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Reactions of 5-benzoyl-/5-carbaldehyde-/5-(3-phenyl-acryloyl)-6-hydroxy-1*H*-pyrimidin-2,4-diones with amines: Anti-cancer and metal sequestering properties

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Reactions of 5-benzoyl- / 5-carbaldehyde- / 5-(3-phenyl-acryloyl)-6-hydroxy-1*H*-pyrimidine-2,4-diones and diamines result in the formation of corresponding enamines. Appreciable anti-cancer activities of compounds **2**, **5**, **6** and **8** at various cell lines of 59 human tumor cell panels have been observed. UV spectral studies of these compounds in solution with $Cu(OAc)_2$ and $FeCl_3$ indicate their interactions with Cu^{+2} and Fe^{+3} ions.

Keywords: 5-Acylpyrimidines, amine, enamines, anti-cancer activities, metal chelators

The metal ions play structural and functional roles in the biological systems through the stabilization of the biomolecules (DNA, RNA, peoteins/enzymes) and participating in the active sites of various enzymes[1-3]. The functions of metal ions like Fe^{+2}/Fe^{+3}, Mn^{+2}, Zn^{+2}, Cu^{+2}, Ni^{+2}, Co^{+2} etc. during the turn over phase of the enzymes ribonucleotide reductase, HIV-Integrase, carbonic anhydrase, plastocyanin etc. have been well documented. The removal of the metal ion from the biosite of an enzyme renders it inactive and this approach has been advantageously used in the drug development programmes. Fe^{+2}/Fe^{+3} and Mn^{+2} chelating agents have been used for blocking the activity of ribonucleotide reductase[4-6] and HIV-In[7,8] enzymes respectively.

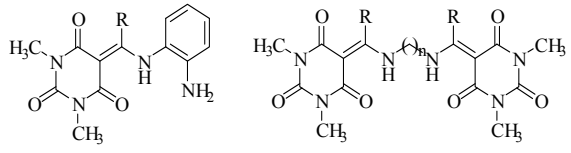
Due to the appropriate placement of the functional groups in salicylidenamines, they have been widely studied for their complexation with various metal ions (Salen-complexes)[9-13] and provide a suitable platform for developing new metal sequestering agents. In continuation with our efforts for developing anti-cancer agents[14-16], here, we have planned to introduce appropriate metal chelating group on pyrimidin-2, 4-diones (**1-3**, **5-9**, **Figure 1**). It was envisaged that the acceptability of the pyrimidine moiety in the biological system and the metal sequestering property of these compounds could help in blocking the activity of the enzyme especially those involved in the propagation of cancer. The synthesis of these molecules (**1-3**, **5-9**; **Figure 1**) has been followed by their screening for anti-cancer activities at 59 human tumor cell lines and studies of their interactions with Cu^{+2} and Fe^{+3} ions on the basis of UV spectral studies.

Appreciable anti-cancer activities of these molecules have been observed at various cell lines.

Chemistry

The synthetic approach, as reported for the reactions of 5-formyl- and 5-acetyl barbituric acids with ω-aminoalkanoic acids and primary amines for procuring corresponding Schiff bases and enamines[17,18], has been followed here to get the desired compounds. 6-Hydroxy-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-carbaldehyde (**10a**) was prepared by the formylation of 1,3-dimethyl-pyrimidin-2,4,6-trione[17]. Compounds **10b** and **10c** were prepared by the microwave assisted cinnamoylation and benzoylation of 1,3-dimethyl-pyrimidin-2,4,6-trione[19,20].

