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Synthesis, characterization, and antifungal activity of novel (*Z*)-*N*-(2-cyano-3-phenylprop-2-en-1-yl)-alkyl/aryl-sulfonamides derived from a Morita–Baylis–Hillman adduct

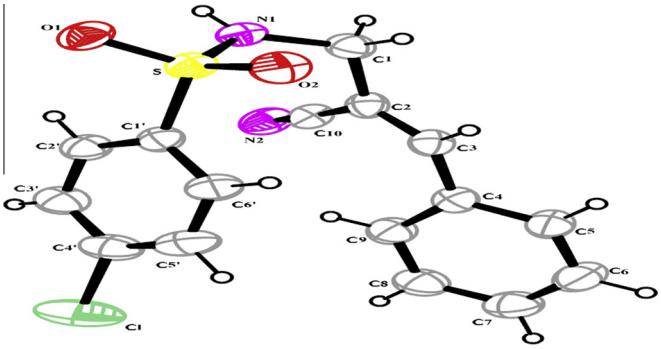
Eder C. Tavares [a,*], Mayura M.M. Rubinger [a], Carlos H.C. Zacchi [a], Simone A. Silva [a], Marcelo R.L. Oliveira [a], Silvana Guilardi [b], Antônio F. de C. Alcântara [c], Dorila Piló-Veloso [c], Laércio Zambolim [d]

[a] *Departamento de Química, Universidade Federal de Viçosa, 36570-900 Viçosa, MG, Brazil*
[b] *Instituto de Química, Universidade Federal de Uberlândia, 38408-100 Uberlândia, MG, Brazil*
[c] *Departamento de Química – ICEx, Universidade Federal de Minas Gerais, 31270-901 Belo Horizonte, MG, Brazil*
[d] *Departamento de Fitopatologia – CCA, Universidade Federal de Viçosa, 36570-900 Viçosa, MG, Brazil*

HIGHLIGHTS

- Nine allyl sulfonamides derived from a Morita–Baylis–Hillman adduct were prepared.
- The highly stereoselective reactions yielded *Z*-isomers, as confirmed by X-ray diffraction.
- Their activity were tested against *Colletotrichum gloeosporioides*.
- Most of these allyl sulfonamides were more active than the primary sulfonamides.

GRAPHICAL ABSTRACT



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ABSTRACT

A series of allyl sulfonamides prepared from the reaction of the Morita–Baylis–Hillman adduct 2-[hydroxy(phenyl)methyl]acrylonitrile with primary sulfonamides (RSO_2NH_2), where R = C_6H_5 (**1**), 4-F—C_6H_4 (**2**), 4-Cl—C_6H_4 (**3**), 4-Br—C_6H_4 (**4**), 4-NO_2—C_6H_4 (**5**), CH_3 (**6**), CH_3CH_2 (**7**), $CH_3(CH_2)_3$ (**8**), and $CH_3(CH_2)_7$ (**9**), were characterized by IR, ^1H and ^{13}C NMR spectroscopies, mass spectrometry and elemental analyses. BLYP/6-31G* calculations suggested stereoselective reactions, resulting in the exclusive formation of the thermodynamically more stable *Z*-products. The *Z*-configuration of the products was confirmed by NOE difference spectroscopy and single crystal X-ray diffraction measurements. The allyl sulfonamides were active against *Colletotrichum gloeosporioides*, an important agent of anthracnose in plants.

Introduction

The Morita–Baylis–Hillman (MBH) reactions are a versatile and powerful carbon–carbon bond-forming method in organic synthesis [1]. MBH reactions can provide in only one-step multifunctionalized compounds which can be used as intermediates

* Corresponding author. Present address: Instituto de Física e Química, Universidade Federal de Itajubá, 37500-903 Itajubá, MG, Brazil. Tel.: +55 3536291220; fax: +55 3536291140.
E-mail address: eder@unifei.edu.br (E.C. Tavares).

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for the preparation of biologically active substances [2], such as sulfonamides. The synthesis of sulfonamides can be considered as a milestone in chemotherapy, mainly due to their action against bacteria. Several compounds bearing sulfonamide groups exhibit other important biological properties, such as antitumor, antiglaucoma and antifungal activities [3].

Colletotrichum is a well-known genus of pathogenic fungi that causes anthracnose in plants. This disease damages trees and food crops, including cereals, legumes and fruits. The regular application of fungicides is the most effective control of anthracnose, although the reduction of effectiveness of commercial fungicides using standard spray schedules has been reported [4]. As a consequence, the use of fungicides of different modes of actions to overcome fungal resistance is an important practice [5]. The discovery of novel antifungals is urgent to increase the structural variety of chemicals available for field applications to control the fungal diseases.

In the present work, the synthetic approach described in the literature [6] for the preparation of *N*-tosylaza–Baylis–Hillman adducts was adapted and applied for the synthesis of nine allyl sulfonamides with aromatic and aliphatic substituents attached to the sulfonyl group (Scheme 1). These new compounds were characterized by elemental analysis, infrared and NMR spectroscopies and mass spectrometry. Additionally, the structures of the compounds **1** and **3** were determined by X-ray diffraction techniques. Effects of the allyl sulfonamides on the growth of *Colletotrichum gloeosporioides* were evaluated *in vitro*.

Experimental

Methods and materials

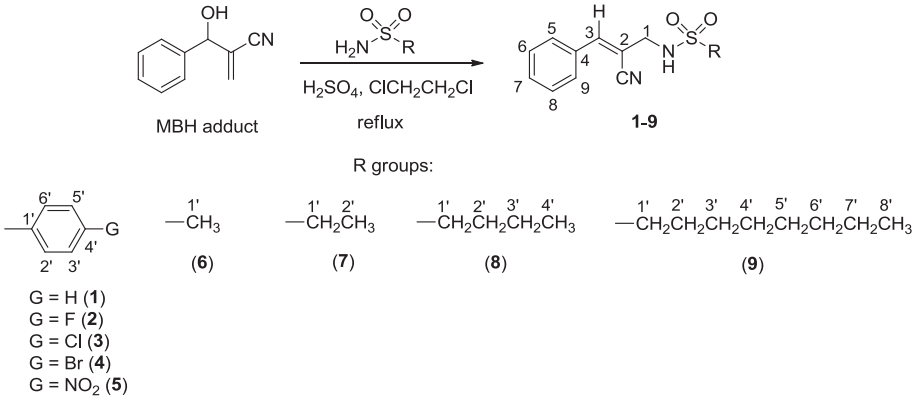
Uncorrected melting points were determined with a MQAPF-302 equipment. Microanalyses for C, H, and N were obtained from a Perkin–Elmer 2400 CHN Elemental Analyzer. The IR spectra (4000–500 cm^{-1}) were recorded on a FT-IR Varian 660 equipment with GladiATR single reflection accessory. The ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a Varian spectrophotometer using $CDCl_3$ or DMSO-*d6* as solvents and TMS as internal standard. COSY, HETCOR and NOEDIF experiments were performed for structural characterization of the reaction products. GC/MS experiments were performed using a Shimadzu QP5050-A mass spectrometer, coupled to a Shimadzu GC17A gas chromatograph (BD1 capillary column, 30 m), 70 eV. Methanesulfonamide, benzenesulfonamide, 4-chlorobenzenesulfonamide, 4-nitrobenzenesulfonamide, 4-fluorobenzenesulfonyl chloride, 4-bromobenzenesulfonyl chloride, methanesulfonyl chloride, ethanesulfonylchloride, butanesulfonyl chloride, and octanesulfonyl chloride were purchased from Aldrich. The R-sulfonamides (R = 4-F-phenyl, 4-Br-phenyl, ethyl, *n*-butyl, and *n*-octyl) were prepared under reflux by the reaction of the corresponding sulfonyl chlorides with concentrated ammonia aqueous solution. The Morita–Baylis–Hillman adduct was prepared from benzaldehyde, as described in the literature [7].

