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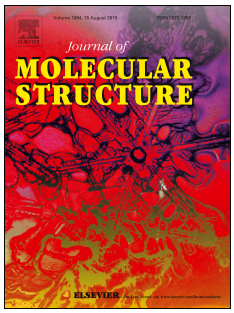

Substituent effect study on the experimental ^{13}C NMR chemical shifts of 3-(substituted phenyl)-3a,4,8,8a-tetrahydro-1,3-dioxepino[5,6-*d*] [1,2] isoxazoles

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Substituent effect study on the experimental ^{13}C NMR chemical shifts of 3-(substituted phenyl)-3a,4,8,8a-tetrahydro-1,3-dioxepino[5,6-*d*] [1,2] isoxazoles

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Abstract

Novel heterocyclic derivatives containing isoxazole ring were synthesized by the 1,3-dipolar cycloaddition reaction of substituted nitrile oxides with *cis*-4,7-dihydro-1,3-dioxepin in the present study. These 3-(substituted phenyl)-3a,4,8,8a-tetrahydro-1,3-dioxepino[5,6-*d*] [1,2] isoxazole derivatives were characterized by their physical constants and IR, ^{1}H NMR, ^{13}C NMR and HRMS data. ^{13}C NMR spectra of studied molecules were measured in Deuterochloroform ($CDCl_3$). The correlation analysis for the substituent-induced experimental ^{13}C NMR chemical shifts (δ, ppm) (SSC) of C=N, C4, C5, C7, C9 and C10 carbons of these isoxazole derivatives have been correlated with various Hammett substituent constants, and Swain-Lupton parameters using single (SSP) and multi-linear (DSP) regression analysis. Negative ρ values were found for correlations of C=N, C4 and C5 carbons. The other carbons were found to have positive ρ values for the electronic effect of substituent on ^{13}C NMR chemical shifts.

Keyword: Isoxazole, Substituent effect, SSP analyses, DSP analyses, ^{13}C NMR chemical shifts.

1. Introduction

The substitution constants (σ), which continue to play an important role in the electron affinity transfer studies of substituents in organic molecules, are the first quantitative

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measurements of the free energy of the electron distribution of substituents in the molecules [1]. Since the substituent constant is related to the electron density of a substitution in the studied region, the correlation with other properties that reflect the electron distribution of the molecule is not surprising. Electron density around the nucleus of interest (^{1}H, ^{11}B, ^{13}C, ^{15}N, ^{17}O, ^{19}F, ^{31}P, ^{33}S) NMR is mostly affected by electron-donating and electron-withdrawing ability of the substituent [2-8].

Many studies in the literature show how substitution constants correlate in a linear fashion with reaction rates, equilibrium constants, corrosion inhibition efficiencies, entropy, enthalpy, free energy, electrochemical and biochemical potential, UV absorption, infrared spectral frequencies, and NMR chemical shifts of various conjugate compounds [9-15]. In our previous work, ^{13}C NMR chemical shift values were related to the transmission of substituent effects both in the heterocyclic rings and on unsaturated side chains attached to substituted organic molecules [16, 17].

Nitrile oxides, $R\text{-}C{\equiv}N^{+}\text{-}O^{-}$, are organic compounds which are well known as synthetic intermediates, especially in the case of preparative heterocyclic compounds because of their high reactivity with unsaturated C=C, C≡C, C=O, C=S, C=P, C≡P and C≡N bonds [18-21]. Generally, isoxazole skeletons are formed by the reaction of nitrile oxides with C-C unsaturated bonds. Nitrile oxides can dimerize easily, to either 1,4,2,5-dioxadiazines or furoxans in the absence of dipolarophiles [22]. Beginning with aldoximes, chlorination and dehydrochlorination processes are carried out in a dry medium for preparation of nitrile oxide [23]. Either N-Chlorosuccinimide or bubbling dry Cl_2 gases into the oxime solution was used as the usual chlorination method. With the addition of base, HCI is spontaneously eliminated

from the molecule and simultaneously nitrile oxide forms. Then nitrile oxide is trapped by using a dipolarophile.

Heterocyclic compounds which contain an isoxazole ring in their structure possess various biological activities. These include anti-microbial [24], anti-inflammatory and analgesic [25], anti-cancer [26], anti-ulcer [27], anti-viral [28], anti-oxidant [29], anti-fungal [30], anti-malarial [31], anti-tubercular [32], anti-hyperglycemic [33], anti-bacterial [34], and cytotoxic [35] effects. Consequently, it is interesting to investigate substituent effects on their spectroscopic properties.

Therefore, the main purpose of this study was to obtain heterocyclic compounds containing an isoxazole ring which may be biologically important. Our other goal was to investigate the substitution effects on the ^{13}C NMR spectroscopic properties of the carbon atoms of interest (especially the CH_2 carbon at ten sigma bond distance from the substituent) in these synthesized compounds. We report the synthesis of eleven new 3-(substituted phenyl)-3a,4,8,8a-tetrahydro-1,3-dioxepino[5,6-*d*] [1,2] isoxazole derivatives and subsequent investigation of the transmission of substituent effects on the ^{13}C NMR chemical shifts using various Hammett substituent constants, and Swain-Lupton parameters and by applying single substituent parameter (SSP) and dual substituent parameter (DSP) analyses.

2. Experimental procedure

All chemicals and analytical grade solvents were purchased from (Aldrich and Fluka) chemical companies. The synthesis of **2(a-k)** series was straightforward as illustrated in Fig. 1. ^{13}C NMR substituent chemical shifts (SCS) of the investigated compounds were recorded in Deuterochloroform ($CDCl_3$) solutions employing Tetramethylsilane (TMS) as an internal

standard. Melting points were determined on Stuart SMP30 apparatus and are uncorrected. The FT-IR spectra of compound **2(a-k)** were recorded on Bruker Alpha II spectrometer, in the region of 4000-400 cm^{-1}. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance III (400 MHz) NMR spectrometer. The HRMS analyses were performed on Water SYNAPT G1 Mass Spectrometer.

3. Synthesis

1,3-Dipolar cycloaddition is the simplest mehod for preparation of dihydroisoxazole derivatives [36-38]. The cycloaddition of nitrile oxides to ***cis***-4,7-dihydro-1,3-dioxepin proceed in $CHCl_3$ to produce a single cycloadduct.

3.1. Synthetic procedures

*3.1.1. 3-phenyl-3a,4,8,8a-tetrahydro-1,3-dioxepino[5,6-d] [1,2] isoxazole **(2a)** (General procedure)*

N-hydroxy-benzenecarboximidoyl chloride (1.29 g, 8.3 mmol) **(1a)** without going forward purification in chloroform (15mL) was added slowly into the mixture of triethylamine (0.5 g, 5 mmol) and *cis*-4,7-Dihydro-1,3-dioxepin (0.6 g, 6 mmol) in chloroform (15 mL) at 0 ^{o}C Then the mixture was warmed at room temperature. The reaction mixture was stirred for two day at room temperature. The reaction mixture was then filtered through filter paper, and the solution was evaporated at reduced pressure. After general work-up, the residue was purified by column chromatography on silica gel using hexane-ethyl acetate (4:1) as eluent. The product was crystallized in (ethyl acetate/petroleum ether, 1:3) to give **(2a)** 400 mg. Yield 30 %; mp 131-131.6 ^{o}C; IR (KBr), ν (cm^{-1}): 3060 (C-H), 2967 (C-H), 2899 (C-H), 1601 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm) : 7.69-7.67 (m, aromatic, 2H), 7.44-7.43 (t, J=2.4, J=3.2, aromatic, 3H), 4.94-4.90 (m, $7CH_2$, 10CH, 2H), 4.69-4.67 (d, J= 6.4, $7CH_2$, H), 4.42-4.37 (dd, J= 3.6, J= 13.6, $9CH_2$, H), 4.17-4.12 (q, J= 7.2, J= 12.8, $5CH_2$, H), 4.05-4.00 (m, 4CH, 9CH, 2H), 3.97-3.93 (dd, J= 3.6, J= 12.6, $5CH_2$, H); ^{13}C NMR ($CDCl_3$), δ (ppm) : 157.42 (C=N), 130.19-126.95 (aromatic C), 98.43 ($7CH_2$), 83.62 (10CH), 68.72 ($9CH_2$), 66.45 ($5CH_2$), 52.01 (4CH); HRMS m/z (ESI/TOF/MS, $[M+H]^+$)calcd for $C_{12}H_{14}NO_3$: 220.0975, Found 220.0979.

