Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy 149 (2015) 920–927

Contents lists available at ScienceDirect

Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy

journal homepage: www.elsevier.com/locate/saa

^{13}C NMR substituent-induced chemical shifts in 4-(substituted phenyl)-3-phenyl-1,2,4-oxadiazol-5(4*H*)-ones (thiones)

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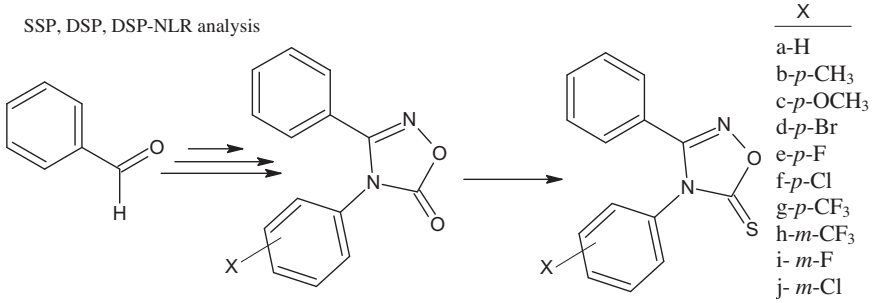
HIGHLIGHTS

- ^{13}C NMR chemical shifts in 4-(substituted phenyl)-3-phenyl-1,2,4-oxadiazol-5(4H)-ones (thiones) were correlated with Hammett substituent constants.
- SSP (single substituent parameter), DSP (dual substituent parameter) and DSP-NLR (dual substituent parameter-non-linear resonance) were applied.
- It has been observed that substituent effects from aryl group are efficiently transmitted to oxadiazole rings.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 6 February 2015
Received in revised form 22 April 2015
Accepted 25 April 2015
Available online 1 May 2015

Keywords:
Oxadiazole ring
SSP analyses
DSP analyses
DSP-NLR analyses
Reverse substituent effect
Hammett correlation

ABSTRACT

In the present, study mostly novel ten 4-(substituted phenyl)-3-phenyl-1,2,4-oxadiazol-5(4*H*)-ones and ten 4-(substituted phenyl)-3-phenyl-1,2,4-oxadiazol-5(4*H*)-thiones were synthesized. These oxadiazole derivatives were characterized by IR, ^{1}H NMR, ^{13}C NMR and elemental analyses. Their ^{13}C NMR spectra were measured in Deuterochloroform ($CDCl_3$). The correlation analysis for the substituent-induced chemical shift (SCS) with Hammett substituent constants (σ), Brown Okamoto substituent constants (σ^+, σ^-), inductive substituent constants (σ_I) and different of resonance substituent constants (σ_R, σ_R^o) were performed using SSP (single substituent parameter), DSP (dual substituent parameter) and DSP-NLR (dual substituent parameter-non-linear resonance) methods, as well as single and multiple regression analysis. Negative ρ values were found for all correlations (reverse substituent effect). The results of all statistical analyses, ^{13}C NMR chemical shift of C=N, C=O and C=S carbon of oxadiazole rings have shown satisfactory correlation.

Introduction

Five membered ring heterocyclic compounds are an important class of compounds due to their use as scaffolds in synthetic chemistry. In this family, many oxadiazole derivatives have demonstrated a wide spectrum of biological activity in both agrochemical and therapeutic areas, such as antioxidant [1], antimicrobial [2], analgesic [3] antiinflammatory, antioxidant and antimicrobial [4], antidiabetic [5] insecticidal [6], antiviral [7], anticancer [8,9], ulcerogenic and lipid peroxidation [10], anticonvulsant [11], antihypertensive [12,13], antiHIV-1 [14], antipyretic [15], tyrosinase [16], antibacterial, antifungal and antitubercular [17], cytotoxic [18], larvicide [19], aryl hydrocarbon receptor [20], antidepressant [21], hypoglycemic and hypolipidemic [22] antituberculosis [23,24], antimalarial [25], pulmonary vasodilatory [26] genotoxic [27] and muscle relaxant [28] activities. Meanwhile, amidoxime derivatives have been shown to have a variety of useful properties. These include antioxidant and lipid peroxidation

http://dx.doi.org/10.1016/j.saa.2015.04.081
1386-1425/

activities [29], antileishmanial and antimicrobial agents [4,30], chelating resin [31], nitric oxide donors [32] and amidine prodrugs [33]. In addition, the main application of these is building blocks, which is related to the construction of 1,2,4-oxadiazoles, 1,2,4-oxadiazines and 1,2,4,5-oxadiazaboroles rings [34–36].

Nowadays scientists have paid more attention to correlate the investigated carbon of the chemical shift of ^{13}C NMR spectra with Hammett substituent constants to explain the substituent effects in organic molecules using SSP (single substituent parameter), DSP (dual substituent parameter) and DSP-NLR (dual substituent parameter non-linear resonance) analysis which are derivatives of Hammett equation. Because when substituent in one section of an organic molecule is varied, reorganization of the electronic framework all through the molecules occurs. This situation can affect the molecule's reactivity, conformation, solubility, biological activity and etc. [34,37].

However, to the best of our knowledge of the activities of oxadiazoles, the substituent effects on the chemical shift of ^{13}C NMR spectra of these molecules have not been previously reported using DSP and DSP-NLR analysis. A number of investigations have previously been reported on SSP analysis on chemical shift ^{13}C NMR spectra of oxadiazoles [34,38]. Therefore, a series of ten 4-(substituted phenyl)-3-phenyl-1,2,4-oxadiazol-5(4*H*)-ones and ten 4-(substituted phenyl)-3-phenyl-1,2,4-oxadiazol-5(4*H*)-thiones were synthesized and ^{13}C NMR substituent chemical shifts (SCS) of investigated compounds were recorded. Additionally, we have also studied the transmission substituent effects on ^{13}C NMR substituent chemical shifts of C=N, C=O and C=S carbons of 4-(substituted phenyl)-3-phenyl-1,2,4-oxadiazol-5(4*H*)-ones (thiones) using SSP, DSP and DSP-NLR equations.

Synthesis

The synthesis of ten 4-(substituted phenyl)-3-phenyl-1,2,4-oxadiazol-5(4*H*)-ones and ten 4-(substituted phenyl)-3-phenyl-1,2,4-oxadiazol-5(4*H*)-thiones straightforward as illustrated in Fig. 1. Melting points were determined on Electrothermal 9200 apparatus and are uncorrected. The FT-IR spectra of compound (**2a**–**j**), (**3a**–**j**) and (**4a**–**j**) were recorded on Bruker Tensor 27 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker DPX-400 (400 MHz) High Performance Digital FT-NMR spectrometer. Elemental analyses were performed on a Costect 4010 elemental combustion system. High Resolution Mass Spectrums were performed on a Agilent Technologies 6224 TOF LC/MS system.

