



Greener synthesis and Hammett spectral Linearity's of some 1-[[3-(furan-2-yl)-5-phenyl-4,5-dihydro-1,2-oxazol-4-yl]methyl]-4-methyl piperazines

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ABSTRACT

We have synthesized eleven numbers of 1-[[3-(furan-2-yl)-5-phenyl-4,5-dihydro-1,2-oxazol-4-yl]methyl]-4-methyl piperazines by hydroxyapatite catalyzed microwave assisted condensation method. The synthesized 1-[[3-(furan-2-yl)-5-phenyl-4,5-dihydro-1,2-oxazol-4-yl]methyl]-4-methyl piperazine compounds were characterized by means of their IR and NMR spectral data. The assigned infrared spectral $\nu_{C=N}$, ν_{C-O-C} stretches(cm^{-1}), NMR chemical shifts of isoxazoline (d) proton, isoxazoline (m) proton, N-CH₃, C=N, C-NH₂ and C-NH₃ (δ , ppm) of these 1-[[3-(furan-2-yl)-5-phenyl-4,5-dihydro-1,2-oxazol-4-yl]methyl]-4-methyl piperazines were assigned and correlated with Hammett substituent constants, F and R parameters using single and multi linear regression analysis. From the results of statistical analyses, the effects of substituents on the above group frequencies were discussed.

Keywords: Piperazines, Hammett substituent constants, IR and NMR spectra, Hammett equation and Regression analyses

1. INTRODUCTION

The Hammett correlation analysis is the study of the relationships between the parameters known as substituent constants and various directly measurable quantities play an important role in physical organic chemistry for the description of the electronic properties of molecule. Spectral data of organic compounds are useful for the prediction of their structure, stereo-chemical and physicochemical properties [1,2]. The quantitative structure activity relationship and quantitative property relationship of the organic substrates are studied from the spectral data associated with their molecular equilibration [3,4]. Spectroscopic data is also very useful for studying the ground state equilibrium of organic molecules through linear relationships [5]. Further the spectral correlation analyses are employed for the study of transition state reaction mechanism [6]. structure activity of biological potentials [7], normal coordinate analysis [8,9], theoretical study of long range interactions in the beta sheet structures of oligo peptides [10], enone-dienol tautomerism [2], density functional theory [11], rotational barriers in selenomides [12] and gas phase reactivity of alkyl sulphides [13].

In recent years, correlation analysis has been applied by chemists to solve spectral problems. Santelli and co-workers [14] have studied the linear-relationships in α , β -unsaturated carbonyl compounds between the half wave reduction potential, the frontier orbital energy and the Hammett σ_p values. Dhimi and Stothers [15] have extensively studied the ^1H NMR spectra of a large number of acetophenones and styrenes with a view to establish the validity of the additivity of substituent effect in aromatic shielding first observed by Lauterber [16]. Savin et al. [17] studied the NMR data of unsaturated ketones of the type $\text{RC}_6\text{H}_4\text{-CH=CH COCH}_3$ and sought Hammett correlations for the ethylenic protons. Solcaniova and Toma [18] have measured ^1H and ^{13}C NMR spectra of substituted styrenes, styryl phenyls and they obtained good Hammett correlations for the olefinic protons and carbons. Nowadays scientists [19] have paid more interest to correlate the group frequencies of spectral data with Hammett substituent constants to explain the substituent effects of organic compounds. Recently Balaji et al., had [20] investigated elaborately the single and multi-substituent effects by spectral data of (*E*)-1-(4-fluoro-3-methylphenyl)-3-phenylprop-2-en-1-ones. Within the above view there is no report available for the study of effect of substituents on the 1-{{[3-(furan-2-yl)-5-phenyl-4,5-dihydro-1,2-oxazol-4-yl]methyl}-4-methyl piperazines through spectral data using regression analysis. Therefore the authors have taken effort to prepare some 1-{{[3-(furan-2-yl)-5-phenyl-4,5-dihydro-1,2-oxazol-4-yl]methyl}-4-methyl piperazines and recorded the infrared and NMR spectra for studying the effect of substituents on the spectral frequencies.

2. EXPERIMENTAL

2.1. General

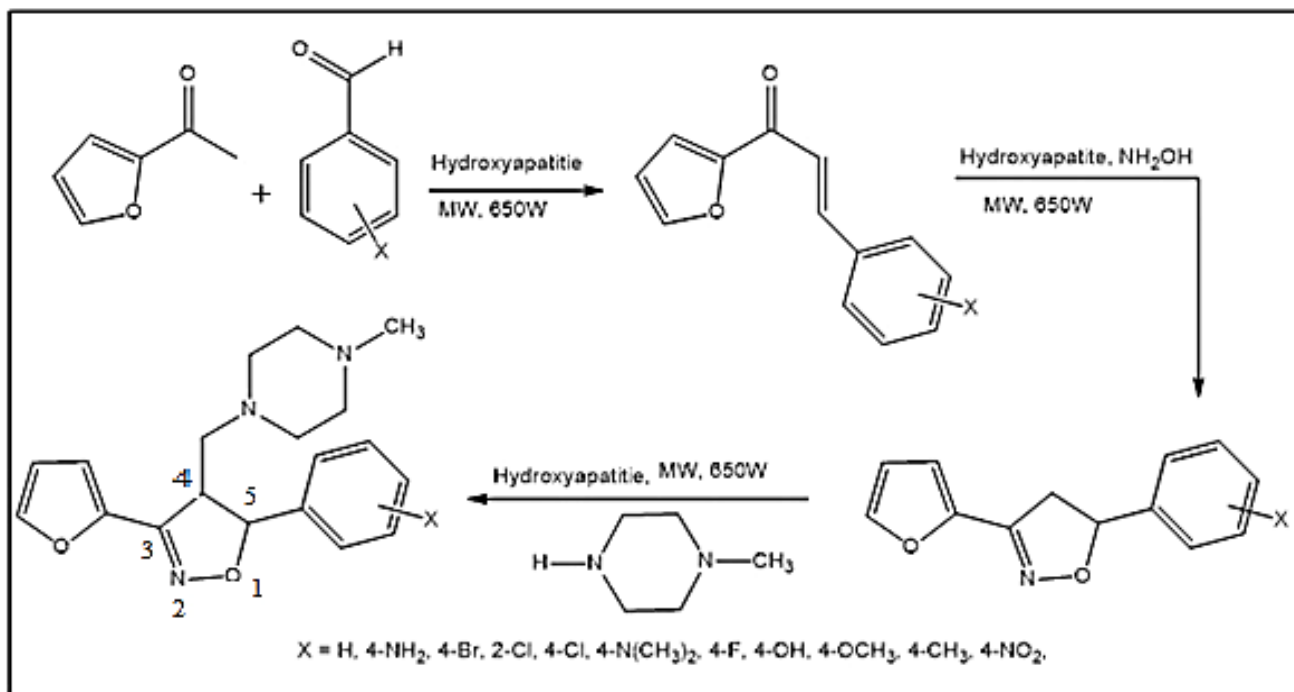
All chemicals were used in this investigation were purchased from Sigma-Aldrich and Merck Chemical companies. Thin layer chromatography (TLC) were used to check the progress and completion of the reaction using silica gel G as an adsorbent (stationary phase) and ethyl acetate and hexane as mobile phase. Open glass capillaries were used to determine the melting point on popular melting point apparatus and are uncorrected. ^1H and ^{13}C nuclear magnetic resonance (^1H & ^{13}C NMR) spectra were recorded on Bruker AV 400 NMR

spectrometer (400 MHz) at 298 K, in appropriate in CDCl_3 solvent. Chemical shifts were reported as δ (ppm) related to TMS as internal standard. The AVATAR-300 Fourier transform spectrophotometer was used for recording infrared spectra (KBr , $4000\text{-}400\text{ cm}^{-1}$) of all compounds in KBr disc.

