An efficient synthesis of 2-(2,2-difluoroethoxy)-6-trifluoromethyl-*n*-(5,8-dimethoxy-1,2,4-triazolo[1,5-c]pyrimidine-2-yl) benzenesulfonamide: penoxsulam

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An efficient nine-step synthesis of 2-(2,2-difluoroethoxy)-6-trifluoromethyl-*N*-(5,8-dimethoxy-1,2,4-triazolo[1,5-c]-pyrimidine-2-yl) benzenesulfonamide has been developed. The starting material 4-nitro-2-(trifluoromethyl)aniline starting material was converted via 2-bromo-4-amino-6-trifluoromethylaniline and 2-bromo-4-acetamido-6-trifluoro-methylbenzenesulfonic acid to 2-bromo-6-trilfuoromethylbenzenesulfonic acid. This was then combined with 2-amino-5,8-dimethoxy-1,2,4-triazolo[1.5-c]pyrimidine to give the target molecule. Compared with the reported method, this approach has advantages in its shorter reaction time, milder reaction conditions and easier purifiction. Moreover, the overall yield has been improved to 22.9% which is twice of that of the reported method.

Keywords: triazolo[1,5-c]pyrimidine benzenesulfonamide, 4-nitro-2-(trifluoromethyl)aniline, benzenesulfonyl chloride, penoxsulam

2-(2,2-Difluoroethoxy)-6-trifluoromethyl-*N*-(5,8-dimethoxy-1,2,4-triazolo[1,5-c]pyrimidine-2-yl) benzenesulfonamide, penoxsulam (**1**), is a novel and effective herbicide developed by Dow AgroSciences in 1999 with the brand name Granite.[1] As a member of the triazolo[1,5-c]pyrimidine sulfonamides class of herbicides, it has been demonstrated competition with the amino acid leucine for binding to acetolactate synthase (ALS) isolated from cotton (*Gossypium hirsutum*).[2] It exhibits higher levels of activity on both grass and broadleaf weeds than other commercial triazolopyrimidine sulfonamides,[3] such as the triazolo[1,5-a]pyrimidine sulfonamides. It is used primarily in rice because of its broad weed control spectrum and safety to rice in effective dose.[4,5]

Most of the research on penoxsulam has been focused on the partitioning,[6] analysis,[7] degradation such as photodegradation,[8] and microbial degradation[9] in water or soil, mechanism of resistance,[10] effect on weeds and safety evaluation.[11] The synthesis and structure-activity of the triazolopyrimidine sulfonamides has also been extensively studied during the past decade.[3]

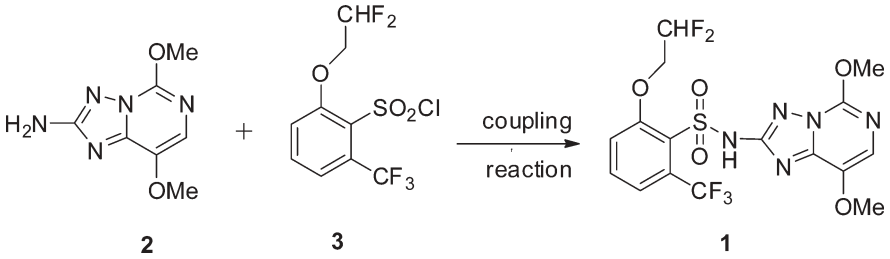
Although there are several methods for the synthesis of triazolo[1,5-c]pyrimidine sulfonamides, such as coupling route and derivative route, it has been reported[3] that penoxsulam could be prepared via the coupling of 2-amino-5,8-dimethoxy-1,2,4-triazolo[1,5-c]pyrimidine (**2**) with 2-trifluoromethyl-6-difluoroethoxybenzenesulfonyl chloride (**3**) (Scheme 1). Methods for the synthesis of compound **2** have been reported in several papers.[12–15] One common high yielding route[16] which used 2-substituted-4-amino-5-methoxypyrimidine as the starting material and did not use hydrazine and cyanogen halide was reported by Dow Agrosciences LLC. In this paper, compound **2** was prepared by Edmonds's method.[15] However, compound **3** has been prepared by a method from the starting material 1-(methoxymethoxy)-3-(trifluoromethyl) benzene.[2] In the original method, a halogen-metal exchange reaction, dimethoxymethyl reaction and etherification took more than 20 hours. Two of the procedures referred above needed the protection of inert nitrogen gas. The reagent 1,2-dipropyl-disulfane discouraged us due to its terrible odour. Moreover, all of the work ups used vacuum distillation to purify the oily intermediates except compound **3**. In short, this is not an attractive method because of the very long reaction times, harsh reaction conditions and complicated work-up. The major problem was the rather low yield (24%) of the coupling reaction to form penoxsulam from compound **2** and **3**, reducing the overall yield of the reported method to 11.0%.

