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Preparation and Promotion of Fruit Growth in Kiwifruit of Fluorinated *N*-Phenyl-*N*′-1,2,3-thiadiazol-5-yl Ureas

ANTONIO ABAD,* CONSUELO AGULLÓ,* ANA CARMEN CUÑAT, RAQUEL JIMÉNEZ, AND CRISTINA VILANOVA

Departamento de Química Orgánica, Facultad de Químicas, Universidad de Valencia, C/Dr. Moliner 50, E-46100 Burjassot, Valencia, Spain

Seventeen phenyl-fluorinated analogues of thidiazuron [*N*-phenyl-*N*′-(1,2,3-thiadiazol-5-yl)urea, TDZ] have been prepared and characterized. The effects of each fluorinated urea on growth and quality of kiwifruits (*Actinidia deliciosa*) were evaluated by comparison with untreated (control) and TDZ-treated fruits. The results obtained showed a clear dependence of the growth-promoting activity of these fluorinated ureas on the pattern and degree of fluorine substitution in the phenyl ring. The most effective for promoting fruit growth was *N*-(2,3,5,6-tetrafluorophenyl)-*N*′-(1′,2′,3′-thiadiazol-5′-yl)urea at 25 ppm (at harvest, treated fruits were 58% heavier than untreated ones) followed by *N*-(3,5-difluorophenyl)-*N*′-(1′,2′,3′-thiadiazol-5′-yl)urea at 10 ppm (50%). Comparatively, TDZ-treated fruits were 31% (10 ppm) and 38% (25 ppm) heavier than untreated ones. The results also indicate that the effects of the more active phenyl-fluorinated ureas on some standard quality parameters of fruits, for example, percent of fruit dry matter content, soluble solids contents, total titratable acids, shape, and internal structure, are similar to those of TDZ. Quantitative structure−activity relationships have been derived for the fruit growth promoting activity of the phenyl-fluorinated analogues of TDZ.

KEYWORDS: ***Actinidia deliciosa*; kiwifruit; cytokinin; phenylurea; fluor; fluorinated; thidiazuron; TDZ; fruit-growth activity; plant hormones; QSAR, substituent-induced chemical shifts**

INTRODUCTION

Control of plant growth with plant hormones has become an important technique in agricultural and horticultural fields, and in recent years substantial research efforts have been devoted to finding new compounds that exhibit cytokinin-like hormonal activity. For some fruit crops, such as kiwifruit (*Actinidia deliciosa*), the production of larger and more uniform fruits has become vital for the economic viability of the crop. Although the use of traditional cultivation practices such as bee-aided pollination and proper fertilization and irrigation may positively affect the quality and size of the fruit, the use of growth promoters gives extraordinary results and is becoming an important technique in this sector. Early studies on kiwifruit growth-promoting hormones begun in 1976 by Hopping (*1*) found that some combinations of endogenous hormones, for example, auxins, gibberellins, and cytokinins, were able to effectively promote fruit growth. Since then, several other compounds have also proved to be effective in improving kiwifruit growth, but the most efficient and best-known of all compounds tested so far is the synthetic phenylurea 1-(2-chloro-4-pyridyl)-3-phenylurea (**1a**), also known as CPPU, forchlorfenuron, or KT-30 (*2*). In fact, CPPU is the active ingredient of several currently marketed formulations used for application not only in kiwifruit but also in other important horticultural crops such as melons, watermelons, and grapes (*3*). Recently, thiadiazuron [1-phenyl-3-(1,2,3-thiadiazol-5-yl)urea, TDZ, **2a**], a compound that is largely used as a defoliant in cotton (*4*), has also proved to be very effective in stimulating kiwifruit growth, producing a weight and size increase in fruits similar to those produced by CPPU (*5*).

The almost equivalent results obtained with CPPU and TDZ in stimulating kiwifruit growth are not surprising, in view of the structural similarity between both compounds that suggests a common molecular mechanism of action. It is thought that the increase in fruit size is due to a specific cell division or expansion in the early stages of fruit development of treated fruits, an effect that has been related with an intrinsic cytokinin activity of these phenylureas (*6*) or an increase in the endogenous cytokinin levels either by inhibiting the action of cytokinin oxidase on the endogenous cytokinins or by stimulating the production of endogenous cytokinins (*7*).

Selective replacement of hydrogen by fluorine has been a successful strategy in agrochemical and medicinal chemistry in the search for compounds with increased biological activity (*8*). More concretely, the introduction of fluorine atoms in the aromatic moiety of biologically active compounds may modify their electronic and physical properties (for example, lipophilicity, acidity, and steric hindrance) (*9*), generally resulting in

* Correspondence should be addressed to Dr. Antonio Abad, Departamento de Química Orgánica, Facultad de Químicas, C/Dr. Moliner 50, 46100 Burjassot (Valencia), Spain (telephone 34-96-3544509; fax 34-96-3544328; e-mail antonio.abad@uv.es).

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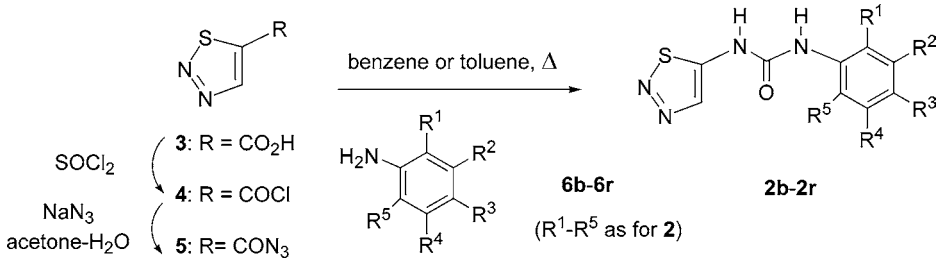
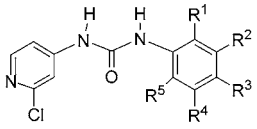
Scheme 1



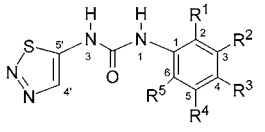
more active and efficient compounds. A recent example is found with fluorinated inhibitors of carbonic anhydrase II (CAII) (*10*, *11*), which show distinct binding modes depending on the patterns and degree of fluorine substitution in the aromatic moiety of the inhibitor.

Some fluorinated analogues of CPPU [1-(2-chloro-4-pyridyl)-3-(2-fluorophenyl)urea (**1b**) (*12*), 1-(2-chloro-4-pyridyl)-3-(3-fluorophenyl)urea (**1c**) (*13*), 1-(2-chloro-4-pyridyl)-3-(4-fluorophenyl)urea (**1d**) (*14*), and 1-(2-chloro-4-pyridyl)-3-(3,5-difluorophenyl)urea (**1e**) (*15*)] have been prepared, and the high cytokinin activity of some of them, for example, **1c**, has been demonstrated in tobacco callus growth in vitro assays. However, the correlation between the patterns and degree of fluorine substitution at the phenyl ring of these compounds and cytokinin activity has not yet been systematically studied. As far as we know, no fluorinated analogue of TDZ has been prepared nor any phenyl-fluorinated urea-type cytokinin tested as a fruit-growth promoter.

We describe in this work the preparation of a small library of mono-, di-, tri-, tetra-, and pentafluorophenyl analogues of TDZ, ureas **2b**−**2r**, and the testing of their growth-promoting



1a: R^1=R^2=R^3=R^4=R^5=H
1b: R^1=F, R^2=R^3=R^4=R^5=H
1c: R^2=F, R^1=R^3=R^4=R^5=H
1d: R^3=F, R^1=R^2=R^4=R^5=H
1e: R^2=R^4=F, R^1=R^3=R^5=H



2a: R^1=R^2=R^3=R^4=R^5=H
2b: R^1=F, R^2=R^3=R^4=R^5=H
2c: R^2=F, R^1=R^3=R^4=R^5=H
2d: R^3=F, R^1=R^2=R^4=R^5=H
2e: R^1=R^2=F, R^3=R^4=R^5=H
2f: R^1=R^3=F, R^2=R^4=R^5=H
2g: R^1=R^4=F, R^2=R^3=R^5=H
2h: R^1=R^5=F, R^2=R^3=R^4=H
2i: R^2=R^3=F, R^1=R^4=R^5=H
2j: R^2=R^4=F, R^1=R^3=R^5=H
2k: R^1=R^2=R^3=F, R^4=R^5=H
2l: R^1=R^2=R^5=F, R^3=R^4=H
2m: R^1=R^3=R^4=F, R^2=R^5=H
2n: R^1=R^3=R^5=F, R^2=R^4=H
2o: R^1=R^2=R^3=R^4=F, R^5=H
2p: R^1=R^2=R^3=R^5=F, R^4=H
2q: R^1=R^2=R^4=R^5=F, R^3=H
2r: R^1=R^2=R^3=R^4=R^5=F

effects on kiwifruits, with respect to weight, size, and some other quality attributes.

