stirred at 0–10 °C for 1.5 h then poured into H_2O (50 mL) at 0–30 °C. The mixture was extracted with toluene (65 mL), and the organic layer was washed successively with 1 M aq HCl (25 mL) containing NaCl (2.5 g) and with brine (15 mL). The organic layer was extracted with 2 M aq NaOH (25 mL) and 1 M aq NaOH (5 mL). Toluene (25 mL) was added to the aqueous layer and the pH was adjusted to 4.5–5.0 with 6 M aq HCl (4.5 mL). EtOAc (25 mL) and activated charcoal (500 mg, Shirasagi A, Wako Pure Chemical Industries, Ltd.) were added, and the mixture was stirred for 1 h. Insoluble materials were filtered off and washed with EtOAc (15 mL). The organic layer of the filtrate was concentrated in vacuo to give crude **13** (4.08 g). An analytical sample of **13** was isolated by column chromatography (silica gel, EtOAc–hexane).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.86 (s, 2 H), 6.78 (t, *J* = 8.8 Hz, 1 H), 7.61–7.69 (m, 1 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 40.5, 113.0 (d, *J* = 4.4 Hz), 113.7 (d, *J* = 21.3 Hz), 120.9 (d, *J* = 14.2 Hz), 139.4 (d, *J* = 8.7 Hz), 157.0 (d, *J* = 3.4 Hz), 160.2 (d, *J* = 267.6 Hz), 196.0.

7-Bromo-4-fluoro-2-[3-(trifluoromethyl)benzylidene]-1-benzothiophen-3(2*H*)-one (8)

To a mixture of crude ketone **13** (4.08 g) and aldehyde **10** (3.18 g, 16.59 mmol) in toluene (8.2 mL) was added piperidine (71 mg, 0.83 mmol, 0.05 equiv). The mixture was stirred at 100 °C for 3 h then EtOH (29 mL) was added at 80 °C. The mixture was cooled to r.t., stirred for 1 h, and then cooled to 0–10 °C for 1 h. The solids were collected by filtration and washed with ice-cold 7:1 EtOH–water (20 mL). The wet solids were dried to give a yellow solid; yield: 5.44 g (72% over 2 steps from **9**); mp 153.9–154.8 °C.

IR (ATR): 456, 482, 506, 525, 578, 631, 653, 675, 684, 731, 767, 806, 814, 871, 907, 925, 946, 1000, 1056, 1075, 1100, 1165, 1189, 1199, 1232, 1261, 1276, 1288, 1299, 1327, 1427, 1459, 1571, 1597, 1693 cm^{-1}.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 7.20 (t, *J* = 9.06 Hz, 1 H) 7.78–7.90 (m, 2 H) 7.95–8.07 (m, 3 H) 8.11 (s, 1 H).

^{13}C NMR (151 MHz, DMSO-d_6): δ = 112.2 (d, *J* = 2.7 Hz), 115.7 (d, *J* = 21.3 Hz), 119.6 (d, *J* = 6.1 Hz), 123.8 (q, *J* = 272.5 Hz), 127.0 (q, *J* = 3.3 Hz), 127.6 (q, *J* = 4.4 Hz), 130.1 (q, *J* = 32.2 Hz), 130.6, 130.8, 132.5, 133.6, 134.3, 140.0 (d, *J* = 9.3 Hz), 147.6 (d, *J* = 3.3 Hz), 159.9 (d, *J* = 264.9 Hz), 184.2.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{16}H_8BrF_4OS$: 402.9415; found: 402.9418.

7-Bromo-4-fluoro-2-[3-(trifluoromethyl)benzyl]-1-benzothiophene (6)