*3.1.2. 3-(4-methylphenyl)-3a,4,8,8a-tetrahydro-[1,3]dioxepino[5,6-d] [1,2] isoxazole **(2b)***

Yield 32 %; mp 161-162.6 ^{o}C; IR (KBr), ν (cm^{-1}): 2984 (C-H), 2958 (C-H), 2912 (C-H),

1599 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm) : 7.58-7.56 (d, J=8, aromatic, 2H), 7.25-7.23 (d, J=8, aromatic, 2H), 4.92-4.87 (m, $7CH_2$, 10CH, 2H), 4.70-4.68 (d, J= 6.0, $7CH_2$, H), 4.40-4.35 (dd, J= 4, J= 13.6, $9CH_2$, H), 4.14-4.09 (q, J= 6.8, J= 12.4, $5CH_2$, H), 4.03-3.97 (m, 4CH, 9CH, 2H), 3.96-3.92 (dd, J= 3.6, J= 12.2, $5CH_2$, H); 2.39 (s, CH_3,3H); ^{13}C NMR ($CDCl_3$), δ (ppm) : 157.36 (C=N), 140.43-125.90 (aromatic C), 98.37 ($7CH_2$), 83.49 (10CH), 68.62 ($9CH_2$), 66.43 ($5CH_2$), 52.07 (4CH), 21.43 (CH_3); HRMS m/z (ESI/TOF/MS, $[M+H]^+$)calcd for $C_{13}H_{16}NO_3$: 234.1132, Found 234.1131.

3.1.3. 3-(4-ethylphenyl)-3a,4,8,8a-tetrahydro-1,3-dioxepino[5,6-d] [1,2] isoxazole ***(2c)*** Yield 30 %; mp 114.6-115.2 ^{o}C; IR (KBr), ν (cm^{-1}): 2960 (C-H), 2911 (C-H), 2874 (C-H), 1599 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm) : 7.60-7.58 (d, J=8.0, aromatic, 2H), 7.27-7.25 (d, J=8.0, aromatic, 2H), 4.93-4.88 (m, $7CH_2$, 10CH, 2H), 4.70-4.68 (d, J= 6.0, $7CH_2$, H), 4.40-4.36 (dd, J= 3.6, J= 13.6, $9CH_2$, H), 4.15-4.10 (q, J= 6.8, J= 12.2, $5CH_2$, H), 4.03-3.98 (m, 4CH, $9CH_2$, 2H), 3.97-3.93 (dd, J= 3.6, J= 12, $5CH_2$, H), 2.72-2.66 (q, J= 7.6, J= 16.7, CH_2, 2H), 1.28-1.24 (t, J= 7.6, J= 8.4, CH_3, 3H); ^{13}C NMR ($CDCl_3$), δ (ppm) : 157.38 (C=N), 146.69-126.11 (aromatic C), 98.37 ($7CH_2$), 83.50 (10CH), 68.61 ($9CH_2$), 66.46 ($5CH_2$), 52.07 (4CH), 21.77 (CH_2), 15.31 (CH_3); HRMS m/z (ESI/TOF/MS, $[M+H]^+$)calcd for $C_{14}H_{18}NO_3$: 248.1288, Found 248.1287.

3.1.4. 3-(4-fluorophenyl)-3a,4,8,8a-tetrahydro-1,3-dioxepino[5,6-d] [1,2] isoxazole ***(2d)*** Yield 30 %; mp 150-151.4 ^{o}C; IR (KBr), ν (cm^{-1}): 2956 (C-H), 2917 (C-H), 2870 (C-H), 1600 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm) : 7.68-7.64 (td, J=5.2, J=8.6, aromatic, 2H), 7.14-7.10 (t, J=8.8, J=9.4, aromatic, 2H), 4.94-4.89 (m, $7CH_2$, 10CH, 2H), 4.66-4.65 (d, J= 6, $7CH_2$, H), 4.41-4.37(dd, J= 3.6, J= 13.8, $9CH_2$, H), 4.16-4.12 (q, J= 6.4, J= 12.4, $5CH_2$, H), 4.01-3.96 (m, 4CH, 9CH, 2H), 3.94-3.90 (dd, J= 3.6, J= 12.6, $5CH_2$, H); ^{13}C NMR ($CDCl_3$), δ (ppm) : 157.47 (C=N), 128.96-116.24 (aromatic C), 98.45 ($7CH_2$), 83.66 (10CH), 68.85 ($9CH_2$), 66.439 ($5CH_2$), 52.08 (4CH); HRMS m/z (ESI/TOF/MS, $[M+H]^+$)calcd for $C_{12}H_{13}FNO_3$: 238.0881, Found 238.0883.

3.1.5. 3-(4-chlorophenyl)-3a,4,8,8a-tetrahydro-1,3-dioxepino[5,6-d] [1,2] isoxazole ***(2e)*** Yield 31 %; mp 165.5-165.8 ^{o}C; IR (KBr), ν (cm^{-1}): 2986 (C-H), 2963 (C-H), 2911 (C-H), 1595 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm) : 7.62-7.60 (d, J=8.0, aromatic, 2H), 7.42-7.40 (d, J=8.4, aromatic, 2H), 4.94-4.91 (m, $7CH_2$, 10CH, 2H), 4.66-4.64 (d, J= 6.0, $7CH_2$, H), 4.42-4.38 (dd, J= 2.8, J= 13.6, $9CH_2$, H), 4.16-4.11 (q, J= 6.8, J= 12.9, $5CH_2$, H), 4.01-3.98 (d, J= 12.4, 4CH, H), 4.00-3.95 (d, J= 16.8, $9CH_2$, H), 3.93-3.90 (d, J= 12.8, $5CH_2$, H); ^{13}C NMR ($CDCl_3$), δ (ppm) : 156.48 (C=N), 136.16-127.32 (aromatic C), 98.46 ($7CH_2$),

83.81 (10CH), 68.86 ($9CH_2$), 66.34 ($5CH_2$), 51.89 (4CH); HRMS m/z (ESI/TOF/MS, $[M+H]^+$)calcd for $C_{12}H_{13}ClNO_3$: 254.0586, Found 254.0583.

3.1.6. 3-(4-bromophenyl)-3a,4,8,8a-tetrahydro-1,3-dioxepino[5,6-d] [1,2] isoxazole ***(2f)*** Yield 29 %; mp 188.6-188.9 ^oC; IR (KBr), ν (cm^{-1}): 2986 (C-H), 2961 (C-H), 2910 (C-H), 1589 (C=N); ^1H NMR (400 MHz, $CDCl_3$), δ (ppm) : 7.58-7.56 (d, J=8.8, aromatic, 2H), 7.55-7.53 (d, J=8.6, aromatic, 2H), 4.94-4.90 (m, $7CH_2$, 10CH, 2H), 4.66-4.64 (d, J= 6.4, $7CH_2$, H), 4.42-4.38 (dd, J= 3.8, J= 13.8, $9CH_2$, H), 4.16-4.11 (q, J= 6.8, J= 12.8, $5CH_2$, H), 4.01-3.95 (m, 4CH, 9CH, 2H), 3.93-3.89 (dd, J= 3.4, J= 12.6, $5CH_2$, H); ^{13}C NMR ($CDCl_3$), δ (ppm) : 156.56 (C=N), 132.20-124.47 (aromatic C), 98.47 ($7CH_2$), 83.84 (10CH), 68.86 ($9CH_2$), 66.34 ($5CH_2$), 51.83 (4CH); HRMS m/z (ESI/TOF/MS, $[M+H]^+$)calcd for $C_{12}H_{13}BrNO_3$: 298.0081, Found 298.0089.

