Synthesis of 2-(2-Fluoro-1-hydroxypropyl)-*N*-(*N*-(hydroxyl-methylcarbamoyl)-carbamimidoylcarbamoyl)pyridine-3-sulfonamide as a Potent Metabolite of Flucetosulfuron

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N-[(4,6-Dimethoxypyrimidin-2-yl)-aminocarbonyl]-2-(1-methoxyacetoxy-2-fluoro-propyl)-3-pyridinesulfonamide (LGC-42153, Flucetosulfuron, Figure 1) is a new herbicide.[1-4] This is a sulfonylurea herbicide, and also include the moieties of chlorosulfuron,[5] flupyrsulfuron-methyl,[6] imazosulfuron,[7] metsulfuron-methyl,[8] and rimsulfuron.[9] This herbicide is known to inhibit acetolactate synthase.[2,3] This herbicide has two asymmetric carbons therein and apply as the mixture of erythro and threo isomers.[1]

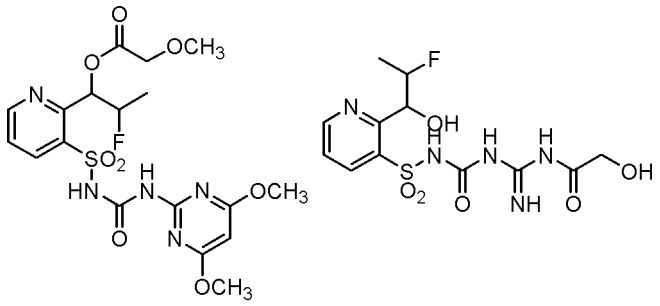
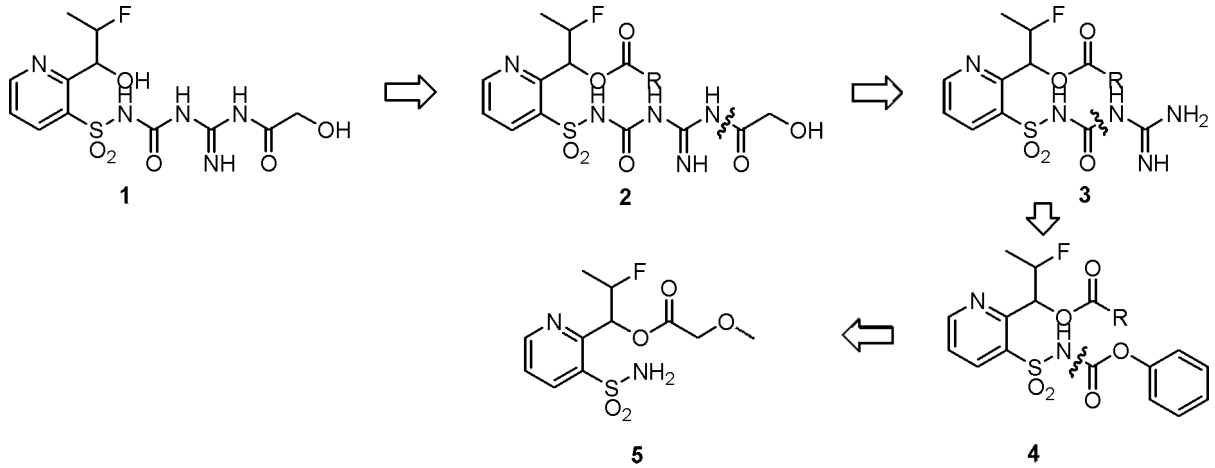


Figure 1. Structure of Flucetosulfuron (LGC-42153) and FCPS (1).

Although the degradation and the metabolism of this new herbicide in soil have been studied,[2,3] the metabolites in soil do not elucidate clearly. Thus, we attempted the synthesis of 2-(2-fluoro-1-hydroxypropyl)-*N*-[*N*-hydroxymethylcarbamoyl)carbamimidoylcarbamoyl]-pyridine-3-sulfonamide (**1**, FCPS, Figure 1) as a potent metabolite of LGC-42153. In this paper, we report the results for the retrosynthesis and the synthesis of FCPS (**1**).

From the retrosynthetic analysis (Scheme 1), we selected 2-fluoro-1-(3-sulfamoylpyridine-2-yl)propyl 2-methoxyacetate (**5**)[1] as the starting material. This method involves the crucial steps such as the formation of the carbamate and the introduction of the guanidine and the 2-hydroxyacetyl moieties.