A mixture of ketone **8** (1.50 g, 3.72 mmol) and THF (7.5 mL) was added dropwise to a mixture of $NaBH_4$ (211 mg, 5.58 mmol, 1.5 equiv) and THF (1.5 mL) at 60 °C, and the mixture was stirred for 0.5 h. MeOH (1.5 mL) was added dropwise at 60 °C, and the mixture was stirred for 1 h then cooled to r.t. 1 M aq HCl (15 mL) was added, and the mixture was extracted with toluene (15 mL). H_2SO_4 (3 mL) was added to the organic layer, and the mixture was stirred at 60 °C for 1 h, then cooled to r.t. The mixture was then washed with H_2O (15 mL then 7.5 mL). The organic layer was concentrated in vacuo to give the crude product. An analytical sample of **6** was isolated by column chromatography (silica gel, EtOAc–hexane).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 4.29 (s, 2 H), 6.91 (dd, *J* = 9.4, 8.3 Hz, 1 H), 7.23 (s, 1 H), 7.35 (dd, *J* = 8.3, 4.2 Hz, 1 H), 7.44–7.51 (m, 2 H), 7.51–7.59 (m, 2 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 36.8, 109.7 (d, *J* = 3.8 Hz), 111.3 (d, *J* = 20.7 Hz), 118.1, 124.1 (q, *J* = 272.5 Hz), 124.1 (q, *J* = 3.6 Hz), 125.5 (q, *J* = 3.8 Hz), 127.4 (d, *J* = 7.6 Hz), 129.3, 129.5 (d, *J* = 20.2 Hz), 131.3 (q, *J* = 32.2 Hz), 132.1, 139.7, 143.6 (d, *J* = 6.5 Hz), 145.4, 156.5 (d, *J* = 251.2 Hz).

Ethyl 3-{4-Fluoro-2-[3-(trifluoromethyl)benzyl]-1-benzothien-7-yl}benzoate (4)

$Pd(OAc)_2$ (33 mg, 0.15 mmol, 0.04 equiv) was added to a mixture of crude product **6**, [3-(ethoxycarbonyl)phenyl]boronic acid (**7**; 1.08 g, 5.58 mmol, 1.5 equiv), (*o*-Tol)$_3$P (181 mg, 0.60 mmol, 0.16 equiv), and 2 M aq Na_2CO_3 (7.4 mL, 14.88 mmol, 4.0 equiv) in DME (15 mL), and the mixture was stirred at 80 °C for 2 h. H_2O (15 mL) was added and the mixture was extracted with toluene (15 mL). Activated charcoal (150 mg) was added to the organic layer, and the mixture was stirred for 0.5 h. Insoluble materials were filtered off, and the filtrate was concentrated in vacuo to give the crude ester **4**. An analytical sample of **4** was isolated by column chromatography (silica gel, EtOAc–hexane).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.39 (t, *J* = 7.0 Hz, 3 H), 4.27 (s, 2 H), 4.40 (q, *J* = 7.1 Hz, 2 H), 7.10 (dd, *J* = 8.7 Hz, 1 H), 7.19–7.31 (m, 2 H), 7.38–7.49 (m, 2 H), 7.49–7.58 (m, 3 H), 7.81 (d, *J* = 7.8 Hz, 1 H), 8.07 (d, *J* = 8.0 Hz, 1 H), 8.29 (t, *J* = 1.7 Hz, 1 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 14.3, 36.7, 61.2, 110.4 (d, *J* = 19.6 Hz), 117.6, 123.9 (q, *J* = 3.8 Hz), 124.1 (q, *J* = 272.3 Hz), 125.1 (d, *J* = 7.6 Hz), 125.5 (q, *J* = 3.8 Hz), 128.9, 129.0, 129.3, 129.3, 129.5, 131.2 (q, *J* = 32.2 Hz), 131.3, 131.7 (d, *J* = 3.8 Hz), 132.1, 132.3, 140.0, 140.1, 141.3 (d, *J* = 6.5 Hz), 144.7, 157.0 (d, *J* = 251.8 Hz), 166.3.

3-{4-Fluoro-2-[3-(trifluoromethyl)benzyl]-1-benzothien-7-yl}benzoic Acid (14)

To a mixture of ester **4** in EtOH (15 mL) was added 2 M aq NaOH (3.7 mL, 7.44 mmol, 2.0 equiv) at r.t. The mixture was stirred at 60 °C for 1.5 h and then 6 M aq HCl (1.3 mL) was added dropwise at 60 °C. Finally, 6 M aq HCl (0.2 mL) was added at r.t. and the mixture was stirred for 1 h. The solids were collected by filtration and washed successively with 70% aq EtOH (6 mL) and water (7.5 mL, 4.5 mL). The wet solids were dried at 50 °C to give a white solid; yield: 1.39 g (87% over 3 steps from **8**); mp 177.6–178.3 °C.