*General procedure for the syntheses of (Z)-N-(2-cyano-3-phenylprop-2-en-1-yl)-alkyl/aryl-sulfonamides (**1**–**9**)*

Concentrated sulfuric acid (54 μL) was added to a solution of the MBH adduct (159 mg, 1.0 mmol) and the appropriate sulfonamide (1.5 mmol) in 1,2-dichloroethane (5 mL). After stirring under reflux for 2–6 h, the reaction was completed (monitored by TLC). Then, water (10 mL) was added and the product was extracted with ethyl acetate (3 × 10 mL). The organic phase was dried over sodium sulfate and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel (hexane:ethyl acetate:dichloromethane 3:1:3). The data obtained for the compounds **1**–**9** are as follows.

(Z)-N-(2-cyano-3-phenylprop-2-en-1-yl)-benzenesulfonamide (**1**): yield 42%; white crystals; m.p. 98.9–99.1 °C; IR (ATR; ν_{max}/cm^{-1}) 3267, 3061, 2214, 1624, 1493, 1446, 1325, 1215, 1156, 1091, 1068, 998, 930, 898, 867, 822, 751, 722, 687, 582, 552, 511, and 479; ^{1}H NMR ($CDCl_3$; 300 MHz) δ3.94 (s; 2H; H1), 5.59 (bs; 1H; NH), 7.06 (s; 1H; H3), 7.33–7.38 (m; 3H; H3′, H4′ and H5′), 7.40–7.50 (m; 3H; H6, H7 and H8), 7.56–7.59 (m; 2H; H5 and H9), 7.86–7.89 (m; 2H; H2′ and H6′); ^{13}C-NMR ($CDCl_3$; 75 MHz) δ 47.2 (C1), 107.0 (C2), 117.5 (CN), 127.4 (C2′ and C6′), 129.0 (C3′and C5′), 129.1 (C5 and C9), 129.4 (C6 and C8), 131.0 (C7), 132.9 (C4′), 133.1 (C4), 140.4 (C1′), 146.0 (C3); MS [*m/z* (%)] 298 (4) $[M]^{+\cdot}$, 157 (100), 155 (28), 140 (37), 115 (12), 77 (87), 51 (41). Anal. Calcd. for $C_{16}H_{14}N_2O_2S$: C, 64.41%; H, 4.73%; N, 9.39%; Found: C, 64.17%; H, 4.71%; N, 9.32%.

(Z)-N-(2-cyano-3-phenylprop-2-en-1-yl)-4-fluorobenzenesulfonamide (**2**): yield 32%; white crystals; m.p. 115.7–116.8 °C; IR (ATR; ν_{max}/cm^{-1}) 3301, 3062, 2923, 2853, 2207, 1730, 1624, 1590, 1492, 1446, 1428, 1335, 1319, 1289, 1233, 1150, 1092, 1071, 1009, 935, 907, 882, 834, 756, 709, 699, 685, 660, 623, 592, 571, 543, 503, 445; ^{1}H NMR ($CDCl_3$; 300 MHz) δ 3.97 (s; 2H; H1), 5.62 (bs; 1H; NH), 7.07–7.15 (m; 3H; H3, H3′ and H5′), 7.35–7.42 (m; 3H; H6, H7 and H8), 7.58–7.62 (m; 2H; H5 and H9), 7.87–7.93 (m; 2H; H2′ and H6′); ^{13}C NMR ($CDCl_3$; 75 MHz) δ 47.4 (C1), 106.4 (C2), 116.7 (d; $^{C\text{-}F}J$ = 22.5 Hz; C3′ and C5′), 117.5 (CN), 129.1 (C5 and C9), 129.2 (C6 and C8), 130.2 (d; $^{C\text{-}F}J$ = 9.7 Hz; C2′ and C6′), 131.3 (C7), 132.6 (C4), 136.3 (d; $^{C\text{-}F}J$ = 3.0 Hz; C1′), 146.3 (C3), 165.4 (d; $^{C\text{-}F}J$ = 254.2 Hz; C4′); MS [*m/z* (%)] 316 (5) $[M]^{+\cdot}$, 157 (100), 155 (38), 140 (35), 130 (9), 115 (10), 95 (39), 51 (15), 44 (25). Anal. Calcd. for $C_{16}H_{13}FN_2O_2S$: C, 60.75%; H, 4.14%; N, 8.86%; Found: C, 60.31%; H, 4.22%; N, 8.77%.



Scheme 1. Syntheses and NMR numbering.

(Z)-N-(2-cyano-3-phenylprop-2-en-1-yl)-4-chlorobenzenesulfonamide (**3**): yield 39%; white crystals; m.p. 128.2–128.4 °C; IR (ATR; ν_{max}/cm^{-1}) 3263, 2925, 2854, 2210, 1627, 1586, 1493, 1474, 1447, 1427, 1394, 1355, 1322, 1277, 1214, 1178, 1155, 1090, 1046, 1011, 932, 908, 870, 834, 825, 704, 629, 505, 481; ^{1}H NMR ($CDCl_3$; 300 MHz) δ 4.00 (s; 2H; H1), 5.11 (bs; 1H; NH), 7.04 (s; 1H; H3), 7.40–7.45 (m; 5H; H6, H7, H8, H3′ and H5′), 7.58–7.61 (m; 2H; H5 and H9), 7.79–7.83 (m; 2H; H2′ and H6′); ^{13}C NMR ($CDCl_3$; 75 MHz) δ 46.6 (C1), 106.4 (C2), 117.3 (CN), 128.9 (C2′ and C6′), 129.1 (C3′ and C5′), 129.2 (C5 and C9), 129.8 (C6 and C8), 131.4 (C7), 132.5 (C4), 138.9 (C4′), 139.9 (C1′), 146.3 (C3); MS [*m/z* (%)] 332 (3) $[M]^{+\cdot}$, 157 (100), 155 (39), 140 (33), 111 (33), 75 (24), 51 (13). Anal. Calcd. for $C_{16}H_{13}ClN_2O_2S$: C, 57.7%; H, 3.94%; N, 8.42%; Found: C, 57.71%; H, 4.09%; N, 8.38%.

(Z)-N-(2-cyano-3-phenylprop-2-en-1-yl)-4-bromobenzenesulfonamide (**4**): yield 35%; white crystals; m.p. 145.0–145.9 °C; IR (ATR; ν_{max}/cm^{-1}) 3234, 2222, 1574, 1492, 1470, 1438, 1345, 1323, 1277, 1160, 1090, 1068, 1007, 992, 933, 903, 817, 776, 735, 720, 698, 686, 629, 604, 570, 547, 514, 481, 470, 430, 415; ^{1}H NMR (DMSO-*d6*; 300 MHz) δ 3.83 (d; 2H; $J_{1,NH}$ = 6 Hz; H1), 7.27 (s; 1H; H3), 7.42–7.45 (m; 3H, H6, H7 and H8), 7.60–7.63 (m; 2H; H5 and H9), 7.72–7.81 (m; 4H; H2′, H6′, H3′ and H5′), 8.47 (t; 1H; $J_{NH,1}$ = 6.0 Hz; NH); ^{13}C NMR (DMSO-*d6*; 75 MHz) δ 47.0 (C1), 108.4 (C2), 118.2 (CN), 127.1 (C4′), 129.2 (C5 and C9), 129.3 (C2′ and C6′), 129.6 (C6 and C8), 131.2 (C7), 133.0 (C3′ and C5′), 133.5 (C4), 140.6 (C1′), 146.0 (C3); MS [*m/z* (%)] 378 (5) $[M]^{+\cdot}$, 221 (8), 157 (100), 155 (63), 140 (43), 130 (13), 115 (14), 77 (18), 51 (15). Anal. Calcd. for $C_{16}H_{13}BrN_2O_2S$: C, 50.94%; H, 3.47%; N, 7.43%; Found: C, 50.93%; H, 3.58%; N, 7.31%.

