Spectral QSAR and QPR study of some (*E*)-4-(((2-hydroxy-6-(substituted phenyl)-1,6-dihydropyrimidin-4-yl)methyl)diazenyl)benzoic acid derivatives

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ABSTRACT

A series of titled compounds were synthesized and recorded the infrared and NMR spectra. The assigned spectral group frequencies were correlated with Hammett substituent constants, F and R parameter. From the statistical analysis results, the effect of substituents on the spectral group frequencies has been studied.

Keywords: Dihydropyrimidines; Diazenyl benzoic acids; IR spectra; NMR spectra; Hammett correlation; QSAR and QPR study

1. INTRODUCTION

Pyrimidine, hydroxy pyrimidine six membered heterocyclic derivatives are important bio-potent molecule as well as in artificial drug synthesis [1,2]. They possess valuable biological activities such as cardiovascular [3], anti-HIV [4], anti-tumour [5], anti-inflammatory [6], anti-tubercular [7], diuretic [8], antimicrobial [9] anti-cancer [9] and antimalarial [10]. Spectroscopic data was applied for predicting the ground state configuration and QSAR and QPR study of chalcones [11], oxazines [12], pyrazoline [13], imines [14], acyl halides, and it esters [15]. Using infrared functional group frequencies such as carbonyl absorpitons, chemists studied the *s-cis* and *s-trans* conformers of chalcones [16], *cis-* and *gauche-* form of acyl esters [15]. From the proton NMR spectral chemical shift(ppm), the E and Z configuration was assigned in alkene [16], alkynes [17] and chalcones [18] derivatives. Recently, Mayavel et al have studied the effect of substituent on the (*E*)-*N*-(substituted benzylidene)-9-ethyl-9*H*-carbazole-3-amine derivatives [19] with IR and NMR spectral data through Hammett equation. Sathiyendiran et al., have studied the spectral correlations of some substituted styryl (*E*)-4-((2-oxopropyl) diazenyl) benzoic acids [20].

Kalyanasundaram and his coworkers have studied the spectral correlation analysis of Hammett substituent constants and biological activities of some (*E*)-1-(4-phenoxyphenyl)-3-phenylprop-2-en-1-ones [21]. Within the above view there is no report available in the literature for the study of effect of substituents through Hammett equation with spectral data

for the titled compounds. In the present study, the authors have taken effort for studying the QSAR and QPR of spectral data of the titled compounds by synthesis and recorded their infrared and NMR spectra.


2. EXPERIMENTAL

2. 1. General

The infrared spectra of all compounds were recorded in SHIMADUZ Fourier Transform IR spectrophotometer using KBr disc technique. The NMR spectra of all compounds were recorded in BRUKER AV 400 type spectrometer, using $CDCl_3$ as a solvent, 400 MHz frequency was applied for recording ^1H, 100 MHz for ^{13}C NMR spectra, taking TMS as standard.

2. 2. Synthesis of (*E*)-4-(((2-hydroxy-6-(substituted phenyl)-1,6-dihydropyrimidin-4-yl) methyl)diazenyl)benzoic acid derivatives