Experimental

Oximes were synthesized according to the literature. For the synthesis of compound (**2**–**4**), literature methods were applied with slight modifications (Fig. 1) [39,40].

Synthetic procedures

*N-(phenyl)-benzamide oxime (**2a**) (general procedure)*

Chlorine gas (2.84 g) was passed through a solution of benzaldehyde oxime (2.42 g, 20 mmol) in dry chloroform (30 mL) while a reaction flask was cooled in an ice-salt bath. After the color turned blue–green, the solution was kept in a refrigerator for one night. Then the solution was evaporated at reduced pressure. Aniline (3.72 g, 40 mmol) was dissolved in benzene (15 mL) in a reaction flask. N-phenyl benzenecarboximidoyl chloride in benzene (20 mL) was added dropwise to this solution with constant stirring at room temperature for 24 h. The precipitate was filtered and the solution was evaporated under reduced pressure. The residual solid was subjected to flash column chromatography (eluent:ethyl acetate/petroleum ether, 1:4) to give N-(phenyl)-benzamide oxime (**2a**) (2.16 g, 51%; mp 128–129.5 °C; IR (KBr), ν (cm^{-1}): 3394.34 (NH), 3153.09–3039.96 (OH), 1639.60 (C=N). HRMS for $C_{13}H_{12}N_2O$ $[M+H]^+$ calculated 213.1022. Found 213.1042.

*Spectroscopic and analytical data of compounds (**2**).*

*N-(4-methylphenyl)-benzamide oxime (**2b**).* Yield 52%; mp 161.5–163 °C, Lit. 163–165 °C [41], 161–162 °C [42]; HRMS for $C_{14}H_{14}N_2O$ $[M+H]^+$ calculated 227.1179. Found 227.1196.

*N-(4-methoxyphenyl)-benzamide oxime (**2c**).* Yield 47%. mp 154.4–157.2 °C. IR (KBr), ν (cm^{-1}): 3395.91 (NH), 3061.45 (OH), 1628.51 (C=N). HRMS for $C_{14}H_{14}N_2O_2$ $[M+H]^+$ calculated 243.1128. Found 243.1148.

*N-(4-bromophenyl)-m-chlorobenzamide oxime (**2d**).* Yield 50%; mp 192–193.5 °C; IR (KBr), ν (cm^{-1}): 3401.82 (NH), 3064.39 (OH), 1645.78 (C=N). HRMS for $C_{13}H_{11}N_2OBr$ $[M+H]^+$ calculated 291.0127. Found 291.0111.

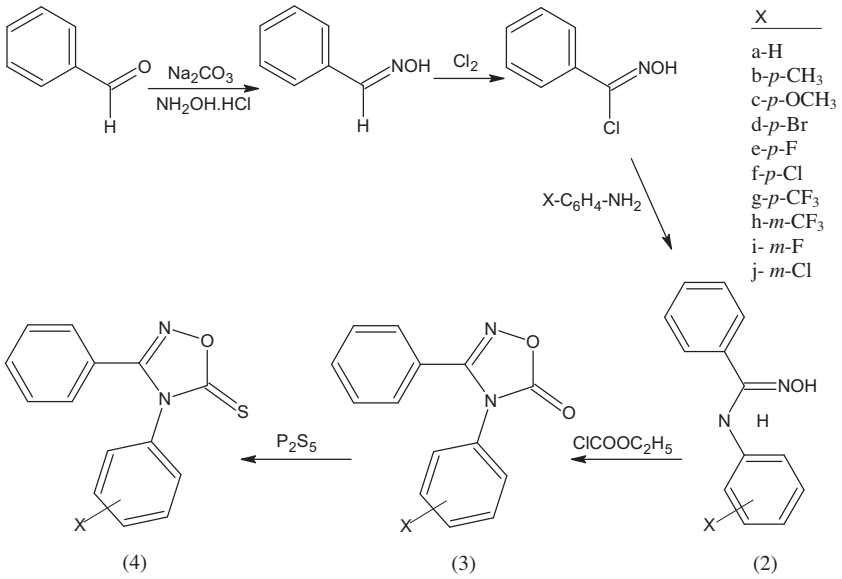


Fig. 1. Synthesis of 4-(substituted phenyl)-3-phenyl-1,2,4-oxadiazole-5(4H)-ones (**3a**–**j**), 4-(substituted phenyl)-3-phenyl-1,2,4-oxadiazole-5(4H)-thiones (**4a**–**j**).

*N-(4-fluorophenyl)-benzamide oxime (**2e**).* Yield 57%; mp 147.5–149 °C; IR (KBr), ν (cm^{-1}): 3353.87 (NH), 3153.77–3104.13 (OH), 1627.11 (C=N). HRMS for $C_{13}H_{11}N_2OF$ $[M+H]^+$ calculated 231.0928. Found 231.0915.

*N-(4-chlorophenyl)-p-bromobenzamide oxime (**2f**).* Yield 49%; mp 182.5–183.6 °C; IR (KBr), ν (cm^{-1}): 3393.59 (NH), 3186.77–3068.74 (OH), 1643.29 (C=N). HRMS for $C_{13}H_{11}N_2OCl$ $[M+H]^+$ calculated 247.0633. Found 247.0621.

*N-(4-(trifluoromethyl)phenyl)-benzamide oxime (**2g**).* Yield 50%; mp 99–101 °C; IR (KBr), ν (cm^{-1}): 3386.45 (NH), 3142.41 (OH), 1626.17 (C=N). HRMS for $C_{14}H_{11}N_2OF_3$ $[M+H]^+$ calculated 281.0896. Found 281.0899.

*N-(3-(trifluoromethyl)phenyl)-benzamide oxime (**2h**).* Yield 50%; mp 100.5–102.7 °C: IR (KBr), ν (cm^{-1}): 3386.37 (NH), 3151.68–3060.41 (OH), 1635.74 (C=N). HRMS for $C_{14}H_{11}N_2OF_3$ $[M+H]^+$ calculated 281.0896. Found 281.0894.

*N-(3-fluorophenyl)-benzamide oxime (**2i**).* Yield 53%; mp 149–151 °C; IR (KBr), ν (cm^{-1}): 3399.26 (NH), 3153.77–3104.13 (OH), 1636.69 (C=N). HRMS for $C_{13}H_{11}N_2OF$ $[M+H]^+$ calculated 231.0928. Found 231.0938.

*N-(3-chlorophenyl)-benzamide oxime (**2j**).* Yield 52%; mp 106–108 °C; IR (KBr), ν (cm^{-1}): 3374.45 (NH), 3157.46–3059.50 (OH), 1633.81 (C=N). HRMS for $C_{13}H_{11}N_2OCl$ $[M+H]^+$ calculated 247.0633. Found 247.0644.