(Z)-N-(2-cyano-3-phenylprop-2-en-1-yl)-4-nitrobenzenesulfonamide (**5**): yield 40%; white crystals; m.p. 205.4–206.0 °C; IR (ATR; ν_{max}/cm^{-1}) 3289, 3108, 2840, 2354, 2208, 1624, 1606, 1523, 1419, 1349, 1307, 1158, 1109, 1079, 736. ^{1}H NMR (DMSO-*d6*; 300 MHz) δ 3.88 (s; 2H; H1), 7.31(s; 1H; H3), 7.43–7.45 (m; 3H; H6; H7 and H8), 7.60–7.63 (m; 2H; H5 and H9), 8.06 (m; 2H; H2′ and H6′), 8.37 (m; 2H; H3′ and H5′); ^{13}C NMR (DMSO-*d6*; 75 MHz) δ 46.9 (C1), 108.1 (C2), 118.2 (CN), 125.3 (C2′ and C6′), 128.9 (C3′ and C5′), 129.2 (C5 and C9), 129.6 (C6 and C8), 131.4 (C7), 133.4 (C4), 146.2 (C3), 146.8 (C1′), 150.2 (C4′); MS [*m/z* (%)] 343 (4) $[M]^{+\cdot}$, 186 (4), 157 (100), 140 (24), 130 (8), 115 (13), 102 (6), 77 (14), 51 (12), 44 (16), 30 (15). Anal. Calcd. for $C_{16}H_{13}N_3O_4S$: C, 55.97%; H, 3.82%; N, 12.24%; Found: C, 56.03%; H, 3.76%; N, 12.30%.

(Z)-N-(2-cyano-3-phenylprop-2-en-1-yl)-methanesulfonamide (**6**): Yield 69%; white solid; m.p. 115.8–116.2 °C; IR (ATR; ν_{max}/cm^{-1}) 3251, 3025, 2932, 2213, 1628, 1494, 1447, 1410, 1309, 1141, 1073, 1061, 969. ^{1}H NMR ($CDCl_3$; 300 MHz) δ 3.05 (s; 3H; H1′), 4.11(dd; 2H; $J_{1,NH}$ = 6.0 Hz; $J_{1,3}$ = 3 Hz; H1), 5.28 (t; 1H, $J_{NH,1}$ = 6.0 Hz; NH), 7.21 (bs; 1H; H3), 7.43–7.47 (m; 3H; H6, H7 and H8), 7.75–7.79 (m; 2H; H5 and H9); ^{13}C NMR ($CDCl_3$; 75 MHz) δ 42.3 (C1′), 47.5 (C1), 107.3 (C2), 117.9 (CN), 129.3 (C5, C6, C8 and C9), 131.4 (C7), 132.7 (C4), 146.3 (C3); MS [*m/z* (%)] 236 (5) $[M]^{+\cdot}$, 219 (1), 157 (100), 155 (95), 140 (73), 130 (20), 115 (24), 102 (18), 77 (32), 63 (12), 51 (24), 44 (47), 40 (81). Anal. Calcd. for $C_{11}H_{12}N_2O_2S$: C, 55.91%; H, 5.12%; N, 11.85%; Found: C, 55.91%; H, 5.15%; N, 11.93%.

(Z)-N-(2-cyano-3-phenylprop-2-en-1-yl)-ethanesulfonamide (**7**): yield 65%; white solid; m.p. 93.7–94.5 °C; IR (ATR; ν_{max}/cm^{-1}) 3259, 2980, 2944, 2215, 2159, 1626, 1574, 1453, 1420, 1383, 1307, 1242, 1139, 1077, 1052, 871; ^{1}H NMR ($CDCl_3$; 300 MHz) δ 1.41 (t; 3H; $J_{2',1'}$ = 9 Hz; H2′), 3.11 (q; 2H; $J_{1',2'}$ = 9 Hz; H1′), 4.08 (dd; 2H; $J_{1,NH}$ = 6 Hz, $J_{1,3}$ = 3 Hz; H1), 5.26 (t; 1H; $J_{NH,1}$ = 6 Hz; NH), 7.20 (bs; 1H; H3), 7.43–7.45 (m; 3H; H6, H7 and H8), 7.75–7.78 (m; 2H; H5 and H9); ^{13}C NMR ($CDCl_3$; 75 MHz) δ 8.5 (C2′), 47.4 (C1), 49.0 (C1′), 107.5 (C2), 117.9 (CN), 129.3 (C5, C6, C8 and C9), 131.3 (C7), 132.8 (C4), 146.2 (C3); MS [*m/z* (%)] 250 (5) $[M]^{+\cdot}$, 235 (2), 219 (1), 157 (100), 155 (52), 140 (11), 130 (18), 115 (20), 102 (14), 77 (27), 63 (6), 51 (18), 44 (30), 40 (44). Anal. Calcd. for $C_{12}H_{14}N_2O_2S$: C, 57.58%; H, 5.64%; N, 11.19%; Found: C, 56.40%; H, 5.85%; N, 11.28%.

(Z)-N-(2-cyano-3-phenylprop-2-en-1-yl)-butanesulfonamide (**8**): yield 54%; white solid; m.p. 99.2–99.7 °C; IR (ATR; ν_{max}/cm^{-1}) 3285, 3056, 2961, 2934, 2873, 2217, 1630, 1497, 1450, 1412, 1315, 1299, 1276, 1143, 1076, 873. ^{1}H NMR ($CDCl_3$; 300 MHz) δ 0.92 (t; 3H; $J_{4',3'}$ = 9 Hz; H4′), 1.43 (sex; 2H; $J_{3',2'} = J_{3',4'}$ = 9 Hz; H3′), 1.78–1.88 (m; 2H; H2′), 3.04–3.11 (m; 2H; H1′), 4.08 (dd; 2H; $J_{1,NH}$ = 6 Hz, $J_{1,3}$ = 3 Hz; H1), 5.18 (t; 1H; $J_{NH,1}$ = 6 Hz; NH), 7.20 (bs; 1H; H3), 7.43–7.45 (m; 3H; H6, H7 and H8), 7.75–7.78 (m; 2H; H5 and H9); ^{13}C NMR ($CDCl_3$; 75 MHz) δ 13.8 (C4′), 21.7 (C3′), 25.8 (C2′), 47.4 (C1), 54.4 (C1′), 107.5 (C2), 117.9 (CN), 129.3 (C5, C6, C8 and C9), 131.3 (C7), 132.8 (C4), 146.2 (C3); MS [*m/z* (%)] 278 (2) $[M]^{+\cdot}$, 252 (1), 157 (100), 140 (51), 130 (13), 115 (15), 102 (8), 89 (3), 77 (14), 57 (20), 44 (8), 41 (36). Anal. Calcd. for $C_{14}H_{18}N_2O_2S$: C, 60.41%; H, 6.52%; N, 10.06%; Found: C, 59.88%; H, 6.58%; N, 10.01%.