The titled pyrimidine derivatives were prepared and their purities were analyzed by the literature method [22]. The general structure of the chalcones is illustrated in Fig. 1.
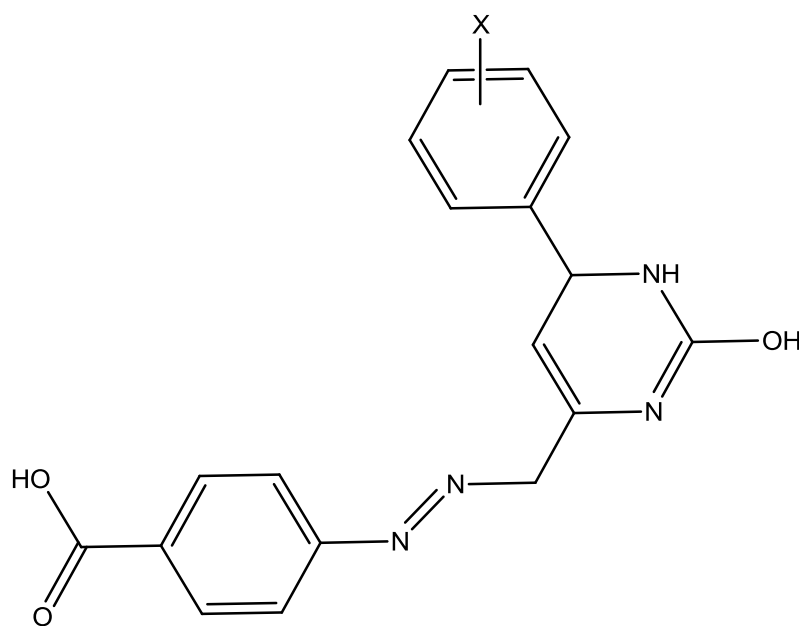
X= H, 3-Br, 2-Cl, 4-Cl, 2-OH, 4-OH, 4-OCH$_3$, 2-NO$_2$, 4-NO$_2$

Fig. 1. (*E*)-4-(((2-hydroxy-6-(substituted phenyl)-1,6-dihydropyrimidin-4-yl)methyl) diazenyl)benzoic acid derivatives.

3. RESULTS AND DISCUSSION

In the present investigations, the authors have evaluated the effect of substituents on the assigned spectral frequencies using Hammett equation with Hammett substituent constants and Swain-Lupton's[23] constants by single and multi-linear regression analysis.

3. 1. IR spectral study

In infrared spectral study, the Hammett equation is employed for evaluation of effect of substituents on the CO, N=N, CN, OH and NH stretches with Hammett substituent constants. In this correlation, the Hammett equation was utilized as,

$$\nu = \rho\sigma + \nu_o \qquad \qquad ...(1)$$

where ν is the frequency for the substituted system, ρ is the reaction constants in terms of intercept, σ is the substituent constants and ν_o is the frequency for the parent member of the series.

The assigned CO, N=N, CN, OH and NH stretches (ν, cm^{-1}) of all (*E*)-4-(((2-hydroxy-6-(substituted phenyl)-1,6-dihydropyrimidin-4-yl)methyl)diazenyl)benzoic acid derivatives are presented in Table 1.

Table 1. The infrared and NMR spectroscopic data of (*E*)-4-(((2-hydroxy-6-(substituted phenyl)-1,6-dihydropyrimidin-4-yl)methyl)diazenyl)benzoic acid derivatives.

| Sl. No. | X | IR (ν, cm^{-1}) | | | | | ^{1}H (δ, ppm) | | | ^{13}C (δ, ppm) | | | |
		CO	N=N	CN	OH	NH	NH	CH$_2$	CH-N	CH=C	CO	CH$_2$	CN
1	H	1683	1483	1594	3410	3214	2.617	2.641	4.521	6.271	170.41	61.641	156.72
2	3-Br	1685	1484	1596	3415	3215	2.623	2.644	4.671	6.073	170.92	61.644	156.81
3	2-Cl	1696	1486	1589	3419	3218	2.597	2.457	4.507	6.523	170.67	62.457	156.97
4	4-Cl	1692	1485	1591	3418	3220	2.373	2.517	4.517	6.497	170.70	62.517	156.81
5	2-OH	1688	1484	1595	3417	3216	2.481	2.501	4.573	5.997	171.73	61.501	156.67

6	4-OH	1693	1482	1597	3416	3211	2.489	2.493	4.567	6.073	170.25	62.493	156.44
7	4OCH$_3$	1679	1479	1581	3401	3208	2.317	2.397	4.490	5.847	170.09	62.397	156.39
8	2-NO$_2$	1698	1488	1599	3422	3229	2.513	2.537	4.657	6.181	172.71	63.537	157.08
9	3-NO$_2$	1697	1490	1598	3421	3224	2.521	2.539	4.598	6.093	172.36	63.539	156.98