In order to overcome these problems, we examined a more efficient method for the synthesis of penoxsulam.

Results and discussion

In the light of the steric hindrance blockade of the difluoroethoxyl group in compound **3**, we put the etherification reaction with 2,2-difluoroethanol after the general coupling reaction. We designed an efficient method for the synthesis of penoxsulam based on the literature[17] which used 4-nitro-2-(trifluoromethyl)-aniline (compound **4**) as the starting material (Scheme 2).

The synthesis of penoxsulam involved bromination, reduction, acetylation, diazotisation, deacetylation, acid hydrolysis, chlorination, coupling and etherification. Compound **4** was reacted with hydrogen bromide and hydrogen peroxide to give **5**. Reduction of **5** in the presence of stannous chloride in ethanol afforded **6**. This was followed by acetylation of the amino group to give **7**. With the amino group protected, compound **7** was diazotised and deacetylated. In the presence of the base sodium ethoxide and *t*-butyl nitrite, the amino group of compound **9** was replaced by hydrogen. Compound **11** was synthesised by chlorination of compound **10** in the presence phosphorus oxychloride and acetonitrile under reflux and then



2 **3** **1**

Scheme 1 The coupling reaction for the synthesis of penoxsulam.

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reacted with **2** to give compound **12** with a high yield in the presence of the catalyst sulfilimine. The target product **1** was formed by etherification. This step was improved by substantial research.