2. 2. General procedure for the preparation of 1-{{3-(furan-2-yl)-5-phenyl-4,5-dihydro-1,2-oxazol-4-yl}methyl}-4-methyl piperazines

Substituted styryl 2-furyl ketones were prepared by microwave assisted condensation of 2-acetyl furon and substituted benzaldehydes. These chalcones were cyclized with hydroxylamine hydrochloride by microwave assisted method gave oxazolines. These oxazolines were subjected to Mannich's reaction with formaldehyde and 1-methyl piperazine. About 0.01 mol of oxazolines, 0.02 mol of formaldehydes and 0.01 mol of 1-methyl piperazine were taken in a 50 mL Borosil beaker and closed with lid. These reactants were mixed well with glass rod and subjected to microwave irradiation of 60-120seconds at 640 Watts (Samsung Grill GW73BD, 100-750 Watts, 2450 MHz, 230V Ac, 50 Hz) (Scheme 1).

The progress of the reaction was monitored by thin layer chromatogram. The reaction mixture was extracted with 25 mL of dichloromethane and evaporation of the solvent gave piperazine derivatives. The yield, analytical and spectroscopic data of synthesized 1-{{3-(furan-2-yl)-5-phenyl-4,5-dihydro-1,2-oxazol-4-yl}methyl}-4-methyl piperazines were presented in Table 1.



Scheme 1. Synthetic route of 1-{{3-(furan-2-yl)-5-phenyl-4,5-dihydro-1,2-oxazol-4-yl}methyl}-4-methyl piperazine derivatives.

Table 1. The yield, physical constants, analytical and spectroscopic data of synthesized 1-{{3-(furan-2-yl)-5-phenyl-4,5-dihydro-1,2-oxazol-4-yl}methyl}-4-methyl piperazines

No	MF	MW	m.p. (°C)	Yield (%)	IR (v, cm ⁻¹)	
					CN	COC
1	C ₁₉ H ₂₃ N ₃ O ₂	325	123-124(122-123)[21]	87	1686	1362
2	C ₁₉ H ₂₄ N ₄ O ₂	340	130-131(128-129) [21]	86	1680	1359
3	C ₁₉ H ₂₂ BrN ₃ O ₂	404	109-110(108) [21]	85	1678	1342
4	C ₁₉ H ₂₂ ClN ₃ O ₂	360	143-144(142) [21]	84	1666	1336
5	C ₁₉ H ₂₂ ClN ₃ O ₂	360	140-141(138-140) [21]	84	1678	1365
6	C ₂₁ H ₂₈ N ₄ O ₂	368	144-145(142-143) [21]	85	1676	1366
7	C ₁₉ H ₂₂ FN ₃ O ₂	343	95-96(94-95) [21]	85	1700	1364
8	C ₁₉ H ₂₃ N ₃ O ₃	341	73-34(70-72) [21]	83	1676	1367
9	C ₂₀ H ₂₅ N ₃ O ₃	355	102-103(102) [21]	82	1667	1360
10	C ₂₀ H ₂₅ N ₃ O ₂	339	134-135(134)[21]	88	1678	1358
11	C ₁₉ H ₂₂ N ₄ O ₄	370	138-139(138) [21]	80	1680	1360
No	¹ H NMR (δ, ppm)			¹³ C NMR (δ, ppm)		
	H ₅ (d, 1H)	H ₄ (m, 1H)	N-CH ₃ (s)	CN	N-CH ₂	N-CH ₃
1	5.34	4.29	2.51	149.92	51.82	46.76
2	5.38	4.20	2.86	150.02	52.42	46.16
3	5.64	4.16	2.58	151.02	51.64	47.06
4	5.53	4.32	2.56	153.02	51.92	47.12
5	5.29	4.36	2.54	149.72	51.79	47.06
6	5.24	4.32	2.55	149.99	52.00	46.77
7	5.38	4.31	2.49	149.87	51.78	46.72

8	5.30	4.33	2.53	149.88	51.88	46.63
9	5.43	4.27	2.55	149.82	51.85	46.68
10	5.36	4.25	2.53	149.91	51.72	46.66
11	5.33	4.30	2.51	149.90	51.80	46.79

3. RESULTS AND DISCUSSION

3. 1. Infrared spectral correlations

Infrared (IR) spectroscopy is a powerful tool for the quantitative study of natural and synthetic molecules. IR spectroscopy can provide information about the nature, concentration and structure of samples at the molecular levels. It is well demonstrated in the literature [22-28] that infrared (IR) stretching frequencies are sensitive probes of electron-density distributions and are useful for studies on the transmission of electronic effects in organic molecules.

The assigned C=N and C-O-C infrared stretching frequencies of 1-{[3-(furan-2-yl)-5-phenyl-4,5-dihydro-1,2-oxazol-4-yl]methyl}-4-methyl piperazines have made correlated with Hammett constants and Swain-Lupton's parameters. The structure parameter correlation involving group frequencies, the employed Hammett equation is shown in equation (1).

$$\nu = \rho \sigma + \nu_0 \quad \dots(1)$$

where ν is the substituted system and ν_0 is the corresponding quantity of unsubstituted system; σ is a Hammett substituent constant, which in principle is characteristics of the substituent only and independent of the nature of reaction. ρ is a reaction constant is depending upon the nature of the reaction (temperature, solvent, catalyst and pressure).

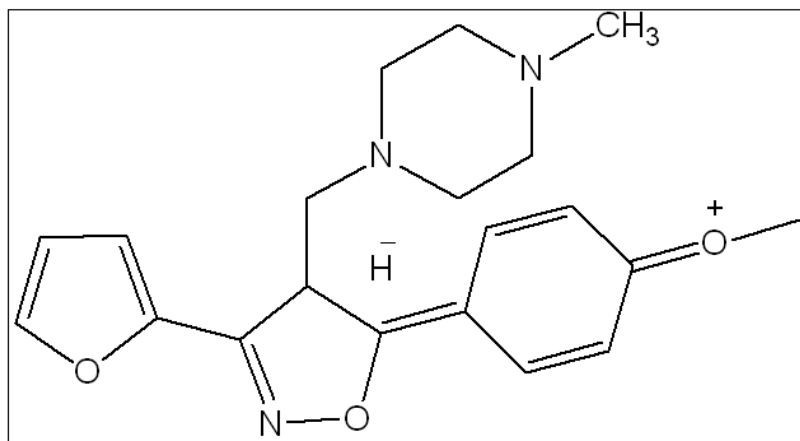


Fig. 1. The resonance-conjugative structure

The results of statistical analyses of 1-[[3-(furan-2-yl)-5-phenyl-4,5-dihydro-1,2-oxazol-4-yl]methyl]-4-methyl piperazines are presented in Table 2. From Table 2, the infrared C=N and C-O-N spectral correlation analyses of 1-[[3-(furan-2-yl)-5-phenyl-4,5-dihydro-1,2-oxazol-4-yl]methyl]-4-methyl piperazines have shown poor correlation ($r < 0.900$) with Hammett substituent constant and Swain-Lupton's parameters. This poor correlation means weak polar, inductive, resonance and field effect of the substituents are unable to predict the reactivity on the C=N and C-O-N stretches and associated with the resonance conjugative structure as shown in Fig. 1. All the correlations have shown negative ρ this means that the reverse substituent effect operates in all the systems.