MATERIALS AND METHODS

Synthetic Procedures. All reactions were carried out with the exclusion of moisture. All NMR spectra were recorded in DMSO-d_6 [(4−6) × 10^{-2} M for ^{1}H and ^{19}F and (1.6−2.3) × 10^{-1} M for ^{13}C] at room temperature on a Bruker AC-300 spectrometer (300.13 MHz for ^{1}H, 282.37 MHz for ^{19}F, and 75.47 MHz for ^{13}C). All ^{1}H NMR chemical shifts are reported in parts per million relative to the residual CHD_2-$SOCD_3$ in DMSO-d_6, set at δ 2.42, and ^{19}F NMR chemical shifts are referenced to $CFCl_3$ as internal reference, which was set at δ 0.000. IR spectra were measured as KBr pellets using a Nicolet Avatar 320 spectrometer. High-resolution mass spectra were recorded with a VG AutoSpec spectrometer using the EI method (70 eV). Column chromatography purification was carried out using Merck silica gel 60, 230−400 mesh. Thin-layer chromatography (TLC) was carried out using TLC C-18 reversed-phase TLC plates with fluorescent indicator (Merck RP-18 F_{254S}). The R_f (retention factor) refers to plates developed in 70:30 methanol/water (v/v). The R_f range was 0.117−0.478.

Synthesis of Ureas 2b−2r. The preparation of phenyl-fluorinated ureas **2b**−**2r** was effected by reaction of 1,2,3-thiadiazole-5-carbonyl azide (**5**), prepared from 1,2,3-thiadiazole-5-carboxylic acid (**3**), with the appropriate commercially available mono-, di-, tri-, tetra-, or pentafluoroanilines, **6b**−**6r** (**Scheme 1**). The preparation and purification of **2j**, **2p**, and **2r** described below are representative examples.

Preparation of 1,2,3-Thiadiazole-5-carbonyl Azide (5). A solution of 1,2,3-thiadiazole-5-carboxylic acid (**3**, 6.0 g, 46 mmol), prepared as described by Arndt (*16*), in $SOCl_2$ (20 mL, 274 mmol) was heated at 80 °C with stirring for 2 h. The excess of $SOCl_2$ was distilled under reduced pressure (40 °C, 210 mmHg) to give an oily residue. Addition of dry toluene (20 mL) and removal of the solvent under vacuum (85 °C, 50 mmHg) afforded crude 1,2,3-thiadiazole-5-carbonyl chloride (**4**) as a yellowish oil (6.8 g).

A solution of the above acyl chloride in dry acetone (25 mL) was dropwise added to a stirred solution of NaN_3 (3.32 g, 52 mmol) in water (20 mL). After 1 h, the reaction mixture was poured into water and extracted with hexane. Combined organic extracts were washed with water and brine, dried ($MgSO_4$), and concentrated under vacuum to give spectroscopically pure 1,2,3-thiadiazole-5-carbonyl azide (**5**, 5.2 g, 74% from acid **3**) as a yellow oil that was used without further purification for the preparation of the ureas.

Preparation of 1-(3,5-Difluorophenyl)-3-(1′,2′,3′-thiadiazol-5′-yl)-urea (2j). To a stirred solution of 3,5-difluoroaniline (**6j**, 417.5 mg, 3.23 mmol) in toluene (2.3 mL) at reflux was added dropwise a solution of **5** (455.6 mg, 2.94 mmol) in toluene (2.3 mL). The reaction mixture was stirred for an additional 1 h at reflux and then cooled to room temperature. The solid was collected by filtration and washed with a 1:1 mixture of hexane/toluene and hexane and dried under vacuum to give pure **2j** (760.3 mg, 92%) as a white solid: mp 227 °C with decomp (from hexane/acetone); R_f 0.170; ^{1}H NMR (DMSO-d_6) δ 11.10 (1H, s, NH3), 9.86 (1H, s, NH1), 8.62 (1H, s, H-4′), 7.22 (2H, dddd, J = 11.8, 2.8. 2.3, and 2.0 Hz, H-2 and H-6), 6.87 (1H, dddd, J = 9.4, 9.4, 2.3, and 2.3 Hz, H-4); ^{19}F NMR (DMSO-d_6) δ −108.7 (s, F-3 and F-5); IR (KBr) 3291, 3169, 3106, 2972, 1710, 1616, 1566, 1477, 1310, 1250, 1196, 1120, 977, 730, 660 cm^{-1}; HRMS, calcd for $C_9H_6F_2N_4OS$ 256.0230, found 256.0232.

Preparation of 1-(2,3,4,6-Tetrafluorophenyl)-3-(1′,2′,3′-thiadiazol-5′-yl)urea (2p). To a stirred solution of 2,3,4,6-tetrafluoroaniline (**6p**, 630 mg, 3.82 mmol) in benzene (3.5 mL) at reflux was added dropwise a solution of **5** (536.0 mg, 458 mmol) in benzene (3.5 mL). The reaction mixture was stirred for an additional 5 h at reflux and then cooled to room temperature. The solid was filtered off and washed successively with a 1:1 mixture of hexane/benzene and hexane. The yellowish solid obtained was subjected to extraction with acetone, and the extracts were evaporated under vacuum to give spectroscopically pure urea **2p** (850.7 mg, 85%): mp 255 °C with decomp (from hexane/acetone); R_f 0.340; ^{1}H NMR (DMSO-d_6) δ 11.36 (1H, s, NH3), 9.28 (1H, s, NH1), 8.57

(1H, s, H-4′), 7.66 (1H, dddd, J = 10.2, 10.2, 7.2, and 2.3 Hz, H-5); ^{19}F NMR (DMSO-d_6) δ −164.3 (ddd, J = 22.7, 22.7, and 10.3 Hz, F-3), −138.1 (dd, J = 22.7 and 4.1 Hz, F-2), −134.8 (dd, J = 22.7 and 4.1 Hz, F-4), −121.1(d, J = 10.3 Hz, F-6); IR (KBr) 3262, 3228, 3164, 3072, 2967, 1702, 1570, 1499, 1484, 1307, 1072, 816, 793 cm^{-1}; HRMS, calcd for $C_9H_4F_4N_4OS$ 292.0042, found 292.0050.

Preparation of 1-(Pentafluorophenyl)-3-(1′,2′,3′-thiadiazol-5′-yl)-urea (2r). To a stirred solution of 2,3,4,5,6-pentafluoroaniline (**6r**, 570.6 mg, 3.08 mmol) in benzene (4 mL) at reflux was slowly added (∼30 min) a solution of **5** (439.2 mg, 2.8 mmol) in the same solvent (4 mL). The reaction mixture was stirred under reflux for 4 h and then concentrated under vacuum, and the solid residue was deposited on a short column of silica gel and eluted with acetone. Evaporation of the solvent under reduced pressure afforded spectroscopically pure urea **2r** (630 mg, 72%): mp 260−265 °C (from DMSO/H_2O); R_f 0.245; ^{1}H NMR (DMSO-d_6) δ 11.44 (1H, s, NH3), 9.52 (1H, s, NH1), 8.58 (1H, s, H-4′); ^{19}F NMR (DMSO-d_6) δ −162.9 (m, F-3 and F-5), −157.0 (t, J = 22.7 and 22.7 Hz, F-4), −145.5 (m, F-2 and F-6); IR (KBr) 3276, 3225, 3006, 1713, 1578, 1528, 1505, 1308, 1197, 970 cm^{-1}; HRMS, calcd for $C_9H_3F_5N_4OS$ 309.9948, found 309.9950.