3.1.7. 3-[4-(trifluoromethyl)phenyl]-3a,4,8,8a-tetrahydro-1,3-dioxepino[5,6-d] [1,2] isoxazole ***(2g)*** Yield 28 %; mp 143.8-145 ^oC; IR (KBr), ν (cm^{-1}): 2999 (C-H), 2936 (C-H), 2883 (C-H), 1605 (C=N); ^1H NMR (400 MHz, $CDCl_3$), δ (ppm) : 7.81-7.79 (d, J=8.0, aromatic, 2H), 7.71-7.69 (d, J=8.4, aromatic, 2H), 4.99-4.95 (m, $7CH_2$, 10CH, 2H), 4.65-4.63 (d, J= 6.4, $7CH_2$, H), 4.45-4.41(dd, J= 3.3, J= 14, $9CH_2$, H), 4.21-4.16 (q, J= 6.4, J= 12.8, $5CH_2$, H), 4.06-3.98 (m, 4CH, 9CH, 2H), 3.95-3.91 (dd, J= 2.8, J= 12.7, 4CH, H); ^{13}C NMR ($CDCl_3$), δ (ppm) : 156.33 (C=N), 132.37-125.91 (aromatic C), 98.56 ($7CH_2$), 84.06 (10CH), 69.07 ($9CH_2$), 66.32 ($5CH_2$), 51.79 (4CH); HRMS m/z (ESI/TOF/MS, $[M+H]^+$)calcd for $C_{13}H_{13}F_3NO_3$: 288.0849, Found 298.0850.

3.1.8. 3-(3-methylphenyl)-3a,4,8,8a-tetrahydro-1,3-dioxepino[5,6-d] [1,2] isoxazole ***(2h)*** Yield 30 %; mp 144.4-146 ^oC; IR (KBr), ν (cm^{-1}): 3002 (C-H), 2970 (C-H), 2895 (C-H), 1596 (C=N); ^1H NMR (400 MHz, $CDCl_3$), δ (ppm) : 7.53 (s, aromatic, H), 7.45-7.43 (d, J=7.6, aromatic, H), 7.34-7.24 (m, aromatic, 2H), 4.94-4.89 (m, $7CH_2$, 10CH, 2H), 4.71-4.69 (d, J= 6.4, $7CH_2$, H), 4.41-4.37 (dd, J= 4.0, J= 13.6, $9CH_2$, H), 4.16-4.11 (q, J= 6.8, J= 12.4, $5CH_2$, H), 4.04-3.99 (m, 4CH, 9CH, 2H), 3.97-3.93 (dd, J= 3.6, J= 12.4, $5CH_2$, H), 2.40 (s, CH_3, 3H); ^{13}C NMR ($CDCl_3$), δ (ppm) : 157.52 (C=N), 138.74-124.04 (aromatic C), 98.42 ($7CH_2$), 83.55 (10CH), 68.67 ($9CH_2$), 66.45 ($5CH_2$), 52.06 (4CH), 21.39 (CH_3); HRMS m/z (ESI/TOF/MS, $[M+H]^+$)calcd for $C_{13}H_{16}NO_3$: 234.1132, Found 234.1130.

3.1.9. 3-(3-chlorophenyl)-3a,4,8,8a-tetrahydro-1,3-dioxepino[5,6-d] [1,2] isoxazole ***(2i)*** Yield 30 %; mp 139.2-141 ^oC; IR (KBr), ν (cm^{-1}): 2995 (C-H), 2956 (C-H), 2883 (C-H), 1596 (C=N); ^1H NMR (400 MHz, $CDCl_3$), δ (ppm) : 7.67 (s, aromatic, H), 7.55-7.53 (d, J=7.2, aromatic, H), 7.42-7.35 (m, aromatic, 2H), 4.96-4.92 (m, $7CH_2$, 10CH, 2H), 4.65-4.63 (d, J= 6.4, $7CH_2$, H), 4.43-4.38 (dd, J= 3.6, J= 14.0, $9CH_2$, H), 4.19-4.14 (q, J= 6.4, J= 12.8,

$5CH_2$, H), 4.01-3.96 (d, J= 14, 4CH, 9CH, 2H), 3.94-3.90 (dd, J= 3.2, J= 12.6, 5CH, H); ^{13}C NMR ($CDCl_3$), δ (ppm) : 156.35 (C=N), 134.96-125.04 (aromatic C), 98.52 ($7CH_2$), 83.88 (10CH), 68.94 ($9CH_2$), 66.40 ($5CH_2$), 51.83 (4CH) HRMS m/z (ESI/TOF/MS, $[M+H]^+$)calcd for $C_{12}H_{13}ClNO_3$: 254.0586, Found 254.0602.

3.1.10. 3-(3-bromophenyl)-3a,4,8,8a-tetrahydro-1,3-dioxepino[5,6-d] [1,2] isoxazole ***(2j)*** Yield 29 %; mp 175-175.8 ^oC; IR (KBr), ν (cm^{-1}): 2991 (C-H), 2954 (C-H), 2882 (C-H), 1595 (C=N); ^1H NMR (400 MHz, $CDCl_3$), δ (ppm) : 7.83 (s, aromatic, H), 7.60-7.55 (td, J=8.4, J=13, aromatic, H), 7.33-7.29 (t, J=8.0, J=8.6, aromatic,2H), 4.96-4.92 (m, $7CH_2$, 10CH, 2H), 4.66-4.64 (d, J= 6.4, $7CH_2$, H), 4.42-4.38 (dd, J= 3.6, J= 13.8, $9CH_2$, H), 4.18-4.14 (q, J= 6.2, J= 12.6, $5CH_2$, H), 4.00-3.95 (m, 4CH, $9CH_2$, 2H), 3.94-3.90 (dd, J= 3.2, J= 12.8, $5CH_2$, H); ^{13}C NMR ($CDCl_3$), δ (ppm) : 156.23 (C=N), 133.09-123.04 (aromatic C), 98.51 ($7CH_2$), 83.88 (10CH), 68.93 ($9CH_2$), 66.37 ($5CH_2$), 51.81 (4CH) HRMS m/z (ESI/TOF/MS, $[M+H]^+$)calcd for $C_{12}H_{13}BrNO_3$: 298.0081, Found 298.0090.

3.1.11. 3-(3-nitrophenyl)-3a,4,8,8a-tetrahydro-1,3-dioxepino[5,6-d] [1,2] isoxazole ***(2k)*** Yield 25 %; mp 138-138.7 ^oC; IR (KBr), ν (cm^{-1}): 2991 (C-H), 2968 (C-H), 2885 (C-H), 1596 (C=N); ^1H NMR (400 MHz, $CDCl_3$), δ (ppm) : 8.45 (s, aromatic, H), 8.29-8.27 (d, J=8, aromatic, H), 8.07-8.05 (d, J=7.6, aromatic, H), 7.66-7.62 (t, J=8.0, J=8.6, aromatic, H), 5.02-4.97 (m, $7CH_2$, 10CH, 2H), 4.60-4.59 (d, J= 6.4, $7CH_2$, H), 4.47-4.43 (dd, J= 3.2, J= 14.0, $9CH_2$, H), 4.27-4.22 (q, J= 5.6 J= 13.2, $5CH_2$, H), 4.11-4.07 (m, 4CH, H), 4.00-3.92 (td, J= 3.2, J= 16, $9CH_2$, $5CH_2$, 2H); ^{13}C NMR ($CDCl_3$), δ (ppm) : 155.66 (C=N), 148.53-121.62 (aromatic C), 98.68 ($7CH_2$), 84.23 (10CH), 69.45 ($9CH_2$), 66.4 ($5CH_2$), 51.71 (4CH); HRMS m/z (ESI/TOF/MS, $[M+H]^+$)calcd for $C_{12}H_{13}BrN_2O_5$: 265.0826, Found 298.0823.

4. Result and Discussion

In this work a series of eleven 3-(substituted phenyl)-3a,4,8,8a-tetrahydro-1,3-dioxepino[5,6-*d*] [1,2] isoxazoles were synthesized and characterized. The sites of interest in the **2(a-k)** series are at C=N, C4, C5, C7, C9 and C10 carbons (Fig.1.). The ^{13}C NMR chemical shifts of the corresponding carbon atoms of compound **2(a-k)** are shown in Table 1. The measurements were performed with a low and constant sample concentration (0.1 M) to

diminish intermolecular associations. The ^{13}C NMR chemical shift values refer to the central peak of $CDCl_3$ which has a value of 77.050 ppm.