A solution of **10a** (1 mmole) and phenylene diamine (1 mmole) was stirred in methanol at 35°C, after usual work up provided compound **1** as yellow solid, m.p. 252°C which could exist in tautomeric forms 'a' and 'b'. Presence of two 1H doublets at δ 8.63 (due to



1-3 **5-9**

Figure 1

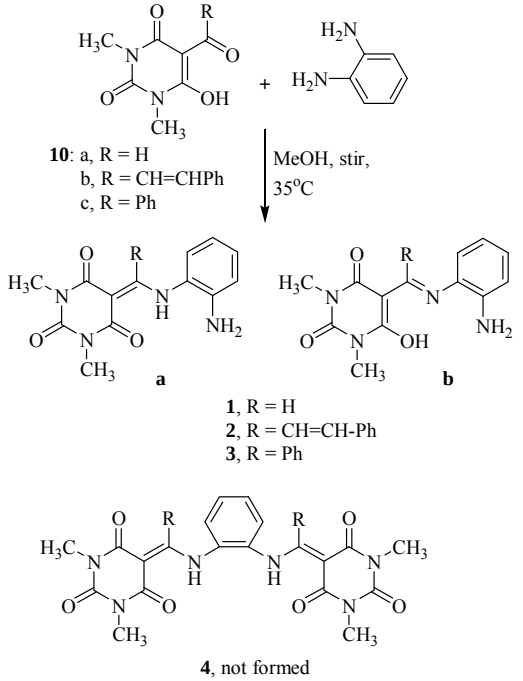
=CH, converted to singlet after adding D_2O) and 12.35 (due to NH, exchangeable with D_2O), besides the signals due to two CH_3 groups at δ 3.36, four ArHs' in the region δ 6.84-7.24 and another D_2O exchangeable signal at δ 12.30 (due to NH_2) in the ^1H NMR spectrum of **1** implies its existence in tautomeric form 'a'. Besides a number of attempts on this reaction, using different molar ratios of **10a** and phenylene diamine, we could not get compound **4**. Under the same reaction conditions as for the synthesis of **1**, the reactions of **10b** and **10c** with phenylene diamine provided the respective compounds **2a** and **3a** (**Scheme I**).

Treatment of **10a** and **10b** with ethylene diamine in methanol at 35°C resulted in the formation of compounds **5** and **6** respectively while the same reaction with **10c** provided compound **7** (**Scheme II**). Likewise, the reactions of **10b** and **10c** with hydrazine in methanol provided the compounds **8** and **9** respectively (**Scheme II**).

Therefore, a very convenient synthetic methodology leads to the formation of a variety of compounds with desirable functionalities introduced at pyrimidine moiety/ies.

Anti-cancer screening

The anti-cancer activities of compounds **2**, **5**, **6** and **8** at 10^{-5} M concentrations have been tested at 59 human tumor cell lines representing leukemia, melanoma, and cancers of the lung, colon, brain, ovary, breast, prostate as well as kidney by the screening unit of NCI, Bethesda, USA following the standard procedure[21-23]. The results of these studies in terms of percent growth of tumor cells at various cell lines have been given in **Table I**. Based upon the preliminary investigations, the anti-cancer activity of compound **6** has further been studied at 59 human tumor cell lines at 10^{-4}, 10^{-5}, 10^{-6}, 10^{-7} and 10^{-8} M concentrations.



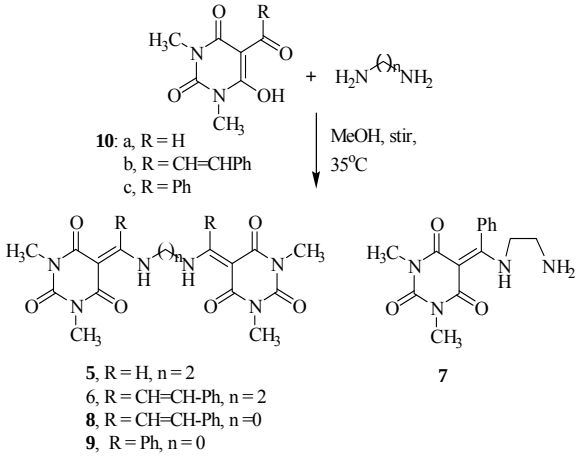
Scheme I

UV based studies of interactions of compounds 2, 5, 6 and 8 with metal ions

The UV spectra of compounds **2, 5, 6** and **8** in CH_3CN at 10^{-4} M concentrations and their 1:2 mixtures with different metal salts in the same solvent and concentrations were recorded. The corresponding λ_{max} and the absorbance values have been given in **Table II**.