*3,4-diphenyl-1,2,4-oxadiazol-5(4H)-one (**3a**) (general procedure)*

Triethylamine (0.6 g, 6 mmol) was added to a stirred solution of N-phenyl-benzamide oxime (**2a**) (1.27 g, 6 mmol) in xylene (15 mL) at r.t., and then ethyl chloroformate was added dropwise (0.72 g, 6 mmol) in xylene (10 mL) and the mixture was refluxed for 9 h. The reaction mixture was filtered through filter paper, and the solution was evaporated at reduced pressure. The crude reaction product was crystallized in ethyl acetate/petroleum ether (1:3) to give (**3a**) (1.1 g, 72%); mp 171.3–171.6 °C; IR (KBr), ν (cm^{-1}): 1771.30 (C=O), 1593.85 (C=N); ^{1}H NMR ($CDCl_3$), δ (ppm): 7.51–7.46 (m, aromatic, 2H), 7.45–7.44 (t, J = 3.2, aromatic, 2H), 7.36–7.36 (d, J = 1.6, aromatic, 2H), 7.35 (s, aromatic, 2H), 7.24–7.21 (m, aromatic, 2H); ^{13}C NMR ($CDCl_3$), δ (ppm): 158.34 (C=O), 157.53 (C=N), 131.99–123.04 (aromatic C). Anal. Calcd for $C_{14}H_{10}N_2O_2$ (238.24): C, 70.58; H, 4.23; N, 11.76. Found C, 70.63; H, 4.63; N, 11.71. HRMS for $C_{14}H_{10}N_2O_2$ $[M+Na]^+$ calculated 261.0635. Found 261.0637.

*Spectroscopic and analytical data of compounds (**3**).*

*4-(4-methylphenyl)-3-phenyl-1,2,4-oxadiazol-5(4H)-one (**3b**).* Yield 60%; mp 164.5–165.8 °C [41], Lit. 165–166 °C [42]; HRMS for $C_{15}H_{12}N_2O_2$ $[M+Na]^+$ calculated 275.0731. Found 275.0785.

*4-(4-methoxyphenyl)-3-phenyl-1,2,4-oxadiazol-5(4H)-one (**3c**).* Yield 61%; mp 158.1–160.2 °C. IR (KBr), ν (cm^{-1}): 1766.99 (C=O), 1606.21 (C=N). ^{1}H NMR ($CDCl_3$), δ (ppm): 7.52–7.48 (m, aromatic, 1H), 7.39–7.38 (d, J = 3.6, aromatic, 4H), 7.18–7.15 (d, J = 8.8, aromatic, 2H), 6.96–6.94 (d, J = 8.8, aromatic, 2H), 3.84 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$), δ (ppm): 158.69 (C=O), 157.64 (C=N), 160.25–115.08 (aromatic C), 55.59 (OCH_3). Anal. Calcd for $C_{15}H_{12}N_2O_3$ (268.27): C, 67.16; H, 4.51; N, 10.44. Found C, 67.34; H, 4.55; N, 10.39. HRMS for $C_{15}H_{12}N_2O_3$ $[M+Na]^+$ calculated 291.0740. Found 291.0743.

*4-(4-bromophenyl)-3-phenyl-1,2,4-oxadiazol-5(4H)-one (**3d**).* Yield 66%; mp 161–163 °C; IR (KBr), ν (cm^{-1}): 1771.29 (C=O), 1603.04 (C=N); ^{1}H NMR ($CDCl_3$), δ (ppm): 7.60–7.58 (d, J = 8.8, aromatic, 2H), 7.54–7.53 (d, J = 7.2, aromatic, H), 7.44–7.36 (m, aromatic, 4H), 7.14–7.11 (d, J = 8.8, aromatic, 2H); ^{13}C NMR ($CDCl_3$), δ (ppm): 157.90 (C=O), 157.23 (C=N), 133.07–122.74 (aromatic C). Anal. Calcd for $C_{14}H_9BrN_2O_2$ (317.13): C, 53.02; H, 2.86; N, 8.83. Found C, 53.22; H, 2.59; N, 8.87. HRMS for $C_{14}H_9N_2O_2Br$ $[M+Na]^+$ calculated 338.9740. Found 338.9719.

*4-(4-fluorophenyl)-3-phenyl-1,2,4-oxadiazol-5(4H)-one (**3e**).* Yield 64%; mp 160–161 °C; IR (KBr), ν (cm^{-1}): 1773.12 (C=O), 1598.58 (C=N); ^{1}H NMR ($CDCl_3$), δ (ppm): 7.53–7.49 (tt, J = 7.2, J = 1.6, aromatic, H), 7.41–7.34 (m, aromatic, 4H), 7.27–7.20 (m, aromatic, 2H), 7.16–7.11 (m, aromatic, 2H); ^{13}C NMR ($CDCl_3$), δ (ppm): 158.23 (C=O), 157.42 (C=N), 163.96–116.88 (aromatic C). Anal. Calcd for $C_{14}H_9FN_2O_2$ (256.23): C, 65.62; H, 3.54; N, 10.93. Found C, 65.79; H, 3.65; N, 10.93. HRMS for $C_{14}H_9N_2O_2F$ $[M+Na]^+$ calculated 279.0540. Found 279.0531.

*4-(4-chlorophenyl)-3-phenyl-1,2,4-oxadiazol-5(4H)-one (**3f**).* Yield 69%; mp 159.5–160.9 °C; IR (KBr), ν (cm^{-1}): 1770.51 (C=O), 1594.38 (C=N); ^{1}H NMR ($CDCl_3$), δ (ppm): 7.56–7.52 (tt, J = 7.2, J = 1.2, aromatic, 2H), 7.45–7.36 (m, aromatic, 5H), 7.21–7.17 (tt, J = 8.8, J = 2, aromatic, 2H); ^{13}C NMR ($CDCl_3$), δ (ppm): 158.00 (C=O), 157.30 (C=N), 135.57–122.74 (aromatic C). Anal. Calcd for $C_{14}H_9ClN_2O_2$ (272.67): C, 61.66; H, 3.33; N, 10.27. Found C, 61.44; H, 3.18; N, 10.23. HRMS for $C_{14}H_9N_2O_2Cl$ $[M+Na]^+$ calculated 295.0245. Found 295.0243.

*3-phenyl-4-[4-(trifluoromethyl)phenyl]-1,2,4-oxadiazol-5(4H)-one (**3g**).* Yield 63%; mp 105–106 °C; IR (KBr), ν (cm^{-1}): 1765.75 (C=O), 1601.67 (C=N); ^{1}H NMR ($CDCl_3$), δ (ppm): 7.71–7.70 (d, J = 7.2, aromatic, 1H), 7.60–7.50 (m, aromatic, 3H), 7.43–7.39 (t, J = 8, aromatic, 3H), 7.35–7.33 (d, J = 7.2, aromatic, 2H); ^{13}C NMR ($CDCl_3$), δ (ppm): 157.74 (C=O), 157.20 (C=N), 132.59–122.54 (aromatic C). Anal. Calcd for $C_{15}H_9F_3N_2O_2$ (306.23): C, 58.83; H, 2.96; N, 9.15. Found C, 58.72; H, 2.67; N, 8.77. HRMS for $C_{15}H_9N_2O_2F$ $[M+Na]^+$ calculated 329.0508. Found 329.0487.

