# organic compounds

# N-(3,4-Difluorophenyl)-3,4-dimethoxy-benzenesulfonamide

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In the title sulfonamide derivative, $C_{14}H_{13}F_2NO_4S$, the dihedral angle between the benzene rings is 66.05 (9)°. The crystal structure is stabilized by weak intermolecular N—H⋯O hydrogen bonds involving the amine and methoxy groups, which link the molecules into a one-dimensional chain. No significant interchain contacts are observed.

## Related literature

For general background on skin-whitening agents, see: Dawley & Flurkey (1993); Nerya *et al.* (2003); Juana *et al.* (1994); Briganti *et al.* (2003). For the synthesis, see: Hussain *et al.* (2003).
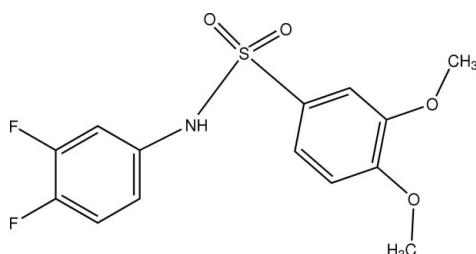


## Experimental

### Crystal data

| | |
|---|---|
| $C_{14}H_{13}F_2NO_4S$ | Monoclinic, $P2_1/c$ |
| $M_r = 329.31$ | $a = 12.2886$ (10) Å |
| $b = 8.5662$ (7) Å | Mo $K\alpha$ radiation |
| $c = 14.5546$ (12) Å | $\mu = 0.26$ mm$^{-1}$ |
| $\beta = 109.655$ (2)° | $T = 295$ (2) K |
| $V = 1442.8$ (2) Å$^3$ | $0.25 \times 0.18 \times 0.15$ mm |
| $Z = 4$ | |

### Data collection

| | |
|---|---|
| Bruker SMART CCD area-detector diffractometer | 9690 measured reflections |
| Absorption correction: multi-scan (*SADABS*; Bruker, 2002) | 3308 independent reflections |
| $T_{min} = 0.928$, $T_{max} = 0.957$ | 1700 reflections with $I > 2\sigma(I)$ |
| | $R_{int} = 0.042$ |

### Refinement

| | |
|---|---|
| $R[F^2 > 2\sigma(F^2)] = 0.044$ | H atoms treated by a mixture of independent and constrained refinement |
| $wR(F^2) = 0.126$ | |
| $S = 0.99$ | |
| 3308 reflections | $\Delta\rho_{max} = 0.19$ e Å$^{-3}$ |
| 204 parameters | $\Delta\rho_{min} = -0.21$ e Å$^{-3}$ |

**Table 1**
Hydrogen-bond geometry (Å, °).

| $D$—H⋯$A$ | $D$—H | H⋯$A$ | $D$⋯$A$ | $D$—H⋯$A$ |
|---|---|---|---|---|
| N7—H7⋯O17$^i$ | 0.76 (3) | 2.48 (3) | 3.180 (3) | 155 (3) |
| N7—H7⋯O19$^i$ | 0.76 (3) | 2.61 (3) | 3.256 (3) | 144 (3) |

Symmetry code: (i) $-x + 2, y + \frac{1}{2}, -z + \frac{1}{2}$.

Data collection: *SMART* (Bruker, 2002); cell refinement: *SAINT* (Bruker, 2002); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *ORTEP-3 for Windows* (Farrugia, 1997); software used to prepare material for publication: *WinGX* (Farrugia, 1999).

## References

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# supporting information

# *N*-(3,4-Difluorophenyl)-3,4-dimethoxybenzenesulfonamide

## Hyon Pil You, Byung Hee Han, Sung Kwon Kang, Chang Keun Sung and Sang Ook Kang

### S1. Comment

Most skin whitening agents currently on the market (Dawley & Flurkey, 1993; Nerya *et al.*, 2003) contain hydroquinone, ascorbic acid, kojic acid (Juana *et al.*, 1994), arbutin, azealic acid, and glycyrrhetinic acid. They include aromatic, methoxy, hydroxyl and carbonyl functional groups in their structures. They are acting as a direct inhibitors of tyrosinase, the enzyme in the skin pigment cells (melanocytes) producing melanin.