An examination of the data in Table 1 shows that the chemical shifts of the investigated carbon atoms depended on the electronic properties of the substituent on the phenyl ring. The electron-withdrawing and electron-donating substituents caused a change in the chemical shifts. The range of chemical shifts for C=N for the studied compounds was 1.885 ppm (from 157.513 to 155.628 ppm), whereas that for C4 was only 0.371 ppm (from 52.047 to 51.676 ppm), for C5 was only 0.126 ppm (from 66.443 to 66.317 ppm), for C7 was only 0.320 ppm (from 98.644 to 98.324 ppm), for C9 was only 0.858 ppm (from 69.421 to 68.563 ppm) and for C10 was only 0.737 ppm (from 84.196 to 83.459 ppm) and shows that changes in electron density for C=N carbon under the influence of substituents in the aryl ring was much larger than for other carbons. The range of the ^{13}C NMR chemical shift values of the C=N carbon (1.885 ppm) value was larger than the value observed for the C=N carbon of the five membered rings in the previous studies (1.342 ppm for diacetate derivatives, 0.438 ppm for 1,2,4-oxadiazole-5-one derivatives, 0.376 ppm for 1,2,4-oxadiazole-5-thione derivatives) [16, 17].

The values in Table 1 reveal that all electron withdrawing substituents caused an upfield shift of C=N carbon, C4 (except *p*-F) and C5 signals. This behavior was contrary to the general tendency for SCS that suggests that the NMR chemical shifts of substituents with either an electron-withdrawing or electron-donating property would be downfield and upfield respectively. The opposite is true for C7, C9 (except *m*-NO_2) and C10 carbons. That is, the electron withdrawing substituents caused a shift downfield.

Among the CH_2 carbons, C5 appeared in mostly upfield while C7 appeared in mostly downfield. Similarly, the chemical shifts of the C9 (CH_2) carbon atom were seen in the upfield when compared to C7 (CH_2) carbon atom (Table1). This was because the C9 (CH_2) carbon atom of the isoxazole derivative is adjacent to a single oxygen atom while the C7 (CH_2) carbon atom is adjacent to two oxygen atoms. Thus, the C7 carbon has the highest chemical shift value among the sp^3 hybridized methylene carbons (CH_2).

The C=N chemical shifts is very characteristic (ca 157 ppm), typical for sp^2 hybridized carbon, bonded to one oxygen or one nitrogen atom [16, 17]. Although the C4 (ca 52 ppm) and C10 (ca 83 ppm) carbons are both sp^3 hybridized methine carbons (CH), the chemical shift values are quite different from each other. When examining the structure of the molecule, it is evident that this difference is due to the electronegative oxygen atom that is near the C10 carbon. Such results were encountered because the estimation of the magnitude of the sign and the substitution chemical shifts was determined by various factors affecting the chemical shift.

The substituent effects on the chemical shifts are typically analyzed by single substituent parameter (SSP) and dual substituent parameter (DSP) approaches, which are represented by Equation 1, 2 and 3 respectively [39]

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

$$SCS = \rho\,\sigma_I + \rho\,\sigma_R + h \quad (2)$$

$$SCS = \rho\,F + \rho\,R + h \quad (3)$$

Where SCS is the ^{13}C NMR chemical shift of investigated carbons, ρ is the proportionality constant reflecting the sensitivity of the ^{13}C NMR chemical shifts to substituent effects which

is dependent upon the nature of the reaction. σ (σ_I, σ_R), F and R are the corresponding substituent constants and h is the intercept.

Equation (1) (the simple Hammett Equation-SSP) uses σ values which express the blending of polar and π-delocalization effects. DSP analysis may be more meaningful than SSP analysis because the SCS are correlated by a linear combination of the inductive (σ_I) or field (F) and various resonance scales (σ_R, σ_R^0, σ_R^+, σ_R^-, R), depending on the electronic demand of the atom under examination [40, 41]. The following substituent constant data were taken from the literature: σ, σ_I, σ_R, F, R [42].

The ^{13}C NMR chemical shifts data were analyzed using Equation (1). The result of SSP analysis is shown in Table 2. The optimal Hammett substituent constants chosen were σ values for C4, C9 and C10, σ_I values for the carbon of the C=N group and C5 and σ^+ values for C7 in the molecules under analysis. The high correlation coefficient (ρ) of the C=N carbon indicated that the chemical shift values of this carbon are most affected by the substituents (Table 2). Figure 2 shows a negative correlations (r: -0.9468) between the chemical shift values of the C4 carbon atom with Hammett σ values. In contrast there was a positive correlation (r: 0.9944) between the ^{13}C NMR chemical shift values of C10 carbon atom with the Hammett substituent constant σ values in Figure 3.

Multi-linear regression analysis yielded slightly better correlation than the single regression analysis and the results of multi-linear regression analysis are shown in Table 3. The variation in the ρ values obtained with different inductive (σ_I, F) and resonance (σ_R, R) parameter combinations were usually small, for example correlation coefficient 0.9838 using F, R and 0.9856 using σ_I, σ_R at the C=N carbon. However, as a result of the correlation

analysis shown in Table 3, the SCS values of the C=N and C4 carbons appear to correlate better with the σ_I, σ_R substituent constants and the other carbon atoms with the F and R values. The results of dual parameter statistical analysis of ^{13}C NMR chemical shifts of C=N, C5, C7 and C9 carbon atoms of 3-(substituted phenyl)-3a,4,8,8a-tetrahydro-1,3-dioxepino[5,6-*d*] [1,2] isoxazole derivatives with Hammett substituent constants (σ_I, σ_R) and Swain-Lupton F and R values have shown satisfactory correlation ($r \geq 0.9$).

The DSP equation provided a slight improvement in fit when compared to the single parameter analysis, except in case of the C4 carbon. The chemical shift of C4 carbon has shown a fair correlation ($r < 0.9$) with multi-linear regression analysis. This can be attributed to weak inductive, resonance and field effects of the substituents on the chemical shifts of the C4 carbon. It was important to notice that a highest correlation coefficient value (r= 0.997) of C10 carbon atom to substituents effects of investigated serie with Swain-Lupton F and R values using dual substituent parameter approaches, which could be called the excellent correlation.

The DSP equation showed, through negative values for each ρ, that reverse substituent effect operates through both the polar and the resonance component of electronic effect for C=N, C4 and C5. The positive ρ_I and ρ_R values show that a normal substituent effect is transmitted through both polar and resonance pathways for C7, C9, C10 carbons. This implies that the normal and reverse substituent effects operate at different carbon atoms of compound **2(a-k)** as illustrated in Fig. 4. The aromatic ring electron-donating substituent increased the electron density at the C7, C9 and C10 carbon atoms (upfield shifts), indicating that normal substituent effect operates at the C7, C9 and C10 carbon atoms, while electron-withdrawing substituents have a reverse effect. An electron-donating substituent caused a decrease in the electron

density at the C=N, C4 and C5 carbons (down field shifts), which was considered to be π-polarization, indicating a reverse substituent effect (RSE) [43, 44].

A similar effect has been observed in other system, examples being in 1,2,4-oxadiazole and 1,2,4-thiadiazole derivatives [10], in (3-(substituted phenyl)-cis-4,5-dihydroisoxazole-4,5-diyl)bis(methylene)diacetate derivatives [16], in N(1)-(4-substituted phenyl)-3-cyano-4,6-dimethyl-2-pyridones [43], in 3-aryl-2-cyanoacrylamides [45], 4-substituted p-terphenls [46], 4-substituted phenyl-4,5-dihydrobenzo[f][1,4]oxazepin-3(2H)-ones(thiones) [47], 5-arylidene-2,4-thiazolidinediones[48] and *N*-1-*p*-substitutedphenyl-5-methyl-4-carboxy uracils [49].

RSE can be termed a π-polarization mechanism [50]. Each π-unit is thought to be polarized separately, the polarization being induced by the substituent dipole in another part of the molecule, not be transmitted via an interventing π-system [44]. This has also been called ‘‘localized polarization” (direct π -polarization) [51]. This interaction can be transmitted through the molecular framework or solvent continuum [50-53]. On the other hand, the terminal atoms of a conjugated π-system show some additional polarization of the whole π-network, which is known as ‘‘extended polarization”. This second type of polarization has been called a field-transmitted resonance-polar effect [16, 17, 54]. Transmission of substituent electronic effects could be presented by mesomeric structures of the investigated isoxazole derivatives of π-polarization in Fig.5.

In the structure of (1) in Fig.5, if X is an electron-donating substituent, a dipole is formed on C-X bond (structure (2)) and this dipole interaction, through the space of the molecule, result in polarization of each individual π-unit (localized polarization). The reverse is true for

electron-withdrawing substituted compounds (structure (4)). The polarization mechanism of each localized π-units, represented by structure (2) and (4), is very important as well as polarization of the entire conjugated of the investigated compound (extended polarization).