IR (ATR): 488, 552, 576, 659, 670, 692, 700, 723, 737, 758, 805, 875, 909, 928, 970, 1069, 1097, 1109, 1149, 1166, 1202, 1231, 1254, 1316, 1417, 1449, 1474, 1578, 1674 cm^{-1}.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 4.44 (s, 2 H), 7.33 (dd, *J* = 10.0, 8.1 Hz, 1 H), 7.44 (dd, *J* = 7.9, 4.9 Hz, 1 H), 7.48 (s, 1 H), 7.56–7.70 (m, 4 H), 7.77 (s, 1 H), 7.88 (d, *J* = 7.8 Hz, 1 H), 8.04 (d, *J* = 7.9 Hz, 1 H), 8.23 (t, *J* = 1.5 Hz, 1 H), 13.20 (br s, 1 H).

^{13}C NMR (151 MHz, DMSO-d_6): δ = 35.2, 110.6 (d, *J* = 19.6 Hz), 117.2, 123.5 (q, *J* = 3.8 Hz), 124.1 (q, *J* = 272.3 Hz), 125.1 (q, *J* = 3.8 Hz), 125.2, 128.4, 128.7 (d, *J* = 19.6 Hz), 128.9, 129.4 (q, *J* = 31.6 Hz), 129.4, 129.6, 131.2 (d, *J* = 3.8 Hz), 131.6, 132.1, 132.8, 139.2, 140.2 (d, *J* = 6.5 Hz), 140.8, 145.8, 156.1 (d, *J* = 250.1 Hz), 166.9.

Anal. Calcd for $C_{23}H_{14}F_4O_2S$: C, 64.18; H, 3.28. Found: C, 64.20; H, 3.31.

N-(2-Amino-2-oxoethyl)-3-{4-fluoro-2-[3-(trifluoromethyl)benzyl]-1-benzothien-7-yl}benzamide (1)

DIPEA (310 mg, 2.40 mmol, 1.2 equiv) was added to a solution of acid **14** (860 mg, 2.00 mmol), 2-aminoacetamide hydrochloride (265 mg, 2.40 mmol, 1.2 equiv), HOBt·H_2O (306 mg, 2.00 mmol, 1.0 equiv), and EDC·HCl (460 mg, 2.40 mmol, 1.2 equiv) in *N*,*N*-dimethylacetamide (8.6 mL) at 0–10 °C, and the mixture was stirred at r.t. for 1 h. H_2O (17.2 mL) and sat. aq $NaHCO_3$ (5.2 mL) were added dropwise to the mixture, and the slurry was stirred for 1 h. The solids were collected by filtration, and the wet solids were washed successively with H_2O (14.6 mL) and *i*-Pr_2O (10 mL). The wet solids were dried over at 50 °C to afford crude **1**. A mixture of crude **1** in 95% aq EtOH (8 mL) was warmed up to 60 °C. H_2O (3.3 mL) was added to the solution at 60 °C, and then more H_2O (1.2 mL) was added at r.t. The mixture was stirred for 1 h, and then the solids were collected by filtration and washed with 60% aq EtOH (2.5 mL). The wet solids were dried at 50 °C to give a white solid; yield: 480 mg (97%); mp 157.2–157.9 °C.

IR (ATR): 409, 432, 461, 486, 509, 531, 573, 659, 671, 698, 751, 804, 817, 910, 1069, 1111, 1165, 1230, 1257, 1326, 1415, 1471, 1578, 1602, 1620, 1678 cm^{-1}.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 3.87 (d, *J* = 4.9 Hz, 2 H), 4.43 (s, 2 H), 7.08 (s, 1 H), 7.34 (t, *J* = 8.9 Hz, 1 H), 7.39–7.51 (m, 3 H), 7.54–7.71 (m, 4 H), 7.76 (s, 1 H), 7.81 (d, *J* = 7.2 Hz, 1 H), 7.97 (d, *J* = 7.2 Hz, 1 H), 8.15 (s, 1 H), 8.83 (s, 1 H).