Tyrosinase is the key enzyme converting the amino acid *L*-tyrosine to melanin, and its inhibitors are target molecules to develop anti-pigmentation agents for skin treatment after sunburn (Briganti *et al.* 2003). The melanin formation by the tyrosinase activity after sunlight exposure causes some dermatological disorders associated with freckles and melasma. Therefore, potent inhibitory agents on melanin formation and tyrosinase should be cosmetically useful for treatment of dermatological disorders.

However, most skin whitening agents have some problems, due to toxicity, low stability of formulation and poor skin permeation. In our work on the development of new whitening agents to complement the inadequacy of current whitening agents and maximize the inhibitory effects of melanin creation, we synthesized the title compound (Fig. 1), *via* a general chemical reaction (Hussain *et al.*, 2003) of 3,4-difluoroaniline with aromatic sulfonyl chloride, and studied its X-ray crystal structure.

The 3,4-dimethoxybenzenesulfonyl and 3,4-difluoroaniline moieties are essentially planar, with a mean deviation of 0.004 Å and 0.010 Å, respectively, from the corresponding least-squares planes. The dihedral angle between benzene rings is 66.05 (9)°. The intermolecular N7—H7···O17[i] and O19[i] [symmetry code: (i) -$x$ + 2, $y$ + 1/2, -$z$ + 1/2] hydrogen bonds (involving the H atom of the amine and O atoms of methoxy groups) allow to form an extensive one-dimensional network along the *b* axis, which stabilizes the crystal structure.

### S2. Experimental

3,4-difluoroaniline and 3,4-dimethoxy benzenesulfonyl chloride were purchased from Sigma Chemical Co. Solvents used for organic synthesis were redistilled before used. All other chemicals and solvents were of analytical grade and used without further purification. The title compound was prepared by the reaction of 3,4-difluoroaniline (1 mmol) with aromatic sulfonyl chloride (1.2 mmol) in triethylamine as a solvent, under stirring. Evaporation of solvent, treatment with water, extraction with methylene chloride and chromatography of the dried solution (MgSO$_4$) on silica gel column (2 / 1 = hexane / ethyl acetate) gave the title compound in 56% yield. Colourless single crystals were obtained by slow evaporation from an ethyl acetate solution, at room temperature.

### S3. Refinement

The amine H atom H7 was located in a difference map and refined freely. The other H atoms were positioned geometrically and refined using a riding model, with C—H = 0.93 Å for aromatic H atoms and 0.96 Å for methyl H

atoms, and with $U_{iso}(H) = 1.2U_{eq}(C)$ for aromatic and $1.5U_{eq}(C)$ for methyl H atoms.
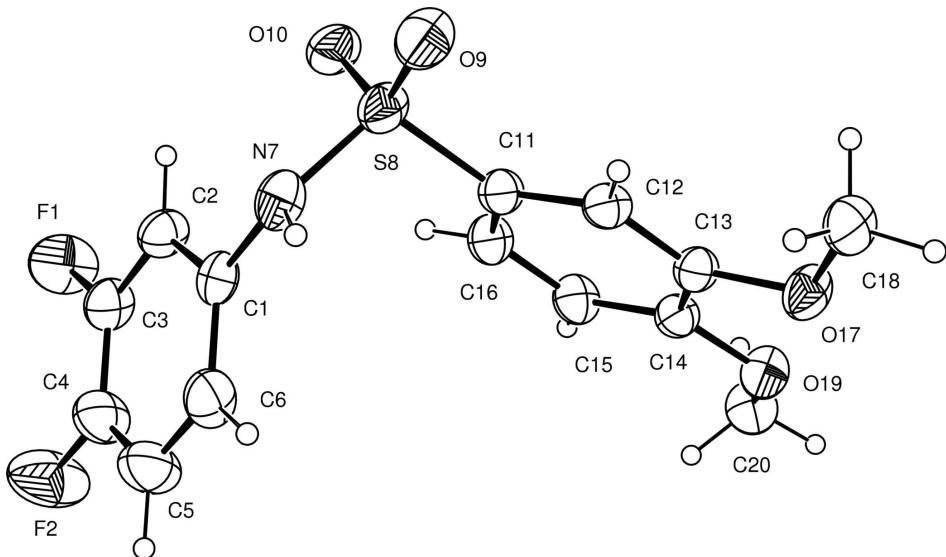