Table 2. Results of statistical analysis of infrared ν (cm^{-1}) C=N, C-O-N stretches, ^1H NMR chemical shifts of isoxazoline (d) proton, isoxazoline (m) proton and N-CH₃ and ^{13}C NMR chemical shifts of C=N, C-NH₂ and C-NH₃ (δ , ppm) of 1-[[3-(furan-2-yl)-5-phenyl-4,5-dihydro-1,2-oxazol-4-yl]methyl]-4-methyl piperazines with Hammett constants σ , σ^+ , σ_I , σ_R and F and R parameters

Freq.	Constt.	r	I	ρ	s	n	Correlated derivatives
Infrared spectral correlations							
CN	σ	0.823	1678.50	-2.21	9.51	11	H, 4-NH ₂ , 4-Br, 2-Cl, 4-Cl, 4-N(CH ₃) ₂ , 4-F, 4-OH, 4-OCH ₃ , 4-CH ₃ , 4-NO ₂
	σ^+	0.810	1678.29	-1.21	9.51	11	H, 4-NH ₂ , 4-Br, 2-Cl, 4-Cl, 4-N(CH ₃) ₂ , 4-F, 4-OH, 4-OCH ₃ , 4-CH ₃ , 4-NO ₂
	σ_I	0.821	1681.05	-8.13	9.35	11	H, 4-NH ₂ , 4-Br, 2-Cl, 4-Cl, 4-N(CH ₃) ₂ , 4-F, 4-OH, 4-OCH ₃ , 4-CH ₃ , 4-NO ₂
	σ_R	0.804	1678.68	0.17	9.57	11	H, 4-NH ₂ , 4-Br, 2-Cl, 4-Cl, 4-N(CH ₃) ₂ , 4-F, 4-OH, 4-OCH ₃ , 4-CH ₃ , 4-NO ₂
	F	0.811	1680.04	-4.36	9.50	11	H, 4-NH ₂ , 4-Br, 2-Cl, 4-Cl, 4-N(CH ₃) ₂ , 4-F, 4-OH, 4-OCH ₃ , 4-CH ₃ , 4-NO ₂
	R	0.807	1677.90	-1.88	9.54	11	H, 4-NH ₂ , 4-Br, 2-Cl, 4-Cl, 4-N(CH ₃) ₂ , 4-F, 4-OH, 4-OCH ₃ , 4-CH ₃ , 4-NO ₂
C-O-N	σ	0.831	1357.66	-7.15	9.99	11	H, 4-NH ₂ , 4-Br, 2-Cl, 4-Cl, 4-N(CH ₃) ₂ , 4-F, 4-OH, 4-OCH ₃ , 4-CH ₃ , 4-NO ₂
	σ^+	0.833	1356.81	-4.22	9.91	11	H, 4-NH ₂ , 4-Br, 2-Cl, 4-Cl, 4-N(CH ₃) ₂ , 4-F, 4-OH, 4-OCH ₃ , 4-CH ₃ , 4-NO ₂
	σ_I	0.825	1361.24	-10.62	10.17	11	H, 4-NH ₂ , 4-Br, 2-Cl, 4-Cl, 4-N(CH ₃) ₂ , 4-F, 4-OH, 4-OCH ₃ , 4-CH ₃ , 4-NO ₂
	σ_R	0.823	1355.39	-10.19	10.22	11	H, 4-NH ₂ , 4-Br, 2-Cl, 4-Cl, 4-N(CH ₃) ₂ , 4-F, 4-OH, 4-OCH ₃ , 4-CH ₃ , 4-NO ₂
	F	0.807	1359.23	-3.53	10.47	11	H, 4-NH ₂ , 4-Br, 2-Cl, 4-Cl, 4-N(CH ₃) ₂ , 4-F, 4-OH, 4-OCH ₃ , 4-CH ₃ , 4-NO ₂
	R	0.831	1354.55	-9.12	9.97	11	H, 4-NH ₂ , 4-Br, 2-Cl, 4-Cl, 4-N(CH ₃) ₂ , 4-F, 4-OH, 4-OCH ₃ , 4-CH ₃ , 4-NO ₂

Proton NMR spectral correlations							
H ₅	σ	0.813	5.38	0.03	0.11	11	H, 4-NH ₂ , 4-Br, 2-Cl, 4-Cl, 4-N(CH ₃) ₂ , 4-F, 4-OH, 4-OCH ₃ , 4-CH ₃ , 4-NO ₂
	σ^+	0.820	5.39	0.03	0.11	11	H, 4-NH ₂ , 4-Br, 2-Cl, 4-Cl, 4-N(CH ₃) ₂ , 4-F, 4-OH, 4-OCH ₃ , 4-CH ₃ , 4-NO ₂
	σ_I	0.810	5.36	0.05	0.11	11	H, 4-NH ₂ , 4-Br, 2-Cl, 4-Cl, 4-N(CH ₃) ₂ , 4-F, 4-OH, 4-OCH ₃ , 4-CH ₃ , 4-NO ₂
	σ_R	0.812	5.40	0.06	0.11	11	H, 4-NH ₂ , 4-Br, 2-Cl, 4-Cl, 4-N(CH ₃) ₂ , 4-F, 4-OH, 4-OCH ₃ , 4-CH ₃ , 4-NO ₂
	F	0.808	5.39	-0.04	0.12	11	H, 4-NH ₂ , 4-Br, 2-Cl, 4-Cl, 4-N(CH ₃) ₂ , 4-F, 4-OH, 4-OCH ₃ , 4-CH ₃ , 4-NO ₂
	R	0.821	5.41	0.07	0.11	11	H, 4-NH ₂ , 4-Br, 2-Cl, 4-Cl, 4-N(CH ₃) ₂ , 4-F, 4-OH, 4-OCH ₃ , 4-CH ₃ , 4-NO ₂
H ₄	σ	0.913	4.28	-0.01	0.06	11	H, 4-NH ₂ , 4-Br, 2-Cl, 4-Cl, 4-N(CH ₃) ₂ , 4-F, 4-OH, 4-OCH ₃ , 4-CH ₃ , 4-NO ₂
	σ^+	0.920	4.27	-0.01	0.06	11	H, 4-NH ₂ , 4-Br, 2-Cl, 4-Cl, 4-N(CH ₃) ₂ , 4-F, 4-OH, 4-OCH ₃ , 4-CH ₃ , 4-NO ₂
	σ_I	0.912	4.27	0.03	0.06	11	H, 4-NH ₂ , 4-Br, 2-Cl, 4-Cl, 4-N(CH ₃) ₂ , 4-F, 4-OH, 4-OCH ₃ , 4-CH ₃ , 4-NO ₂
	σ_R	0.927	4.26	-0.07	0.06	11	H, 4-NH ₂ , 4-Br, 2-Cl, 4-Cl, 4-N(CH ₃) ₂ , 4-F, 4-OH, 4-OCH ₃ , 4-CH ₃ , 4-NO ₂
	F	0.919	4.26	0.04	0.06	11	H, 4-NH ₂ , 4-Br, 2-Cl, 4-Cl, 4-N(CH ₃) ₂ , 4-F, 4-OH, 4-OCH ₃ , 4-CH ₃ , 4-NO ₂
	R	0.929	4.26	-0.05	0.05	11	H, 4-NH ₂ , 4-Br, 2-Cl, 4-Cl, 4-N(CH ₃) ₂ , 4-F, 4-OH, 4-OCH ₃ , 4-CH ₃ , 4-NO ₂
N-CH ₃	σ	0.800	2.56	0.01	0.01	11	H, 4-NH ₂ , 4-Br, 2-Cl, 4-Cl, 4-N(CH ₃) ₂ , 4-F, 4-OH, 4-OCH ₃ , 4-CH ₃ , 4-NO ₂
	σ^+	0.810	2.56	0.01	0.10	11	H, 4-NH ₂ , 4-Br, 2-Cl, 4-Cl, 4-N(CH ₃) ₂ , 4-F, 4-OH, 4-OCH ₃ , 4-CH ₃ , 4-NO ₂
	σ_I	0.834	2.60	-0.14	0.10	11	H, 4-NH ₂ , 4-Br, 2-Cl, 4-Cl, 4-N(CH ₃) ₂ , 4-F, 4-OH, 4-OCH ₃ , 4-CH ₃ , 4-NO ₂
	σ_R	0.823	2.59	0.10	0.10	11	H, 4-NH ₂ , 4-Br, 2-Cl, 4-Cl, 4-N(CH ₃) ₂ , 4-F, 4-OH, 4-OCH ₃ , 4-CH ₃ , 4-NO ₂
	F	0.832	2.60	-0.13	0.10	11	H, 4-NH ₂ , 4-Br, 2-Cl, 4-Cl, 4-N(CH ₃) ₂ , 4-F, 4-OH, 4-OCH ₃ , 4-CH ₃ , 4-NO ₂
	R	0.825	2.59	0.07	0.10	11	H, 4-NH ₂ , 4-Br, 2-Cl, 4-Cl, 4-N(CH ₃) ₂ , 4-F, 4-OH, 4-OCH ₃ , 4-CH ₃ , 4-NO ₂
Carbon-13 NMR spectral correlations							
C=N	σ	0.928	150.31	0.62	0.98	11	H, 4-NH ₂ , 4-Br, 2-Cl, 4-Cl, 4-N(CH ₃) ₂ , 4-F, 4-OH, 4-OCH ₃ , 4-CH ₃ , 4-NO ₂
	σ^+	0.928	150.38	0.34	0.98	11	H, 4-NH ₂ , 4-Br, 2-Cl, 4-Cl, 4-N(CH ₃) ₂ , 4-F, 4-OH, 4-OCH ₃ , 4-CH ₃ , 4-NO ₂