*3-phenyl-4-[3-(trifluoromethyl)phenyl]-1,2,4-oxadiazol-5(4H)-one (**3h**).* Yield 68%; mp 105–106.2 °C; IR (KBr), ν (cm^{-1}): 1773.06 (C=O), 1607.29 (C=N); ^{1}H NMR ($CDCl_3$), δ: 7.64–7.62 (d, J = 7.6, aromatic, 1H), 7.53–7.43 (m, aromatic, 3H), 7.35–7.31 (t, J = 8, aromatic, 3H), 7.27–7.25 (d, J = 7.2, aromatic, 2H); ^{13}C NMR ($CDCl_3$), δ (ppm): 157.74 (C=O), 157.21 (C=N), 132.57–121.68, (aromatic C). Anal. Calcd for $C_{15}H_9F_3N_2O_2$ (306.23): C, 58.83; H, 2.96; N, 9.15. Found C, 58.95; H, 2.39; N, 9.19. HRMS for $C_{15}H_9N_2O_2F$ $[M+Na]^+$ calculated 329.0508. Found 329.0494.

*4-(3-fluorophenyl)-3-phenyl-1,2,4-oxadiazol-5(4H)-one (**3i**).* Yield 71%; mp 129–132.5 °C; IR (KBr), ν (cm^{-1}): 1780.91 (C=O), 1607.90 (C=N); ^{1}H NMR ($CDCl_3$), δ (ppm): 7.55–7.50 (td, J = 7.2, J = 1.6, aromatic, 1H), 7.44–7.33 (m, aromatic, 5H), 7.19–7.14 (m, aromatic, 1H), 7.03–7.00 (dd, J = 6.8, J = 1.6 aromatic, 2H); ^{13}C NMR ($CDCl_3$), δ (ppm): 157.86 (C=O), 157.29 (C=N), 164.00–114.39 (aromatic C). Anal. Calcd for $C_{14}H_9FN_2O_2$ (256.23): C, 65.62; H, 3.54; N, 10.93. Found C, 65.50; H, 3.56; N, 10.53. HRMS for $C_{14}H_9N_2O_2F$ $[M+Na]^+$ calculated 279.0540. Found 279.0526.

*4-(3-chlorophenyl)-3-phenyl-1,2,4-oxadiazol-5(4H)-one (**3j**).* Yield 53%; mp 147–148.3 °C; IR (KBr), ν (cm^{-1}): 1769.96 (C=O), 1581.25 (C=N); ^{1}H NMR ($CDCl_3$), δ (ppm): 7.55–7.51 (td, J = 7.2, J = 1.6, aromatic, 1H), 7.44–7.34 (m, aromatik, 6H), 7.31–7.30 (t, J = 3.2, aromatic, 1H), 7.09–7.07 (m, aromatik, 1H), ^{13}C NMR ($CDCl_3$), δ (ppm): 157.86 (C=O), 157.24 (C=N), 135.48–122.65 (aromatic C). Anal. Calcd for $C_{14}H_9ClN_2O_2$ (272.67): C, 61.66; H, 3.33; N, 10.27. Found C, 61.39; H, 3.17; N, 10.26. HRMS for $C_{14}H_9N_2O_2Cl$ $[M+Na]^+$ calculated 295.0245. Found 295.0233.

*3,4-diphenyl-1,2,4-oxadiazole-5(4H)-thione (**4a**) (general procedure)*

Compound (**3a**) (1.1 g, 4.33 mmol) was refluxed with P_2S_5 (0.466 g, 2 mmol) in xylene for 35 h. The reaction mixture was filtered and xylene was evaporated under reduced pressure. The crude product was purified by flash column chromatography, using ethyl acetate-petroleum ether (1:4) as eluent. The residue was crystallized from ethanol. (R_f: 0.55). The product recrystallized from ethanol to give (**4a**) (0.49 g, Yield 40%; mp 172–173.3 °C; IR (KBr), ν (cm^{-1}): 1590.95 (C=N), 1327.10 (C=S); ^{1}H NMR ($CDCl_3$), δ (ppm): 7.52–7.47 (m, aromatic, 4H), 7.38–7.26 (m, aromatic, 6H); ^{13}C NMR ($CDCl_3$), δ (ppm): 187.26(C=S), 158.78 (C=N),

133.45–121.71 (aromatic C). Anal. Calcd for $C_{14}H_{10}N_2OS$ (254.30): C, 66.12; H 3.96; N 11.02; S 12.61 Found C, 66.40; H 3.93; N 10.78; S 12.22. HRMS for $C_{14}H_{10}N_2OS$ $[M+H]^+$ calculated 255.0587. Found 255.0576.

*Spectroscopic and analytical data of compounds (**4**).*

*4-(4-methylphenyl)-3-phenyl-1,2,4-oxadiazole-5(4H)-thione (**4b**).* Yield 30%; mp 164.5–166 °C, Lit. 164–165 °C [41], Lit. 163–165 °C [42]; HRMS for $C_{15}H_{12}N_2OS$ $[M+H]^+$ calculated 269.0743. Found 269.0731.

*(4-methoxyphenyl)-3-phenyl-1,2,4-oxadiazole-5(4H)-thione (**4c**).* Yield 39%; mp 180.8–181.7 °C. IR (KBr), ν (cm^{-1}): 1607.16 (C=N), 1329.44 (C=S). ^1H NMR ($CDCl_3$), δ (ppm): 7.54–7.50 (m, aromatic, 1H), 7.41–7.38 (m, aromatic, 4H), 7.23–7.21 (d, J = 8.8, aromatic, 2H), 7.02–7.00 (d, J = 8.8, aromatic, 2H), 3.87 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$), δ (ppm): 187.64 (C=S), 158.86 (C=N), 160.69–115.24 (aromatic C), 55.61 (OCH_3). Anal. Calcd for $C_{15}H_{12}N_2O_2S$ (284.33): C, 63.36; H, 4.25; N, 9.85; S 11.28 Found C, 63.60; H 4.21; N 9.76; S 11.08. HRMS for $C_{15}H_{12}N_2O_2S$ $[M+H]^+$ calculated 285.0692. Found 285.0688.