^{13}C NMR (151 MHz, DMSO-d_6): δ = 35.2, 42.5, 110.5 (d, *J* = 19.1 Hz), 117.2, 123.5 (q, *J* = 3.8 Hz), 124.2 (q, *J* = 272.5 Hz), 125.1 (q, *J* = 3.8 Hz), 125.2, 127.0, 127.0, 128.6 (d, *J* = 19.6 Hz), 128.9, 129.3 (q, *J* = 31.6 Hz), 129.7, 130.3, 131.6 (d, *J* = 3.8 Hz), 132.8, 134.9, 139.0, 140.3 (d, *J* = 6.5 Hz), 140.9, 145.8, 156.1 (d, *J* = 250.1 Hz), 166.0, 170.9.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{25}H_{19}F_4N_2O_2S$: 487.1103; found: 487.1094.

Acknowledgment

We thank Dr. David Cork for his help in preparing the manuscript.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1378746.

References

(1) Sawzdargo, M.; Nguyen, T.; Lee, D. K.; Lynch, K. R.; Cheng, R.; Heng, H. H. Q.; George, S. R.; O'Dowd, B. F. *Mol. Brain Res.* **1999**, *64*, 193.

(2) (a) Setoh, M.; Ishii, N.; Kono, M.; Miyanohana, Y.; Shiraishi, E.; Harasawa, T.; Ota, H.; Odani, T.; Kanzaki, N.; Aoyama, K.; Hamada, T.; Kori, M. *J. Med. Chem.* **2014**, *57*, 5226. (b) Komatsu, H.; Maruyama, M.; Yao, S.; Shinohara, T.; Sakuma, K.; Imaichi, S.; Chikatsu, T.; Kuniyeda, K.; Sui, F. K.; Peng, L. S.; Zhuo, K.; Mun, L. S.; Han, T. M.; Matsumoto, Y.; Hashimoto, T.; Miyajima, N.; Ito, Y.; Ogi, K.; Habata, Y.; Mori, M. *PLoS One* **2014**, *9*, e90134. (c) Setoh, M.; Kobayashi, T.; Tanaka, T.; Baba, A. WO 2009107391, **2009**.

(3) (a) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893. (b) Berrade, L.; Aisa, B.; Ramirez, M. J.; Galiano, S.; Guccione, S.; Moltzau, L. R.; Levy, F. O.; Nicoletti, F.; Battaglia, G.; Molinaro, G.; Aldana, I.; Monge, A.; Perez-Silanes, S. *J. Med. Chem.* **2011**, *54*, 3086. (c) Qin, Z.; Kastrati, I.; Chandrasena, R. E. P.; Liu, H.; Yao, P.; Petukhov, P. A.; Bolton, J. L.; Thatcher, G. R. J. *J. Med. Chem.* **2007**, *50*, 2682. (d) Flynn, B. L.; Hamel, E.; Jung, M. K. *J. Med. Chem.* **2002**, *45*, 2670. (e) Hsiao, C.-N.; Kolasa, T. *Tetrahedron Lett.* **1992**, *33*, 2629.

(4) (a) Fouad, I.; Mechbal, Z.; Chane-Ching, K. I.; Adenier, A.; Maurel, F.; Aaron, J.-J.; Vodicka, P.; Cernovska, K.; Kozmik, V.; Svoboda, J. *J. Mater. Chem.* **2004**, *14*, 1711. (b) Jung, K. H.; Kim, K. H.; Lee, D. H.; Jung, D. S.; Park, C. E.; Choi, D. H. *Org. Electron.* **2010**, *11*, 1584. (c) Pu, S.; Li, M.; Fan, C.; Liu, G.; Shen, L. *J. Mol. Struct.* **2009**, *919*, 100. (d) Um, M.-C.; Kwak, J.; Hong, J.-P.; Kang, J.; Yoon, D. Y.; Lee, S. H.; Lee, C.; Hong, J.-I. *J. Mater. Chem.* **2008**, *18*, 4698.