Data for 1-(2-Fluorophenyl)-3-(1′,2′,3′-thiadiazol-5′-yl)urea (2b): yield 89%; mp 242 °C with decomp (from hexane/acetone); R_f 0.309; ^{1}H NMR (DMSO-d_6) δ 10.97 (1H, s, NH3), 9.16 (1H, s, NH1), 8.64 (1H, s, H-4′), 7.94 (1H, ddd, J = 8.1, 8.1 and 1.8 Hz, H-6), 7.24 (1H, ddd, J = 11.2, 7.7, and 1.5 Hz, H-3), 7.15 (1H, ddd, J = 8.1, 7.7, and 1.5 Hz, H-5), 7.10 (1H, dddd, J = 7.7, 7.7, 5.1, and 1.8 Hz, H-4)' ^{19}F NMR (DMSO-d_6) δ −127.3 (s); IR (KBr) 3269, 3208, 3028, 1698, 1629, 1561, 1529, 1308, 1184, 755, 731 cm^{-1}; HRMS, calcd for $C_9H_7FN_4OS$ 238.0325, found 238.0318.

Data for 1-(3-Fluorophenyl)-3-(1′,2′,3′-thiadiazol-5′-yl)urea (2c): yield 82%; mp 238 °C with decomp (from hexane/acetone); R_f 0.266; ^{1}H NMR (DMSO-d_6) δ 10.92 (1H, s, NH3), 9.65 (1H, s, NH1), 8.61 (1H, s, H-4′), 7.43 (1H, ddd, J = 11.7, 2.0, and 2.0 Hz, H-2), 7.32 (1H, ddd, J = 8.0, 8.0, and 7.5 Hz, H-5), 7.21 (1H, ddd, J = 8.0, 2.0, and 2.0 Hz, H-6), 6.83 (1H, dddd, J = 8.3, 8.0, 2.0, and 2.0 Hz, H-4); ^{19}F NMR (DMSO-d_6) δ −111.6 (s); IR (KBr) 3275, 3146, 2940, 1701, 1613, 1556, 1487, 1441, 1301, 1277, 1194, 872, 816, 794 cm^{-1}; HRMS, calcd for $C_9H_7FN_4OS$ 238.0325, found 238.0331.

Data for 1-(4-Fluorophenyl)-3-(1′,2′,3′-thiadiazol-5′-yl)urea (2d): yield 93%; mp 259 °C with decomp (from hexane/acetone); R_f 0.309; ^{1}H NMR (DMSO-d_6) δ 10.86 (1H, s, NH3), 9.45 (1H, s, NH1), 8.59 (1H, s, H-4′), 7.47 (2H, ddd, J = 8.9, 5.0, and 2.0 Hz, H-2 and H-6), 7.13 (2H, ddd, J = 8.9, 8.9, and 2.1 Hz, H-3 and H-5); ^{19}F NMR (DMSO-d_6) δ −119.2 (s); IR (KBr) 3288, 3146, 3108, 2948, 1702, 1624, 1574, 1509, 1302, 1203, 1187, 1161, 835, 817, 795 cm^{-1}; HRMS, calcd for $C_9H_7FN_4OS$ 238.0325, found 238.0326.

Data for 1-(2,3-Difluorophenyl)-3-(1′,2′,3′-thiadiazol-5′-yl)urea (2e): yield 90%; mp 229−230 °C (from hexane/acetone); R_f 0.255; ^{1}H NMR (DMSO-d_6) δ 11.06 (1H, s, NH3), 9.39 (1H, s, NH1), 8.67 (1H, s, H-4′), 7.78 (1H, dddd, J = 8.1, 6.8, 2.0, and 2.0 Hz, H-6), 7.16 (2H, m, H-4 and H-5 overlapped); ^{19}F NMR (DMSO-d_6) δ −151.4 (d, J = 21.1 Hz, F-2), −138.0 (d, J = 21.1 Hz, F-3); IR (KBr) 3278, 3221, 3040, 1708, 1634, 1577, 1542, 1479, 1314, 1264, 1191, 975 cm^{-1}; HRMS, calcd for $C_9H_6F_2N_4OS$ 256.0230, found 256.0226.

Data for 1-(2,4-Difluorophenyl)-3-(1′,2′,3′-thiadiazol-5′-yl)urea (2f): yield 83%; mp 225 °C with decomp (from hexane/acetone); R_f 0.298; ^{1}H NMR (DMSO-d_6) δ 11.04 (1H, s, NH3), 9.18 (1H, s, NH1), 8.63 (1H, s, H-4′), 7.84 (1H, ddd, J = 9.0, 8.7, and 6.4 Hz, H-6), 7.30 (1H, ddd, J = 11.3, 8.9, and 2.5 Hz, H-3), 7.06 (1H, ddd, J = 8.7, 8.7, and 2.5 Hz, H-5); ^{19}F NMR (DMSO-d_6) δ −121.1 (s, F-2), −114.6 (s, F-4); IR (KBr) 3226, 3146, 3039, 2952, 1698, 1576, 1505, 1305, 1301, 1249, 1204, 1107, 843 cm^{-1}; HRMS, calcd for $C_9H_6F_2N_4OS$ 256.0230, found 256.0240.

Data for 1-(2,5-Difluorophenyl)-3-(1′,2′,3′-thiadiazol-5′-yl)urea (2g): yield 83%; mp 255 °C with decomp (from DMSO/H_2O); R_f 0.223; ^{1}H NMR (DMSO-d_6) δ 11.04 (1H, s, NH3), 9.36 (1H, s, NH1), 8.69 (1H, s, H-4′), 7.85 (1H, ddd, J = 10.0, 6.4, and 3.2 Hz, H-6), 7.31 (1H, ddd, J = 10.4, 9.2, and 5.1 Hz, H-3), 6.92 (1H, dddd, J = 9.2, 8.5, 3.2, and 3.2 Hz, H-4); ^{19}F NMR (DMSO-d_6) δ −133.1 (d, J = 15.5 Hz, F-2), −116.1 (d, J = 15.5 Hz, F-5); IR (KBr) 3262, 3210, 3022, 1701, 1641, 1579, 1545, 1500, 1320, 1246, 1194, 820, 746 cm^{-1}. HRMS, calcd for $C_9H_6F_2N_4OS$ 256.0230, found 256.0243.

Data for 1-(2,6-Difluorophenyl)-3-(1′,2′,3′-thiadiazol-5′-yl)urea (2h): yield 92%; mp 216 °C with decomp (from DMSO/H_2O); R_f 0.479; ^{1}H NMR (DMSO-d_6) δ 11.27 (1H, s, NH3), 9.10 (1H, s, NH1), 8.56 (1H, s, H-4′), 7.37 (1H, dddd, J = 8.1, 8.1, 6.5, and 6.5 Hz, H-4), 7.17 (2H, m, H-3 and H-5); ^{19}F NMR (DMSO-d_6) δ −118.1 (s, F-2 and F-6); IR (KBr) 3255, 3174, 2993, 1698, 1561, 1470, 1313, 1245, 1190, 1002, 777, 702 cm^{-1}; HRMS, calcd for $C_9H_6F_2N_4OS$ 256.0230, found 256.0222.

Data for 1-(3,4-Difluorophenyl)-2-(1′,2′,3′-thiadiazol-5′-yl)urea (2i): yield 83%; mp 239 °C with decomp (from hexane/acetone); R_f 0.223; ^{1}H NMR (DMSO-d_6) δ 10.99 (1H, s, NH3), 9.66 (1H, s, NH1), 8.61 (1H, s, H-4′), 7.61 (1H, ddd, J = 13.0, 7.4, and 2.5 Hz, H-2), 7.36 (1H, ddd, J = 9.6, 9.6, and 9.4 Hz, H-5), 7.22−7.19 (1H, m, H-6); ^{19}F NMR (DMSO-d_6) δ −136.6 (d, J = 23.2 Hz, F-3), −144.7 (d, J = 23.2 Hz, F-4); IR (KBr) 3286, 3243, 3143, 3115, 2956, 1702, 1627, 1585, 1547, 1518, 1302, 1272, 1239, 1204, 1192, 854, 818 cm^{-1}; HRMS, calcd for $C_9H_6F_2N_4OS$ 256.0230, found 256.0236.