(Z)-N-(2-cyano-3-phenylprop-2-en-1-yl)-octanesulfonamide (**9**): yield 45%; white solid; m.p. 98.1–98.3 °C; IR (ATR; ν_{max}/cm^{-1}) 3266, 3057, 2962, 2928, 2955, 2215, 1626, 1450, 1417, 1317, 1265, 1213, 1139, 1076, 874, 734, 691; ^{1}H NMR ($CDCl_3$; 300 MHz) δ 0.87 (t; 3H; $J_{8',7'}$ = 9 Hz; H8′), 1.24–1.41 (m; 10H; H3′, H4′, H5′, H6′ and H7′), 1.76–1.89 (m; 2H; H2′), 3.04–3.10 (m; 2H; H1′), 4.09 (dd; 2H; $J_{1,NH}$ = 6 Hz, $J_{1,3}$ = 3 Hz; H1), 5.11 (t; 1H; $J_{NH,1}$ = 6 Hz; NH), 7.20 (bs; 1H; H3), 7.43–7.45 (m; 3H; H6, H7 and H8), 7.75–7.78 (m; 2H; H5 and H9); ^{13}C NMR ($CDCl_3$; 75 MHz) δ 14.3 (C8′), 22.8 (C7′), 23.9 (C6′), 28.4 (C5′), 29.2 (C4′), 29.3 (C3′), 31.9 (C2′), 47.4 (C1), 54.7 (C1′), 107.5 (C2), 117.9 (CN), 129.2 (C5, C6, C8 and C9), 131.3 (C7), 132.7 (C4), 146.2 (C3); MS [*m/z* (%)] 334 (1) $[M]^{+\cdot}$, 281 (1), 252 (2), 235 (1), 207 (3), 157 (100), 140 (28), 130 (8), 115 (13), 96 (1), 77 (7), 57 (15), 44 (33) and 40 (11). Anal. Calcd. for $C_{18}H_{26}N_2O_2S$: C, 64.64%; H, 7.84%; N, 8.37%; Found: C, 64.42%; H, 7.94%; N, 8.39%.

X-ray crystallography

Suitable single crystals of compounds **1** and **3** were obtained from their solutions in a chloroform and petroleum ether mixture. Room temperature diffraction intensities for compounds **1** and **3** were measured on an Enraf–Nonius Kappa-CCD diffractometer using graphite-monochromated MoKα radiation (0.71073 Å). Data collections were made using the COLLECT program [8] and the final unit cell parameters were derived from all reflections. Integration, reduction and scaling of X-ray data were performed with the HKL Denzo–Scalepack programs [9]. The structures were solved by direct methods with SHELXS-97 [10] and refined by full-matrix least squares method on F^2 using the SHELXL-97 [10], with anisotropic atomic displacement parameters for non-hydrogen atoms. All hydrogen atoms were stereochemically positioned and refined with the riding model. The WinGX [11] program was used to prepare the material for publication. Structural analysis and figures were made using the MERCURY [12] and ORTEP-3 [13] programs. The crystal data and results of the analyses are listed in Table 1.

Computational calculations

Log*P* of the compounds **1–9** and of the parent primary sulfonamides were calculated using the program ACD/log*P*.

Theoretical studies were carried out using the Gaussian 09 software package [14]. The geometries obtained from PM3 semi-empirical calculations were used as initial models in geometry optimizations employing DFT calculations with the Pople's split valence basis set 6-31G*. BLYP exchange–correlation functional was used in DFT calculations. The optimized geometries were

Table 1
Crystal data and details of diffraction experiments for compounds **1** and **3**.

Compound	**1**	**3**
Empirical formula	$C_{16}H_{14}N_2O_2S$	$C_{16}H_{13}N_2O_2SCl$
Formula weight (g mol^{-1})	298.35	332.79
Temperature (K)	293(2)	293(2)
Crystal system/space group	Monoclinic/P2$_1$/a	Triclinic/P-1
Unit cell dimensions		
a (Å)	7.6794(2)	7.1657(3)
b (Å)	22.9914(4)	10.2707(5)
C (Å)	8.4481(2)	11.6729(6)
α (°)	90	92.165(3)
β (°)	94.308(1)	104.699(3)
γ (°)	90	107.685(3)
Volume (Å^3), Z	1487.38(6), 4	785.53(6), 2
Calculated density (g/cm^3)	1.332	1.407
Absorption coefficient (mm^{-1})	0.223	0.384
F(000)	624	344
Crystal size (mm)	0.289 × 0.265 × 0.232	0.653 × 0.081 × 0.035
θ range for data collection (°)	3.00–26.74	2.94–27.49
Limiting indices	−9, 9; −28, 29; 0, 10	−9, 8; −13, 13; 0, 14
Reflections collected/ unique	15101/ 3131	7309/3521
R (int)	0.0320	0.1406
Observed reflections [$I > 2\sigma(I)$]	2152	1807
Parameters refined	190	199
Goodness-of-fit on F^2	1.060	0.915
Final *R* indices [$I > 2\ \sigma\ (I)$]	$R = 0.0537$, $wR = 0.1585$	$R = 0.0561$, $wR = 0.1325$
R indices (all data)	$R = 0.0771$, $wR = 0.1723$	$R = 0.1226$, $wR = 0.1537$
Max.; min. in $\Delta\rho$ map (e A^{-3})	0.340; −0.406	0.421; −0.331

$R_1 = \Sigma\ (||F_o| - |F_c||)/\Sigma\ |F_o|$; $wR_2 = [\Sigma w(|F_o^2| - |F_c^2|)^2/\Sigma w|F_o^2|^2]^{1/2}$.

characterized as true minima on the potential energy surface (PES) when all harmonic frequencies were real. The electronic-nuclear energy (*E*) of the optimized geometries was given in atomic unit (Hartree). These theoretical methodologies have been efficiently employed in the study of different organic compounds [15–20].

Biological assay

The antifungal activity of **1–9** was evaluated by the *Poisoned food* technique [21] against *C. gloeosporioides*. Discs of mycelia of the fungus (diameter of 6 mm) were placed on the center of Petri dishes containing 6 mL of the culture medium (PDA) homogeneously mixed with the tested compounds at the concentration of 1.5 mM, dimethylsulfoxide (1% v/v), and the antibiotic chloramphenicol (Pfizer) (0.5% v/v). Each treatment consisted of four repetitions and the dishes were incubated at 25 °C for 9 days. The diameter of the fungus colony was measured with the aid of a caliper every 24 h from the second day of incubation. Effects of the parent primary sulfonamides were also tested, under the same conditions. The control (negative check treatment, four repetitions) was prepared with PDA, dimethylsulfoxide and chloramphenicol. Results were analyzed using Tukey's test at $P = 0.05$.