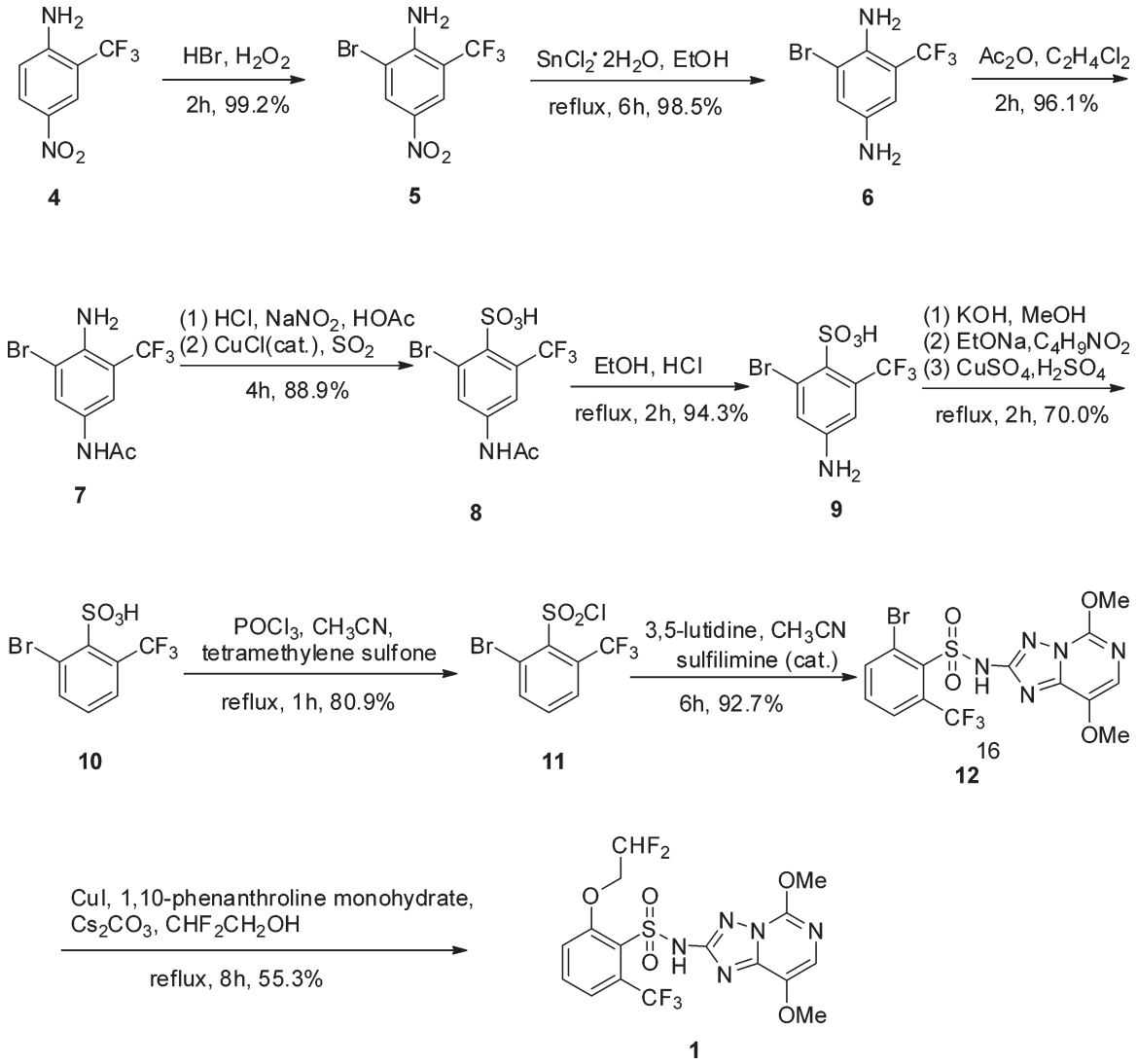
In order to optimise the route, the next step was to find the best parameters for each stage. Hydrogen bromide together with hydrogen peroxide and bromine alone were used as reagents for the bromination reaction. Considering the volatility and poisonous nature of bromine, we chose hydrogen bromide and hydrogen peroxide as the bromination reagent. In this reaction, the temperature was the key parameter. The golden yellow substrate did not dissolve well in the polar solvent below 50 °C. When the temperature reached 80 °C, there would be a danger due to the presence of hydrogen peroxide. A better result was obtained at 60–70 °C. In the second reduction step, different reducing agents, such as stannous chloride in ethanol, iron in acetic acid and zinc dust in acetic acid were screened at 78–80 °C. The results showed that the optimum yield was obtained in the presence of stannous chloride. The metal reducing agents made the postprocessing difficult and product **6** was impure due to the unreacted metals and less compound **7** was formed in the next step. The remaining steps could be easily accomplished in our hands and are not discussed in detail. The diazotisation was a classical reaction in organic synthesis in which the temperature was the key parameter. The transformation of compound **7** to **8** proceeded under acidic conditions and the best result was obtained at 0 °C. The conversion of **9** to **10** proceeded under basic conditions and the best result was obtained at 55 °C.

In order to decrease the steric hindrance the condensation of **11** with **2** was accomplished successfully with a yield of up to 92.7% and this was followed by the etherification of **12** to get **1**.

This method shortened the reaction time to less than 8 hours and improved the efficiency considerably. The conditions were mild and the reagents that were used were inexpensive. Moreover most of the intermediates were isolated by filtration without recourse to column chromatography, making the post-processing more convenient. Finally the overall yield improved to 22.9% which is twice of that of the reported process (11.0%).