Data for 1-(2,3,4-Trifluorophenyl)-3-(1′,2′,3′-thiadiazol-5′-yl)urea (2k): yield 91%; mp 263 °C with decomp (from hexane/acetone); R_f 0.223; ^{1}H NMR (DMSO-d_6) δ 11.07 (1H, s, NH3), 9.37 (1H, s, NH1), 8.64 (1H, s, H-4′), 7.64 (1H, dddd, J = 9.0, 9.0, 5.3, and 2.3 Hz, H-6), 7.29 (1H, dddd, J = 10.2, 9.0, 9.0, and 2.1 Hz, H-5); ^{19}F NMR (DMSO-d_6) δ −160.8 (dd, J = 22.6 and 20.6 Hz, F-3), −146.4 (dd, J = 20.6 and 2.1 Hz, F-2), −141.1 (dd, J = 22.6 and 2.1 Hz, F-4); IR (KBr) 3268, 3013, 1698, 1635, 1518, 1478, 1306, 1251, 1191, 1022, 818, and 685 cm^{-1}; HRMS, calcd for $C_9H_5F_3N_4OS$ 274.0136, found 274.0138.

Data for 1-(2,3,6-Trifluorophenyl)-3-(1′,2′,3′-thiadiazol-5′-yl)urea (2l): yield 88%; mp 256 °C with decomp (from hexane/acetone); R_f 0.426; ^{1}H NMR (DMSO-d_6) δ 11.34 (1H, s, NH3), 9.32 (1H, s, NH1), 8.58 (1H, s, H-4′), 7.47 (1H, dddd, J = 9.6, 9.6, 9.6, and 4.9 Hz, H-4), 7.23 (1H, dddd, J = 9.6, 9.6, 4.5, and 2.3 Hz, H-5); ^{19}F NMR (DMSO-d_6) δ −141.4 (dd, J = 22.7 and 14.5 Hz, F-3), −140.2 (d, J = 22.7 Hz, F-2), −122.6 (d, J = 14.5 Hz, F-6); IR (KBr) 3211, 3174, 2999, 1708, 1638, 1574, 1557, 1486, 1306, 1254, 1190, 1000, 815 cm^{-1}; HRMS, calcd for $C_9H_5F_3N_4OS$ 274.0136, found 274.0127.

Data for 1-(2,4,5-Trifluorophenyl)-3-(1′,2′,3′-thiadiazol-5′-yl)urea (2m): yield 89%; mp 245 °C (from hexane/acetone); R_f 0.181; ^{1}H NMR (DMSO-d_6) δ 11.01 (1H, s, NH3), 9.34 (1H, s, NH1), 8.67 (1H, s, H-4′), 7.99 (1H, ddd, J = 12.4, 8.1, and 8.1 Hz, H-6), 7.66 (1H, ddd, J = 10.7, 10.7, and 7.5 Hz, H-3); ^{19}F NMR (DMSO-d_6) δ −142.0 (dd, J = 23.7 and 13.4 Hz, F-5), −141.1 (d, J 2= 3.7 Hz, F-4), −128.6 (d, J = 13.4 Hz, F-2); IR (KBr) 3273, 3034, 2999, 1698, 1650, 1582, 1532, 1506, 1434, 1302, 1213, 1202, 1192, 782, 737 cm^{-1}; HRMS, calcd for $C_9H_5F_3N_4OS$ 274.0136, found 274.0138.

Data for 1-(2,4,6-Trifluorophenyl)-3-(1′,2′,3′-thiadiazol-5′-yl)urea (2n): yield 77%; mp 244−245 °C (from hexane/acetone); R_f 0.426; ^{1}H NMR (DMSO-d_6) δ 11.30 (1H, s, NH3), 9.02 (1H, s, NH1), 8.55 (1H, s, H-4′), 7.31 (2H, dd, J = 8.9 and 8.3 Hz, H-3 and H-5); ^{19}F NMR (DMSO-d_6) δ −114.9 (d, J = 6.2 Hz, F-2 and F-6), −108.6 (s, F-4); IR (KBr) 3230, 3142, 3081, 3029, 2967, 1686, 1545, 1514, 1445, 1296, 1244, 1124, 1031, 1000, 866, 823, 708 cm^{-1}; HRMS, calcd for $C_9H_5F_3N_4OS$ 274.0136, found 274.0136.

Data for 1-(2,3,4,5-Tetrafluorophenyl)-3-(1′,2′,3′-thiadiazol-5′-yl)-urea (2o): yield 79%; mp 263−266 °C (from hexane/acetone); R_f 0.117; ^{1}H NMR (DMSO-d_6) δ 11.07 (1H, s, NH3), 9.56 (1H, s, NH1), 8.68 (1H, s, H-4′), 7.86 (1H, dddd, J = 12.4, 9.9, 7.7, and 2.4 Hz, H-6); ^{19}F NMR (DMSO-d_6) δ −163.2 (dd, J = 22.7 and 22.6 Hz, F-4), −156.6 (dd, J = 22.6 and 21.7 Hz, F-3), −151.4 (dd, J = 21.7 and 9.3 Hz, F-2), −139.3 (dd, J = 22.7 and 9.3 Hz, F-5); IR (KBr) 3163, 3084, 2999, 1701, 1652, 1591, 1526, 1481, 1308, 1245, 1201, 1184, 1015, 964, 951, 713 cm^{-1}; HRMS, calcd for $C_9H_4F_4N_4OS$ 292.0042, found 292.0033.

Data for 1-(2,3,5,6-Tetrafluorophenyl)-3-(1′,2′,3′-thiadiazol-5′-yl)-urea (2q): yield 70%; mp 255−258 °C (from hexane/acetone); R_f 0.340; ^{1}H NMR (DMSO-d_6) δ 11.39 (1H, s, NH3), 9.55 (1H, s, NH1), 8.60 (1H, s, H-4′), 7.88 (1H, dddd, J = 10.7, 10.7, 7.5, and 7.5 Hz, H-4); ^{19}F NMR (DMSO-d_6) δ −145.9 (dd, J = 23.7 and 11.3 Hz, F-2 and F-6), −139,7 (dd, J = 23.7 and 11.3 Hz, F-3 and F-5); IR (KBr) 3284,

3249, 3189, 3021, 1721, 1567, 1519, 1483, 1309, 1198, 1178, 937 cm^{-1}; HRMS, calcd for $C_9H_4F_4N_4OS$ 292.0042, found 292.0047.

Effects of Phenyl-fluorinated Ureas 2b−2r on Kiwifruit Growth. The experiments were performed at the end of May 2002 in Almussafes (Valencia, Spain) on mature vines of *Actinidia deliciosa* (A. Chev.) of the cv. Hayward with cv. Matua and Tomuri at 50% as pollinizer (8:1). The vines used were from the same orchard blocks. The treatment consisted of dipping fruits for ~5 s, ~2 weeks after full bloom, into an aqueous solution of each urea at 10 or 25 ppm. The solutions were prepared by first dissolving the corresponding urea (100 mg) in a 3:2 mixture of 1-methyl-2-pyrrolidone/DMSO (20 mL), and then this solution was slowly added with vigorous stirring to a volume of water adequate to obtain the urea concentration (w/v) used for the treatments. Between 100 and 120 uniform fruits of three different vines were used in each treatment. All treatments were effected in two consecutive days. Control fruits were also dipped for ~5 s in an aqueous solution of a 3:2 mixture of 1-methyl-2-pyrrolidone/DMSO (0.2% v/v).