Results and discussion

Synthesis and characterization

Compounds **1–9** were prepared as shown in Scheme 1, which also displays the numbering used for the NMR assignments. Experimental data for compound **6** have been previously published [6]. The methodology initially employed was based on the procedure described for the preparation of compound **6**, in the presence of $MeSO_3H$ (1.2 mL, *ca.* 18 mmol) [6]. Nevertheless, the use of this catalyst led to very low yields of the allyl sulfonamides (up to 30%), due to the hydrolysis of the nitrile group and also to the reaction of the MBH with the methanesulfonate nucleophile, as indicated by CG–MS. Thus, the reduction of the amount of $MeSO_3H$ improved the yields, but better results (up to 69%) were achieved using diluted H_2SO_4 (54 μL, *ca.* 1 μmol) as catalyst. However, the hydrolysis products were still observed in some extent by CG–MS, together with the formation of very small amounts of the disubstituted sulfonamides. The formation of *E*-isomers was not observed.

Compounds **1–9** were structurally characterized by CG–MS, elemental analysis, and by infrared and NMR spectroscopies. Spectroscopic data obtained for **6** are in accordance with the literature [6]. However, the literature reports that **6** melts at the range of 103–104 °C with decomposition, while we observed a clear melting point at 115.8–116.2 °C, with no evidence of decomposition.

The molecular ion peaks were observed in the mass spectra of all allyl sulfonamides, which also exhibited the base peak at *m/z* 157 due to the common fragment $[C_{10}H_9N_2]^+$. Their molecular formulae and purity were confirmed by elemental analyses of C, H and N.

The infrared spectra of **1–9** showed bands at 3301–3234 and 2222–2207 cm^{-1}, assigned to the N—H and C≡N stretching frequencies, respectively. The presence of the SO_2 group was confirmed by the νSO_{2as} and νSO_{2sym} bands at 1325–1307 and 1214–1139 cm^{-1}, respectively. The expected bands due to νC=C were observed at 1630–1574 cm^{-1}.

In the ^{1}H NMR spectrum of the MBH adduct, two signals are observed at δ 6.02 and 6.10 which are assigned to the sp^2-CH$_2$ methylenic hydrogens H1 and H3 [7]. In the NMR spectra of **1–9** these signals were substituted by one signal at δ 4 (H1) characteristic for the sp^3-CH$_2$-N moiety, while the signal of H3, now an sp^2-CH hydrogen atom, was shifted to δ 7.1–7.3. Further, the H1 signal appeared as a singlet in the spectra of **1–3** and **5**, and as a doublet in the spectrum of **4**, or a double–doublet in the spectra of **6–9**. These multiplicities are due to coupling constants of ca. 6 Hz with the N—H hydrogen atom (observed in the spectra of compounds **4** and **6–9**), and of ca. 3 Hz with H3 (observed in the spectra of compounds **6–9**). Coherently, the NH signal appeared as a triplet (*J* ca. 6 Hz) in the range of δ 5.1–5.6 in the spectra of **6–9** ($CDCl_3$) and at δ 8.5 in the spectrum of **4** (DMSO-*d6*).

The H1 (ca. δ 4) and H3 (δ 7.0–7.3) signals were correlated to the ^{13}C NMR signals, respectively at ca. δ 47 (in the C—C single bonds region) and at δ 146 (in the C=C region), in the HETCOR experiments for compounds **1–9**.

As compounds **6–9** have only the aromatic ring from the MBH adduct, the remaining signals observed in the region from 7 to 8 ppm in their ^{1}H NMR spectra were easily assigned to the hydrogen atoms H6, H7, H8 (δ 7.4–7.5) and H5, H9 (δ 7.7–7.8). This pattern could also be recognized in the spectra of compounds **1–5**, as exemplified in Fig. 1, what helped the identification of the hydrogen signals of the aromatic sulfonamide groups.

From the spectra of the sulfonamides **6–9** it was also possible to recognize the signals of the aromatic carbons C4 (ca. δ 133) and C7 (ca. δ 131) in all spectra. The signals of C5, C6, C8 and C9 were superposed at ca. δ 129 in the spectra of **6–9**. In the spectra of **1–5** the region around δ 129 was complicated by other signals from the sulfonamides aromatic R groups. In the spectrum of compound **2** (Fig. 2), the assignments of these signals were straightforward due to the coupling constants of the carbon and fluorine atoms, allowing the identification of the signals of C4′ (δ 165.4, $J = 254.2$ Hz), C3′ and C5′ (δ 116.7, $J = 22$ Hz), C2′ and C6′ (δ 130.2, $J = 9.7$ Hz) and C1′ (δ 136.3, $J = 3$ Hz).

The HETCOR contour maps confirmed the assignments of the NMR signals in the aromatic region. For example, for compound

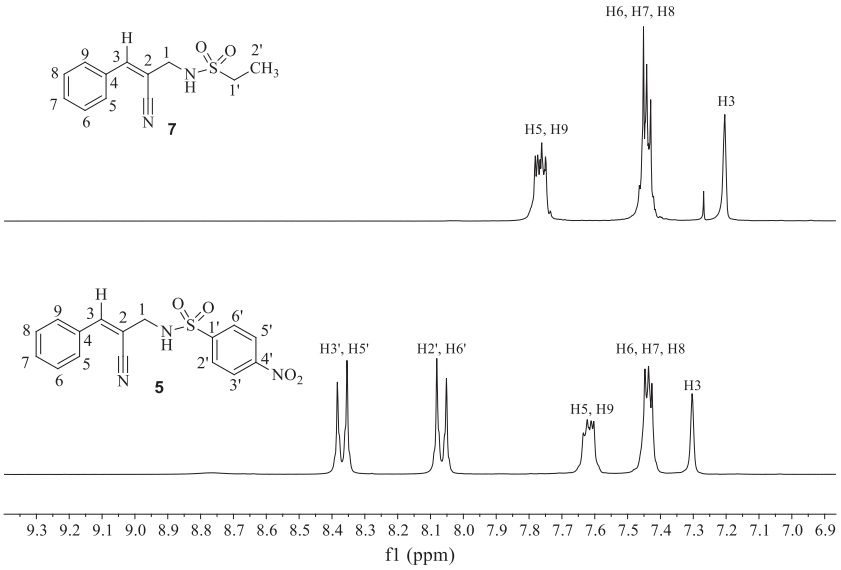


Fig. 1. Fragments of the ^{1}H NMR spectra of compounds **5** and **7** showing the region of the aromatic hydrogen signals.

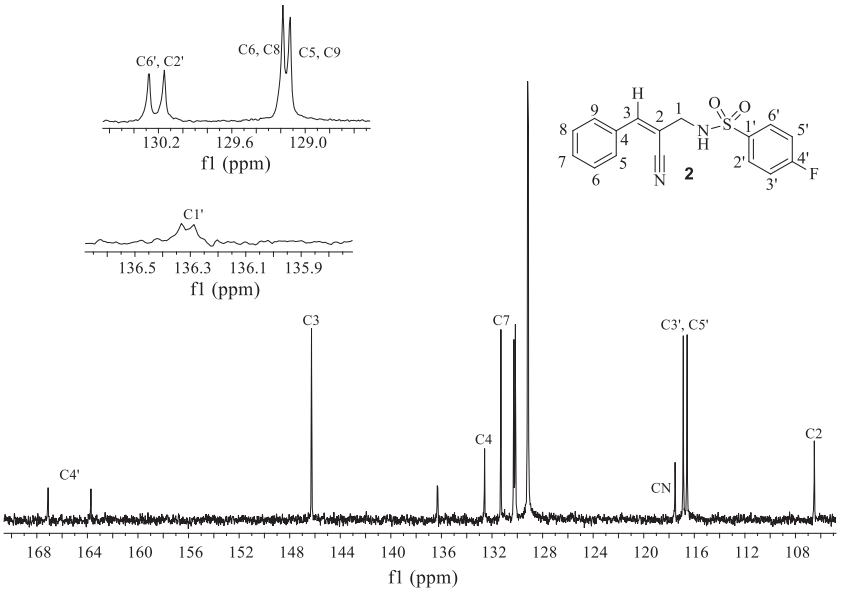


Fig. 2. Fragment of the ^{13}C NMR spectrum of compound **2** showing the region of the aromatic carbon signals.