Conclusion

An efficient synthesis of 2-(2,2-difluoroethoxy)-6-trifluoromethyl-*N*-(5,8-dimethoxy-1,2,4-triazolo[1,5-c]pyrimidine-2-yl) benzenesulfonamide has been developed which used 4-nitro-2-(trifluoromethyl)aniline as the starting material. Compared with the reported method, this approach has advantages in its shorter reaction time, milder reaction conditions, and easier work-up. Moreover, the overall yield has been improved to 22.9% which is twice of that of the reported method.



Scheme 2 An efficient synthesis of penoxsulam (overall yield 22.9%).

Experimental

Reagents and solvents were obtained from commercial suppliers and used without purification.Column chromatography was conducted on silica gel (100–200 mesh) from Qingdao Ocean Chemical Factory. 2-Amino-5,8-dimethoxy-1,2,4-triazolo[1,5-c]pyrimidine (compound **2**) was prepared by Edmonds's method.[15] Melting points were recorded on a XT-4 melting point apparatus from Taike, Beijing. ^{1}H NMR spectra were obtained in either $CDCl_3$, DMSO-d_6 or D_2O, used as purchased, and were recorded on a Bruker 300 MHz, and referenced to an internal standard of tetramethylsilane (TMS ^{1}H: δ 0.00). ^{1}H–^{1}H couplings are assumed to be first order and peak multiplicity is reported as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or br (broad). Mass spectroscopic data were obtained on a Bruker Esruire 3000 Plus series chromatograph (ESI). IR spectra were measured using a ThermoFisher Nicolet 470 FT-IR spectrometer. High-resolution mass spectrometry (HRMS) was performed using a Waters Micromass LCT Premier spectrometer. Reactions were monitored by thin layer chromatography (TLC) on GF254 silica gel plates and visualised with ZF-20D ultraviolet analytic apparatus.

2-Bromo-4-nitro-6-trifluoromethylaniline (**5**): Compound **4** (67.9 g, 0.329 mol) and 40% hydrogen bromide (73.1 g, 0.36l mol) were placed in a round bottomed flask (500 mL) at room temperature. The resultant reaction mixture was stirred for 10 min and then heated to 60–70 °C. 30% hydrogen peroxide (40.5 g, 0.357 mol) diluted with water (40 mL) was added slowly to the resultant suspension for 1 h and the reaction mixture was stirred for 2 h at 60–70 °C. The precipitated solid was filtered off with suction, washed with water (800 mL) and dried at 60 °C to afford **5** as yellow powder. Yield: 93.2 g (99.2%). The spectroscopic data of the yellow solid was in accordance with the reported values.[14] m.p. 136–128 °C (lit.[14] 138–140 °C).^{1}H NMR ($CDC1_3$, 300 MHz): δ 5.44 (br s, 2H, NH_2), 8.38 (d, 1H, J = 2.4 Hz, Ar H-5), 8.52 (d, 1H, J = 2.7 Hz, Ar H-3). IR (KBr), v/cm^{-1}: 3494, 3388, 3200, 1623, 1516, 1482, 1315, 1122, 917, 743, 708, 686.

2-Bromo-4-amino-6-trifluoromethylaniline (**6**): Stannous chloride (27.1 g, 0.120 mol) was added to a suspension of **5** (11.4 g, 0.04 mol) and ethanol (80 mL), and the resultant reaction mixture was heated to reflux for 3 h. The ethanol was completely distilled off below 55 °C under reduced pressure and the residue was made alkaline to pH = 11–12 with 20% aqueous sodium hydroxide solution (300 mL). Then ethyl acetate (200 mL) was introduced and stirred for 30 min. The unwanted solid was filtered and washed with ethyl acetate (50 mL). The resultant filtrate was poured into a tap funnel and the organic solution was washed with water (200 mL×2), and dried with anhydrous sodium sulfate (10 g). The solvent was removed under reduced pressure to afford **6** as a tan solid. Yield: 10.0 g (97.1%). m.p. 45–47 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.34 (br s, 2H, NH_2), 4.19 (br s, 2H, NH_2), 6.80 (d, 1H, J = 2.4 Hz, Ar H), 7.02 (d, 1H, J = 2.4 Hz, Ar H). IR (KBr), v/cm^{-1}: 3483, 3445, 3391, 3364, 3297, 3197, 1620, 1485, 1231, 1111, 936, 872, 697. HRMS: calcd for $C_7H_6BrF_3N_2$ [M-H]$^-$ 252.9588, found 252.9590.