The treated and control fruits were harvested in the second week of October, ~140 days after the treatment, and their weight, diameter, length, structure (proportion among outer and inner pericarp and core), flesh firmness, total titratable acids, number of seeds, dry matter of the fruits, and content of soluble solids were measured paralleling the methodology previously followed by other authors on related studies with CPPU (*5*, *17*). All of the fruits from each treatment were used to determine the final fresh weight and to estimate fruit shape (calculating length/average diameter and maximum/minimum diameter ratios and by counting the number of fruits having a protruding distal end). The rest of the properties were determined for only fruits in those experiments that produced a significant increment of average fruit weight with respect to the control. Twenty-five fruits were randomly selected from each treatment and used to estimate the average internal structure by measuring, on the cross-sectional area, the maximum and minimum diameters of the inner pericarp and core and weighing the core. The same fruits were used to examine the number of seeds visible on the cut surface, to estimate the seed content, and to measure the total soluble solids content, expressed as °Brix, using a hand refractometer. Fifteen fruits per treatment were oven-dried at 105 °C to constant weight for the determination of the percentage of dry matter of the fruit. Total titratable acidity was determined by titrating a known volume of fruit juice with 0.1 N NaOH to the end point of pH 8.1, and the results were expressed as percentage of citric acid. Fruit firmness was measured at harvest on two pared sides of each fruit (10 measurements/treatment) using a hand-held penetrometer with an 8-mm-diameter plunger.

Statistical Analysis. Results were processed by an analysis of variance (ANOVA), and statistical significance was determined by Student's test. Statistical analyses were performed with the software package SPSS 10.0.6 for Windows obtained from SPSS España, Madrid, Spain (1999).

RESULTS AND DISCUSSION

Preparation of Fluorinated Ureas 2a−2r. 1-(Fluorophenyl)-3-(1′,2′,3′-thiadiazol-5′-yl)ureas **2a**−**2r** were prepared in high yield and in a straightforward way by reaction of 1,2,3-thiadiazole-5-carbonyl azide (**5**) with the appropriate fluorinated aniline in refluxing toluene, except in the case of the less nucleophilic tetra- and pentafluorinated anilines, **6o**, **6p**, **6q**, and **6r**, for which benzene at reflux was used as the solvent (**Scheme 1**). In these cases, the use of the higher temperature resulted in lower yields, as a consequence of the formation of substantial amounts of symmetric 1,3-bis(1,2,3-thiadiazol-5-yl)urea. The carbonyl azide (**5**) has been previously described in the literature (*18*) and may be prepared using conventional procedures from 1,2,3-thiadiazole-5-carboxylic acid (**3**). First, **3** is transformed into the corresponding acid chloride **4** by treatment with thionyl chloride, which is then reacted at room temperature with sodium azide in aqueous acetone. All of the ureas prepared were confirmed by ^1H, ^{13}C, and ^{19}F NMR, IR, and high- and low-resolution mass spectra. A complete assignment of the spectroscopic data for all of them is given in **Tables 6**, **7**, and **8** of the Supporting Information.

Table 1. Effects of Treatments with TDZ (**2a**) and Ureas **2b**–**2r** on Fruit Weight at Harvest[a]

urea (ppm)	fresh wt (g)	urea (ppm)	fresh wt (g)
control (0)	115.0 ± 22.9		
TDZ (10)	150.2 ± 13.0 (30.6)	**2j** (10)	172.5 ± 30.8 (50.0)
TDZ (25)	159.0 ± 11.3 (38.2)	**2j** (25)	159.5 ± 22.5 (38.7)
2b (10)	133.2 ± 16.2 (15.8)	**2k** (10)	120.4 ± 16.3 (4.7)
2b (25)	163.5 ± 20.1 (42.2)	**2k** (25)	136.1 ± 15.9 (18.3)
2c (10)	149.3 ± 15.9 (29.8)	**2l** (10)	147.8 ± 5.7 (28.5)
2c (25)	138.8 ± 10.5 (20.7)	**2l** (25)	124.6 ± 9.9 (8.31)
2d (10)	120.3 ± 12.5 (4.6)	**2m** (10)	121.8 ± 14.4 (5.9)
2d (25)	123.1 ± 9.9 (7.0)	**2m** (25)	137.6 ± 17.7 (19.6)
2e (10)	158.2 ± 20.5 (37.5)	**2n** (10)	141.0 ± 10.9 (22.6)
2e (25)	144.7 ± 18.2 (25.8)	**2n** (25)	136.0 ± 10.2 (18.3)
2f (10)	119.0 ± 9.8 (3.5)	**2o** (10)	105.7 ± 13.9 (–8.0)
2f (25)	138.8 ± 9.2 (20.7)	**2o** (25)	93.4 ± 9.2 (–18.8)
2g (10)	116.2 ± 16.5 (1.0)	**2p** (10)	131.9 ± 6.5 (14.7)
2g (25)	108.6 ± 15.4 (–5.6)	**2p** (25)	133.0 ± 4.4 (15.7)
2h (10)	126.5 ± 8.1 (10.0)	**2q** (10)	153.7 ± 23.8 (33.6)
2h (25)	132.6 ± 8.7 (15.3)	**2q** (25)	181.3 ± 25.2 (57.6)
2i (10)	144.2 ± 17.6 (25.4)	**2r** (10)	135.0 ± 6.1 (17.4)
2i (25)	136.3 ± 18.9 (18.5)	**2r** (25)	138.9 ± 8.8 (20.7)

[a] Values are fruit weight at harvest ± standard deviation. Values in parentheses represent the percentage of fruit weight with respect to control, calculated by $(fw_t - fw_c)/fw_c \times 100$, where fw_t = fresh weight of treated fruit and fw_c = fresh weight of control

Effect of Fluorinated Urea Treatments on Fruit Growth. The fruits treated with TDZ and most of the fluorinated analogue ureas showed a rapid increase in diameter such that differences in growth with respect to control began to be clearly visible after the first 2 weeks. Those treatment differences observed after 2 weeks were still present at harvest (**Table 1**). As may be observed, most of the urea treatments produced, to more or less extent, an increase in fresh fruit weight with respect to the control. The only exceptions were the ureas **2g** and **2o**, which even at the highest concentration showed a significantly antagonist effect on the fruit weight. Interestingly, some of the fluorinated ureas produced a larger increase in weight than TDZ, the effect produced by **2j** and **2q** at 10 and 25 ppm, respectively, being particularly notable.

It is interesting to note that, as deduced from the data given in **Table 1**, there seems to be a different dose−response for some of the fluorinated ureas. Thus, whereas ureas **2a**, **2b**, **2d**, **2f**, **2h**, **2k**, **2m**, **2p**, **2q**, and **2r** are all more active at 25 ppm than at 10 ppm, ureas **2c**, **2e**, **2i**, **2j**, **2l**, and **2n** are less active at 25 ppm than at 10 ppm. This is not particularly surprising in view of the results previously obtained in cytokinin activity studies of other phenyl ureas, for which the dose−response curves showed a characteristic parabolic shape with the optimum concentration for maximum cytokinin activity varying substantially over a wide concentration range depending on the urea substituents (*19*).