	σ_I	0.828	149.92	1.18	0.98	11	H, 4-NH ₂ , 4-Br, 2-Cl, 4-Cl, 4-N(CH ₃) ₂ , 4-F, 4-OH, 4-OCH ₃ , 4-CH ₃ , 4-NO ₂
	σ_R	0.813	150.42	0.56	1.01	11	H, 4-NH ₂ , 4-Br, 2-Cl, 4-Cl, 4-N(CH ₃) ₂ , 4-F, 4-OH, 4-OCH ₃ , 4-CH ₃ , 4-NO ₂
	F	0.817	150.06	0.67	1.01	11	H, 4-NH ₂ , 4-Br, 2-Cl, 4-Cl, 4-N(CH ₃) ₂ , 4-F, 4-OH, 4-OCH ₃ , 4-CH ₃ , 4-NO ₂
	R	0.924	150.54	0.68	0.99	11	H, 4-NH ₂ , 4-Br, 2-Cl, 4-Cl, 4-N(CH ₃) ₂ , 4-F, 4-OH, 4-OCH ₃ , 4-CH ₃ , 4-NO ₂
C-NH ₂	σ	0.818	51.86	0.08	0.21	11	H, 4-NH ₂ , 4-Br, 2-Cl, 4-Cl, 4-N(CH ₃) ₂ , 4-F, 4-OH, 4-OCH ₃ , 4-CH ₃ , 4-NO ₂
	σ^+	0.812	51.86	0.03	0.21	11	H, 4-NH ₂ , 4-Br, 2-Cl, 4-Cl, 4-N(CH ₃) ₂ , 4-F, 4-OH, 4-OCH ₃ , 4-CH ₃ , 4-NO ₂
	σ_I	0.844	51.98	0.38	0.19	11	H, 4-NH ₂ , 4-Br, 2-Cl, 4-Cl, 4-N(CH ₃) ₂ , 4-F, 4-OH, 4-OCH ₃ , 4-CH ₃ , 4-NO ₂
	σ_R	0.805	51.88	0.02	0.21	11	H, 4-NH ₂ , 4-Br, 2-Cl, 4-Cl, 4-N(CH ₃) ₂ , 4-F, 4-OH, 4-OCH ₃ , 4-CH ₃ , 4-NO ₂
	F	0.832	51.96	0.26	0.20	11	H, 4-NH ₂ , 4-Br, 2-Cl, 4-Cl, 4-N(CH ₃) ₂ , 4-F, 4-OH, 4-OCH ₃ , 4-CH ₃ , 4-NO ₂
	R	0.803	51.88	0.02	0.21	11	H, 4-NH ₂ , 4-Br, 2-Cl, 4-Cl, 4-N(CH ₃) ₂ , 4-F, 4-OH, 4-OCH ₃ , 4-CH ₃ , 4-NO ₂
C-NH ₃	σ	0.827	46.77	0.16	0.26	11	H, 4-NH ₂ , 4-Br, 2-Cl, 4-Cl, 4-N(CH ₃) ₂ , 4-F, 4-OH, 4-OCH ₃ , 4-CH ₃ , 4-NO ₂
	σ^+	0.829	46.79	0.09	0.26	11	H, 4-NH ₂ , 4-Br, 2-Cl, 4-Cl, 4-N(CH ₃) ₂ , 4-F, 4-OH, 4-OCH ₃ , 4-CH ₃ , 4-NO ₂
	σ_I	0.854	46.58	0.61	0.23	11	H, 4-NH ₂ , 4-Br, 2-Cl, 4-Cl, 4-N(CH ₃) ₂ , 4-F, 4-OH, 4-OCH ₃ , 4-CH ₃ , 4-NO ₂
	σ_R	0.805	46.74	0.06	0.27	11	H, 4-NH ₂ , 4-Br, 2-Cl, 4-Cl, 4-N(CH ₃) ₂ , 4-F, 4-OH, 4-OCH ₃ , 4-CH ₃ , 4-NO ₂
	F	0.824	46.61	0.45	0.25	11	H, 4-NH ₂ , 4-Br, 2-Cl, 4-Cl, 4-N(CH ₃) ₂ , 4-F, 4-OH, 4-OCH ₃ , 4-CH ₃ , 4-NO ₂
	R	0.803	46.77	0.02	0.27	11	H, 4-NH ₂ , 4-Br, 2-Cl, 4-Cl, 4-N(CH ₃) ₂ , 4-F, 4-OH, 4-OCH ₃ , 4-CH ₃ , 4-NO ₂
r = Correlation co-efficient; ρ = Slope; I = Intercept; s = Standard deviation; n = Number of substituents							

All the single-regression analyses of C=N and C-O-C have shown poor correlation so it is decided to go for multi-regression analyses. The multi-regression analysis gave good correlation with Swain-Lupton's [33] σ_I , σ_R substituent constants, F and R parameters. The generated multi-regression analysis equations are given in (2-5).

$$v_{C=N} (\text{cm}^{-1}) = 1681.73(\pm 6.742) - 8.554(\pm 2.631)\sigma_I + 2.072(\pm 0.146)\sigma_R \quad \dots(2)$$

(R = 0.921, n = 11, P > 95%)

$$v_{C=N} (\text{cm}^{-1}) = 1679.39(\pm 6.700) - 4.039(\pm 1.765)F - 1.420(\pm 0.152)R \quad \dots(3)$$

(R = 0.912, n = 11, P > 95%)

$$\nu_{\text{C-O-C}} (\text{cm}^{-1}) = 1358.58(\pm 7.211) - 8.950(\pm 2.481)\sigma_{\text{I}} - 8.213(\pm 2.104)\sigma_{\text{R}} \quad \dots(4)$$

$$(R = 0.931, n = 11, P > 95\%)$$

$$\nu_{\text{C-O-C}} (\text{cm}^{-1}) = 1355.10(\pm 7.034) - 1.509(\pm 0.109)F - 8.947(\pm 2.773)R \quad \dots(5)$$

$$(R = 0.932, n = 11, P > 95\%)$$

3. 2. NMR Spectral Correlation

The NMR spectra of synthesized 1-[[3-(furan-2-yl)-5-phenyl-4,5-dihydro-1,2-oxazol-4-yl]methyl]-4-methyl piperazine compounds under investigation have been recorded in deuteriochloroform solution, employing tetramethylsilane (TMS) as the internal standard. In nuclear magnetic resonance spectra, the ^1H and ^{13}C chemical shifts (δ , ppm) depend on the electronic environment of the nuclei concerned. The assigned chemical shifts (ppm) have been correlated [29-32] with reactivity parameters using Hammett equation [34-36] in the form of equation (6)

$$\delta = \rho\sigma + \delta_0 \quad \dots (6)$$

where δ_0 is the frequency for the parent member of the series.

3. 2. 1. ^1H NMR spectral correlation

The assigned proton NMR chemical shift values (δ , ppm) of synthesized 1-[[3-(furan-2-yl)-5-phenyl-4,5-dihydro-1,2-oxazol-4-yl]methyl]-4-methyl piperazine compounds have been correlated with various Hammett constants, F and R parameters using single and multi-regression analysis. The results of statistical analysis are presented in Table 2.