*4-(4-bromophenyl)-3-phenyl-1,2,4-oxadiazole-5(4H)-thione (**4d**).* Yield 28%; mp 150.8–151.6 °C; IR (KBr), ν (cm^{-1}): 1600.89 (C=N), 1320.06 (C=S); ^1H NMR ($CDCl_3$), δ (ppm): 7.67–7.63 (d, J = 8.4, aromatic, 2H), 7.56–7.52 (t, J = 7.2, aromatic, 1H), 7.43–7.34 (m, aromatic, 4H), 7.21–7.19 (d, J = 8.8, aromatic, 2H); ^{13}C NMR ($CDCl_3$), δ (ppm): 186.88 (C=S), 158.50 (C=N), 133.34–121.43 (aromatic C). Anal. Calcd for $C_{14}H_9BrN_2OS$ (333.20): C, 50.46; H 2.72; N 8.41; S 9.62 Found C, 50.63; H 2.72; N 8.42; S 10.25. HRMS for $C_{14}H_9N_2OSBr$ $[M+H]^+$ calculated 332.9692. Found 332.9673.

*4-(4-fluorophenyl)-3-phenyl-1,2,4-oxadiazole-5(4H)-thione (**4e**).* Yield 27%; mp 185–187.1 °C; IR (KBr), ν (cm^{-1}): 1597.21 (C=N), 1326.87 (C=S); ^1H NMR ($CDCl_3$), δ (ppm): 7.54–7.50 (d, J = 7.2, aromatic, 1H), 7.41–7.37 (t, J = 7.6, aromatic, 2H), 7.34–7.27 (m, aromatic, 4H), 7.22–7.18 (d, J = 8.8, aromatic, 2H); ^{13}C NMR ($CDCl_3$), δ (ppm): 187.21 (C=S), 158.66 (C=N), 164.40–117.15 (aromatic C). Anal. Calcd for $C_{14}H_9FN_2OS$ (272.30): C, 61.75; H 3.33; N 10.29; S 11.78 Found C, 61.78; H 3.42; N 10.26; S 11.57. HRMS for $C_{14}H_9N_2OSF$ $[M+H]^+$ calculated 273.0492. Found 273.0444.

*4-(4-chlorophenyl)-3-phenyl-1,2,4-oxadiazole-5(4H)-thione (**4f**).* Yield 28%; mp 162.5–163.5 °C; IR (KBr), ν (cm^{-1}): 1601.06 (C=N), 1329.61 (C=S); ^1H NMR ($CDCl_3$), δ (ppm): 7.55–7.23 (m, aromatic, 9H); ^{13}C NMR ($CDCl_3$), δ (ppm): 186.97 (C=S), 158.57 (C=N), 136.53–121.47 (aromatic C). Anal. Calcd for $C_{14}H_9ClN_2OS$ (288.75): C, 58.23; H 3.14; N 9.70; S 11.10 Found C, 58.40; H 2.94; N 9.75; S 11.20. HRMS for $C_{14}H_9N_2OSCl$ $[M+H]^+$ calculated 289.0197. Found 289.0172.

*3-phenyl-4-[4-(trifluoromethyl)phenyl]-1,2,4-oxadiazole-5(4H)-thione (**4g**).* Yield 29%; mp 176.7–178 °C; IR (KBr), ν (cm^{-1}): 1605.75 (C=N), 1336.24 (C=S); ^1H NMR ($CDCl_3$), δ (ppm): 7.79–7.77 (d, J = 8, aromatic, 1H), 7.68–7.64 (t, J = 8, aromatic, 1H), 7.58–7.51 (m, aromatic, 3H), 7.41–7.38 (d, J = 8, aromatic, 2H), 7.32–7.30 (d, J = 7.6, aromatic, 2H); ^{13}C NMR ($CDCl_3$), δ (ppm): 186.73 (C=S), 158.50 (C=N), 133.98–121.29 (aromatic C). Anal. Calcd for $C_{15}H_9F_3N_2OS$ (322.31): C, 55.90; H 2.81; N 8.69; S 9.95 Found C, 55.59; H 2.43; N 8.42; S 9.62. HRMS for $C_{15}H_9N_2OSF_3$ $[M+H]^+$ calculated 323.0460. Found 323.0459.

*3-phenyl-4-[3-(trifluoromethyl)phenyl]-1,2,4-oxadiazole-5(4H)-thione (**4h**).* Yield 28%; mp 175.5–176.8 °C; IR (KBr), ν (cm^{-1}): 1601.39 (C=N), 1329.60 (C=S); ^1H NMR ($CDCl_3$), δ (ppm): 7.80–7.10 (m, aromatic, 9H); ^{13}C NMR ($CDCl_3$), δ (ppm): 186.85 (C=S), 158.55 (C=N), 132.54–115.71 (aromatic C). Anal. Calcd for $C_{15}H_9F_3N_2OS$ (322.31): C, 55.90; H 2.81; N 8.69; S 9.95 Found C, 55.58; H 2.75; N 8.89; S 9.57. HRMS for $C_{15}H_9N_2OSF_3$ $[M+H]^+$ calculated 323.0460. Found 323.0458.

*4-(3-fluorophenyl)-3-phenyl-1,2,4-oxadiazole-5(4H)-thione (**4i**).* Yield 25%; mp 178.3–181.3 °C; IR (KBr), ν (cm^{-1}): 1600.65 (C=N), 1330.49 (C=S); ^1H NMR ($CDCl_3$), δ (ppm): 7.81–7.09 (m, aromatic, 9H); ^{13}C NMR ($CDCl_3$), δ (ppm): 186.84 (C=S), 158.55 (C=N), 132.62–115.68 (aromatic C). Anal. Calcd for $C_{14}H_9FN_2OS$ (272.30): C, 61.75; H 3.33; N 10.29; S 11.78 Found C, 62.17; H 3.36; N 10.05; S 11.39. HRMS for $C_{14}H_9N_2OSF$ $[M+H]^+$ calculated 273.0492. Found 273.0463.

*4-(3-chlorophenyl)-3-phenyl-1,2,4-oxadiazole-5(4H)-thione (**4j**).* Yield 28%; mp 184.6–185 °C; IR (KBr), ν (cm^{-1}): 1583.53 (C=N), 1329.14 (C=S); ^1H NMR ($CDCl_3$), δ (ppm) 7.55–7.49 (m, aromatic, 2H), 7.47–7.33 (m, aromatic, 6H), 7.18–7.16 (m, 1H); ^{13}C NMR ($CDCl_3$), δ (ppm): 186.86 (C=S), 158.49 (C=N), 135.64–121.40. Anal. Calcd for $C_{14}H_9ClN_2OS$ (288.75): C, 58.23; H 3.14; N 9.70; S 11.10 Found C, 58.23; H 3.20; N 9.87; S 11.68. HRMS for $C_{14}H_9N_2OSCl$ $[M+H]^+$ calculated 289.0197. Found 289.0174.