**Figure 1**

The molecular structure of the title compound, showing the atom-numbering scheme and 30% probability ellipsoids.

### *N*-(3,4-Difluorophenyl)-3,4-dimethoxybenzenesulfonamide

*Crystal data*
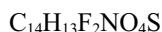
| | |
|---|---|
| $C_{14}H_{13}F_2NO_4S$ | $F(000) = 680$ |
| $M_r = 329.31$ | $D_x = 1.516$ Mg m$^{-3}$ |
| Monoclinic, $P2_1/c$ | Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å |
| Hall symbol: -P 2ybc | Cell parameters from 1598 reflections |
| $a = 12.2886$ (10) Å | $\theta = 2.8–23.5°$ |
| $b = 8.5662$ (7) Å | $\mu = 0.26$ mm$^{-1}$ |
| $c = 14.5546$ (12) Å | $T = 295$ K |
| $\beta = 109.655$ (2)° | Block, colourless |
| $V = 1442.8$ (2) Å$^3$ | $0.25 \times 0.18 \times 0.15$ mm |
| $Z = 4$ | |

*Data collection*

| | |
|---|---|
| Bruker SMART CCD area-detector diffractometer | 3308 independent reflections |
| | 1700 reflections with $I > 2\sigma(I)$ |
| $\varphi$ and $\omega$ scans | $R_{int} = 0.042$ |
| Absorption correction: multi-scan (*SADABS*; Bruker, 2002) | $\theta_{max} = 27.5°$, $\theta_{min} = 1.8°$ |
| | $h = -15\rightarrow14$ |
| $T_{min} = 0.928$, $T_{max} = 0.957$ | $k = -11\rightarrow9$ |
| 9690 measured reflections | $l = -18\rightarrow18$ |

*Refinement*

| | |
|---|---|
| Refinement on $F^2$ | H atoms treated by a mixture of independent and constrained refinement |
| Least-squares matrix: full | |
| $R[F^2 > 2\sigma(F^2)] = 0.044$ | $w = 1/[\sigma^2(F_o^2) + (0.0426P)^2 + 0.5561P]$ |
| $wR(F^2) = 0.126$ | where $P = (F_o^2 + 2F_c^2)/3$ |
| $S = 0.99$ | $(\Delta/\sigma)_{max} = 0.001$ |
| 3308 reflections | $\Delta\rho_{max} = 0.19$ e Å$^{-3}$ |
| 204 parameters | $\Delta\rho_{min} = -0.21$ e Å$^{-3}$ |
| 0 restraints | |

Extinction correction: *SHELXL97* (Sheldrick, 2008), Fc\*=kFc[1+0.001xFc²*λ*³/sin(2*θ*)]⁻¹ᐟ⁴

Extinction coefficient: 0.0349 (19)

*Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²)*

|  | $x$ | $y$ | $z$ | $U_{iso}$*/$U_{eq}$ |
|---|---|---|---|---|
| F1 | 0.37106 (16) | 0.1400 (3) | −0.04021 (13) | 0.0975 (7) |
| F2 | 0.3788 (2) | 0.0318 (3) | 0.13264 (17) | 0.1271 (9) |
| C1 | 0.6212 (2) | 0.3457 (3) | 0.11332 (19) | 0.0492 (7) |
| C2 | 0.5338 (2) | 0.2966 (3) | 0.0306 (2) | 0.0584 (8) |
| H2 | 0.5288 | 0.3352 | −0.0304 | 0.07* |
| C3 | 0.4554 (2) | 0.1914 (4) | 0.0395 (2) | 0.0609 (8) |
| C4 | 0.4593 (3) | 0.1366 (4) | 0.1281 (2) | 0.0753 (10) |
| C5 | 0.5430 (3) | 0.1849 (5) | 0.2102 (2) | 0.0885 (12) |
| H5 | 0.5454 | 0.1475 | 0.2708 | 0.106* |
| C6 | 0.6248 (2) | 0.2906 (4) | 0.2030 (2) | 0.0692 (9) |
| H6 | 0.6826 | 0.3245 | 0.2591 | 0.083* |
| N7 | 0.7042 (2) | 0.4591 (3) | 0.1068 (2) | 0.0595 (7) |
| H7 | 0.738 (2) | 0.489 (4) | 0.158 (2) | 0.062 (10)* |
| S8 | 0.78080 (6) | 0.43912 (9) | 0.03547 (5) | 0.0595 (3) |
| O9 | 0.84833 (17) | 0.5777 (2) | 0.04834 (17) | 0.0802 (7) |
| O10 | 0.70295 (15) | 0.3991 (3) | −0.05866 (13) | 0.0709 (6) |
| C11 | 0.8750 (2) | 0.2809 (3) | 0.07756 (18) | 0.0490 (7) |
| C12 | 0.9910 (2) | 0.3073 (3) | 0.13211 (17) | 0.0478 (6) |
| H12 | 1.0184 | 0.4087 | 0.1468 | 0.057* |
| C13 | 1.0644 (2) | 0.1829 (3) | 0.16380 (17) | 0.0472 (6) |
| C14 | 1.0231 (2) | 0.0296 (3) | 0.14189 (18) | 0.0480 (6) |
| C15 | 0.9086 (2) | 0.0050 (3) | 0.0875 (2) | 0.0559 (7) |
| H15 | 0.8809 | −0.0962 | 0.0724 | 0.067* |
| C16 | 0.8350 (2) | 0.1300 (3) | 0.0554 (2) | 0.0566 (7) |
| H16 | 0.7579 | 0.1128 | 0.0187 | 0.068* |
| O17 | 1.17904 (15) | 0.1936 (2) | 0.21844 (13) | 0.0614 (5) |
| C18 | 1.2333 (2) | 0.3419 (4) | 0.2277 (2) | 0.0669 (9) |
| H18A | 1.3129 | 0.3326 | 0.2681 | 0.1* |
| H18B | 1.1949 | 0.4141 | 0.2569 | 0.1* |
| H18C | 1.2288 | 0.3792 | 0.1643 | 0.1* |
| O19 | 1.10296 (15) | −0.0832 (2) | 0.17753 (14) | 0.0599 (5) |
| C20 | 1.0682 (3) | −0.2409 (3) | 0.1507 (2) | 0.0668 (8) |
| H20A | 1.132 | −0.3098 | 0.1805 | 0.1* |
| H20B | 1.0441 | −0.2514 | 0.0811 | 0.1* |
| H20C | 1.005 | −0.2674 | 0.1727 | 0.1* |

*Atomic displacement parameters (Å²)*

|  | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{12}$ | $U^{13}$ | $U^{23}$ |
|---|---|---|---|---|---|---|
| F1 | 0.0780 (12) | 0.1205 (18) | 0.0749 (12) | −0.0470 (12) | 0.0005 (10) | −0.0069 (11) |
| F2 | 0.1139 (17) | 0.160 (2) | 0.1037 (16) | −0.0684 (17) | 0.0321 (14) | 0.0185 (15) |
| C1 | 0.0374 (13) | 0.0490 (16) | 0.0540 (17) | 0.0026 (12) | 0.0060 (12) | −0.0074 (13) |