(5) (a) Gabriele, B.; Mancuso, R.; Lupinacci, E.; Veltri, L.; Salerno, G.; Carfagna, C. *J. Org. Chem.* **2011**, *76*, 8277. (b) Duan, Z.; Ranjit, S.; Liu, X. *Org. Lett.* **2010**, *12*, 2430. (c) Wang, Z.; Geng, W.; Wang, H.; Zhang, S.; Zhang, W.-X.; Xi, Z. *Tetrahedron Lett.* **2011**, *52*, 6997. (d) Benati, L.; Montevecchi, P. C.; Spagnolo, P. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1659. (e) Hari, D. P.; Hering, T.; König, B. *Org. Lett.* **2012**, *14*, 5334. (f) Clark, P. D.; Kirk, A.; Yee, J. G. K. *J. Org. Chem.* **1995**, *60*, 1936. (g) Lin, C.-H.; Chen, C.-C.; Wu, M.-J. *Chem. Eur. J.* **2013**, *19*, 2578.

(6) (a) Capozzi, G.; Melloni, G.; Modena, G. *J. Chem. Soc. C* **1970**, 2621. (b) Jones, C. D.; Jevnikar, M. G.; Pike, A. J.; Peters, M. K.; Black, L. J.; Thompson, A. R.; Falcone, J. F.; Clemens, J. A. *J. Med. Chem.* **1984**, *27*, 1057. (c) Pinney, K. G.; Bounds, A. D.; Dingeman, K. M.; Mocharla, V. P.; Pettit, G. R.; Bai, R.; Hamel, E. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1081.

(7) (a) Sun, L.-L.; Deng, C.-L.; Tang, R.-Y.; Zhang, X.-G. *J. Org. Chem.* **2011**, *76*, 7546. (b) Kashiki, T.; Shinamura, S.; Kohara, M.; Miyazaki, E.; Takimiya, K.; Ikeda, M.; Kuwabara, H. *Org. Lett.* **2009**, *11*, 2473.

(8) (a) Ebata, H.; Miyazaki, E.; Yamamoto, T.; Takimiya, K. *Org. Lett.* **2007**, *9*, 4499. (b) Zhou, Y.; Liu, W.-J.; Ma, Y.; Wang, H.; Qi, L.; Cao, Y.; Wang, J.; Pei, J. *J. Am. Chem. Soc.* **2007**, *129*, 12386. (c) Hessian, K. O.; Flynn, B. L. *Org. Lett.* **2003**, *5*, 4377. (d) Larock, R. C.; Yue, D. *Tetrahedron Lett.* **2001**, *42*, 6011. (e) Flynn, B. L.; Verdier-Pinard, P.; Hamel, E. *Org. Lett.* **2001**, *5*, 651.

(9) (a) Kuhn, M.; Falk, F. C.; Paradies, J. *Org. Lett.* **2011**, *13*, 4100. (b) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (c) Bryan, C. S.; Braunger, J. A.; Lautens, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 7064.

(10) (a) Yu, H.; Zhang, M.; Li, Y. *J. Org. Chem.* **2013**, *78*, 8898. (b) Newman, S. G.; Aureggi, V.; Bryan, C. S.; Lautens, M. *Chem. Commun.* **2009**, 5236. (c) Lu, W.-D.; Wu, M.-J. *Tetrahedron* **2007**, *63*, 356. (d) Kunz, T.; Knochel, P. *Angew. Chem. Int. Ed.* **2012**, *51*, 1958.

(11) Liu, K.; Jia, F.; Xi, H.; Li, Y.; Zheng, X.; Guo, Q.; Shen, B.; Li, Z. *Org. Lett.* **2013**, *15*, 2026.

(12) Nakamura, I.; Sato, T.; Yamamoto, Y. *Angew. Chem. Int. Ed.* **2006**, *45*, 4473.

(13) Godoi, B.; Schumacher, R. F.; Zeni, G. *Chem. Rev.* **2011**, *111*, 2937.

(14) Inamoto, K.; Arai, Y.; Hiroya, K.; Doi, T. *Chem. Commun.* **2008**, 5529.