4 (R = C_6H_4Br) the signal at δ 129.2 (C5 and C9) is correlated to the hydrogen signal at δ 7.60–7.63 (H5 and H9) while the slightly lower field signal at δ 129.6 (C6 and C8) is correlated to the multiplet at δ 7.42–7.45 (H7, H6 and H8), which is also correlated to the signal of C7 (δ 131.2). The signal of C2′ and C6′ (δ 129.3) could be identified due to its correlation with the signal of the hydrogen atoms of the sulfonamide group (δ 7.72–7.81). In turn, this hydrogen signal is also correlated to the signal of C3′ and C5′ (δ 133.0).

The *Z* configuration of the allyl sulfonamides could be determined by NMR, through the irradiation of the H3 signal in NOE difference spectroscopy, producing the enhancement of the H1 signal. This stereochemistry assignment was unambiguously confirmed by X-ray diffraction analysis after the isolation of the allyl sulfonamides **1** and **3** as single crystals from chloroform–petroleum ether solutions.

X-ray crystallography

The molecular structures of **1** and **3** with the atom numbering scheme are given in Figs. 3 and 4, respectively. Some important bond lengths, bond angles and torsion angles are listed in Table 2. Compound **1** crystallizes in the monoclinic system while compound **3** crystallizes in the triclinic system (Table 1). Both compounds exhibit *Z*-configuration and all bonds and angles are similar and within normally expected ranges.

The sulfur atoms in both molecules have a distorted tetrahedral coordination, similar to other reported sulfonamide structures [22–24], probably due to non-bonded intramolecular distances. The contact distances O1—O2, O1—N1, O2—N1, O1—C1′ and O2—C1′ are in the range of 2.4–2.6 Å, resulting in structures with less steric interferences [22]. The S=O bond lengths present

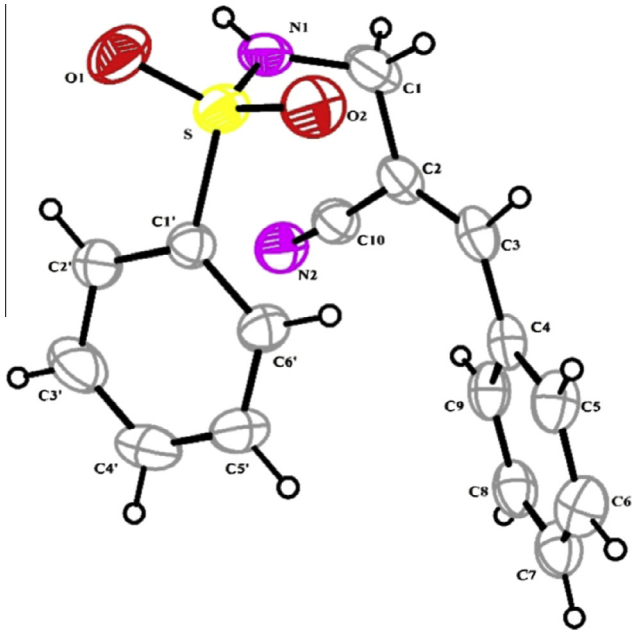


Fig. 3. An ORTEP-3 view of **1**, showing 30% probability displacement ellipsoids.

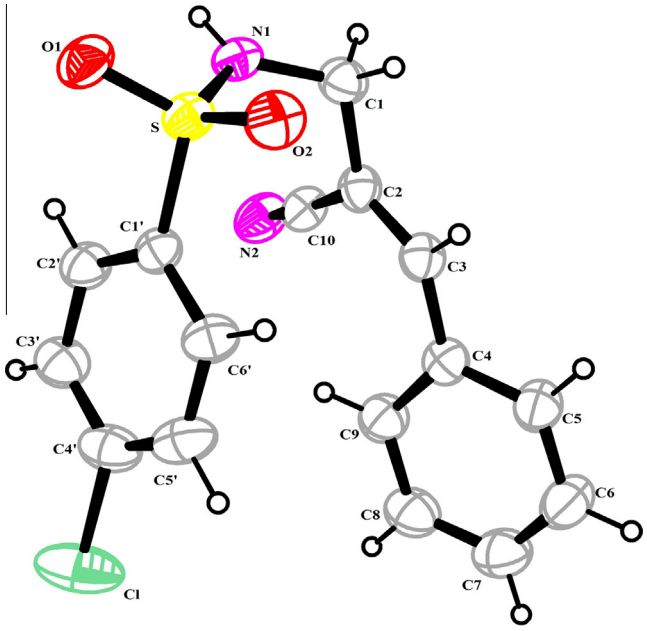


Fig. 4. An ORTEP-3 view of **3**, showing 30% probability displacement ellipsoids.

shorter values than those in *N*,*N*′-polymethylenebis-sulfonamides while the S—N and S—C bond lengths have similar values [23]. The S—N and S—C distances are shorter than the corresponding single-bond distances. These bond shortenings have been attributed to $d\pi$–$p\pi$ interactions between these atoms.

The C10—N2 bond length of 1.142(3) Å in **1**, and 1.138(3) Å in **3** is consistent with a triple bond, while the C1—N1 bond length of 1.460(3) Å in both compounds fits in the value for a single bond. The angle C1—N1—S are 121.9(2)° and 121.1(2)°, respectively in **1** and **3**, which are consistent with the partial sp^2 hybrid character of the N1 atom. The C2—C3 distance confirms the double bond character.

The mean plane of the phenyl ring (C4—C9) forms dihedral angles of 47.06(7)° and 20.83(8)° with the mean plane of the benzene ring (C1′—C6′) for the compounds **1** and **3**, respectively. In compound **3**, the chlorine atom is in the same plane defined by the benzene ring (the root mean square deviation to the fitted atoms is 0.016(4) Å). The substitution of one hydrogen atom at the 4-position of the benzene ring by chlorine atom alters the molecular conformation (torsion angles in Table 2) and the intermolecular architecture displayed by the compound **1**.

Only one intramolecular C6′—H6′···O2 interaction is observed in the structure of **1**, while in **3**, two intramolecular interactions (C6′—H6′···O2 and C1—H1a···O2) are observed. In the crystal packing, both compounds form inversion-related dimmers through N1—H1···N2 hydrogen bond, resulting in a twelve membered ring motif R_2^2 (12) (Table 3). The dimeric unit represents the basic supramolecular element of the crystal structures. In **1**, these dimers are linked by C3—H3···O2 interactions in the plane *ab* and C5—H5···Π contacts (the centroid acceptor Π correspond to the phenyl ring with donor–acceptor distance of 3.634(2) Å) forming a three-dimensional supramolecular framework. In **3**, these dimers are linked by C3—H3···O2 interactions to form layers in the plane *ac* and the adjacent layers were stacked via van der Waals interactions (Figs. 5 and 6). These intramolecular interactions led to the pronounced U shape conformation observed for the molecules **1** and **3** (Figs. 3 and 4).