2-Bromo-4-acetamido-6-trifluoromethylaniline (**7**): A round bottomed flask (250 mL) fitted with an additional funnel, thermometer and compound **6** (40.3 g, 0.141 mol) and 1, 2-dichloroethane (150 mL) was introduced. The resultant reaction mixture was stirred for 30 min at room temperature, and then acetic anhydride (17.3 g, 0.169 mol) was added slowly. The temperature was maintained at 50 °C for 2 h. The solvent was distilled off below 55 °C under reduced pressure, and then the residue was filtered, washed with water (200 mL) and dried in a vacuum oven at 50 °C to afford **7** as a grey solid. Yield: 45.1 g (96.1%). m.p. 152–154 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.01 (s, 3H, CH3), 5.21 (br s, 2H, NH2), 7.68 (s, 1H, Ar H), 7.98 (s, 1H, Ar H), 9.95 (s, 1H, NH). IR (KBr), v/cm^{-1}: 3472, 3358, 3287, 3236, 3174, 3120,1661, 1608, 1551, 1485, 1281, 1111, 877, 703, 695. ESI-MS *m/z*: 319.0, 321 [base peak, M+23, M+25= 1:1]. HRMS: calcd for $C_9H_8BrF_3N_2O$ [M-H]$^-$ 294.9694, found 294.9699.

2-Bromo-4-acetamido-6-trifluoromethybenzenesulfonic acid (**8**): A round bottomed flask (250 mL) fitted with an additional funnel, thermometer and mechanical stirrer was charged with compound **7** (30.0 g, 0.101 mol), acetic acid (60 mL), 37% hydrochloric acid (90 mL) and 98% sulfuric acid (2 mL). The resultant reaction mixture was stirred for 30 min and cooled to 0–2 °C. 25% Aqueous sodium nitrite solution (8.5 g, 0.123 mol) was slowly added to the cold solution at 0–5 °C. The resultant suspension was stirred at this temperature for 1 h until a completely clear solution was formed. The solution obtained above was added to a mixture of the catalyst cuprous chloride (0.2 g, 0.001 mol) and sulfur dioxide dissolved in acetic acid (60 mL) in an ice bath. Then the resulting suspension was stirred for 2.5 h at 0–5 °C. The precipitated product was filtered, washed with water (200 mL) and dried in a vacuum oven at 50 °C to afford **8** as an off-white solid. Yield: 34.2 g (88.9%). m.p. 182–184 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.07 (s, 3H, CH3), 7.9 (d, 1H, J = 1.7 Hz, Ar H), 8.11 (d, 1H, J = 1.7 Hz, Ar H), 10.41 (s, 1H, NH), 12.20 (br s, 1H, SO3H). IR (KBr), v/cm^{-1}: 3445, 3316, 3253, 3173, 3091, 1683, 1584, 1524, 1392, 1304, 1193, 1157, 882, 696. ESI-MS *m/z*: 360.1 [base peak, M-1]. HRMS: calcd for $C_9H_7BrF_3NO_4S$ [M-H]$^-$ 359.9153, found 359.9156.