In the case of electron-donating substituents, resonance interaction in the extended conjugate system can be represented by the structure (3) and with an electron-withdrawing substituent (structure (5)) has an effect against the polarization cause. The net result is that the electron-withdrawing substituents increase the electron density at the C=N, C4 and C5 carbons, hence increased shielding, caused an upfield shift. Conversely, the electron-donating substituents reduces the electron density at C=N, C4, and C5 carbons in the molecules under study, thereby causing increased deshielding leading to downfield shifts.

The regression coefficient ($\rho_{I,}$ ρ_R) values of the investigated molecules were the lowest for the C5 atom. This indicated that the electron density around the C5 carbon atom exhibited a low sensitivity to the effects of phenyl substituents. This value (ρ) was also the highest at the C=N carbon atom. This result is consistent with the expected effects because C=N is the closest carbon to the substituent. According to Table 3, this high substituent effect is effectively a result of inductive effects ($\rho_{I(F)} > \rho_R$).

The magnitude and sign of ρ should have enable an understanding of the transfer mechanism of the substitution effect. The ρ_I values in Table 3 show the dependence of the inductive effects as a distance-dependent phenomenon from the substituent. It can be seen from Table 3 that DSP analysis of C=N shows the largest ρ_I value among the investigated carbon atoms of compound **2(a-k)**. This carbon is directly bonded to the substituted-phenyl ring meaning that resonance effects were minimal but the inductive effect was greatly dominant ($\rho_{R=}$ - 0.426±0.258, $\rho_{I=}$ - 2.221±0.203 with Swain-Lupton F and R values). According to this

generally accepted view, the inductive effect appears to be increased due to the shorter distance between the substituent in the phenyl side and the C=N carbon atom isoxazole derivatives.

The correlation coefficient of C7 carbon was r: 0.9882 (using F, R values) (ρ_F: 0.318, ρ_R: 0.323) with a normal substituent effect and was believed to be connected through a space-type of transmission which becomes significant at this carbon. As the C7 carbon is far from the substituent (ten bond away), essentially the electronic effect transmitted by bond should be weaker as it moves away from the substituent. This means that the systematic electronic effects on the entire molecule are transmitted. In addition, although the C7 atom of the dioxepane ring was not directly conjugated with the substituted-phenyl ring, it was approximately equal to the polar and resonance effects as indicated by $\lambda = \rho_R / \rho_F = 0.97$ with F and R parameters.

The DSP analysis also showed that the ratio of resonance to inductive effects ($\lambda = \rho_R / \rho_{I(F)}$) changed considerably from one series to another, indicating that a single parameter equation would be inadequate for data analysis [44]. The field effects varied with changing position of each investigated atom in the molecular structure of the studied compounds [55]. λ values were less than 1, indicating that the inductive effect was more important than resonance effect in the C=N and C5 carbons in the studied molecules. The observed ρ_I and ρ_R values for other carbons indicated a similar contribution from the field and resonance effects, considering the λ values are approximately equal to 1.

In addition, it is well known that the difference between SSP analyses and DSP analyses is meaningless, exactly within the λ range, (about 0.5 to 1.5). Most of our results were in this

range. However, DSP analyses provided slightly better fits in this study, except for the C4 atom. Moreover, even in those cases where the correlation coefficients (r) using the two types of analysis was similar, DSP analyses provided important additional information, not obtainable from SSP analyses, for example, the relative size of the ρ_I and ρ_R values [56].

5. Conclusion

A number of 3-(substituted phenyl)-3a,4,8,8a-tetrahydro-1,3-dioxepino[5,6-*d*] [1,2] isoxazole derivatives were synthesized by a 1,3-dipolar cycloaddition reaction of substituted nitrile oxides with *cis*-4,7-dihydro-1,3-dioxepin in the presence Et_3N and chloroform. A linear relationship was shown to exist between the ^{13}C NMR chemical shift values of these compounds and Hammett sigma constants and F&R parameters using both single and multi-linear regression analysis. However using the multiple regression analysis, slightly larger correlation coefficients were obtained. The results of DSP analysis of ^{13}C NMR chemical shifts of C=N, C5, C7 and C9 carbon atoms with Hammett substituent constants (σ_I, σ_R) and Swain-Lupton F and R values showed satisfactory correlation. Although poor correlation between the substitution parameters of the C4 carbon were observed, excellent correlation was found at the C10 (CH) carbon in this study. In addition, a normal substitution effect operates on carbon atoms C7, C9 and C10, while the reverse substitution effect on C=N, C4 and C5 carbons was seen.

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Supplementary materials

IR, ^1H NMR, ^{13}C NMR and HRMS spectral data of the all newly synthesized compounds and COSY and HMQC spectral data of 2a are added part of Supplementary materials.

References

[1] R. W. Taft, J. Am. Chem. Soc. 79 (1957) 1045-1049.
[2] K. O. Jeon, S-Y. S. Yu, C-K. Lee, Bull. Korean Chem. Soc. 23 (2002) 1241-1246.
[3] P.Balakrishnan, A.L.Baumstark, D.W.Boykin, Tetrahedron Lett. 25 (1984) 169-172.
[4] J. Herna´ndez, F. M. Goycoolea, D. Zepeda-Rivera, J. Jua´rez-Onofre, K. Martı´nez, J. Lizardi, M. Salas-Reyes, B. Gordillo, C. Vela´zquez-Contreras, O. Garcı´a-Barradas, S. Cruz-Sa´nchezd, Z. Domı´nguez, Tetrahedron 62 (2006) 2520-2528.
[5] A. R. Siedle, G. M. Bodner, Inorg. Chem. 12 (1973) 2091-2094.
[6] R. Musió , O. Sciacovelli, J. Org. Chem. 57 (1992) 1195-1198.
[7]B. Gierczyk, M. Zalas, M. Kaźmierczak, J. Grajewski, R. Pankiewicz, B. Wyrzykiewicz, Magn. Reson. Chem. 49 (2011) 648-654.
[8]B. Gierczyk, M. Ceglowski, M. Kaźmierczak, M. Zalas, Magn. Reson. Chem. 50 (2012) 637-641.
[9] H. Ağırbaş, Y. Kara, Phosphorus sulfur. 179 (2004) 1435-1443.
[10] Y. Dürüst, M. Yıldırım, Monatsh. Chem.141 (2010) 961-973.
[11] S. Jovanović, D. Mijin, M. Mišić-Vuković, ARKIVOC 10 (2006) 116-128.
[12] Y. Dürüst, N. Dürüst, M. Akca, J. Chem. Eng. Data 52 (2007) 718-720.
[13] S. G. Sagdinc, Y. S. Kara, Prot. Met. Phys. Chem. S. 50 (2014) 111-116.
[14] G. Thirunarayanan, World Sci.News, 53 (2016) 138-156.
[15]M.H.Schofield, M-A. Sorel, R. J.Manalansan, D.P.Richardson, J.H.Markgraf, Magn. Reson. Chem. 44 (2006) 851-855.
[16] Yesim S. Kara, Spectrochim. Acta A 151 (2015) 723-730.
[17] Yesim S. Kara, Spectrochim. Acta A 149 (2015) 920-927.
[18] T. Ishikawa, J. Urano, S. Ikeda, Y. Kobayashi, S. Saito, Angew. Chem. Int. Ed. Engl. 41 (2002) 1586-1588.
[19]Henry Feuer, Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis: Novel Strategies in Synthesis, Second Edition, 1807 (2007) 67-70.
[20]L. Shen, Y. Ye, Y. Luo, L. Liu, Phosphorus Sulfur. 185 (2010) 680-687.
[21] R. R. Gupta, A. Hasner, Topic in Heterocyclic Chemistry, Synthesis of heterocycles via Cycloaddition II, Springer, 2008, 1-69.
[22] P. Quadrelli, A. G. Invemizzi, M. Falzoni, P. Caramella, Tetrahedron, 53 (1997) 1787-1796.
[23] B. Touaux, F. Texier-Boullet, J. Hamelin, Heteroat. Chem. 9 (1998) 351-354.
[24] S. S. Basha, K. Divya, A. Padmaja, V. Padmavathi, Res. Chem. Intermed. 41 (2015) 10067-10083.
[25] A. A. Abu-Hashem, M. El-Shazly, Med. Chem. 14 (2018) 356-371.
[26] J. P. Yong, C. Z. Lu, X. Wu, Anti-cancer Agents Med. Chem. 15 (2015) 131-136.
[27] S. S. Undare, N. J. Valekar, A. A. Patravale, D. K. Jamale, S. S. Vibhute, L. S. Walekar, G. Kolekar, M. B. Deshmukh, P. V. Anbhule, Bioorg. Med. Chem. Lett. 26 (2016) 814-818.
[28] A. K. Patick, M. A. Brothers, F. Maldonado, S. Binford, O. Maldonado, S. Fuhrman, A. Petersen, G. J. Smith, L. S. Zalman, L. A. Burns-Naas, J. Q. Tran, Antimicrob. Agents Chemother. 49 (2005) 2267-2275.
[29] S. Durgamma, P. R. Reddy, V. Padmavathi, A. Padmaja, J. Heterocyclic Chem. 53 (2016) 738-747.
[30] K. C. Gautam, D. P. Singh, Chem. Sci. Trans. 2 (2013) 992-996.
[31] J. Ferna´ndez, J. Chicharro, J. M. Bueno, M. Lorenzo, Chem. Commun. 66 (2016) 10190-10192.
[32] K. M. Naidu, S. Srinivasarao, N. Agnieszka, A. Kopec´ Ewa, M. M. K. Kumar, K. V. G. C. Sekhar, Bioorg. Med. Chem. Lett. 26 (2016) 2245-2250.