Since flucetosulfuron applies as the mixture of erythro and threo isomers,[1] we attempted to synthesize the racemate **1** from 2-fluoro-1-(3-sulfamoylpyridin-2-yl)propyl 2-methoxyacetate (**5**). Reaction of **5** with phenylchloroformate as a carbonyl source under basic condition afforded compound **4** in excellent yield. Compound **4** was treated with guanidine hydrochloride in the presence of potassium carbonate to give chemoselectively acetate **3** in 91% yields. Compound **2** was prepared in the reaction of **3** with acetoxyacetyl chloride



Scheme 1. Retrosynthesis of FCPS (1)

under basic condition, and the resulting compound **2** was treated *in situ* with ammonium hydroxide in methanol at room temperature to afford target FCPS **1** as the racemate in 75% yield. The structures of the products were established by IR, NMR and elemental analysis.

In summary, 2-(2-fluoro-1-hydroxypropyl)-*N*-[*N*-(hydroxymethylcarbamoyl)carbamimidoyl-carbamoyl]pyridine-3-sulfonamide (**1**, FCPS) as racemate is successfully prepared from 2-fluoro-1-(3-sulfamoylpyridin-2-yl)propyl 2-methoxyacetate (**5**) *via* 3 steps in 67% overall yield. Our methods such as the formation of the carbamte and the introduction of the guanidinyl moiety may be useful in the synthesis of drugs and agrochemicals. In addition, the protected carbamate **4** may be a useful material for the synthesis of *N*-substituted urea. Further works including matching up to unknown metabolites and the toxicity test are under way in our laboratory.

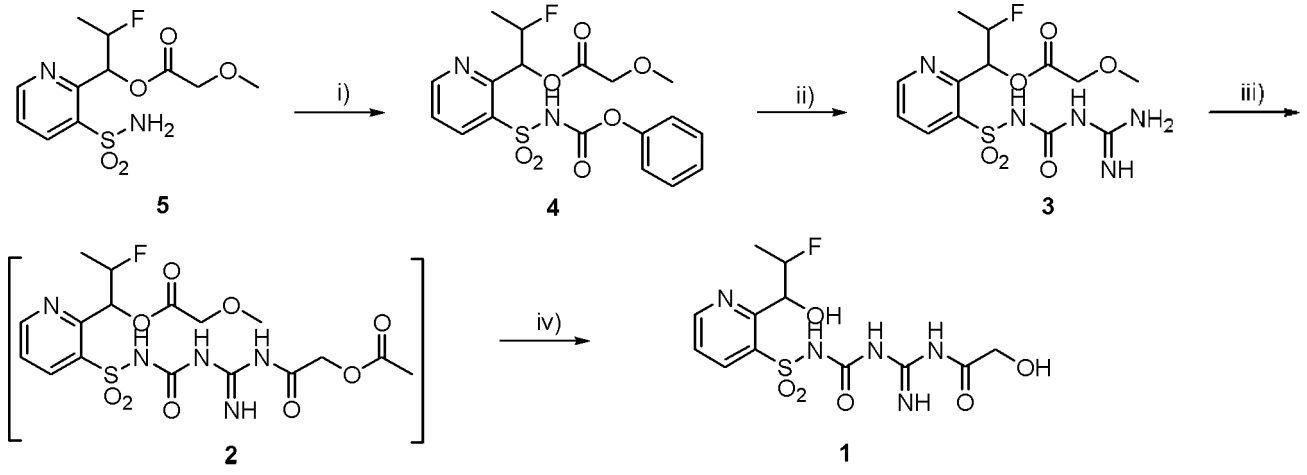
Experimental Section

General. Melting points were determined with Thomas-Hoover capillary apparatus and uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on Brüker FT-NMR DRX 300 spectrophotometer with chemical shift values reported in δ units (ppm) relative to an internal standard (TMS). IR spectra were obtained on Mattson Genesis Series FT-IR spectrophotometer. Elemental analyses were performed with a CHNS-932 (Leco).