| C2 | 0.0499 (16) | 0.0634 (19) | 0.0522 (17) | −0.0065 (14) | 0.0044 (13) | 0.0047 (14) |
| C3 | 0.0480 (16) | 0.069 (2) | 0.0555 (18) | −0.0104 (15) | 0.0037 (14) | −0.0058 (15) |
| C4 | 0.0615 (19) | 0.088 (3) | 0.075 (2) | −0.0210 (18) | 0.0223 (17) | 0.0036 (19) |
| C5 | 0.074 (2) | 0.134 (4) | 0.057 (2) | −0.015 (2) | 0.0207 (18) | 0.008 (2) |
| C6 | 0.0520 (17) | 0.096 (3) | 0.0530 (19) | −0.0028 (17) | 0.0093 (14) | −0.0121 (17) |
| N7 | 0.0462 (13) | 0.0581 (16) | 0.0618 (17) | −0.0029 (12) | 0.0019 (12) | −0.0102 (13) |
| S8 | 0.0460 (4) | 0.0573 (5) | 0.0647 (5) | −0.0070 (4) | 0.0048 (3) | 0.0101 (4) |
| O9 | 0.0582 (12) | 0.0579 (14) | 0.1098 (18) | −0.0137 (10) | 0.0090 (12) | 0.0198 (12) |
| O10 | 0.0543 (11) | 0.0896 (17) | 0.0556 (12) | −0.0054 (10) | 0.0009 (9) | 0.0153 (11) |
| C11 | 0.0422 (14) | 0.0530 (17) | 0.0480 (15) | −0.0059 (13) | 0.0102 (12) | 0.0031 (13) |
| C12 | 0.0480 (14) | 0.0453 (16) | 0.0459 (15) | −0.0115 (12) | 0.0102 (12) | −0.0005 (12) |
| C13 | 0.0420 (14) | 0.0526 (17) | 0.0427 (14) | −0.0059 (13) | 0.0084 (11) | 0.0005 (12) |
| C14 | 0.0469 (14) | 0.0473 (17) | 0.0482 (15) | −0.0036 (13) | 0.0138 (12) | 0.0015 (12) |
| C15 | 0.0509 (16) | 0.0509 (17) | 0.0643 (18) | −0.0130 (14) | 0.0171 (14) | −0.0060 (14) |
| C16 | 0.0418 (14) | 0.062 (2) | 0.0598 (18) | −0.0137 (14) | 0.0092 (13) | −0.0027 (15) |
| O17 | 0.0470 (10) | 0.0523 (12) | 0.0707 (13) | −0.0082 (9) | 0.0010 (9) | 0.0051 (10) |
| C18 | 0.0486 (16) | 0.061 (2) | 0.078 (2) | −0.0199 (14) | 0.0042 (14) | 0.0031 (16) |
| O19 | 0.0563 (11) | 0.0441 (12) | 0.0732 (13) | −0.0037 (9) | 0.0138 (10) | −0.0016 (9) |
| C20 | 0.0727 (19) | 0.0473 (18) | 0.081 (2) | −0.0054 (16) | 0.0270 (17) | −0.0061 (16) |