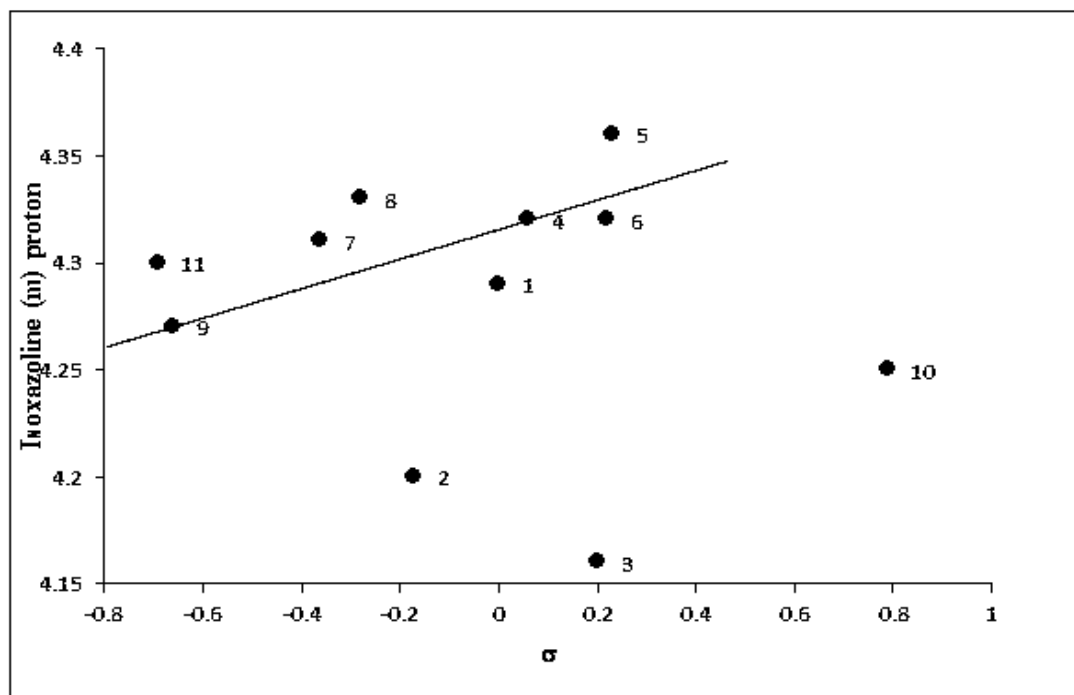


Fig. 2. Plot of ^1H chemical shifts (δ , ppm) of isoxazoline (m) proton of 1-[[3-(furan-2-yl)-5-phenyl-4,5-dihydro-1,2-oxazol-4-yl]methyl]-4 methyl piperazines Vs σ .

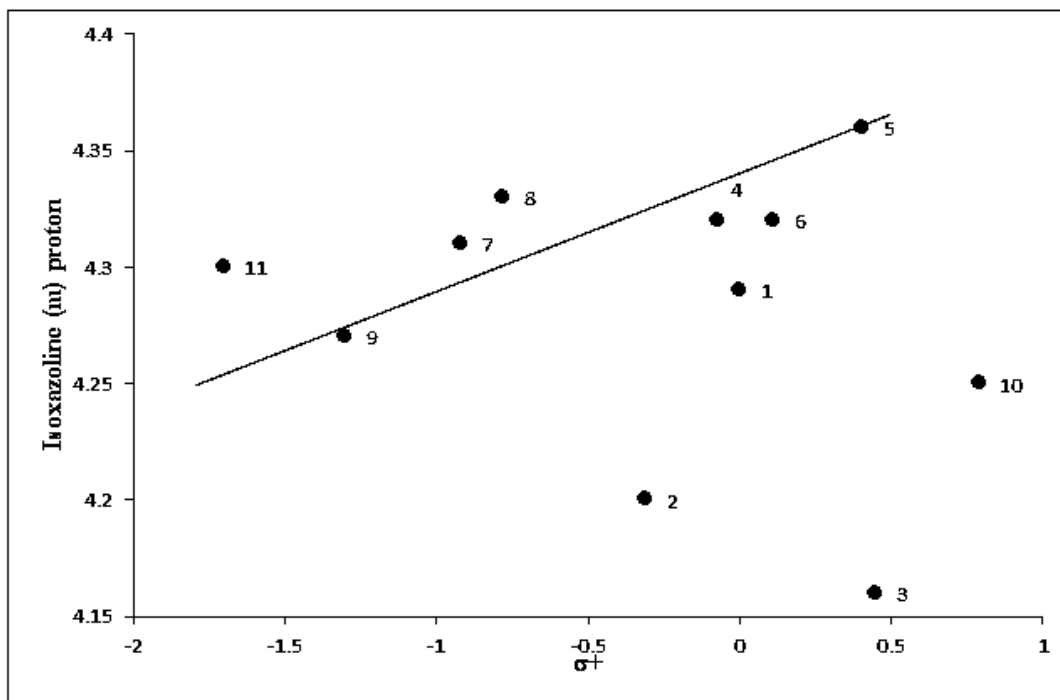


Fig. 3. Plot of ^1H chemical shifts (δ , ppm) of isioxazoline (m) proton of 1-{[3-(furan-2-yl)-5-phenyl-4,5-dihydro-1,2-oxazol-4-yl]methyl}-4 methyl piperazines Vs σ .

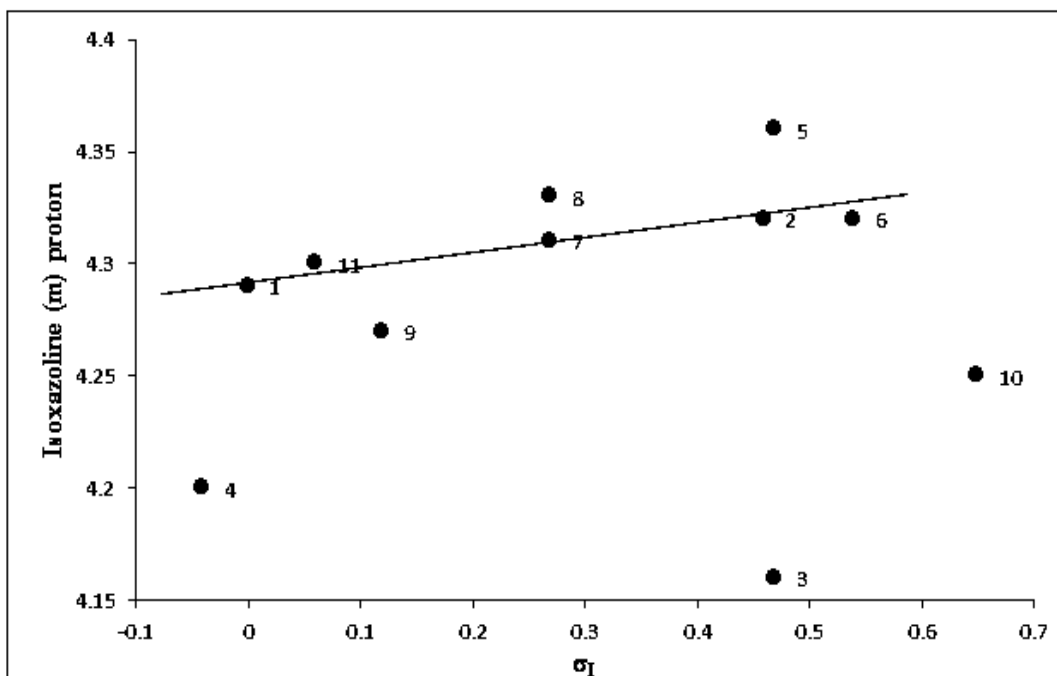


Fig. 4. Plot of ^1H chemical shifts (δ , ppm) of isioxazoline (m) proton of 1-{[3-(furan-2-yl)-5-phenyl-4,5-dihydro-1,2-oxazol-4-yl]methyl}-4 methyl piperazines Vs σ_I .