[33] A. Kumar, R. A. Maurya, S. Sharma, P. Ahmad, A. B. Singh, A. K. Tamrakar, A. K. Srivastava, Bioorg. Med. Chem. 17 (2009) 5285-5292.
[34] K. A. Parmar, S. N. Prajapati, S. A. Joshi, K. V. Goswami, Anup N. Patel, Der Chemica Sinica 2 (2011) 100-110.
[35] P. S. Rao, C. Kurumurthy, B. Veeraswamy, Y. Poornachandra, C. G. Kumar, B. Narsaiah, Bioorg. Med. Chem. Lett. 24 (2014) 1349-1351.
[36] K. Jiang, Y. Jin, J. Lin, Tetrahedron 73 (2017) 6662-6668.
[37]I.Gaamoussi, I.Fichtali, A. Tama, E. Hadrami, D. Armentano,G. De Munno, M. Julve, S.Stiriba, J. Mol. Struct., 1048 (2013) 130-137
[38]G. Motyan , A. Baji , I. Zupko , E. Frank, J. Mol. Struct. 1110 (2016) 143-149.
[39] C. K. Leee, I. S. H. Lee, Bull. Korean Chem Soc. 29 (2008) 2205-2208.
[40] G. Thirunarayanan, M. Gopalakrishnan, G. Vanangamudi, Spectrochim. Acta A 67 (2007) 1106-1112.
[41] G. Thirunarayanan, G. Vanangamudi, Spectrochim. Acta Part A. 81 (2011) 390-396.
[42] C. Hansch, A. Leo, R. W. Taft, Chem. Rev. 97 (1991) 165-195.
[43] A. D. Marinkovic, N. V. Valentıc, D. Z. Mıjın, G. G. Uscumlıc, B. Z. Jovanovic, J. Serb. Chem. Soc. 73 (2008) 513-524.
[44] J. Bromilov, R. T. C. Brownlee, D. J. Craik, P. R. Fiske, J. E. Rowe, M. Sadek, J. Chem. Soc. Perkin Trans II. 5 0 (1981) 753-759.
[45] S.P.Bhattacharyya, A.De, A.K.Chakravarty, J.S.A.Brunskill, D.F.Ewing, J.Chem. Soc. Perkin Trans II. 3 0 (1985) 473-478.
[46] N. K. Wilson, R. D. Zehr, J. Org. Chem. 47 (1982) 1184-1188.
[47] H. Agirbas, B. Kemal, J. Mol. Struct. 1053 (2013) 61–65.
[48]M.P. Rancic, N. P. Trišovic , M. K. Milcic , I. A. Ajaj , A. D. Marinkovic, J. Mol. Struct. 1049 (2013) 59–68.
[49] F. H. Assaleh, A. D. Marinkovic, B. Z. Jovanovic, J. Csanadi, J. Mol. Struct. 833 (2007) 53-57.
[50] W. F. Reynolds, Prog. Phys. Org. Chem. 14 (1983) 165-203.
[51] R.T.C. Brownlee,D. J. J. Craik, J. Chem. Soc. Perkin Trans. II (1981) 760-764.
[52] A. D. Marinkovic, B. Z. Jovanovic, N. Todorovic, I. O. Juranic, J. Mol. Struct. 920 (2009) 90-96.
[53] K. Neuvonen, F. Fülöp, H. Neuvonen, A. Kock, E. Kleinpeter, K. Pihlaja, J. Org. Chem. 70 (2005) 10670-10678.
[54] K. Neuvonen, F. Fülöp, H. Neuvonen, K. Pihlaja, J. Org. Chem.59 (1994) 5895-5900.
[55] A. D. Marinković, D. Brkić, J. S. Martinović, D. Z. Mijin, M. Milčić, S. D. Petrović, Chem. Ind. Chem. Eng. Quarterly 19 (2013) 67-78.
[56] M. Christl, H. Leininger, E. Brunn, J. Org. Chem. 47 (1982) 661-666.

Figure Capture

Fig.1. Synthesis of 3-(substituted phenyl)-3a,4,8,8a-tetrahydro-1,3-dioxepino[5,6-*d*] [1,2] isoxazoles **2(a-k)**.

Fig.2. Plot of ^{13}C NMR chemical shifts of C4 carbon atom against Hammett substituent constants σ values.

Fig.3. Plot of ^{13}C NMR chemical shifts of C10 carbon atom against Hammett substituent constants σ values.

Fig.4. The patterns of the substituent effect of compounds **2(a-k)** in term ^{13}C NMR shifts.

Fig.5. Mesomeric structures with the contribution of π-polarization in 3-(substituted phenyl)-3a,4,8,8a-tetrahydro-1,3-dioxepino[5,6-*d*] [1,2] isoxazole derivatives **2(a-k).**

Table 1
^{13}C NMR chemical shifts (ppm) of 3-(substituted phenyl)-3a,4,8,8a-tetrahydro-1,3-dioxepino[5,6-*d*][1,2] isoxazoles **2(a-k)**.

Substituent(x)	**δ C=N** [a]	**δ C4** [a]	**δ C5** [a]	**δ C7** [a]	**δ C9** [a]	**δ C10** [a]
a (H)	157.388	51.978	66.426	98.403	68.684	83.591
b (*p*-CH_3)	157.330	52.036	66.400	98.335	68.588	83.459
c (*p*-C_2H_5)	157.335	52.031	66.412	98.324	68.563	83.460
d (*p*-F)	156.445	52.047	66.358	98.423	68.824	83.630
e (*p*-Cl)	156.458	51.870	66.317	98.444	68.835	83.790
f (*p*-Br)	156.544	51.814	66.318	98.451	68.843	83.817
g (*p*-CF_3)	156.336	51.797	66.326	98.564	69.070	84.063
h (*m*-CH_3)	157.513	52.047	66.443	98.410	68.662	83.536
i (*m*-Cl)	156.321	51.807	66.375	98.491	68.919	83.853
j (*m*-Br)	156.215	51.789	66.349	98.494	68.913	83.868
k (*m*-NO_2)	155.628	51.676	66.411	98.644	69.421	84.196

[a] Chemical shifts of the synthesized 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) for 2**(a-k).**