The results of statistical analysis [11-16,18-21] are shown in Table 2. From the table 2, the correlation of νCO stretches of all compounds gave satisfactory correlation for Hammett σ, σ$^+$, and σ$_I$ constants. The Hammett σ$_I$ constants, F and R parameters were fail in correlations. This due to the inability of effect of substituents on the carbonyl group and associated with the resonance-conjugative structure as shown in Fig. 2. All correlations gave positive ρ values. This may mean that the normal substituent effects operated in all system.
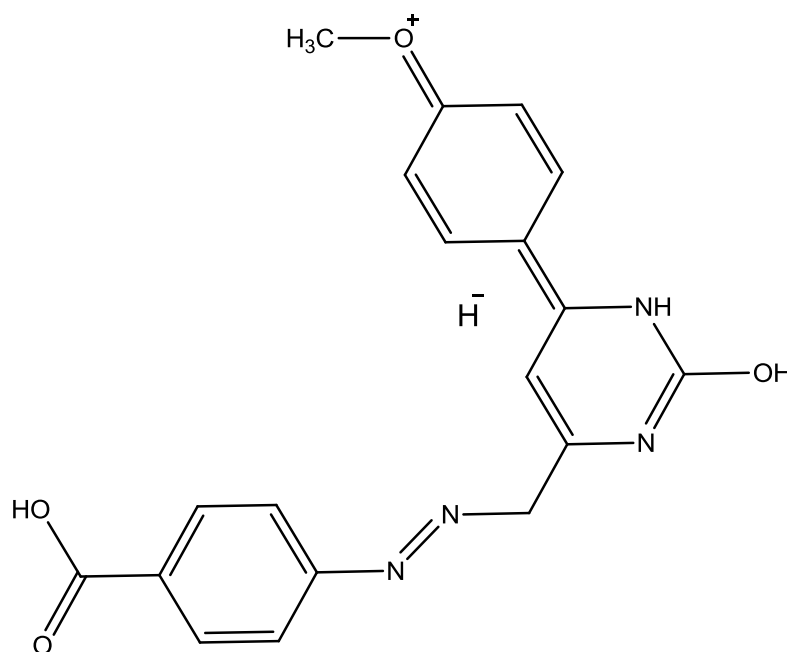

Fig. 2. The resonance-conjugative structure.

The N=N stretches (ν, cm^{-1}) of pyrimidine derivatives were produced satisfactory correlation coefficient with Hammett substituent constants and F and R parameters along with positive ρ values.

The C=N stretches (v, cm^{-1}) of pyrimidine derivatives were produced poor correlation coefficient with Hammett substituent constants and F and R parameters along with positive ρ values. The reasons for the poor correlation of this stretches are stated earlier and associated with resonance-conjugated structure as shown in Fig. 2.

The OH stretches (v, cm^{-1}) of pyrimidine derivatives were produced poor correlation coefficient with Hammett σ, σ^+, σ_I constants and F parameters. The resonance components of the substitutes were fail in correlation. All correlation gave positive ρ values. The reasons for the failure correlation of this stretches were stated earlier and associated with resonance-conjugated structure as shown in Fig. 2.

The NH stretches (v, cm^{-1}) of pyrimidine derivatives were produced satisfactory correlation coefficient with Hammett substituent constants and F and R parameters along with positive ρ values.

Among these correlations some of the correlation gave poor coefficients. They are worthwhile when they are subjected to multi-regression analysis. In multi parameter correlation with Swain-Lupton's [18] parameters, these stretches produced satisfactory correlations. The generated multi-regression analysis equations are shown in (2-11).

Table 2. Results of statistical analysis of IR, ^{1}H NMR and ^{13}C-NMR spectral values of (E)-4-(((2-hydroxy-6-(substituted phenyl)-1,6-dihydropyrimidin-4-yl)methyl) diazenyl)benzoic acid derivatives with Hammett σ, σ^+, σ_I, σ_R constants, F and R parameters.