Computational calculations

The stereochemistry of the allyl sulfonamides was investigated using theoretical methodology. Scheme 2 shows one possible

Table 2
Selected bond lengths (Å), bond angles (°) and torsion angles (°) for **1** and **3**.

Compound	**1**	**3**
Bond lengths		
S—O(1)	1.4203(18)	1.4292(19)
S—O(2)	1.4287(16)	1.4280(19)
S—N(1)	1.611(2)	1.607(2)
S—C(1′)	1.760(2)	1.764(3)
N(1)—C(1)	1.469(3)	1.460(3)
N(2)—C(10)	1.142(3)	1.138(3)
C(1)—C(2)	1.515(4)	1.514(4)
C(2)—C(3)	1.340(3)	1.332(4)
C(2)—C(10)	1.430(3)	1.433(4)
C(3)—C(4)	1.461(3)	1.456(4)
C(4′)—Cl	–	1.739(3)
Bond angles		
O(1)—S—O(2)	120.07(11)	120.25(12)
O(1)—S—N(1)	106.22(11)	106.16(12)
O(2)—S—N(1)	106.61(11)	107.18(12)
O(1)—S—C(1′)	107.16(11)	107.30(12)
O(2)—S—C(1′)	108.63(10)	107.56(13)
N(1)—S—C(1′)	107.57(9)	107.87(11)
S—N(1)—C(1)	121.82(16)	121.06(18)
C(1)—C(2)—C(10)	114.3(2)	114.5(2)
C(2)—C(10)—N(2)	174.9(3)	175.2(3)
C(10)—C(2)—C(3)	123.0(2)	122.9(3)
C(1)—C(2)—C(3)	122.5(2)	122.6(3)
N(1)—C(1)—C(2)	115.1(2)	115.2(2)
C(2)—C(3)—C(4)	129.8(2)	131.2(3)
Torsion angles		
O(1)—S—N(1)—C(1)	165.17(17)	169.87(19)
O(2)—S—N(1)—C(1)	36.03(19)	40.2(2)
C(1′)—S—N(1)—C(1)	−80.34(19)	−75.4(2)
O(1)—S—C(1′)—C(2′)	35.4(2)	51.0(2)
O(1)—S—C(1′)—C(6′)	−147.04(17)	−128.9(2)
O(2)—S—C(1′)—C(2′)	166.47(17)	−178.3(2)
O(2)—S—C(1′)—C(6′)	−15.9(2)	1.8(2)
S—N(1)—C(1)—C(2)	63.5(3)	67.1(3)
N(1)—C(1)—C(2)—C(3)	−116.4(3)	−112.5(3)
N(1)—C(1)—C(2)—C(10)	58.2(3)	67.0(3)
C(2)—C(3)—C(4)—C(5)	−149.7(2)	160.1(3)
C(2)—C(3)—C(4)—C(9)	28.3(4)	−21.6(5)

Table 3
Hydrogen-bond geometry (Å, °) in the crystal structures of **1** and **3**.

D—H···A	d(D—H)	d(H···A)	d(D···A)	<(DH···A)
*Compound **1***				
C(6′)—H(6′)···O(2)	0.93	2.58	2.940(3)	103.6
N(1)—H(1)···N(2)^{i}	0.86	2.38	3.033(3)	133.5
C(3)—H(3)···O(2)^{ii}	0.93	2.57	3.424(3)	153.3
C(5)—H(5)···C_g^{iii}	0.93	2.95	3.633(2)	131
*Compound **3***				
C(6′)—H(6′)···O(2)	0.93	2.52	2.894(4)	104.4
C(1)—H(1a)···O(2)	0.97	2.60	2.926(3)	99.9
N(1)—H(1)···N(2)^{iv}	0.86	2.30	2.980(3)	136.0
C(3)—H(3)···O(2)^{v}	0.93	2.68	3.405(3)	134.9

Symmetry codes: (i) 1 − *x*, −*y*, −*z*; (ii) ½ + *x*, ½ − *y*, *z*; (iii) −½ + *x*, ½ − *y*, *z*; (iv) 2 − *x*, −*y*, 2 − *z*; (v) 1 − *x*, −*y*, 1 − *z*. C_g is the centroid of the C4—C9 ring.

mechanism for the formation of compounds **1**–**9** from the MBH adduct and the corresponding sulfonamides. The reaction can occur *via* intermediates A or B, providing the isomeric *Z* or *E* products, respectively.

BLYP/6-31G* geometry optimizations were carried out for the corresponding intermediates A and B considering the formation of compounds **1**–**9** *via* the proposed mechanism shown in Scheme 2. The energy values obtained for the intermediates A are lower than those obtained for the intermediates B (ΔE = 2.25, 1.91, 1.91, 1.91, 1.86, 1.97, 1.89, 1.94, and 1.93 kcal/mol, respectively for the formation of **1**–**9**). Although the energy differences between the intermediates A and B are small, these theoretical results suggest that the formation of the *Z*-isomers are energetically favorable. Similar results were obtained when the *Z* and *E* allyl sulfonamides **1**–**9** were compared. The *Z*-isomers of **1** to **9** showed lower energy values in relation to the corresponding *E*-isomers (ΔE = 1.17, 1.62, 1.26, 1.26, 1.56, 2.72, 1.60, 0.86, and 1.66 kcal/mol, respectively).

Thus, the BLYP/6-31G* geometry optimization calculations suggested that the lower energy of the intermediates A (Scheme 2) contributes to the formation of the corresponding Z-isomers. Moreover, as expected, the *Z*-isomers are the thermodynamically favored products.

Although the aprotic solvent of low dielectric constant (1,2-dichloroethane) would not favor the formation of carbocations, a possible variation of the mechanism shown in Scheme 2 could involve the elimination of water, forming a benzylic cation, from which the formation of the most stable Z-product should be favored.

The reaction could also occur *via* S_N2', as proposed by Basavaiah [1]. In this mechanism, the addition of the sulfonamide and the elimination of water are simultaneous. The reaction stereoselectivity in this case could be reasoned considering the greater steric hindrance of the transition state leading to the isomer *E* [1b]. Thus, *via* an S_N2' mechanism, the isomer *Z* would still be the main product.

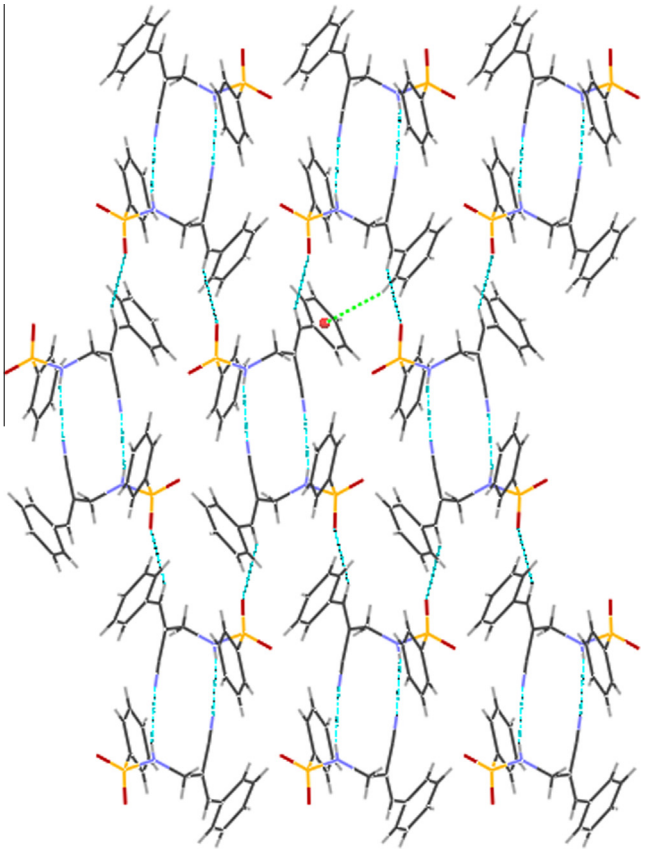


Fig. 5. Packing diagram of **1**, in the *ab* plane.