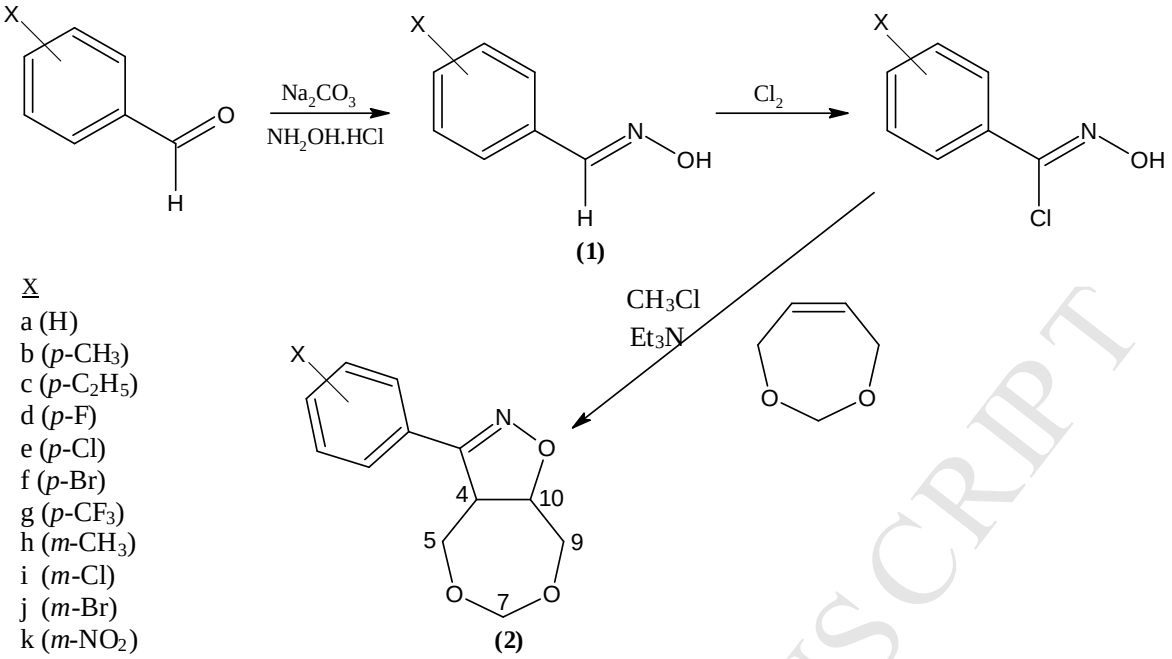
Atom	sigma	r[a]	ρ[b]	h[c]	n[d]
3C=N	σ	-0.9154	-1.938±0.284	157.060±0.096	11
3C=N	σ^+	-0.7232	-1.123±0.480	156.864±0.140	7
3C=N	σ^-	-0.7392	-1.229±0.501	156.957±0.145	7
3C=N	σ_I	-0.9787	-1.800±0.169	157.281±0.059	7
3C=N	σ_R	0.1549	-0.569±1.622	156.900±0.276	7
4C	σ	-0.9468	-0.434±0.049	51.984±0.017	11
4C	σ^+	-0.8651	-0.301±0.078	51.947±0.023	7
4C	σ^-	-0.9037	-0.336±0.071	51.973±0.021	7
4C	σ_I	-0.5967	-0.246±0.148	52.000±0.052	7
4C	σ_R	-0.4816	-0.396±0.322	51.893±0.055	7
5C	σ	-0.4209	-0.066±0.047	66.389±0.016	11
5C	σ^+	-0.6846	-0.102±0.049	66.368±0.014	7
5C	σ^-	-0.7385	-0.118±0.048	66.377±0.014	7
5C	σ_I	-0.9120	-0.161±0.032	66.405±0.011	7
5C	σ_R	0.0954	0.034±0.157	66.369±0.027	7
7C	σ	0.9743	0.316±0.024	98.391±0.008	11
7C	σ^+	0.9864	0.253±0.019	98.414±0.006	7
7C	σ^-	0.9725	0.267±0.029	98.394±0.008	7
7C	σ_I	0.7422	0.226±0.091	98.364±0.032	7
7C	σ_R	0.4226	0.256±0.246	98.451±0.042	7
9C	σ	0.9542	0.808±0.084	68.690±0.028	11
9C	σ^+	0.9505	0.532±0.078	68.758±0.023	7
9C	σ-	0.9439	0.566±0.089	68.716±0.026	7
9C	σ_I	0.8269	0.548±0.167	68.636±0.058	7
9C	σ_R	0.2827	0.374±0.568	68.816±0.096	7
10C	σ	0.9944	0.830±0.030	83.590±0.010	11
10C	σ^+	0.9807	0.680±0.061	83.669±0.018	7
10C	σ-	0.9901	0.735±0.046	83.614±0.013	7
10C	σ_I	0.7463	0.613±0.245	83.535±0.085	7
10C	σ_R	0.4296	0.704±0.662	83.770±0.112	7

[a] Correlation coefficient, [b]Weighting coefficient ratio, [c]Intercept, [d] Number of compound in correlation.

Table 3 Result of the DSP analyses of ^{13}C NMR chemical shifts (ppm) for **2(a-k)**.

Scale	Atom	r[a]	ρ_R[b]	ρ_F/ρ_I[b]	h[c]	λ[d]
(F,R)	C=N	0.9838	-0.426±0.258	-2.221±0.203	157.327±0.068	0.19
(σ_I,σ_R)	C=N	0.9856	-0.442±0.323	-1.861±0.162	157.244±0.061	0.24
(F,R)	C-4	0.8876	-0.416±0.149	-0.377±0.117	51.957±0.039	1.10
(σ_I,σ_R)	C-4	0.8967	-0.572±0.189	-0.324±0.095	51.953±0.036	1.76
(F,R)	C-5	0.9369	-0.045±0.048	-0.204±0.038	66.410±0.013	0.22
(σ_I,σ_R)	C-5	0.9257	-0.058±0.069	-0.169±0.035	66.401±0.013	0.34
(F,R)	C-7	0.9882	0.318±0.036	0.323±0.029	98.385±0.010	0.98
(σ_I,σ_R)	C-7	0.9861	0.401±0.053	0.281±0.026	98.399±0.010	1.43
(F,R)	C-9	0.9841	0.577±0.092	0.751±0.073	68.666±0.024	0.77
(σ_I,σ_R)	C-9	0.9809	0.726±0.134	0.647±0.067	68.697±0.134	1.12
(F,R)	C-10	0.9970	0.861±0.050	0.884±0.039	83.587±0.013	0.97
(σ_I,σ_R)	C-10	0.9947	1.121±0.088	0.766±0.044	83.628±0.017	1.46

[a] Correlation coefficient, [b] Weighting coefficient ratio, [c] Intercept, [d] λ- the ratio of resonance to inductive effects, ρ_R / ρ_I .



X
a (H)
b (*p*-CH_3)
c (*p*-C_2H_5)
d (*p*-F)
e (*p*-Cl)
f (*p*-Br)
g (*p*-CF_3)
h (*m*-CH_3)
i (*m*-Cl)
j (*m*-Br)
k (*m*-NO_2)

Fig.1. Synthesis of 3-(substituted phenyl)-3a,4,8,8a-tetrahydro-1,3-dioxepino[5,6-*d*] [1,2] isoxazoles **2(a-k)**.

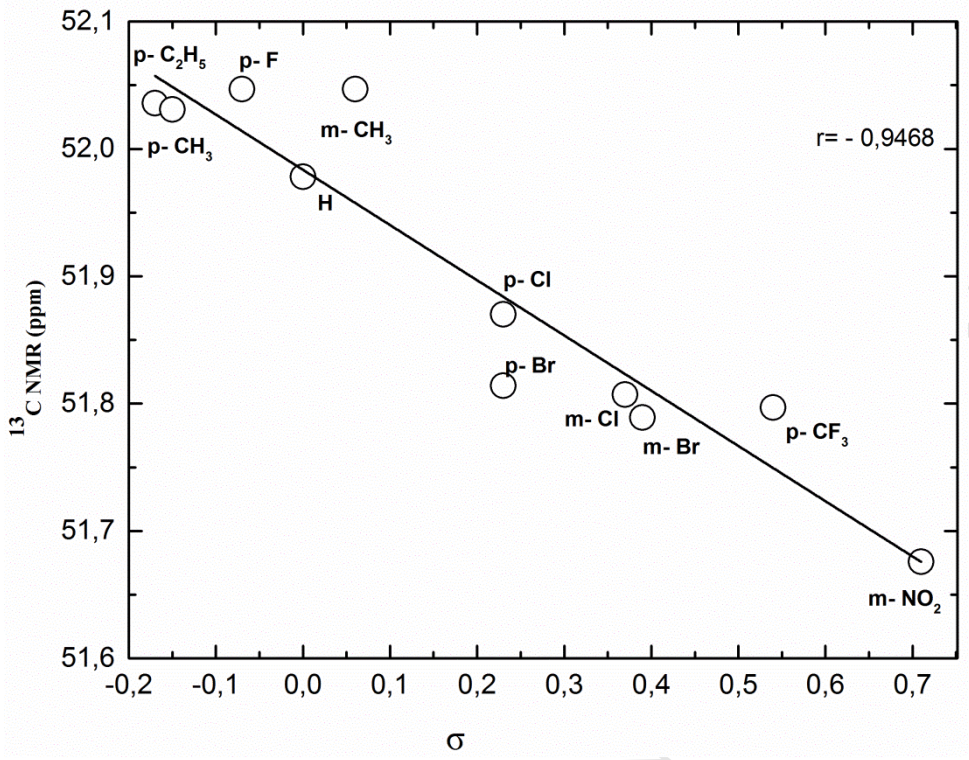


Fig.2. Plot of ^{13}C NMR chemical shifts of C4 carbon atom against Hammett substituent constants σ values.