The results obtained in the above experiments show diverse degrees of growth-promoting activity for the different fluorinated analogues of TDZ that logically should be attributable to the pattern of fluorine substitution. Despite being quite different biological systems, the results obtained in our field experiments agree relatively well with the conclusions previously obtained from in vitro studies of phenyl substituent requirements for high cytokinin activity of phenylureas (*20*). Thus, a clear correspondence is found between the high efficacy of the 3,5-difluorophenyl urea **2j**, the most active at 10 ppm, and the in

Table 2. Data for Compounds **2a**–**2r**

urea	fluorine substitution pattern	TLC log P^a	ΣF^b	$SCS_{NH1}{}^a$	$SCS_{NH3}{}^a$	$A_{10}{}^c$
2a	TDZ	1.52	0.00	0.00	0.00	0.306
2b	2-F	1.57	0.54	–0.26	0.15	0.158
2c	3-F	1.65	0.42	0.23	0.10	0.298
2d	4-F	1.57	0.43	0.03	0.04	0.046
2e	2,3-F_2	1.67	0.96	–0.03	0.24	0.375
2f	2,4-F_2	1.59	0.97	–0.24	0.22	0.035
2g	2,5-F_2	1.72	0.96	–0.06	0.22	0.010
2h	2,6-F_2	1.28	1.08	–0.32	0.45	0.100
2i	3,4-F_2	1.72	0.85	0.24	0.17	0.254
2j	3,5-F_2	1.82	0.84	0.44	0.28	0.500
2k	2,3,4-F_3	1.72	1.39	–0.05	0.25	0.047
2l	2,3,6-F_3	1.37	1.50	–0.10	0.52	0.285
2m	2,4,5-F_3	1.80	1.39	–0.08	0.18	0.059
2n	2,4,6-F_3	1.37	1.51	–0.40	0.48	0.226
2o	2,3,4,5-F_4	1.91	1.81	0.14	0.25	–0.080
2p	2,3,4,6-F_4	1.52	1.93	–0.14	0.54	0.146
2q	2,3,5,6-F_5	1.52	1.92	0.13	0.57	0.336
2r	2,3,4,5,6-F_5	1.69	2.34	0.10	0.62	0.174

[a] TLC log *P*, SCS_{NH1}, and SCS_{NH3} have estimated uncertainties of <±3%, based on separate measurements. [b] Swain–Lupton *F* values used are scaled by aromatic ring position (ortho, meta, para) following the procedure described in Williams, S. G.; Norrington, F. E. *J. Am. Chem. Soc.* **1976**, *98*, 508. [c] $A_{10} = (fw_t - fw_c)/fw_c$ (fw_t = fresh weight of treated fruit; fw_c = fresh weight of control) at 10 ppm.

vitro activity of the 3,5-difluorophenyl analogue of the *N*-oxide of CPPU (*21*). As with **2j**, an increment in activity at 10 ppm is observed in the less fluorinated ureas by meta fluorination at the phenyl ring, for example, **2b** versus **2e**, **2d** versus **2i**, or **2h** versus **2l**, although this effect disappears or even inverts with increasing fluorination, for example, **2m** versus **2o**. The effect of para substitution by fluorine is also significant, generally resulting in a diminution of activity, for example, **2a** versus **2d**, **2b** versus **2f**, or **2e** versus **2k**, which should be in accordance with the reduced cytokinin activity observed for the structurally related 1-(2-chloro-1-oxypyridin-4-yl)-3-(4-fluorophenyl)urea with respect to the parent compound in the chlorophyll retention bioassay (*22*). Ortho fluorination of the phenyl ring does not produce a uniform effect on activity, but, in general, the presence of the fluorine atom at C-2 and/or C-6 does not seem to have a particularly detrimental effect on activity. Even some of the ortho fluorinated ureas produce a remarkable increase in activity with respect to the parent TDZ, as the symmetrically fluorinated urea **2q**, by far, the most active of all these ureas at 25 ppm. The great activity of this tetrafluorinated urea shows that the steric effects produced by the fluorine atoms, which could also affect the conformational disposition between the ureido and phenyl moieties, do not seem to influence very negatively the interaction of the fluorinated phenyl moiety with the specific local receptor site. In fact, and with the exception of only urea **2o**, all of the polyfluorinated ureas produce an increase in fruit weight with respect to the control.

We have estimated the hydrophobicity of ureas **2a**−**2r** by determining the corresponding TLC log *P* values using an adaptation of the procedure used by Henrie for related ureas (*22*). These values are given in **Table 2**. As can be seen, the degree and pattern of fluorine substitution of the benzene ring have a significant influence in the overall hydrophobicity of these ureas. There does not seem to be a good-quality correlation between the overall hydrophobicity and the growth-promoting activity for the whole group of fluorinated ureas. However, there is a good correlation between hydrophobicity and activity for a subset of nine ureas (**2a**, **2c**, **2h**, **2i**, **2l**, **2m**, **2n**, **2o**, and **2q**), for which a nonlinear regression analysis gave the eq 1,

$$A_{10} = -7.057\ (\pm 0.848) + 9.614\ (\pm 1.081)\ \text{TLC log } P - 3.128\ (\pm 0.340)\ (\text{TLC log } P)^2$$
$$(n = 9,\ r^2 = 0.949,\ s = 0.036,\ F = 56) \qquad (1)$$

where A_{10} expresses the activity at 10 ppm [$A_{10} = (fw_t - fw_c)/fw_c$, see **Table 2**]. The remaining nine ureas (**2b**, **2d**, **2e**, **2f**, **2g**, **2j**, **2k**, **2p**, and **2r**) form a group with intermediate or high hydrophobicity that does not correlate with activity.

Figure 1 shows the set of data points relating TLC log *P* and activity values given in **Table 2** and illustrates the parabolic relationship of the activity to TLC log *P* for the first subgroup of ureas mentioned above, showing for them an optimum hydrophobicity close to TLC log $P = 1.53$.

The lack of a good correlation between TLC log *P* and activity for the entire group of ureas, and particularly the fact that two ureas with nearly identical hydrophobicities, for example **2p** versus **2q** or **2a**, produced a very different effect on fruit weight, suggests that other factors besides overall hydrophobicity may also influence the activity. In this respect, we noted an interesting correlation between the activity of the whole library of ureas with the Swain−Lupton substituent parameter *F* (see ΣF in **Table 2**) and the substituent-induced chemical shifts observed for the NH protons of the urea bridge (SCS_{NH1} and SCS_{NH3}, **Table 2**) as shown by eq 2,

$$A_{10} = 0.244\ (\pm 0.050) + 0.416\ (\pm 0.114)\ SCS_{NH1} + 1.078\ (\pm 0.245)\ SCS_{NH3} - 0.319\ (\pm 0.074)\ \Sigma F$$
$$\beta^* = 0.587 \qquad \beta^* = 1.348 \qquad \beta^* = -1.301 \qquad (2)$$
$$(n = 18,\ r^2 = 0.664,\ s = 0.096,\ F = 9)$$

which may be considerably improved if the values of four ureas are excluded from the analysis (ureas **2d**, **2e**, **2g**, and **2h**, the data points that fit worst to the correlation line) as shown by eq 3

$$A_{10} = 0.286\ (\pm 0.031) + 0.346\ (\pm 0.065)\ SCS_{NH1} + 1.193\ (\pm 0.147)\ SCS_{NH3} - 0.369\ (\pm 0.043)\ \Sigma F \quad (3)$$
$$\beta^* = 0.523 \qquad \beta^* = 1.568 \qquad \beta^* = -1.632$$
$$(n = 14,\ r^2 = 0.906,\ s = 0.052,\ F = 32)$$

and **Figure 2**. [Results from a parallel study have shown that all of the ureas exist in the solvent used for recording their NMR data (DMSO-d_6 solutions) as monomers in the trans−trans conformation, which is strongly stabilized by formation of a three-center bond between the ureido protons (NH) and the oxygen atom of the sulfoxide moiety. No significant variations are observed in the chemical shifts of the NH hydrogens with the concentration of the fluorinated urea (at least over a 3-fold concentration range). It is interesting to note that there is a good linear dependence between the chemical shift of the ureido hydrogens and both *F* and *R* substituent constants (Swain−Lupton model). These results will be published elsewhere.]

Because the ΣF factor measures the field-inductive effects of the fluorine atoms on the phenyl moiety of each urea, both equations seem to reveal the importance of the electronic interactions of this region of the urea framework with its specific receptor site, an aspect that could be more significant to their

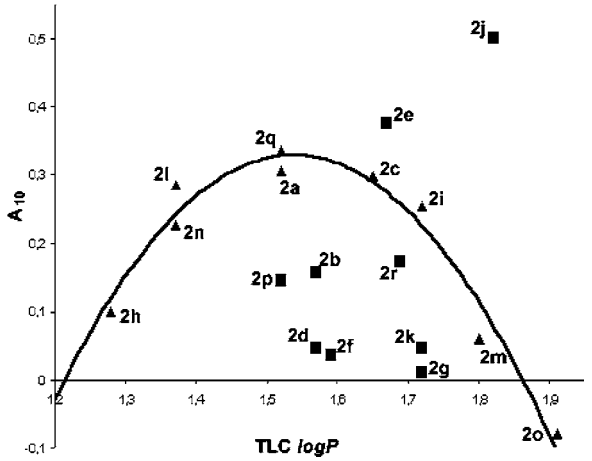


Figure 1. Parabolic relationship of growth-promoting activity of fluorinated analogues of TDZ to TLC log *P* expressed by eq 1. Squares represent data points not included in the quadratic curve-of-best-fit drawn.