Discussion

The data for anti-cancer activities of compounds **2**, **5**, **6** and **8** at 10^{-5} M concentration in terms of the percent growth of treated cells has been given in **Table I**. For compound **2**, the mean of growth percent at all the cell lines is 90.35. The percent growth less than 90.35 at individual cell lines on treatment with compound **2** indicate the higher sensitivity of that cell line for this compound. Compound **2** is showing 44, 41 and 33% growth inhibition of K-562, RPMI-8226 and CCRF-CEM tumor cell lines of leukemia and 43% growth inhibition of HCT-116 cell line of colon cancer. Compound **5,** with 90.27 mean value of percent growth, shows the maximum growth inhibition (~93%) of CCRF-CEM cell line of



Scheme II

Table I — Percent growth of cancer cell when treated with compounds **2**, **5**, **6** and **8** at 10^{-5} *M* concentration

Panel/Cell Line	Percent growth			
	2	5	6	8
Leukemia				
CCRF-CEM	67.34	7.42	39.02	76.82
HL-60 (TB)	-39.36	-59.98	38.22	49.40
K-562	55.89	34.54	46.33	56.06
MOLT-4	-43.53	-46.64	65.37	63.78
RPMI-8226	58.68	80.63	39.58	59.43
SR	-19.67	-21.85	28.89	83.01
Non-small cell lung cancer				
A549/ATCC	103.01	100.19	83.11	109.59
EKVX	82.04	101.76	80.53	99.28
HOP-62	104.85	90.68	30.05	92.28
HOP-92	82.43	86.22	77.61	71.63
NCI-H226	97.86	92.28	95.92	94.36
NCI-H23	94.16	97.01	77.08	86.16
NCI-H322M	104.60	89.26	81.76	93.32
NCI-H460	103.83	106.91	62.00	100.72
NCI-H522	90.31	105.03	86.77	91.87
Colon cancer				
COLO 205	95.04	101.25	90.94	99.53
HCC-2998	90.01	92.22	91.31	87.71
HCT-116	56.70	81.14	55.40	97.71
HCT-15	91.52	107.50	63.51	70.96
HT29	72.07	97.13	67.96	90.40
KM12	106.59	98.75	66.75	95.52
SW-620	106.06	106.81	92.81	103.45
CNS cancer				
SF-268	114.16	105.07	57.39	92.63
SF-295	105.20	101.18	58.81	92.63
SF-539	106.85	93.91	69.62	112.22
SNB-19	100.58	97.64	80.58	97.03
SNB-75	90.73	88.29	75.53	83.50
U251	100.554	102.17	65.45	101.57
Ovarian cancer				
IGROV1	77.38	106.37	90.64	102.45
OVCAR-3	104.90	101.96	78.59	92.20
OVCAR-4	101.01	112.14	83.13	95.06
OVCAR-5	83.36	83.66	93.49	75.97
OVCAR-8	106.56	103.09	75.15	105.06
SK-OV-3	110.27	106.55	94.40	103.34
Renal cancer				
786-0	103.27	112.99	87.62	111.34
A498	130.25	126.52	91.51	98.64
ACHN	99.26	101.42	83.05	87.74
CAKI-1	101.52	94.42	89.41	105.01
RXF 393	109.25	111.28	75.35	107.75
SN12C	96.09	95.58	77.23	97.67
TK-10	133.98	116.06	120.13	116.73
UO-31	83.37	84.70	73.87	84.23
Prostate cancer				
PC-3	77.71	90.45	66.41	81.66
DU-145	116.73	109.83	61.92	101.97
Breast cancer				
MCF7	99.02	107.87	48.71	97.65
NCI/ADR-RES	96.46	104.45	85.34	82.59
MDA-MB-2321/ATCC	91.40	101.17	92.56	93.16
HS 578T	109.59	112.30	84.90	111.11
MDA-MB-435	95.55	93.69	65.68	104.26
BT-549	120.77	118.36	73.45	113.95
T-47D	85.55	96.12	68.02	87.77
Mean	90.35	90.27	73.41	92.40