### Geometric parameters (Å, º)

| | | | |
|---|---|---|---|
| F1—C3 | 1.343 (3) | C11—C12 | 1.398 (3) |
| F2—C4 | 1.354 (3) | C12—C13 | 1.372 (4) |
| C1—C6 | 1.375 (4) | C12—H12 | 0.93 |
| C1—C2 | 1.382 (3) | C13—O17 | 1.369 (3) |
| C1—N7 | 1.434 (4) | C13—C14 | 1.405 (4) |
| C2—C3 | 1.357 (4) | C14—O19 | 1.350 (3) |
| C2—H2 | 0.93 | C14—C15 | 1.379 (3) |
| C3—C4 | 1.359 (4) | C15—C16 | 1.378 (4) |
| C4—C5 | 1.352 (4) | C15—H15 | 0.93 |
| C5—C6 | 1.383 (4) | C16—H16 | 0.93 |
| C5—H5 | 0.93 | O17—C18 | 1.420 (3) |
| C6—H6 | 0.93 | C18—H18A | 0.96 |
| N7—S8 | 1.628 (3) | C18—H18B | 0.96 |
| N7—H7 | 0.76 (3) | C18—H18C | 0.96 |
| S8—O10 | 1.424 (2) | O19—C20 | 1.431 (3) |
| S8—O9 | 1.424 (2) | C20—H20A | 0.96 |
| S8—C11 | 1.754 (3) | C20—H20B | 0.96 |
| C11—C16 | 1.381 (4) | C20—H20C | 0.96 |
| | | | |
| C6—C1—C2 | 119.3 (3) | C13—C12—C11 | 119.6 (2) |
| C6—C1—N7 | 119.9 (2) | C13—C12—H12 | 120.2 |
| C2—C1—N7 | 120.7 (3) | C11—C12—H12 | 120.2 |
| C3—C2—C1 | 119.2 (3) | O17—C13—C12 | 125.1 (2) |
| C3—C2—H2 | 120.4 | O17—C13—C14 | 114.6 (2) |
| C1—C2—H2 | 120.4 | C12—C13—C14 | 120.3 (2) |
| F1—C3—C2 | 120.1 (3) | O19—C14—C15 | 125.5 (2) |

| | | | |
|---|---|---|---|
| F1—C3—C4 | 118.5 (3) | O19—C14—C13 | 114.9 (2) |
| C2—C3—C4 | 121.4 (3) | C15—C14—C13 | 119.6 (3) |
| C5—C4—F2 | 120.7 (3) | C16—C15—C14 | 120.1 (3) |
| C5—C4—C3 | 120.4 (3) | C16—C15—H15 | 119.9 |
| F2—C4—C3 | 118.9 (3) | C14—C15—H15 | 119.9 |
| C4—C5—C6 | 119.3 (3) | C15—C16—C11 | 120.5 (2) |
| C4—C5—H5 | 120.3 | C15—C16—H16 | 119.8 |
| C6—C5—H5 | 120.3 | C11—C16—H16 | 119.8 |
| C1—C6—C5 | 120.3 (3) | C13—O17—C18 | 118.3 (2) |
| C1—C6—H6 | 119.8 | O17—C18—H18A | 109.5 |
| C5—C6—H6 | 119.8 | O17—C18—H18B | 109.5 |
| C1—N7—S8 | 123.2 (2) | H18A—C18—H18B | 109.5 |
| C1—N7—H7 | 109 (2) | O17—C18—H18C | 109.5 |
| S8—N7—H7 | 115 (2) | H18A—C18—H18C | 109.5 |
| O10—S8—O9 | 120.03 (13) | H18B—C18—H18C | 109.5 |
| O10—S8—N7 | 107.04 (13) | C14—O19—C20 | 117.3 (2) |
| O9—S8—N7 | 105.36 (14) | O19—C20—H20A | 109.5 |
| O10—S8—C11 | 107.51 (13) | O19—C20—H20B | 109.5 |
| O9—S8—C11 | 108.15 (12) | H20A—C20—H20B | 109.5 |
| N7—S8—C11 | 108.29 (13) | O19—C20—H20C | 109.5 |
| C16—C11—C12 | 119.9 (2) | H20A—C20—H20C | 109.5 |
| C16—C11—S8 | 120.0 (2) | H20B—C20—H20C | 109.5 |
| C12—C11—S8 | 120.0 (2) | | |

*Hydrogen-bond geometry (Å, º)*

| D—H···A | D—H | H···A | D···A | D—H···A |
|---|---|---|---|---|
| N7—H7···O17[i] | 0.76 (3) | 2.48 (3) | 3.180 (3) | 155 (3) |
| N7—H7···O19[i] | 0.76 (3) | 2.61 (3) | 3.256 (3) | 144 (3) |

Symmetry code: (i) −x+2, y+1/2, −z+1/2.