Frequency	Constant	r	I	ρ	s	n	Correlated derivatives
v CO (cm^{-1})	σ	0.905	1688.55	9.440	5.77	9	H, 3-Br, 2-Cl, 4-Cl, 2-OH, 4-OH, 4-OCH$_3$, 2-NO$_2$, 4-NO$_2$
	σ^+	0.905	1689.87	6.052	5.95		
	σ_I	0.907	1681.30	22.777	5.01		
	σ_R	0.844	1692.11	10.260	6.55		
	F	0.917	1680.45	24.553	4.98		
	R	0.832	1692.23	8.185	6.58		
v N=N (cm^{-1})	σ	0.986	1483.46	6.655	1.73	9	H, 3-Br, 2-Cl, 4-Cl, 2-OH, 4-OH, 4-OCH$_3$, 2-NO$_2$, 4-NO$_2$
	σ^+	0.986	1484.37	4.562	1.72		
	σ_I	0.917	1480.13	11.444	2.31		
	σ_R	0.908	1486.18	8.343	2.51		
	F	0.972	1479.87	11.889	2.01		
	R	0.907	1486.42	7.181	2.39		
vC=N (cm^{-1})	σ	0.849	1592.25	6.566	5.24	9	H, 3-Br, 2-Cl, 4-Cl, 2-OH, 4-OH, 4-OCH$_3$, 2-NO$_2$, 4-NO$_2$
	σ^+	0.843	1593.17	3.954	5.42		
	σ_I	0.830	1590.16	8.197	5.73		
	σ_R	0.843	1595.10	9.057	5.43		
	F	0.837	1589.14	10.652	5.59		

	R	0.836	1594.96	6.270	5.61	
νOH (cm⁻¹)	σ	0.906	3413.84	9.742	5.32	9
	σ⁺	0.915	3415.17	6.789	5.24	
	σ_I	0.916	3407.70	20.026	5.22	
	σ_R	0.831	3417.28	9.416	6.36	
	F	0.966	3406.87	21.777	5.19	
	R	0.884	3417.56	8.150	6.29	
νNH (cm⁻¹)	σ	0.908	3214.99	13.567	3.18	9
	σ⁺	0.900	3216.87	8.871	3.72	
	σ_I	0.907	3208.32	23.011	4.55	
	σ_R	0.907	3220.56	17.098	4.81	
	F	0.907	3207.79	23.961	4.71	
	R	0.907	3221.03	14.677	4.61	
δNH (ppm)	σ	0.833	2.489	0.831	0.10	
	σ⁺	0.905	2.500	0.085	0.09	
	σ_I	0.711	2.500	0.115	0.11	
	σ_R	0.831	2.532	0.148	0.10	
	F	0.806	2.516	0.033	0.11	
	R	0.840	2.537	0.129	0.10	
δCH₂ (ppm)	σ	0.838	2.513	0.070	0.07	9
	σ⁺	0.844	2.522	0.056	0.07	
	σ_I	0.809	2.538	0.034	0.08	
	σ_R	0.905	2.554	0.156	0.06	
	F	0.813	2.547	0.056	0.08	
	R	0.905	2.557	0.123	0.07	
δCH-N (ppm)	σ	0.906	4.551	0.093	0.05	9
	σ⁺	0.904	4.562	0.051	0.06	
	σ_I	0.905	4.504	0.162	0.05	
	σ_R	0.839	4.858	0.095	0.06	
	F	0.905	4.459	0.192	0.05	
	R	0.831	4.583	0.063	0.06	
δCH=C (ppm)	σ	0.828	6.143	0.151	0.22	9
	σ⁺	0.846	6.166	0.167	0.21	

Substituents column (spanning):
- For νOH: H, 3-Br, 2-Cl, 4-Cl, 2-OH, 4-OH, 4-OCH₃, 2-NO₂, 4-NO₂
- For νNH, δNH, δCH₂, δCH-N, δCH=C: H, 3-Br, 2-Cl, 4-Cl, 2-OH, 4-OH, 4-OCH₃, 2-NO₂, 4-NO₂