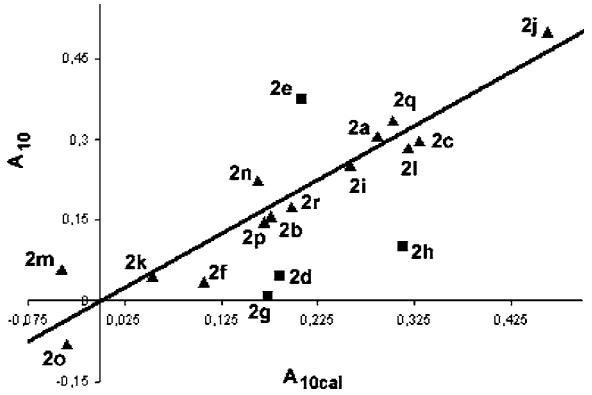


Figure 2. Plot of A_{10} versus a linear combination of SCS_{NH1}, SCS_{NH3}, and Swain–Lupton *F* constant ($A_{10calcd}$ as expressed by eq 3). Squares represent data points not included in the line-of-best-fit drawn.

activity than the global transport process measured by the overall hydrophobicity. On the other hand, the dependence of the activity on the SCSs may be associated with the capacity of the ureido N−H protons of the urea bridge to participate in hydrogen-bonding interactions, a factor that has been suggested to play an important role in the cytokinin activity of *N*-phenyl- and *N*-pyridylureas and related carbamates (*23*). The consideration of these two factors leads to the conclusion that two of the main effects produced by fluorination of the benzene ring, for example, changes in the acidity of the ureido hydrogens and alteration of electron donor/acceptor capacity of the phenyl ring, are important for the cytokinin-like activity of these fluorinated ureas. Thus, an enhancement of acidity of the ureido protons results in an increase in activity, whereas a lowering of the phenyl ring electronic density leads to a lesser activity. The highest activity should result from a subtle balance of both effects.

The above conclusion will explain the elevated activity of tetrafluorinated urea **2q** as opposed to the rest of the highly fluorinated ureas, because the relatively large inductive-field effect associated with the polyfluorinated phenyl ring is compensated by the acidity of the ureido protons, particularly the N3−H proton, to which should probably be added a very favorable overall hydrophobicity for an efficient transport to the receptor. On the other hand, the urea **2j**, one of the most hydrophobic fluorinated ureas, has an adequate combination of the inductive effects associated with the fluorine atoms and acidity of the ureido N−H that results in a very high activity.

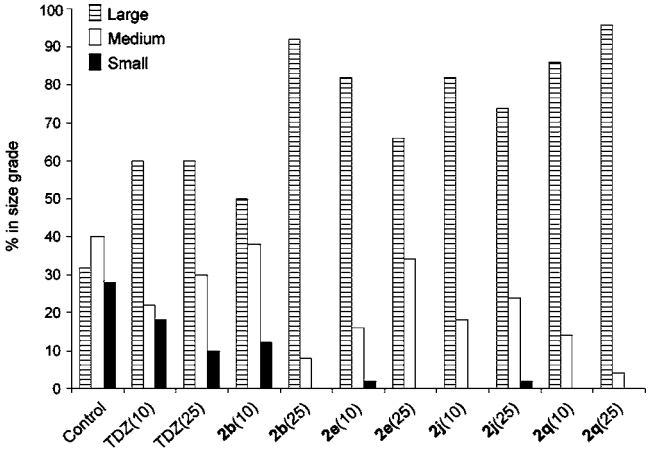


Figure 3. Effect of fruit size distribution in response to phenyl-fluorinated urea treatments

Effects of Fluorinated Urea Treatments on Fruit Quality Properties. A more detailed evaluation of the effects caused by the urea treatments on some commercially important fruit properties was effected on a reduced selection of experiments. In particular, the fruits harvested from control experiments and treatments with TDZ (**2a**) and ureas **2b**, **2e**, **2j**, and **2q** were selected for this evaluation. Additionally to the increase in the average fruit weight, the treatment with the more active ureas resulted in a greater uniformity and size grade increase for the fruits obtained. As graphically expressed in **Figure 3**, the percentage of large size fruits (weight ≥ 135 g), medium size fruits (110 ≤ weight ≤ 135 g), and small size fruits (weight ≤ 110 g) changed substantially from control to TDZ-treated fruits and from these to the rest of fluorinated urea-treated fruits. In the latter case, few fruits of small size were obtained, and most of the fruits were of the largest size, the results obtained with **2b** and **2q** at 25 ppm and with **2e** and **2j** at 10 ppm being particularly relevant.

As a consequence of the increase in size, the treatments with these ureas also resulted in an increase in the length and diameter of the fruits (**Table 3**). Although a slight elongation of the fruits treated with the more active ureas was observed, as shown by the relationship between the length and average diameter, in general, the global fruits shape was not affected very negatively. It is interesting to note that a modification of the shape of the fruits treated with TDZ at 10 ppm was observed, with more rounded fruits being obtained in this experiment. This result contrasts with that obtained at the higher concentration; the treatment with TDZ at 25 ppm did not cause any change in the relative diameters and lengths. Previous studies with TDZ and CPPU showed that the effect of the treatments with these ureas on the relative diameter and length of the fruits is not regular; in some cases CPPU or TDZ treatments caused more fruit growth in the diameter than in length (*5*), whereas in other cases the treatment did not cause any significant change in the relative diameters and lengths (*24*). As previously noted, an increase in the percentage of fruits having a protruding distal end was observed for all of the treated fruits, an effect that was appreciably more marked in the fruits treated with the more active ureas.

The effect of treatments on fruit internal structure is also evident by comparison of the data given in **Table 4**. As can be seen from these data, all of the treatments caused a similar modification of the relative proportion of the fruit tissues that led to fruits with proportionally smaller cores than untreated fruits. These results contrast with those previously obtained with

Table 3. Effects of Phenyl-fluorinated Urea Treatments on Fruit Size and Shape at Harvest[a]

urea (ppm)	length (mm)	max diameter (mm)	min diameter (mm)	D_{max}/D_{min}	length/av diameter	protruding distal end (% fruits)
control (0)	66.7 g	58.6 e	52.8 e	1.11 ab	1.20 c	6 d
TDZ (10)	67.4 g	62.9 cd	57.4 abcd	1.10 b	1.12 d	26 c
TDZ (25)	70.8 ef	61.6 a	56.2 bcd	1.10 b	1.20 c	28 c
2b (10)	70.2 fg	61.8 d	55.0 de	1.13 ab	1.20 c	50 b
2b (25)	74.2 bcd	66.0 b	57.8 abc	1.14 ab	1.20 c	72 ab
2e (10)	74.2 bcd	64.9 bc	56.7 abcd	1.15 ab	1.22 bc	52 b
2e (25)	73.1 cdef	61.9 d	55.3 d	1.12 ab	1.25 ab	36 c
2j (10)	76.8 ab	66.3 b	56.8 ab	1.11 ab	1.23 abc	84 a
2j (25)	75.4 cd	64.9 bc	55.9 cd	1.16 a	1.25 ab	52 b
2q (10)	75.4 bc	65.0 bc	58.4 ab	1.11 ab	1.22 bc	32 c
2q (25)	79.4 a	66.8 b	59.1 a	1.11 ab	1.22 bc	40 c

[a] In each column, means followed by the same letter are not significantly different at $P \leq 0.05$.