2-Bromo-4-amino-6-trifluoromethybenzenesulfonic acid (**9**): A round bottomed flask (250 mL) fitted with an additional funnel and mechanical stirrer was charged with compound **8** (28.0 g, 0.074 mol), 37% hydrochloric (20 mL) and ethanol (100 mL). The resulting mixture was heated under reflux for 2 h, and then cooled to room temperature. The solvent was removed in vacuum. The residue was filtered, washed with ethanol (10 mL) and dried in a vacuum oven at 50 °C to afford **9** as a white solid. Yield: 22.2 g (94.3%). m.p. >250 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.02 (s, 1H, Ar H), 7.15 (s, 1H, Ar H), 7.64 (br s, 3H, NH_2, SO_3H). IR (KBr), v/cm^{-1}: 3433, 3097, 3021, 2676, 1608,1561, 1509, 1298, 1234, 1161, 1115, 1076, 877, 700, 676. ESI-MS *m/z*: 317.9 [base peak, M-1]. HRMS: calcd for $C_7H_5BrF_3NO_3S$ [M-H]$^-$ 317.9047, found 317.9050.

2-Bromo-6-trifluoromethybenzenesulfonic acid (**10**): A round bottomed flask (250 mL) fitted with a thermometer and mechanical stirrer was charged with n-butyl alcohol (37.0 g, 0.50 mol), water (10 mL) and 98% sulfuric acid (14 mL). The resultant mixture was stirred and cooled to 0–2 °C. The cold suspension was slowly added to 20% aqueous sodium nitrite solution (38.0 g, 0.55 mol) for 1 h. The solution obtained above was transferred to a funnel and the organic layer was washed with aqueous sodium bicarbonate (200 mL) and sodium chloride solution (150 mL) and dried with anhydrous sodium sulfate (10 g). The solvent was evaporated to afford a yellow oil (36.1 g) of butyl nitrite.

Another round bottomed flask (100 mL) fitted with a thermometer and mechanical stirrer was charged with **9** (15.9 g, 0.05 mol), sodium (1.2 g, 0.052 mol) and anhydrous ethanol (50 mL). The resultant reaction mixture was stirred and cooled to 0–2 °C. Butyl nitrite (17.0 g, 0.068 mol) obtained above was added. After the ester was added, the solution was heated to 60 °C for 3 h. The resulting solution was cooled to 0 °C, followed by the addition of cuprous chloride (0.8 g, 0.004 mol) catalyst and concentrated sulfuric acid (15 mL). It was then refluxed for 2 h. The solution was filtered, extracted with ethyl acetate (150 mL) and water (100 mL×2), dried with anhydrous sodium sulfate (10 g) and the solvent was removed to obtained yellow oil. Yield: 10.7 g (70.0%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.99 (s, 1H, SO3H), 7.34–7.40 (t, 1H, J = 7.9 Hz, Ar H-4), 7.75 (d, 1H, J = 7.9 Hz, Ar H-5), 7.92 (d, 1H, J = 7.8 Hz, Ar H-3). IR (KBr), v/cm^{-1}: 3475, 3419, 3167, 2120, 1634, 1401, 1238, 1221, 793, 731, 690, 634, 624. ESI-MS *m/z*: 302.9 [base peak, M-1]; HRMS calcd for $C_7H_4BrF_3O_3S$ [M-1]$^-$ 302.8938, found 302.8942.

2-Bromo-6-trifluoromethybenzenesulfonyl chloride (**11**): 10% Aqueous potassium hydroxide solution (40 g) was added to compound **10** (15.2 g, 0.05 mol) in methanol at room temperature to generate the potassium salt of compound **10** (17.1 g, 0.05 mol).

A suspension of this potassium salt of compound **10** (3.4 g, 9.9 mol) in acetonitrile (8 mL), was treated with tetramethylene sulfone (2.5 g, 21 mol) and phosphorus oxychloride (5.0 g, 32 mmol). The resultant mixture was stirred and heated to reflux for 1 h. The mixture was then cooled to room temperature, diluted to ice water (40 mL) and extracted with dichloromethane (100 mL). The organic layer was washed with water (100 mL×2), dried with anhydrous sodium sulfate (10 g), filtered and the solvent removed in vacuum to afford the crude product as tan oil. The oil was purified by column chromatography (SiO_2, 0–20%, EtOAc/hexane) to afford **11** as light yellow solid. Yield: 2.6 g (80.9%). m.p. 40–42 °C. This compound was not stable in the analysis of ^{1}H NMR spectra and mass spectra, and the sulfonyl chloride group was easily hydrolysed to sulfonic acid. Its structure could be confirmed by its easy conversion to compound **12**.