Results and discussion

The chemical shifts in ^{13}C NMR spectra are frequently used for the study of the transmission of electronic effects of substituents in organic molecules. Because ^{13}C NMR chemical shifts are very sensitive to electron density distribution and monitors of the molecular structure. The most successful analyses of substituent effects on the chemical shifts have been used Hammett-type applications, using SSP, DSP and DSP-NLR analysis methods. The DSP analysis method extension of the Hammett approach has proven particularly useful [43]. The DSP-NLR analysis method is a successful equation in the modeling of long-range substituent effects, which is derivatives of Hammett equation [44]. The substituent-induced change in the chemical shift, SCS (substituent-inducted chemical shift) is based on the principles of linear free energy relationships (LFER) for SSP analysis method using substituent parameters such as the Hammett σ values [45,46] and Brown Okamoto σ^+ and σ^- values [46–48] (Eq. (1)) equations in the form:

$$SCS = \rho\sigma(\sigma^+, \sigma^-) + h \quad (1)$$

where SCS are the ^{13}C chemical shifts for a substituted compound relative to the unsubstituted compound, ρ is the proportionality constant reflecting the sensitivity of the ^{13}C NMR chemical shifts to substituent effects, σ (σ^+, σ^-) is the corresponding substituent constant, and h is the intercept [49,50].

Although the SSP analysis uses an additive blend of inductive and resonance parameters of substituents given as σ (σ^+, σ^-) values, there is present a satisfactory description of substituent effects in Eq. (1). The transmission of electronic effects of substituent effects is to divide the total electronic effect of a substituent into field or inductive and resonance contributions, that is, to use a dual substituent parameter (DSP) [51].In the dual-substituent parameter equation:

$$SCS = \rho_I\sigma_I + \rho_R\sigma_R + h \quad (2)$$

$$SCS = \rho_I\sigma_I + \rho_R\sigma_R^o + h \quad (3)$$

In the dual substituent parameter (DSP), the extended Hammett equation (Eqs. (2) and (3)), SCS are correlated by a linear combination of inductive σ_I and four different resonance constants (σ_R^+, σ_R^o, σ_R^-, σ_R^{BA}), depending on the electronic demand [52], where ρ_I and ρ_R parameters evaluate the sensitivity of ^{13}C NMR chemical shift to the change of the substituent nature.In the dual-substituent parameter non-linear resonance equation:

$$SCS = \rho_I\sigma_I + \rho_R\sigma_R^o/(1 - \varepsilon\,\sigma_R^o) + h \quad (4)$$

In the dual-substituent parameter non-linear resonance equation (DSP-NLR) (Eq. (4)), SCS are correlated by σ_I and differing σ_R constant, which allows the resonance constant to vary with electron demand of the site [53]. DSP-NLR equation includes an

electron demand parameter, ε, where ρ_I and ρ_R parameters evaluate the sensitivity of ^{13}C NMR chemical shift to the change of the substituent nature.

The ^{13}C NMR substituent chemical shifts (SCS) (^{13}C NMR chemical shifts of the corresponding carbon atom, caused by a substituent relative to unsubstituted compound) of 4-(substituted phenyl)-3-phenyl-1,2,4-oxadiazol-5(4*H*)-ones (thiones) respectively are given in Table 1. ^{13}C NMR substituent chemical shifts (SCS) of the investigated compounds were recorded in $CDCl_3$ solutions employing TMS as an internal standard. The chemical shift of the unsubstituted compound relative to the residual solvent center signal at 77.050 ppm. The measurements were performed with a low and constant sample concentration. Inspection of the data in Table 1 shows that the effects of the phenyl ring substituents on the chemical shifts of investigated carbons in (**3a–j**) and (**4a–j**) are electronic in origin. While the electron acceptor substituents in substituted phenyl ring increase the electron density (upfield shifts) on ^{13}C NMR substituent chemical shifts of C=N, C=O and C=S carbons of (**3a–j**) and (**4a–j**), electron donor substituents cause a decrease (downfield shifts) on the same carbons. This is contrary to the general idea that electron donor substituents cause shielding, while electron acceptors cause deshielding [54]. The ^{13}C NMR substituent chemical shifts (SCS) data were analyzed by SSP, DSP and DSP-NLR treatment. Values of various selected Hammett substituent constants (σ, σ^+, σ^-, σ_I, σ_R, σ_R^o) using Eqs. (1)–(4) are taken from the literature [55–60].

The SCS data were analyzed by Eq. (1) (σ, σ^+, σ^-) using single regression analysis. The obtained results are given in Table 2 for the (**3a**–) and (**4a–j**). That the correlation with σ gave better correlation than σ^+ and σ^- implies that there is no significant resonance interaction between the substituent and C=N, C=O, C=S groups for (**3a–j**) and (**4a–j**), because it is separated by an intervening atom. According to observed ρ values for four investigated carbons, it is apparent that chemical shifts of C=O and C=S carbons of oxadiazole rings show as increased susceptibility to substituent effects compared to C=N carbons of oxadiazoles rings. This is because these groups are nearer to the substituent of phenyl ring than C=N group. From the sign of the constants ρ in correlation from Table 2, it can be concluded that the effects of substituent on the phenyl ring have negative values ($\rho < 0$), that is, a reverse substituent effect (RSE).

Qualitatively RSE can be understood on the basis of the so-called π-polarization mechanism, first proposed by Reynolds et al. [61] and later characterized in a more detailed fashion by Bromilow et al. [60,63]. Each π-unit (a double bond, triple bond or aromatic ring system) is thought to be polarized separately, the polarization being induced by the substituent dipole in another part of the molecule. This interaction can be transmitted through the molecular framework [64]. This interaction is called localized polarization because each π-unit is polarized separately. The other method is called extended π-polarization [62]. This second polarization is called field-transmitted resonance-polar effects [65,66]. All correlation gave negative ρ values, and it is evident that the reverse substituent effect operates on all oxadiazole rings. Consequently, the polarization of the C=N, C=O and C=S groups of oxadiazoles ring by electron-acceptor substituent leads to an increase in the π-electron density and upfield ^{13}C NMR substituent chemical shift.

Transmission of substituent effects could be presented by mesomeric structures of the investigated oxadiazole rings and contribution of π-polarization (localized polarization and extended π-polarization) (Fig. 2.).

In reverse substituent effect, the aromatic ring substituents such as *p*-Br, *p*-F and *p*-Cl (electron-acceptor substituent) cause an increase of the electron density on the same carbon atoms (upfield shift) (Structure 3, 4 in Fig. 2.), while *p*-CH_3 and *p*-OCH_3 (electron-donor substituent) cause a decrease of electron density at C=N, C=O, C=S (downfield shift) (Structure 5, 6 in Fig. 2.), which is considered to be π-polarization mechanism [67]. A similar effect has been observed in N-(Substituted phenyl)-2-cyanoacetamides [52], N(1)-(4-substituted phenyl)-3-cyano-4,6-dimethyl-2-pyridones [67], 4-substituted phenyl-4,5-dihydrobenzo[*f*][1,4]oxazepin-3(2H)-ones(thiones) [64], 1,4-Disubstituted benzenes [53] 1-(substituted phenyl)-6,7-dimethoxy-3,4-dihydro- and -1,2,3,4-tetrahydroisoquinolines [37], 2-(9H)-fluorene-4-yl[3-(substituted phenyl)oxiran-2-yl]methanone [67] and in other conjugated side chain systems.