Antifungal assay

The synthesized allyl sulfonamides (**1**–**9**) were tested *in vitro* for their growth inhibitory activity against *C. gloeosporioides* using the *Poisoned Food* method [21]. The biological tests included the primary parent sulfonamides for comparison. The bioassay results are summarized in Table 4.

No straightforward relation between their structures and the biological activities was observed. Nevertheless, some general

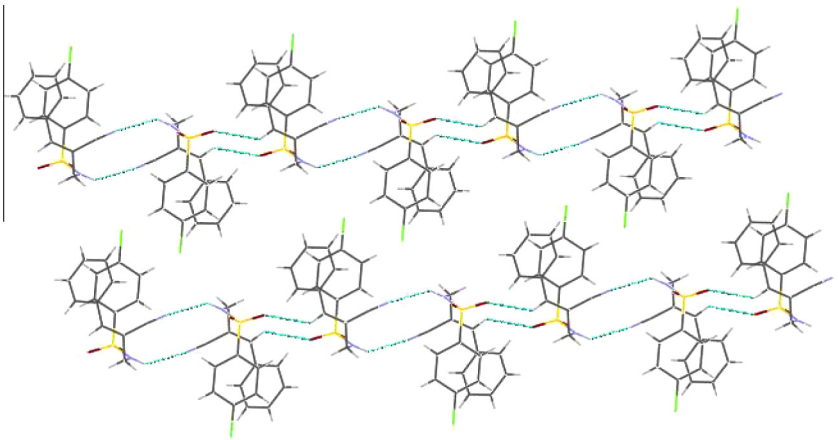
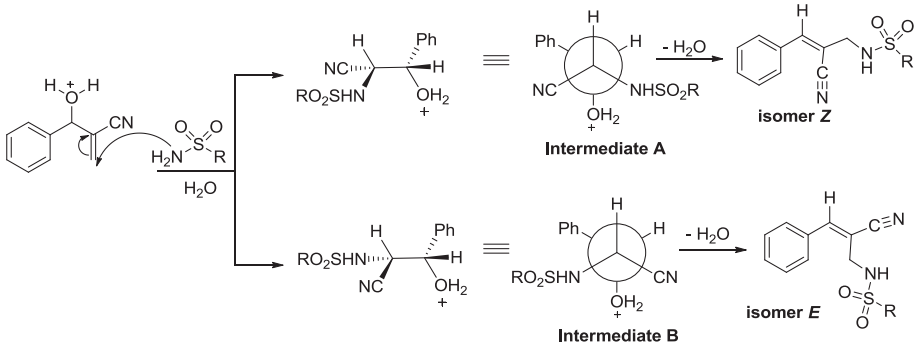


Fig. 6. Packing diagram of **3**.



Scheme 2. A possible mechanism for the formation of *Z* and *E* isomers from the MBH adduct and sulfonamides.

Table 4
Percentage of mycelial growth inhibition of *C. gloesporoides* after 9 days of incubation at 25 °C in the presence of allyl sulfonamides **1–9** and the corresponding primary sulfonamides containing the same *R* groups, and the log*P* of the tested compounds.

R	Sulfonamides		Allyl sulfonamides **1–9**	
	Inhibition %	log*P*	Inhibition %	log*P*
H	20 c	0.33	48 i	3.85
F	15 b	0.64	23 c	4.17
Cl	21 c	0.84	22 c	4.80
Br	32 ef	1.36	15 b	4.89
O_2N	31 de	0.65	43 h	4.05
$-CH_3$	0 a	−1.29	34 f	1.93
$-CH_2CH_3$	0 a	−0.76	38 g	2.46
$-CH_2CH_2CH_2CH_3$	0 a	0.31	42 h	3.52
$-CH_2CH_2CH_2CH_2$ $CH_2CH_2CH_2CH_3$	39 c	2.43	22 d	5.65

Inhibition % = $(dc - dt)/dc \times 100$; where *dc* = average diameter (in mm) of fungal colony in control, *dt* = average diameter (in mm) of fungal colony in the treatment. Values followed by different letters are significantly different by the Tukey test at 5% probability.

features can be clearly pointed out. Except for compounds **4** and **9**, the allyl sulfonamides were more active than the parent primary sulfonamides. Among the allyl sulfonamides with aliphatic moieties, it was observed an increase in the activity with the increase of the chain length from 1 to 4 carbon atoms. However, the replacement of the *n*-butyl group (compound **8**) by the much longer *n*-octyl group (compound **9**) had a detrimental effect on the antifungal activity. These facts indicated that the lipophilicity of the compounds is an important factor, showing lower and upper limits.

The partition coefficient (log*P*) is related to the lipophilicity of a substance and can be an useful information for the prediction of the permeability of the cell membranes to the agrochemicals [25]. Thus, log*P* values were calculated and are displayed in Table 4. These results indicated that the higher activity of the 4-bromophenyl- and octyl- sulfonamides when compared to the other primary sulfonamides, might be related to their favorable values of log*P* (Table 4).

The allyl sulfonamides **1**, **5** and **8** were the most active compounds, showing log*P* values between 3.52 and 4.05. The electron withdrawing substituents (F, Cl, Br) did not improve the activity of the aromatic sulfonamides, except for the nitro group which provided the second best result. The literature suggests that the nitro group, especially in the *para* position on the aromatic ring with respect to the sulfonyl group, can be reduced in the biological medium to form the oxime, and the amine afterwards [26]. Thus, the nitro group could act as an additional active site for the inhibition of the fungal growth.

Conclusion

Nine allyl sulfonamides (**1**–**9**) were synthesized from the reaction of a Morita–Baylis–Hillman adduct with primary sulfonamides. All compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR, MS and elemental analysis techniques. The allyl sulfonamide **6** is already described but its characterization by elemental analysis and mass spectrometry is reported here for the first time. All compounds exhibited the *Z* configuration, confirmed by NOE difference spectroscopy and by single crystal X-ray diffraction measurements. Theoretical calculations confirmed that the formation of the *Z* isomers are thermodynamically favored when compared to the *E* isomers. The results of X-ray diffraction analysis show that the N—H···N hydrogen bond is the main force stabilizing the pairs of centrosymmetric dimers present in the compounds **1** and **3** crystals. These dimers interact through C—H···O contacts forming layers in the plane *ab* for compound **1** and in the plane *ac* for compound **3**. The three-dimensional supramolecular framework is stabilized by the intermolecular C—H···Π contacts in **1** and by van der Waals forces in **3**. The compounds **1–9** were active against *C. gloeosporioides*. Compounds **1**, **5** and **8** showed the best results, and were considerably more active than the parent primary sulfonamides. Thus the biological activity of the allyl sulfonamides are worth of further investigation, for their potential application as agrochemicals.

Supplementary material

Details on data collection, refinement and crystallographic data in CIF format for structures **1** and **3** have been deposited at the Cambridge Crystallographic Data Centre, No. CCDC 977967 and 977968. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44 1223 336 033; email: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

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