	σ_I	0.816	6.104	0.177	0.23		
	σ_R	0.830	6.221	0.258	0.22		
	F	0.801	6.164	0.021	0.23		
	R	0.841	6.247	0.287	0.21		
δCO (ppm)	σ	0.907	170.81	1.698	0.66	9	H, 3-Br, 2-Cl, 4-Cl, 2-OH, 4-OH, 4-OCH$_3$, 2-NO$_2$, 4-NO$_2$
	σ^+	0.906	171.05	1.024	0.75		
	σ_I	0.906	169.93	2.994	0.75		
	σ_R	0.905	171.44	1.803	0.87		
	F	0.907	169.70	3.531	0.68		
	R	0.905	171.48	1.058	0.86		
δCH_2 (ppm)	σ	0.834	62.513	0.072	0.07	9	H, 3-Br, 2-Cl, 4-Cl, 2-OH, 4-OH, 4-OCH$_3$, 2-NO$_2$, 4-NO$_2$
	σ^+	0.844	62.522	0.056	0.07		
	σ_I	0.709	62.538	0.088	0.08		
	σ_R	0.905	62.558	0.157	0.06		
	F	0.813	62.413	0.087	0.07		
	R	0.824	62.173	0.411	0.07		
δCN (ppm)	σ	0.903	156.68	0.506	0.10	9	H, 3-Br, 2-Cl, 4-Cl, 2-OH, 4-OH, 4-OCH$_3$, 2-NO$_2$, 4-NO$_2$
	σ^+	0969	156.74	0.370	0.05		
	σ_I	0.906	156.46	0.778	0.18		
	σ_R	0.907	156.88	0.645	0.17		
	F	0.906	156.47	0.736	0.20		
	R	0.908	156.91	0.587	0.14		

r = correlation coefficient; I = intercept; ρ = slope; s = standard deviation; n = number of correlated derivatives

$$\nu C{=}O(cm^{-1}) = 1682.09(\pm 5.392) + 21.644(\pm 10.417)\sigma_I + 1.803(\pm 0.812)\sigma_R \qquad ...(2)$$
$$(r = 0.971, n = 9, P > 95\ \%)$$

$$\nu C{=}O(cm^{-1}) = 1682.04(\pm 5.134) + 22.607(\pm 10.183)F + 3.180(\pm 0.612)R \qquad ...(3)$$
$$(r = 0.973, n = 9, P > 95\ \%)$$

$$\nu N{=}N(cm^{-1}) = 1482.38(\pm 2.063) + 8.221(\pm 4.092)\sigma_I + 5.313(\pm 3.178)\sigma_R \qquad ...(4)$$
$$(r = 0.983, n = 9, P > 95\ \%)$$

$$\nu N{=}N(cm^{-1}) = 1482.54(\pm 1.775) + 8.667(\pm 5.521)F + 5.216(\pm 2.118)R \qquad ...(5)$$
$$(r = 0.987, n = 9, P > 95\ \%)$$

$$\nu C=N (cm^{-1}) = 1593.56(\pm 5.760) + 3.324(\pm 11.248)\sigma_I + 7.715(\pm 0.818)\sigma_R \qquad ...(6)$$
$$(r = 0.944, n = 9, P > 90\ \%)$$

$$\nu C=N (cm^{-1}) = 1591.40(\pm 5.683) + 7.882(\pm 1.125)F + 4.527(\pm 1.654)R \qquad ...(7)$$
$$(r = 0.989, n = 9, P > 95\ \%)$$

$$\nu OH (cm^{-1}) = 3408.82(\pm 5.550) + 18.700(\pm 10.838)\sigma_I + 2.109(\pm 0.854)\sigma_R \qquad ...(8)$$
$$(r = 0.965, n = 9, P > 95\ \%)$$

$$\nu OH\ (cm^{-1}) = 3408.80(\pm 5.281) + 19.420(\pm 10.474)F + 3.580(\pm 1.304)R \qquad ...(9)$$
$$(r = 0.968, n = 9, P > 95\ \%)$$

$$\nu NH (cm^{-1}) = 3213.58(\pm 3.931) + 16.292(\pm 7.673)\sigma_I + 10.744(\pm 6.055)\sigma_R \qquad ...(10)$$
$$(r = 0.984, n = 9, P > 95\ \%)$$

$$\nu NH\ (cm^{-1}) = 3213.22(\pm 3.295) + 17.326(\pm 6.536)F + 10.841(\pm 3.931)R \qquad ...(11)$$
$$(r = 0.989, n = 9, P > 95\ \%)$$