DSP analyses have been employed to estimate the importance of resonance and field or inductive effects of synthesized compounds. The statistical results of extended Hammett equation, σ_I and σ_R, σ_I and σ_R^o with C=N, C=O and C=S are given in Table 3. The results of the correlation analysis in Table 3 imply that the SCS values of the C=N, C=O and C=S carbons correlate better with σ_R substituent constants than σ_R^o substituent constants. The ρ_R values depend on the use of σ_R substituent constants. It should be noted that all the DSP correlations are a satisfactory description of the transmission of substituent effects at the investigated carbons.

Much better correlation for investigated carbons is obtained with DSP-NLR equation (Eq. (4)) than DSP equations (Eqs. (2) and (3)). Results from Table 4 indicate that the best correlation of SCS of carbon atoms of C=N groups are obtained using DSP-NLR equations ($r \geqslant 0.98$) in (**3a–j**) and (**4a–j**), but in view of the inability of σ constant to produce individually satisfactory correlation, using SSP equation for C=O and C=S ($r \geqslant 0.98$) in (**3a–j**) and (**4a–j**). The observed ρ_I and ρ_R values from Table 4 ($\rho_I > \rho_R$) show the prevalent polar effect at all carbon atoms of oxadiazole rings. The calculated values λ for C=O, C=N, C=S and C=N atoms are: 0.55, 0.36, 0.59 and 0.37, respectively at DSP-NLR analyses. Calculation of the λ parameter (for the same carbons) gave the following results: 1.07, 0.90, 1.17 and 0.91, respectively at DSP analyses (using σ_R^o substituent constants). Comparison of the values of λ at DSP analyses (Eq. (3)) with those at DSP-NLR analyses (Eq. (4)) indicates a significant decrease for all investigated carbons, which have the high electron demand parameters. This situation could be explained by the fact that the localized π-polarization effect is dominant at the carbons of C=N, C=O and C=S groups. It can be noted that ρ_I and, ρ_R values are negative at all investigated carbon atoms. Demand for electrons ($\varepsilon = -1.34$) is also observed for carbon atoms of the C=O group of the oxadiazole ring. This value of ε is

Table 1
^{13}C NMR chemical shifts (ppm) of 4-(substituted phenyl)-3-phenyl-1,2,4-oxadiazol-5(4*H*)-ones (**3a–j**) and 4-(substituted phenyl)-3-phenyl-1,2,4-oxadiazol-5(4*H*)-thiones (**4a–j**).

Substituent (*x*)	Oxadiazole-5(4H)-ones δ(C=O) ppm[a,b]	Oxadiazole-5(4H)-ones δ(C=N) ppm[a,b]	Oxadiazole-5(4H)-thiones δ(C=S) ppm[a,b]	Oxadiazole-5(4H)-thiones δ(C=N) ppm[a,b]
a (H)	158.311	157.503	187.214	158.726
b (*p*-CH_3)	0.216	0.067	0.246	0.085
c (*p*-OCH_3)	0.379	0.133	0.425	0.135
d (*p*-Br)	−0.407	−0.269	−0.339	−0.186
e (*p*-F)	−0.077	−0.087	−0.004	−0.062
f (*p*-Cl)	−0.313	−0.204	−0.245	−0.159
g (*p*-CF_3)	−0.575	−0.305	−0.485	−0.223
h (*m*-CF_3)	−0.567	−0.291	−0.366	−0.172
i (*m*-F)	−0.447	−0.210	−0.374	−0.176
j (*m*-Cl)	−0.447	−0.262	−0.351	−0.241

[a] ^{13}C NMR chemical shifts (in ppm) expressed relative to the unsubstituted compound, downfield shifts are positive. Solvent is $CDCl_3$.
[b] Chemical shifts of the unsubstituted compounds relative to the residual solvent signal at 77.050 ppm.

Table 2
Result of the SSP analyses of the ^{13}C NMR chemical shifts (ppm) of 4-(substituted phenyl)-3-phenyl-1,2,4-oxadiazol-5(4*H*)-ones (**3a–j**) and 4-(substituted phenyl)-3-phenyl-1,2,4-oxadiazol-5(4*H*)-thiones (**4a–j**).

Compound	C	σ	ρ	h	r	n
(**3a–j**)	C=O	σ	−1.2471 ± 0.0821	−0.0048 ± 0.0265	−0.9852	10
	C=O	σ^+	−0.7631 ± 0.1045	−0.1664 ± 0.0451	−0.9645	7
	C=O	σ^-	−0.0180 ± 0.0561	−1.0615 ± 0.1747	−0.9499	7
	C=N	σ	−0.5708 ± 0.0566	−0.0470 ± 0.0183	−0.9672	10
	C=N	σ^+	−0.3624 ± 0.0644	−0.1283 ± 0.0278	−0.9422	7
	C=N	σ^-	−0.5029 ± 0.1028	−0.0580 ± 0.0330	−0.9257	7
(**4a–j**)	C=S	σ	−1.1333 ± 0.0297	0.0557 ± 0.0297	−0.9778	10
	C=S	σ^+	−0.7264 ± 0.0986	−0.1021 ± 0.0425	−0.9651	7
	C=S	σ^-	−1.0076 ± 0.1697	0.0388 ± 0.0545	−0.9477	7
	C=N	σ	−0.4731 ± 0.0563	−0.0185 ± 0.0182	−0.9538	10
	C=N	σ^+	−0.2981 ± 0.0542	−0.0827 ± 0.0234	−0.9398	7
	C=N	σ^-	−0.4097 ± 0.0907	−0.0253 ± 0.0291	−0.9144	7