Table 4. Effects of Phenyl-fluorinated Urea Treatments on Fruit Structure at Harvest[a]

urea (ppm)	D_{max} of inner pericarp + core/D_{max} of fruit	D_{min} of inner pericarp + core/D_{min} of fruit	D_{max} of core/ D_{max} of fruit	D_{min} of core/ D_{min} of fruit	core fw/ fruit fw (%)	seed no.
control (0)	0.64 ab	0.58 a	0.34 ab	0.24 a	8.7 a	50.6 ab
TDZ (10)	0.63 b	0. 52 c	0.30 b	0.18 b	5.0 c	43.2 b
TDZ (25)	0.65 ab	0.55 abc	0.30 b	0.20 b	4.9 c	43.4 b
2b (10)	0.66 ab	0.56 abc	0.35 ab	0.20 b	6.7 b	50.6 ab
2b (25)	0.68 a	0.52 c	0.36 a	0.19 b	6.0 bc	43.4 b
2e (10)	0.66 ab	0.53 bc	0.35 ab	0.19 b	5.6 bc	43.8 b
2e (25)	0.67 ab	0.57 ab	0.34 ab	0.20 b	5.6 bc	54.5 a
2j (10)	0.64 ab	0.53 bc	0.34 ab	0.18 b	5.6 bc	46.8 ab
2j (25)	0.64 ab	0.53 bc	0.33 ab	0.18 b	5.7 bc	50.8 ab
2q (10)	0.66 a	0.53 bc	0.33 ab	0.19 b	5.3 c	43.2 b
2q (25)	0.64 ab	0.53 bc	0.31 ab	0.19 b	4.9 c	43.2 b

[a] In each column, means followed by the same letter are not significantly different at $P \leq 0.05$.

Table 5. Changes in Flesh Firmness, Soluble Carbohydrates, and Total Titratable Acids at Harvest and after 13 Days at 25 °C As Affected Phenyl-fluorinated Urea Treatments[a]

	flesh firmness (kgf)		soluble carbohydrates (°Brix)		total titratable acids (g of citric acid/L of juice)		
urea (ppm)	at harvest	13 days after harvest	at harvest	13 days after harvest	at harvest	13 days after harvest	dry matter content (% fw)
control (0)	7.6 a	4.2 c	6.2 f	9.7 b	17.2 b	16.3 a	15.9 a
TDZ (10)	5.7 cde	1.5 d	7.4 de	13.1 a	15.0 f	14.3 e	12.5 cd
TDZ (25)	4.7 e	1.5 d	7.7 cde	12.5 a	14.9 f	14.7 d	12.9 b
2b (10)	6.7 abc	5.7 ab	8.1 abc	8.4 c	15.9 d	15.4 c	12.8 bc
2b (25)	6.6 abc	6.2 a	8.3 ab	8.2 c	15.9 d	15.9 b	13.0 b
2e(10)	6.8 ab	5.0 bc	8.4 a	8.6 bc	15.8 d	15.3 c	13.0 b
2e (5)	5.7 cde	4.2 c	8.3 ab	9.1 b	15.5 e	15.1 c	12.0 efg
2j (10)	6.1 bcd	5.5 abc	8.2 abc	8.0 c	16.5 c	14.5 h	12.1 ef
2j (25)	7.0 ab	4.7 bc	7.8 bcd	8.5 c	16.5 c	15.8 b	12.3 de
2q (10)	6.6 abc	1.6 d	7.2 e	12.7 a	17.6 a	15.7 b	11.9 fg
2q (25)	5.1 de	1.8 d	7.1 e	12.3 a	14.9 f	13.9 f	11.7 g

[a] In each column, means followed by the same letter are not significantly different at $P \leq 0.05$.

TDZ, which caused an increase in the size of all the tissues of the fruits without changing their relative proportions (*5*). An important modification of the shape of the core was also observed in all of the treated fruits, being appreciably flatter than in the control fruits (see **Figure 4** of the Supporting Information). No significant variation in the number of seeds was observed between the fruits of different treatments, nor with respect to control. Similar observations have also been made in previous studies with TDZ and CPPU (*5*, *17*).

Fruit ripening at harvest was affected by all of the treatments. Comparison of the values of flesh firmness and total soluble solid content of treated and control fruits indicates that the treatments advance fruit ripening with respect to untreated fruits more or less proportionally to the increase in fruit weight (**Table 5**). This observation is also in agreement with the results previously obtained on kiwifruit treatments with TDZ and CPPU. However, although the more active ureas produced a more rapid fruit ripening, the effect is in general less pronounced for the fluorinated ureas than for TDZ. A very interesting observation deduced from the data referring to the postharvest period is the substantially slower ripening of the fruits treated with some of the more active fluorinated ureas with respect to both control and TDZ-treated fruits. In fact, of all the ureas studied, only the polyfluorinated urea **2q** showed a behavior

similar to that of TDZ. The effect of the treatments on maturation was also confirmed by the lower total titratable acidity measured for treated fruits with respect to untreated ones.

Finally, the effect of the treatments with the fluorinated ureas on dry matter content at harvest was also determined (**Table 5**). In concordance with the results previously described for TDZ and CPPU treatments, all of the fluorinated ureas also produced an important decrease in the percentage of dry matter of fruit at harvest that was not very different from that produced by TDZ (*2*). [The data set corresponding to the different measured or calculated agronomical variables (length, maximum diameter, minimum diameter, D_{max}/D_{min}, length/average diameter, percent of fruits with protruding distal end, D_{max} of inner pericarp + core/D_{max} of fruit, D_{min} of inner pericarp + core/D_{min} of fruit, D_{max} of core/D_{max} of fruit, D_{min} of core/D_{max} of fruit, core fw/fruit fw, flesh firmness, soluble carbohydrates, total titratable acids, and dry matter content) was also statistically analyzed with principal component analysis (PCA), which revealed that the variance in this data set is explained by a three-component model to 92%. According to this analysis the agronomical parameters corresponding to the kiwifruits treated with the more active fluorinated ureas (**2b**, **2e**, **2j**, and **2q**) are statistically homogeneous, different from those corresponding to TDZ-treated and control fruits. A good linear correlation ($r^2 = 0.877$) is obtained between the fresh fruit weights and the first principal component derived from the PCA.]

Conclusion. A relatively large number of fluorinated analogues of TDZ have been prepared and evaluated as kiwifruit growth regulators. The results show that most of these 1-fluorophenyl-3-(1,2,3-thiadiazol-5-yl)ureas are able to stimulate kiwifruit growth to more or less extent depending on the degree and pattern of fluorine substitution of the phenyl ring. It has been concluded from the structure−activity relationship studies performed on this group of fluorinated ureas that two of the main effects produced by fluorination of the benzene ring, for example, changes in the acidity of the ureido hydrogens and alteration of electron donor/acceptor capacity of the phenyl ring, could be the key in determining the growth-promoting activity of these fluorinated ureas.

The results also indicate that the effects of the more active phenyl-fluorinated ureas on some standard quality parameters of fruits, for example, percent of fruit dry matter content, soluble solids contents, total titratable acids, shape, and internal structure, are relatively similar to those of TDZ. Interestingly and in contrast to TDZ, some phenyl-fluorinated ureas are able to stimulate fruit growth without accelerating the ripening process after harvest.

From a potential profitability point of view, the great increase of fruit size promoted at low concentrations by the 3,5-difluorinated analogue of TDZ (urea **2j**) is particularly relevant, which suggests the possibility of using it as an active ingredient in formulations for kiwifruit applications.

SAFETY

Special care must be taken to avoid inhalation of vapors of thionyl chloride. Although we have not had problems with the handling of solutions of acyl azide **5**, special safety precautions must be observed when it is handled without solvent, because a violent explosion may occur under certain conditions (e.g., heat, rapid solidification after evaporation of the solvent, or radiation). In particular, on one occasion we had a violent explosion when a small sample (~2 g) of **5** was allowed to solidify in the freezer at −20 °C.

Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra and mass spectra of compounds **2b**−**2r**; tables with completed ^{1}H, ^{13}C, and ^{19}F NMR chemical shifts and coupling constants assignments (**Tables 6**, **7**, and **8**, respectively); photograph of representative longitudinal and equatorial cross sections of untreated and treated kiwifruits (**Figure 4**). This material is available free of charge via the Internet at http://pubs.acs.org.

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