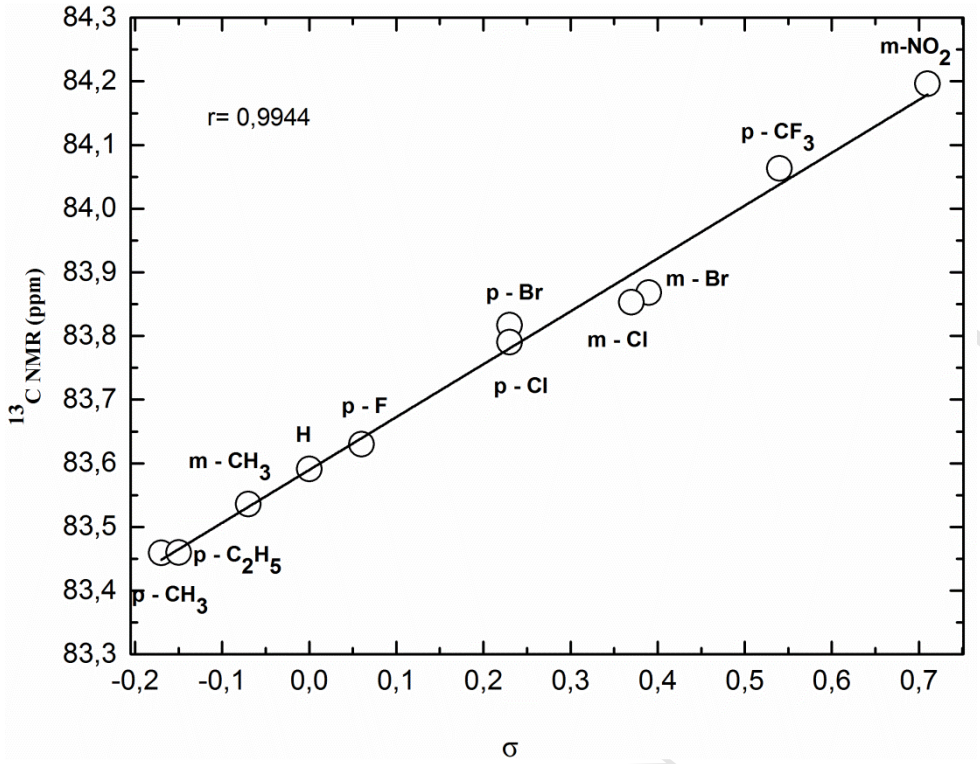


Fig.3. Plot of ^{13}C NMR chemical shifts of C10 carbon atom against Hammett substituent constants σ values.

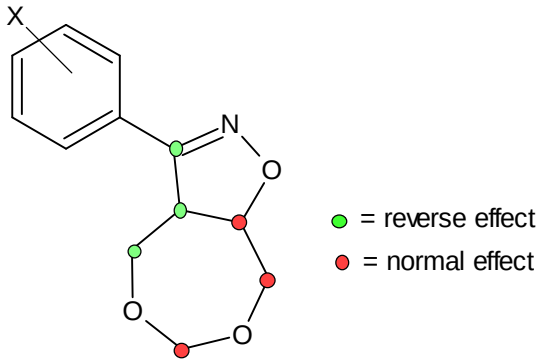


Fig.4. The patterns of the substituent effect of compounds **2(a-k)** in term ^{13}C NMR shifts.

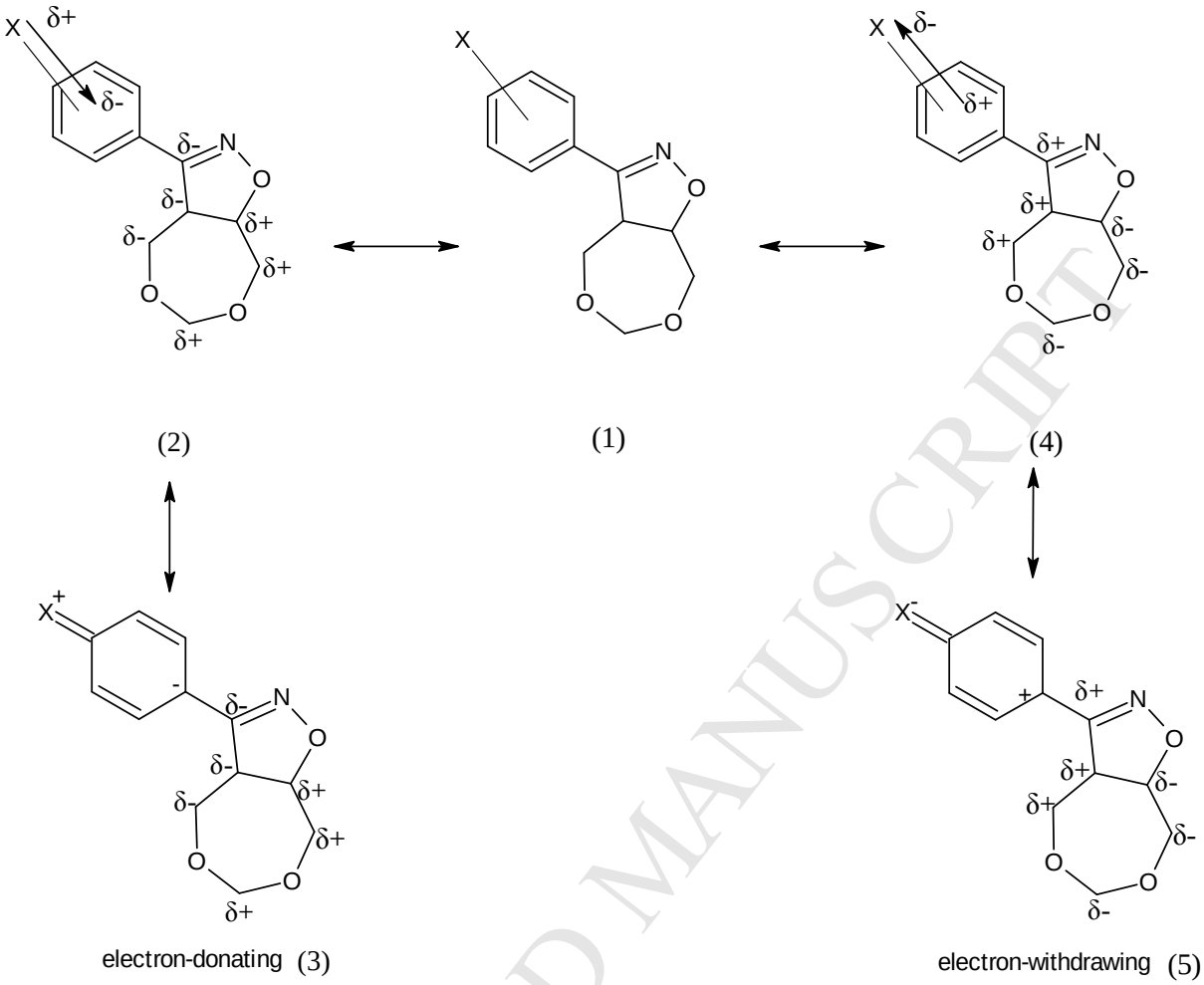


Fig.5. Mesomeric structures with the contribution of π-polarization in 3-(substituted phenyl)-3a,4,8,8a-tetrahydro-1,3-dioxepino[5,6-*d*] [1,2] isoxazole derivatives **2(a-k).**

* Negative ρ values were found for at C=N, C4, C5 carbons for SSP (Single substituent parameter) and DSP (Dual substituent parameter) analysis.

* Positive ρ values were found for at C7, C9 and C10 carbons with same analyses methods.

* It has been observed that substituent effects from phenyl ring are efficiently transmitted to isoxazole ring and 1,3-dioxepane ring.