2-Fluoro-1-(3-(*N*-(phenoxycarbony)sulfamoyl)pyridine-2-yl)propyl 2-methoxyacetate (4): A mixture of **5** (1 g, 3.26 mmol), K_2CO_3 (0.54 g, 3.92 mmol), phenylchloroformate (0.49 mL, 3.92 mmol) and acetonitrile (25 mL) was stirred at room temperature for 49 hours. After evaporating the solvent under reduced pressure, the product was extracted with H_2O/CH_2Cl_2 (2:7, v/v). The organic layer was dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography (EtOAc) to give compound **4** in 98% (1.37 g) yield: mp 118 - 119 °C. IR (KBr): 3081, 3017, 2990, 1751, 1668, 1564, 1491, 1282, 1196, 938, 877, 750 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.60 (m, 1H), 8.20 (m, 1H), 7.44 - 6.90 (m, 7H), 5.52 - 5.34 (m, 1H), 4.13 (s, 2H), 3.32 (s, 3H), 1.36 (m, 3H). ^{13}C NMR(75 MHz, DMSO-d_6): δ 169.3, 157.2, 153.0, 140.3, 138.2, 129.1, 129.1, 124.2, 123.1, 122.6, 122.4, 90.7, 88.4, 74.6, 74.3, 69.3, 58.85, 15.1, 14.81. Elemental Anal. Calcd for $C_{18}H_{19}FN_2O_7S$: C, 50.70; H, 4.49; N, 6.57; S, 7.52: Found: C, 50.74; H, 4.53; N, 6.62; S, 7.58

1-(3-(*N*-(Carbamimidoylcarbamoyl)sulfamoyl)pyridin-2-yl)-2-fluoropropyl 2-methoxyacetate (3): A solution of compound **4** (3 g, 7.03 mmol), K_2CO_3 (1.07 g, 7.72 mmol), guanidine hydrocholide (0.74 g, 7.72 mmol) and methanol (30 mL) was refluxed for17 hours. After cooling to room temperature, the solvent was evaporated under reduced pressure. The residue was recrystallized from MeOH/Ether (1:7, v/v) to give compound **3** in 91% (2.51g) yield; mp 40 - 41 °C. IR (KBr): 3439, 3405, 3075, 2952, 2830, 1693, 1667, 1650, 1594, 1422, 1403, 1333, 1292, 1197, 1146, 1111, 977, 865, 757 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.61 (d, 1H, J = 2.94 Hz), 8.17 (d, 1H, J = 7.88 Hz), 7.42 - 7.38 (m, 1H), 5.75 - 5.70 (m, 1H), 5.22 - 5.02 (m, 1H), 3.54 (s, 2H), 3.28 (s, 3H), 1.31 (m, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 169.6, 152.0, 151.5, 151.4, 139.2, 136.6, 124.3, 90.8, 88.5, 74.2, 73.9, 69.2, 58.8, 15.5, 15.2. Elemental Anal. Calcd for $C_{13}H_{18}FN_5O_6S$: C, 39.89; H, 4.64; N, 17.89; S, 8.19; Found: C, 39.91; H, 4.67; N, 17.92; S, 8.22.

***N*-(*N*-(2-(2-Fluoro-1-hydroxypropyl)pyridin-3-ylsulfonyl-carbamoyl)carbamimidoyl)-2-hydroxyacetamide (1):** A mixture of acetate **3** (3 g, 7.66 mmol), K_2CO_3 (1.16 g, 8.43 mmol), acetoxyacetylchloride (0.9 mL, 8.43 mmol) and MeOH (35 mL) was stirred at room temperature for 28 hours. The solvent was evaporated under reduced pressure to give the compound **2** (3.2 g). Compound **2** was dissolved in MeOH (30 mL), NH_4OH (5 mL) was added and then the mixture was stirred at room temperature for 8 hours. NH_3 gas was removed by N_2 gas. After evaporating the solvent, the residue was recrystallized from MeOH/diethyl ether (2:7, v/v) to give the product **1** as brown crystal in 76% (1.9 g) yield: mp = 38 - 39 °C. IR (KBr): 3418, 3402, 3093, 2951, 2827, 1667, 1594, 1428, 1270, 1032, 1019, 937, 850, 742 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.74 (d, 1H, J = 3.55 Hz), 8.44 (d, 1H, J = 8.01 Hz), 7.49 - 7.45 (m, 1H), 5.88 - 5.83 (m, 1H), 5.21 - 5.01 (m,



Scheme 2. Synthesis of FCPS (**1**). i) phenylchloroformate, K_2CO_3, CH_3CN, room temperature. ii) $NH_2C(=NH)NH_2$, HCl, K_2CO_3, MeOH, reflux. iii) acetoxyacetylchloride, K_2CO_3, MeOH, room temperature. iv) NH_4OH, MeOH, room temperature.

1H), 3.52 (s, 2H), 1.44 (m, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 157.77, 156.85, 156.77, 151.55, 138.23, 137.58, 122.82, 92.81, 90.56, 71.50, 71.17, 52.00, 15.45, 15.16. Elemental Anal. Calcd for $C_{12}H_{16}FN_5O_6S$: C, 38.20; H, 4.27; N, 18.56; F, 5.03; S, 8.50; Found: C, 38.22; H, 4.29; N, 18.59; F, 5.05; S, 8.53.

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