3. 2. ^{1}H NMR Spectral study

In nuclear magnetic resonance spectra, the ^{1}H or the ^{13}C chemical shifts (δ, ppm) depend on the electronic environment of the nuclei concerned. These chemical shifts of hydrazide have been correlated with reactivity parameters. Thus the Hammett equation was used in the form as shown in (12).

$$\text{Log } \delta = \text{Log } \delta_0 + \rho\sigma \qquad ...(12)$$

where δ_0 is the chemical shift of the corresponding parent compound.

The NH$_2$, CH$_2$, CH-NH and CH=C proton chemical shifts (δ, ppm) of pyrimidines have been assigned and correlated with Hammett substituent constants using single and multi-linear regression analysis [11-16,18-21]. The results of statistical analysis are shown in Table 2. From Tale 2, the correlation of NH proton chemical shifts (δ, ppm) of pyridines with Hammett σ^+ constant only satisfactory. The Hammett σ, σ_I, σ_R constant, F and R parameters were fail in correlations.

A satisfactory correlation were obtained for CH$_2$ proton chemical shifts (δ, ppm) of pyridines with Hammett σ_R constant and R parameter. The remaining Hammett sigma constants and F parameters were fail in correlation.

The correlation of CH-N proton chemical shifts (δ, ppm) of pyridines gave satisfactory coefficients with Hammett σ, σ^+, σ_I constant and F parameter. The resonance components of the substituents were fail in correlation.

A poor correlation were observed for the correlation of CH=C proton chemical shifts (δ, ppm) of pyridines with Hammett substituent constants F and R parameters. All correlations gave positive ρ values. This is implies that the normal substituent effect operates in all system. The reason for failure in correlations of assigned proton chemical shifts were already stated earlier and is associated with the resonance-conjugative structure as shown in Fig. 2.

Some of the chemical shifts of assigned NH$_2$, CH$_2$, CH-NH and CH=C proton chemical shifts (δ, ppm) of pyrimidines have shown poor correlation in single parameter analysis. While seeking these chemical shifts are worthwhile, they are indulged in multi-parameter correlation. They produced satisfactory correlation either inductive and resonance

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components or field and resonance components combined. The generated multi-regression equations are shown in (13-20).

$$\delta NH(ppm) = 2.592(\pm0.107) + 0.103(\pm0.021)\sigma_I + 0.198(\pm0.106)\sigma_R \qquad ...(13)$$
$$(r = 0.943, n = 9, P > 90 \%)$$

$$\delta NH(ppm) = 2.959(\pm0.105) + 0.103(\pm0.020)F + 0.158(\pm0.102)R \qquad ...(14)$$
$$(r = 0.946, n = 9, P > 90 \%)$$

$$\delta CH_2(ppm) = 2.634(\pm0.069) + 0.172(\pm0.134)\sigma_I + 0.219(\pm0.101)\sigma_R \qquad ...(15)$$
$$(r = 0.964, n = 9, P > 95 \%)$$

$$\delta CH_2(ppm) = 2.625(\pm0.070) + 0.152(\pm0.109)F + 0.156(\pm0.084)R \qquad ...(16)$$
$$(r = 0.961, n = 9, P > 95 \%)$$

$$\delta CH\text{-}N(ppm) = 4.522(\pm0.062) + 0.135(\pm0.012)\sigma_I + 0.042(\pm0.001)\sigma_R \qquad ...(17)$$
$$(r = 0.954, n = 9, P > 95 \%)$$