(15) (a) Duez, S.; Steib, A. K.; Knochel, P. *Org. Lett.* **2012**, *14*, 1951. (b) Shrestha, S.; Hwang, S. Y.; Lee, K.-H.; Cho, H. *Bull. Korean Chem. Soc.* **2005**, *26*, 1138. (c) Lapointe, D.; Fagnou, K. *Org. Lett.* **2009**, *11*, 4160. (d) Imamura, M.; Nakanishi, K.; Suzuki, T.; Ikegai, K.; Shiraki, R.; Ogiyama, T.; Murakami, T.; Kurosaki, E.; Noda, A.; Kobayashi, Y.; Yokota, M.; Koide, T.; Kosakai, K.; Ohkura, Y.; Takeuchi, M.; Tomiyama, H.; Ohta, M. *Bioorg. Med. Chem.* **2012**, *20*, 3263. (e) Robbins, D. W.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2013**, *52*, 933.

(16) (a) Anderson, N. G. *Practical Process Research and Development: A Guide for Organic Chemists*, 2nd ed.; Elsevier Academic Press: Amsterdam, **2012**. (b) Repič, O. *Principles of Process Research and Chemical Development in the Pharmaceutical Industry*; Wiley: New York, **1998**.

(17) Varedian, M.; Langer, V.; Bergquist, J.; Gogoll, A. *Tetrahedron Lett.* **2008**, *49*, 6033.

(18) Kurosawa, K.; Morita, Y. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 635.

(19) (a) Burger, U.; Bringhen, A. O. *Helv. Chim. Acta* **1989**, *72*, 93. (b) Sainsbury, M.; Webb, B.; Schinazi, R. *J. Chem. Soc., Perkin Trans. 1* **1975**, 289.

(20) The selectivity was determined by ^{1}H NMR.

Ethyl [(2-Bromo-5-fluorophenyl)sulfanyl]acetate (12)

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.27 (t, *J* = 7.2 Hz, 3 H), 3.68 (s, 2 H), 4.21 (q, *J* = 7.2 Hz, 2 H), 6.79 (t, *J* = 8.3 Hz, 1 H), 7.09 (dd, *J* = 9.3, 2.8 Hz, 1 H), 7.49 (t, *J* = 7.5 Hz, 1 H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 14.1, 35.4, 61.9, 114.4 (d, *J* = 22.3 Hz), 115.6 (d, *J* = 25.6 Hz), 117.4 (d, *J* = 3.3 Hz), 134.0 (d, *J* = 8.2 Hz), 139.0 (d, *J* = 8.2 Hz), 162.1 (d, *J* = 249.0 Hz), 168.6.

Ethyl [(4-Bromo-3-fluorophenyl)sulfanyl]acetate (Regioisomer of 12)

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.25 (t, *J* = 7.1 Hz, 3 H), 3.64 (s, 2 H), 4.19 (q, *J* = 7.3 Hz, 2 H), 7.05 (ddd, *J* = 8.4, 2.2, 0.8 Hz, 1 H), 7.17 (dd, *J* = 9.0, 2.1 Hz, 1 H), 7.46 (dd, *J* = 8.2, 7.3 Hz, 1 H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 14.1, 36.3, 61.8, 107.3 (d, *J* = 21.3 Hz), 117.3 (d, *J* = 24.5 Hz), 126.1 (d, *J* = 3.3 Hz), 133.7, 136.9 (d, *J* = 7.1 Hz), 159.0 (d, *J* = 250.1 Hz), 169.1.

(21) Eggers, K.; Fyles, T. M.; Montoya-Pelaez, P. J. *J. Org. Chem.* **2001**, *66*, 2966.

(22) (a) Fukuda, N.; Kajiwara, T.; Katou, T.; Majima, K.; Ikemoto, T. *Synlett* **2013**, *24*, 1438. (b) Fukuda, N.; Izumi, M.; Ikemoto, T. *Tetrahedron Lett.* **2015**, *56*, 3905.

(23) Zhang, T. Y. *Handbook of Green Chemistry and Technology*; Clark, J.; Macquarrie, D., Eds.; Blackwell Science: Oxford, **2002**, 312.

(24) Rueping, M.; Vila, C.; Szadkowska, A.; Koenigs, R. M.; Fronert, J. *ACS Catal.* **2012**, *2*, 2810.