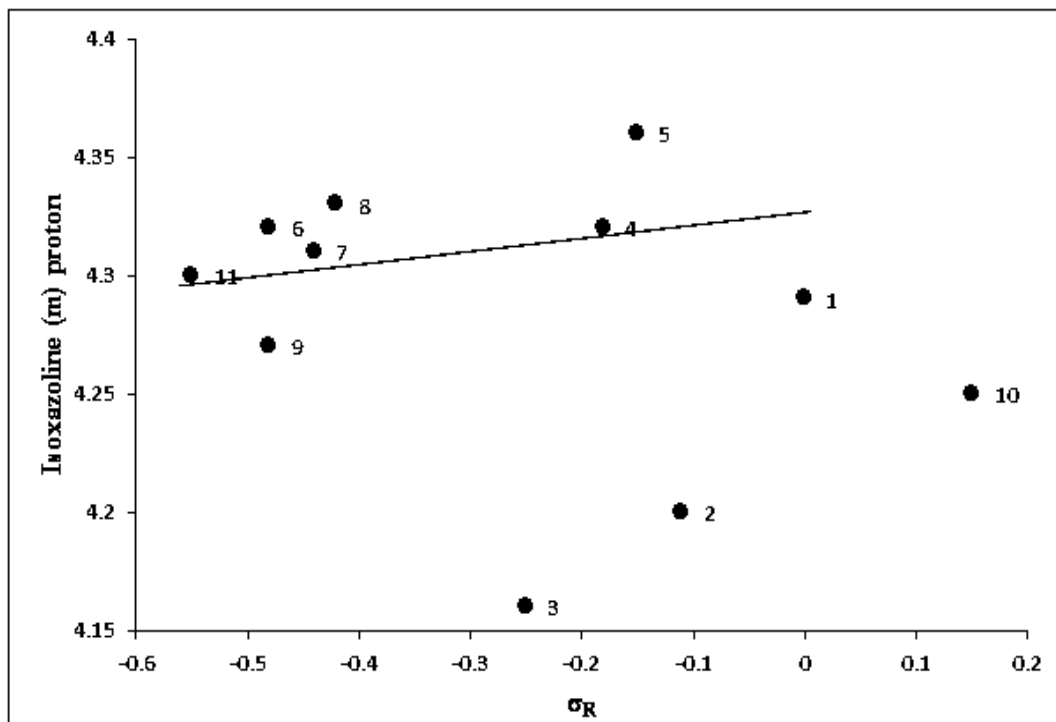


Fig. 5. Plot of ^1H chemical shifts (δ , ppm) of isioxazoline (m) proton of 1-[[3-(furan-2-yl)-5-phenyl-4,5-dihydro-1,2-oxazol-4-yl]methyl]-4 methyl piperazines Vs σ_R .

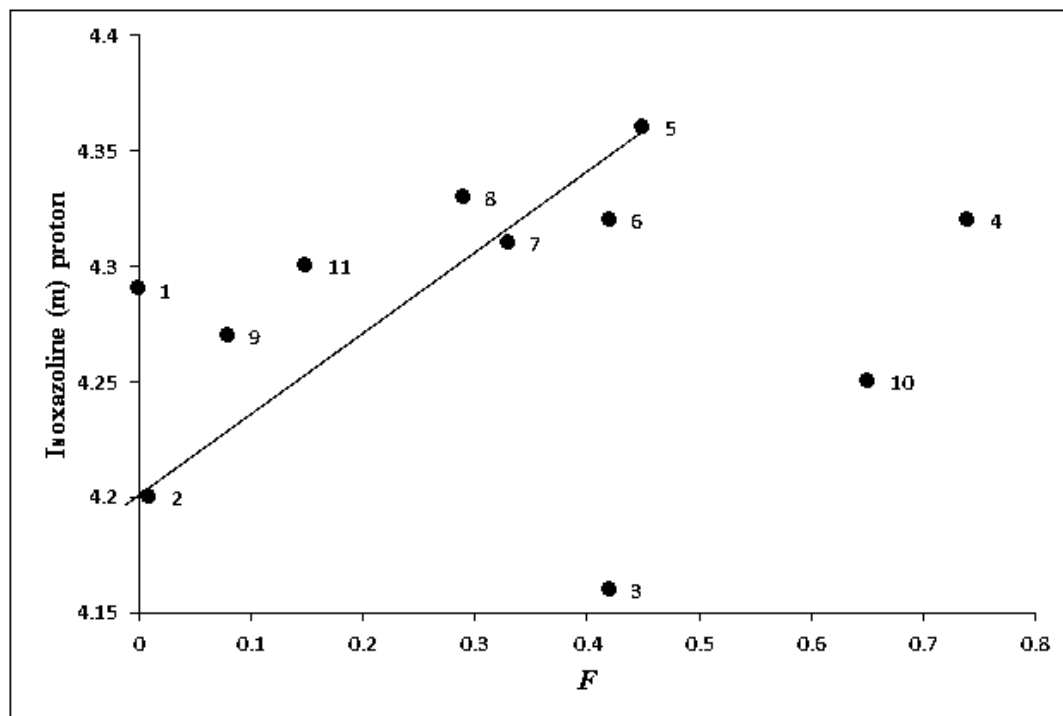


Fig. 6. Plot of ^1H chemical shifts (δ , ppm) of isioxazoline (m) proton of 1-[[3-(furan-2-yl)-5-phenyl-4,5-dihydro-1,2-oxazol-4-yl]methyl]-4 methyl piperazines Vs F .

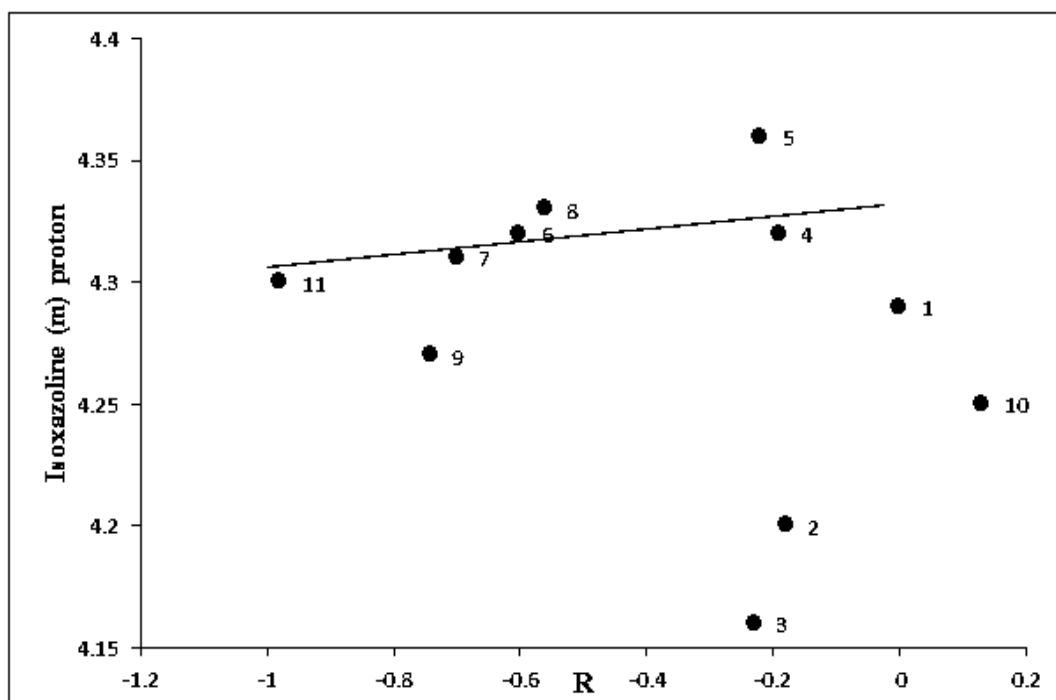


Fig. 7. Plot of ^1H chemical shifts (δ , ppm) of isoxazoline (m) proton of 1-[[3-(furan-2-yl)-5-phenyl-4,5-dihydro-1,2-oxazol-4-yl]methyl]-4 methyl piperazines Vs R .

From the Table 2, the isoxazole (d) proton chemical shift (δ , ppm) values with Hammett substituent constants and F and R parameters fail in correlation. All the correlation except F parameter have shown positive ρ value. This means operation of normal substituent effect operates in all the systems. The failure in correlation is associated with the conjugative structure shown in Fig. 1. The results of statistical analyses of isoxazoline (m) proton chemical shifts (ppm) with Hammett substituents are shown in Table 3. The isoxazoline (m) proton chemical shifts with Hammett σ and σ^+ , σ_R and R constants give satisfactory correlation excluding 2-Cl, 4-CH₃ and 4-NO₂ substituents. The Hammett constant σ_I and F have shown satisfactory correlation except 2-Cl, 4-Cl and 4-NO₂ substituents. In this cause, all the correlations have shown positive ρ values. It indicates the operation of normal substituent effect operates in all the systems. The single parameter correlations are shown in Figs. 2-7.