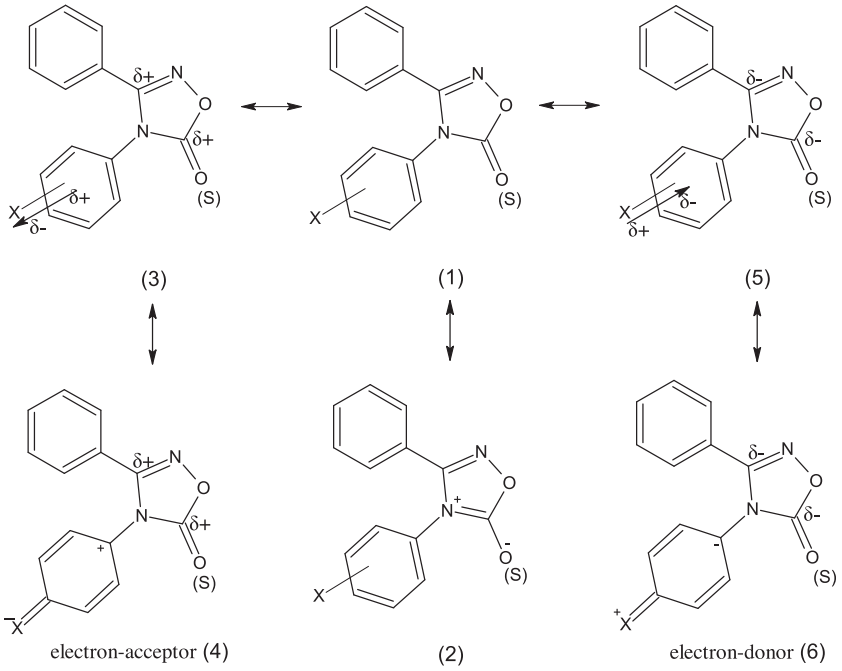


Fig. 2. Mesomeric structures with the contribution of π-polarization in 4-(substituted phenyl)-3-phenyl-1,2,4-oxadiazole-5(4H)-ones (**3a–j**), 4-(substituted phenyl)-3-phenyl-1,2,4-oxadiazole-5(4H)-thiones (**4a–j**).

Table 3
Result of the DSP analyses of ^{13}C NMR chemical shifts (ppm) of 4-(substituted phenyl)-3-phenyl-1,2,4-oxadiazol-5(4*H*)-ones (**3a–j**) and 4-(substituted phenyl)-3-phenyl-1,2,4-oxadiazol-5(4*H*)-thiones (**4a–j**).

Series	Atom	r	ρ_I	ρ_R	h	λ	n
3(σ_I,σ_R)	C=O	0.9786	−1.0932 ± 0.1552	−1.2847 ± 0.1760	0.0009 ± 0.0606	1.18	7
3($\sigma_I$$\sigma_R^o$)	C=O	0.9513	−1.2779 ± 0.2421	−1.3731 ± 0.2966	0.0294 ± 0.0895	1.07	7
3(σ_I,σ_R)	C=N	0.9655	−0.5901 ± 0.0978	−0.5647 ± 0.1095	−0.0148 ± 0.0380	0.96	7
3($\sigma_I$$\sigma_R^o$)	C=N	0.9345	−0.6625 ± 0.1387	−0.5974 ± 0.1700	−0.0023 ± 0.0513	0.90	7
4(σ_I,σ_R)	C=S	0.9735	−0.9699 ± 0.1632	−1.2648 ± 0.1850	0.0212 ± 0.0638	1.30	7
4($\sigma_I$$\sigma_R^o$)	C=S	0.9402	−1.1499 ± 0.2523	−1.3444 ± 0.3092	0.0500 ± 0.0933	1.17	7
4(σ_I,σ_R)	C=N	0.9541	−0.4429 ± 0.0765	−0.2958 ± 0.0867	0.0067 ± 0.0299	0.67	7
4($\sigma_I$$\sigma_R^o$)	C=N	0.9381	−0.5391 ± 0.1097	−0.4923 ± 0.1345	0.0158 ± 0.0406	0.91	7

Table 4
Result of the DSP-NLR analyses of ^{13}C NMR chemical shifts (ppm) 4-(substituted phenyl)-3-phenyl-1,2,4-oxadiazol-5(4*H*)-ones (**3a–j**) and 4-(substituted phenyl)-3-phenyl-1,2,4-oxadiazol-5(4*H*)-thiones (**4a–j**).

Series	Atom	r	ρ_I	ρ_R	ε	h	λ	n
3	C=O	0.9815	−1.2642 ± 0.1492	−0.6990 ± 0.0889	−1.34	0.0339 ± 0.0551	0.55	7
	C=N	0.9760	−0.6372 ± 0.0832	−0.2321 ± 0.0369	−1.61	−0.0003 ± 0.0310	0.36	7
4	C=S	0.9756	−1.1338 ± 0.1613	−0.6676 ± 0.0934	−1.37	0.0543 ± 0.0596	0.59	7
	C=N	0.9830	−0.5188 ± 0.0571	−0.1922 ± 0.0253	−1.61	0.0172 ± 0.0212	0.37	7

similar to the value for carbonyl group of N-1-*p*-substituted phenyl-5-methyl-4-carboxy uracils, which is $\varepsilon = -1.38$ [50]. The electron demand for carbon atoms of C=N groups are $\varepsilon = -1.61$ for (**3a–j**) and (**4a–j**), which indicates a higher deficiency of electron density than the C=O and C=S ($\varepsilon = -1.37$) carbons. Lower electron demand at carbon atoms of C=O and C=S groups than C=N groups at the oxadiazole ring could be attributed to delocalization of the lone pair of nitrogen atoms to carbonyl and thiocarbonyl groups (Structure 2 in Fig. 2.). Higher electron demand at carbons of C=S groups than C=O groups could be explained by poor overlap between sulfur ($3sp^2$ orbital) atom and carbon ($2sp^2$ orbital) atom. This situation should polarize C=S bond further than C=O bond [64].

The correlation between the SCS values of the investigated carbon atoms and substituent parameters using DSP-NLR equation shows that the electron demand parameter of these atoms is considerable. This result could probably be explained by higher polarizability π-electrons due to the vicinity of electronegative heteroatoms (O, N, S). DSP-NLR equation has been most the successful in the treatment of SCS values for series that had large λ values at DSP analyses [68]. The calculated λ values are small from Table 3 at the investigated two series, so excellent correlations are not obtained with DSP-NLR analysis. This could be explained by the fact that the substituent effect is transferred from phenyl ring to oxadiazole ring by π, n conjugation, which is poor interaction compared with π, π conjugation. The net results of SSP, DSP and DSP-NLR analyses, ^{13}C NMR chemical shift of C=N, C=O and C=S carbons of oxadiazole rings have shown satisfactory correlation with single and multiple regression analysis. The satisfactory correlation implies that the substituent effects are electronic in origin.

Conclusion

The assigned spectral ^{13}C NMR chemical shifts (ppm) of carbon atoms of C=N, C=O and C=S groups have been correlated with various substituent constants using single and multiple regression analysis. From the results of statistical analyses, ^{13}C NMR chemical shift of C=N, C=O and C=S carbon atoms of oxadiazole rings have shown satisfactory correlation with single and multiple regression analysis. All attempted correlations involving substituent parameters gave only negative ρ values. This shows that the reverse substituent effect operates in the investigated oxadiazole rings. The net result is that the electron-donor substituents decrease the electron density on C=N, C=O and C=S carbon in (**3a–j**) and (**4a–j**), but electron-acceptor substituents increase the electron density at the same carbon. For all investigated carbons $\rho_I > \rho_R$ indicates a dominant role for the polar effect.

Acknowledgements

We would like to thank the Research Fund of Kocaeli University (2014/071) for financial support of this research.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.saa.2015.04.081.

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