$$\delta CH\text{-}N(ppm) = 4.503(\pm0.059) + 0.177(\pm0.117)F + 0.024(\pm0.007)R \qquad ...(18)$$
$$(r = 0.959, n = 9, P > 95 \%)$$

$$\delta CH\text{=}C(ppm) = 6.214(\pm0.242) + 0.020(\pm0.004)\sigma_I + 0.250(\pm0.037)\sigma_R \qquad ...(19)$$
$$(r = 0.930, n = 9, P > 90 \%)$$

$$\delta CH\text{=}C(ppm) = 6.328(\pm0.225) + 0.179(\pm0.044)F + 0.326(\pm0.026)R \qquad ...(20)$$
$$(r = 0.944, n = 9, P > 90 \%)$$

3. 3. ^{13}C NMR Spectral study

The CO, CH$_2$, and CN carbon chemical shifts (δ, ppm) of pyrimidine derivatives have been assigned and correlated with Hammett substituent constants using single and multi-linear regression analysis [11-16,18-21].

The results of statistical analysis are shown in Table 2. From Table 2, the correlation of CO carbon chemical shifts (δ, ppm) of hydrazides with Hammett substituent constants and F and R parameters were satisfactory. The correlation of CH$_2$ carbon chemical shifts (δ, ppm) were fail in correlation with Hammett substituent constants and F and R parameters. The CN carbon chemical shifts (δ, ppm) pyrimidines were shows satisfactory correlation with Hammett substituent constants and f and R parameters. The failure in correlation is due to the reasons stated earlier and was associated with the resonance-conjugative structure as shown in Figure 2.

The chemical shifts (δ, ppm) of CH$_2$ pyrimidines have shown poor correlation in single parameter analysis. While seeking these chemical shifts (δ, ppm) CO, CH$_2$, and CN are worthwhile, they are indulged in multi-parameter correlation. They produced satisfactory correlation either inductive and resonance components or field and resonance components combined. The generated multi-regression equations are shown in (21-26)

$$\delta CO(ppm) = 170.303(\pm0.772) + 2.468(\pm1.508)\sigma_I + 0.839(\pm0.011)\sigma_R \qquad ...(21)$$
$$(r = 0.969, n = 9, P > 95 \%)$$

$$\delta CO(ppm) = 170.125(\pm 0.663) + 3.017(\pm 0.131)F + 0.840(\pm 0.079)R \qquad ...(22)$$
$$(r = 0.978, n = 9, P > 95 \text{ \%})$$

$$\delta CH_2(ppm) = 62.625(\pm 0.070) + 0.152(\pm 0.013)\sigma_I + 0.156(\pm 0.081)\sigma_R \qquad ...(23)$$
$$(r = 0.969, n = 9, P > 95 \text{ \%})$$

$$\delta CH_2(ppm) = 62.613(\pm 0.172) + 0.817(\pm 0.032)F + 0.217(\pm 0.013)R \qquad ...(24)$$
$$(r = 0.970, n = 9, P > 95 \text{ \%})$$

$$\delta CN(ppm) = 156.66(\pm 0.153) + 0.491(\pm 0.219)\sigma_I + 0.453(\pm 0.236)\sigma_R \qquad ...(25)$$
$$(r = 0.982, n = 9, P > 95 \text{ \%})$$

$$\delta CN(ppm) = 156.719(\pm 0.127) + 0.436(\pm 0.021)F + 0.491(\pm 0.015)R \qquad ...(26)$$
$$(r = 0.987, n = 9, P > 95 \text{ \%})$$

4. CONCLUSIONS

A series of dihydropyimidine methyl diazenyl benzoic acid derivatives have been prepared and recorded their IR and NMR spectra. The assigned spectral group frequencies were correlated with Hammett substituent constants, F and R parameters. From the results of statistical analysis, almost all frequencies were shown satisfactorily correlations in both single and multi-parameter correlation analysis. There is a normal substituent effect operates in all systems evident with positive ρ values.

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