The results of statistical analyses of phenazine N-CH₃ proton chemical shift values (δ , ppm) with Hammett constants are shown in Table 2. From the Table 2, the phenazine N-CH₃ proton chemical shifts (δ , ppm) with Hammett substituent constants and Swain-Lupton's constants have shown fail in correlation. The failure in correlations is due to the reasons stated earlier and associated with the resonance-conjugative structure as shown in the Fig 1. All the correlation except (σ_I & F) parameters have shown positive ρ values. This is attributed to the weak polar, inductive, field and resonance effects of the substituents. Most of the single regression analyses have shown poor correlation, it is decided to go for multi-regression analyses. The multi-regression produced satisfactory correlations with Hammett substituent constants and F and R parameters [33]. The multi correlation equations are given in (7) - (12).

$$\text{Isoxazoline (d) (H)} = 5.385(\pm 0.086) + 0.041(\pm 0.011)\sigma_I + 0.055(\pm 0.021)\sigma_R \quad \dots(7)$$

$$(R = 0.915, n = 11, P > 95\%)$$

$$\text{Isoxazoline (d) (H)} = 5.432(\pm 0.082) - 0.057(\pm 0.021)F + 0.077(\pm 0.032)R \quad \dots(8)$$

$$(R = 0.924, n = 11, P > 95\%)$$

$$\text{Isoxazoline (m) (H)} = 4.246(\pm 0.042) + 0.047(\pm 0.015)\sigma_I - 0.081(\pm 0.029)\sigma_R \quad \dots(9)$$

$$(R = 0.932, n = 11, P > 95\%)$$

$$\text{Isoxazoline (m) (H)} = 4.241(\pm 0.040) + 0.060(\pm 0.019)F - 0.057(\pm 0.017)R \quad \dots(10)$$

$$(R = 0.924, n = 11, P > 95\%)$$

$$\text{N-CH}_3 = 2.655(\pm 0.068) - 0.177(\pm 0.013)\sigma_I + 0.144(\pm 0.014)\sigma_R \quad \dots(11)$$

$$(R = 0.946, n = 11, P > 95\%)$$

$$\text{N-CH}_3 = 2.649(\pm 0.067) - 0.153(\pm 0.113)F + 0.092(\pm 0.013)R \quad \dots(12)$$

$$(R = 0.944, n = 11, P > 95\%)$$

3. 2. 2. ^{13}C NMR spectral correlation

The assigned ^{13}C chemical shifts (δ , ppm) of C=N carbons are presented in Table 1. The chemical shifts (δ , ppm) are correlated [29-32] with Hammett substituent constants and F and R parameters using single and multi-linear regression analysis. The results of statistical analysis are presented in Table 2. From the Table 2, the ^{13}C chemical shifts (δ , ppm) of C=N carbons of produced satisfactory correlation with Hammett constant σ and σ^+ excluding 4-Br and 4- NO_2 substituents.

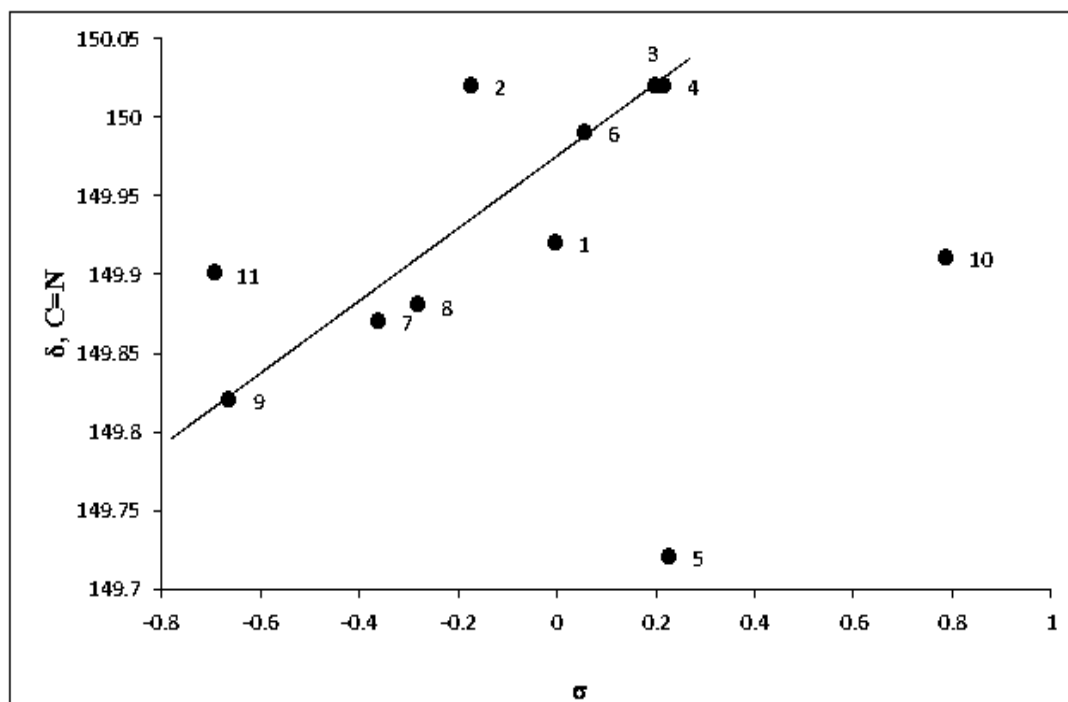


Fig. 8. Plot of ^{13}C chemical shifts (δ , ppm) of C=N of 1-[[3-(furan-2-yl)-5-phenyl-4,5-dihydro-1,2-oxazol-4-yl]methyl]-4 methyl piperazines Vs σ .

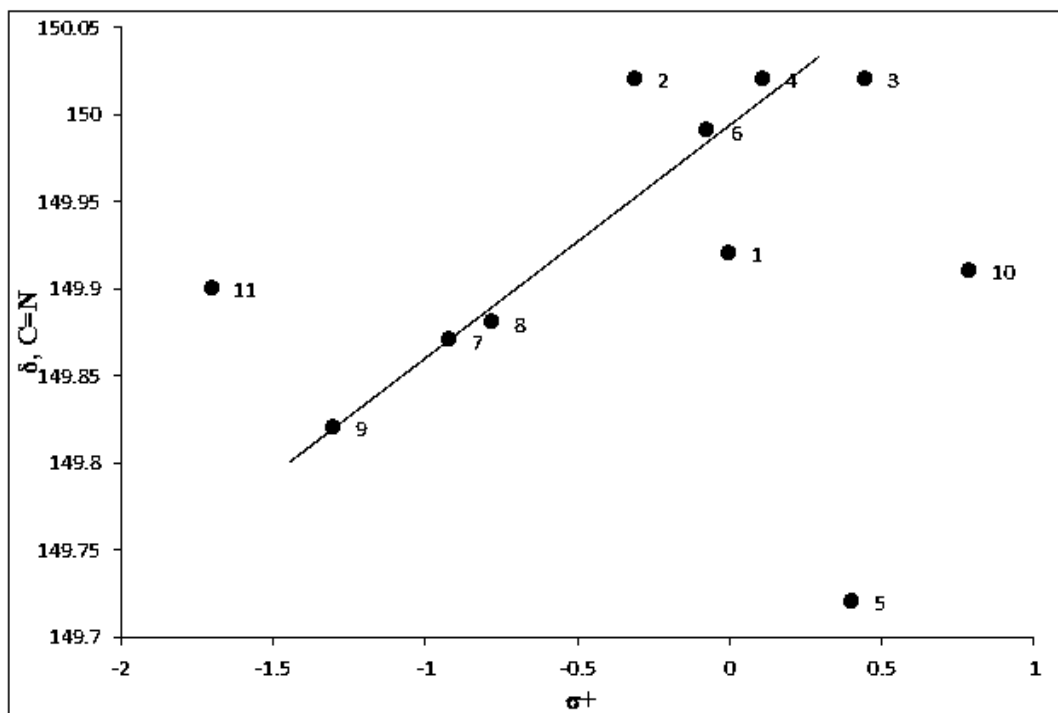


Fig. 9. Plot of ^{13}C chemical shifts (δ , ppm) of C=N of 1- $\{[3\text{-}(\text{furan-2-yl})\text{-5-phenyl-4,5-dihydro-1,2-oxazol-4-yl]methyl}\}$ -4 methyl piperazines Vs σ^+ .