2-Bromo-6-trifluoromethyl-N-(5,8-dimethoxy-1,2,4-triazolo[1,5-c] pyrimidine-2-yl)benzenesulfonamide (**12**): Compound **2** (1.42 g, 4.4 mmol) dissolved in anhydrous acetonitrile was added to a suspension of anhydrous 3,5-lutidine (2.86 g, 26.7 mmol), compound **11** (0.78 g, 5 mmol) and catalyst sulfilimine (0.10 g, 0.3 mmol). The resultant mixture was stirred and heated to 45 °C for 24 h. The solution was cooled to room temperature, acidified by 15% sulfuric acid (20 mL) and stirred for 30 min. A solid was precipitated from the solution, filtered, rinsed with water (50 mL) and dried in a vacuum oven at

50 °C to afford compound **12** as a white powder. Yield: 1.9 g (92.7%). m.p. 181–182 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.86 (s, 3H, CH3), 4.09 (s, 3H, CH3), 5.81 (s, 1H, NH), 7.60 (s, 1H, Ar H), 7.70 (t, 1H, Ar H), 8.08–8.15 (q, 2H, Ar). IR (KBr), v/cm^{-1}: 3431, 3247, 1637, 1572, 1537, 1513, 1398, 1374, 1293, 1177, 1153, 813, 688, 599. ESI-MS *m/z*: 482.0, 484.0 [base peak, M+1, M+3]. HRMS: calcd for $C_{14}H_{11}BrF_3N_5O_4S$ $[M+H]^+$ 481.9745, found 481.9749.

2-(2,2-Difluoroethoxy)-6-trifluoromethyl-N-(5,8-dimethoxy-1,2,4-triazolo[1,5-c]pyrimidine-2-yl) benzenesulfonamide (**1**): A dry round bottomed flask (50 mL) under N_2 was charged with compound (2.5 g, 5 mmol), copper iodide (0.05 g, 0.25 mmol), 8-hydroxyquinoline (0.073 g, 0.5 mmol) and tribasic potassium phosphate (2.12 g, 10 mmol). Difluoroethanol (8 mL) was slowly injected to the mixture. The resultant mixture was heated to reflux for 20 h. Most of the solvent difluoroethanol was removed under reduced pressure. The remaining residue was diluted with ethyl acetate (50 mL), washed with water (50 mL) and dried with anhydrous sodium sulfate. The organic layer was collected and the solvent removed under reduced pressure to afford crude tan oil. The oil was purified by column chromatography (SiO_2, 0–25%, MeOH/EtOAc) to afford compound **1** as a white solid. Yield: 1.4 g (55.3%). The spectroscopic data of the white solid was in accordance with the reported values.[3] m.p. 220–221 °C (lit.[3] 223–224 °C). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.85 (s, 3H, CH3), 4.06 (s, 3H, CH3), 4.46–4.54 (t, 2H, J = 12.0 Hz, CHF2), 6.34–6.70 (tt, 1H, J = 56.7 Hz), 7.58 (s, 1H, CH), 7.62–7.66 (m, 2H, J = 6.5 Hz, Ar), 7.75–7.77 (d, 1H, J = 7.9 Hz), 11.94 (s, 1H, NH). IR (KBr), v/cm^{-1}: 3463, 3362, 3127, 3003, 2359, 2324, 1638, 1537, 1314, 1315, 1179, 1158, 942, 801, 630. ESI-MS *m/z*: 484.2 [base peak, M+1]; HRMS calcd for $C_{16}H_{14}F_5N_5O_5S$ 484.0714, found $[M+H]^+$ 484.0716.

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