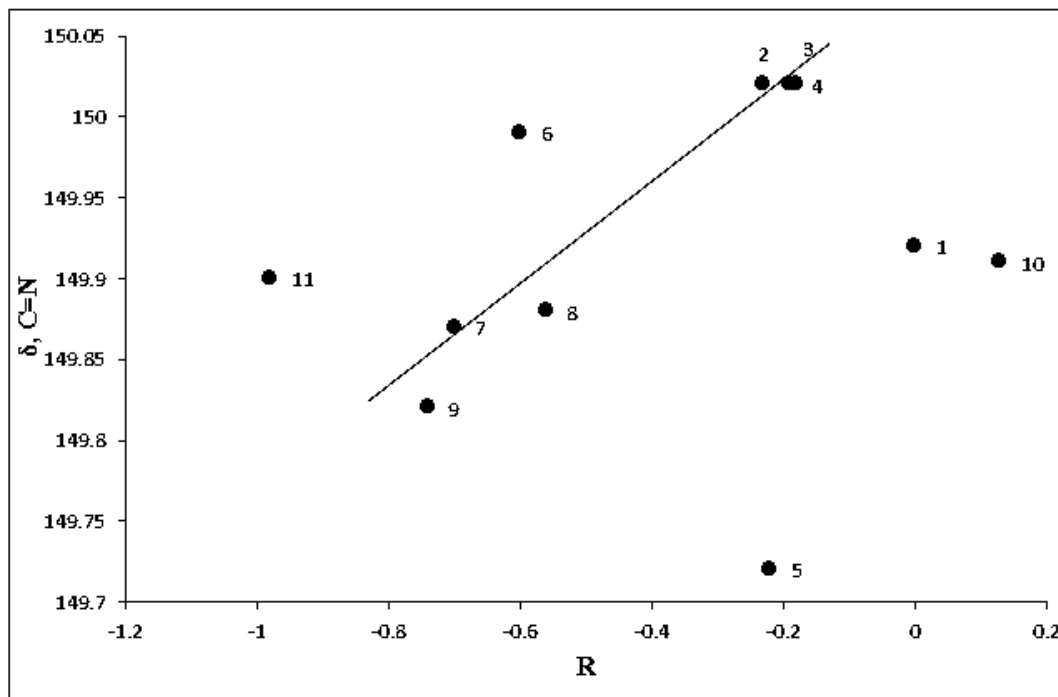


Fig. 10. Plot of ^{13}C chemical shifts (δ , ppm) of C=N of 1- $\{[3\text{-}(\text{furan-2-yl})\text{-5-phenyl-4,5-dihydro-1,2-oxazol-4-yl]methyl}\}$ -4 methyl piperazines Vs R.

All the correlation except those with parent (H), 4-Br and 4-NO₂ substituent have shown satisfactory correlation with Hammett constant R parameter. When the substitutions include the regression reduce the correlation considerable. The remaining Hammett constant namely σ_I , σ_R and F and R parameters have shown poor correlations. The failure in correlations is due to the reasons stated earlier and associated with the resonance-conjugative structure as shown in the Fig 1. The results of statistical analyses of C-NH₂ and C-NH₃ carbon chemical shifts (ppm) with Hammett substituents are shown in Table 2. From the Table 2, the C-NH₂ and C-NH₃ carbon produced poor correlation with all the Hammett substituent constant this poor correlation is due to weak polar, inductive, field and resonance effects of the substituents. All correlations gave positive ρ values. This supports that the normal substituent effects operate in all systems. The reason for failure of correlation was stated earlier and associated with resonance conjugative structure as shown in Fig. 1. In view of the inability of prediction of effect of substituents on the C=N, C-NH₂ and C-NH₃ carbon chemical shifts (δ , ppm), they are worthwhile and produce satisfactory correlations when seeking in multi-regression analysis with Swain-Lupton's [20] σ_I , σ_R substituent constants, F and R parameters. The single parameter correlations are shown in Figs. 8-10. The results of statistical analysis of C-NH₂ and C-NH₃ carbon chemical shifts (δ , ppm) with Hammett substituents are shown in Table 2. From the Table 2, the C-NH₂ and C-NH₃ carbon shift's produced poor correlation this poor correlation is due to weak polar, inductive, field and resonance effects of the substituents. All correlations gave positive ρ values. This supports that the normal substituent effects operate in all systems. The reason for failure of correlation was stated earlier and associated with resonance conjugative structure as shown in Fig. 1. In view of the inability of prediction of effect of substituents on the C=N, C-NH₂ and C-NH₃ carbon chemical shifts (δ , ppm), they are worthwhile and produce satisfactory correlations when seeking in multi-regression analysis with Swain-Lupton's [33] σ_I , σ_R substituent constants, F and R parameters. The generated multi-regression analysis equations are given in (13-18).

$$\delta C=N \text{ (ppm)} = 150.033(\pm 0.706) - 1.119(\pm 0.149)\sigma_I + 0.321(\pm 0.148)\sigma_R \quad \dots(13)$$

$$(R = 0.929, n = 11, P > 95\%)$$

$$\delta C=N \text{ (ppm)} = 150.351(\pm 0.695) + 0.532(\pm 0.135)F + 0.625(\pm 0.096)R \quad \dots(14)$$

$$(R = 0.927, n = 11, P > 95\%)$$

$$\delta C-NH_2 \text{ (ppm)} = 52.025(\pm 0.138) - 0.406(\pm 0.277)\sigma_I + 0.112(\pm 0.028)\sigma_R \quad \dots(15)$$

$$(R = 0.945, n = 11, P > 95\%)$$

$$\delta C-NH_2 \text{ (ppm)} = 51.984(\pm 0.143) - 0.278(\pm 0.028)F + 0.052(\pm 0.019)R \quad \dots(16)$$

$$(R = 0.933, n = 11, P > 95\%)$$

$$\delta C-NH_3 \text{ (ppm)} = 46.515(\pm 0.165) + 0.654(\pm 0.332)\sigma_I - 0.205(\pm 0.347)\sigma_R \quad \dots(17)$$

$$(R = 0.957, n = 11, P > 95\%)$$

$$\delta C-NH_3 \text{ (ppm)} = 46.605(\pm 0.178) + 0.465(\pm 0.348)F - 0.023(\pm 0.248)R \quad \dots(18)$$

$$(R = 0.942, n = 11, P > 95\%)$$

4. CONCLUSIONS

In the present investigation, we have synthesized 1-{{[3-(furan-2-yl)-5-phenyl-4,5-dihydro-1,2-oxazol-4-yl]methyl}-4 methyl piperazines have been synthesized by 4-methyl piperazine compounds by greener method. The synthesized 1-{{[3-(furan-2-yl)-5-phenyl-4,5-

dihydro-1,2-oxazol-4-yl)methyl}-4-methyl piperazines were characterized by their physical constants, analytical and spectroscopic data. The assigned infrared spectral $\nu_{\text{C=N}}$, $\nu_{\text{C-O-C}}$ stretches (cm^{-1}), NMR chemical shifts of isoxazoline (d) proton, isoxazoline (m) protons, N-CH₃, C=N, C-NH₂ and C-NH₃ (δ , ppm) of these 1-[[3-(furan-2-yl)-5-phenyl-4,5-dihydro-1,2-oxazol-4-yl)methyl]-4-methyl piperazines were assigned and correlated with Hammett substituent constants, F and R parameters using single and multi linear regression analysis. The ¹H NMR spectral correlation of isoxazoline (m) protons have shown satisfactory correlation with all the Hammett substituent constants.

The ¹³C NMR chemical shift values C=N (δ , ppm) have shown satisfactory correlation with Hammett constant σ , σ^+ and R parameters. The multi-correlation analysis have shown satisfactory correlations with spectral data of 1-[[3-(furan-2-yl)-5-phenyl-4,5-dihydro-1,2-oxazol-4-yl)methyl]-4-methyl piperazines.

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