Table II — UV spectral data of compounds **2**, **5**, **6** and **8** at 10^{-4} M conc.

Compd	λ_{max} in nm (A)		
	Pure compd	Compd + M^{+}	
		Cu^{+2}	Fe^{+3}
2	367 (1.62), 342 (1.93) 223 (0.94)	326 (0.70), 213 (1.68)	361 (1.23), 304 (1.19), 236 (1.74)
5	313 (0.80). 290 (0.80) 217 (0.76)	317 (0.61), 213 (1.70)	361 (1.08), 305 (1.14), 236 (1.7)
6	301 (0.70), 240 (0.53)	305 (0.60), 213 (1.71)	361(1.01), 305 (1.01), 237 (1.6)
8	298 (0.26), 258.5 (0.80), 220 (1.53)	317.5 (0.58), 218 (1.85)	361 (1.04), 305 (1.05), 237.5 (1.68)

leukemia and 65% inhibition of tumor cells of K-562 cell line. The best growth inhibitions with compound **6** have been observed at the cell lines of leukemia with a maximum of 71% at SR cell line. Moreover, 70% and 52% inhibition of tumor cell growth has been observed at HOP-62 and MCF7 cell lines of non-small cell lung cancer and breast cancer respectively, along with appreciable inhibitions of some cell lines of colon cancer, CNS cancer, ovarian cancer, renal cancer and prostate cancer, when treated with compound **6**. This compound with mean percent growth inhibition 73.41 is the most efficacious of all the four compounds investigated here. The growth inhibitory activities of compound **8** are scattered over a number of cell lines. The best results with compound **8** have been observed on all the cell lines of leukemia along with 28, 29, 24 and 18% growth inhibitions of HOP-92, HCT-15, OVCAR-8 and PC-3 cell lines of non-small cell lung cancer, colon cancer, ovarian cancer and prostate cancer, respectively.

Therefore, of the four compounds investigated here for anti-cancer activities, compound **6** has shown the best results and has been further investigated at lower concentrations. The percentage growth inhibitions of various cell lines by compound **6** at 10^{-4}, 10^{-5}, 10^{-6}, 10^{-7} and 10^{-8} *M* concentrations depict its average GI_{50} over all the 59 human tumor cell lines 1.65×10^{-5} *M* which is quite similar to the average GI_{50} of 5-fluorouracil[24] (1.77×10^{-5} *M*), a clinically used anti-cancer drug. For certain cell lines like HL-60(TB) and RPMI-8226 of leukemia; NCI-H460 of non-small cell lung cancer and SK-MEL-28 of melanoma, the GI_{50} of compound **6** has been observed at micro-molar concentrations (Complete 4 page anti-cancer data for compound **6** could be obtained from the author via e-mail).

The interactions of these compounds (**2**, **5**, **6** and **8**) with Cu^{+2} and Fe^{+3} ions were investigated on the basis of UV spectral studies. All the four molecules show considerable change in the λ_{max} when mixed with a solution of $Cu(OAc)_2$ and $FeCl_3$ in CH_3CN at 10^{-4} M concentration (**Table II**) which indicates the interactions of these molecules with Cu^{+2} and Fe^{+3} ions and supports the idea of the design of these molecules.

Although the cellular target has not been defined in the anti-cancer studies, but the results are quite in agreement with the UV spectral data of the compounds especially the shifts in λ_{max} when mixed with $FeCl_3$. Compound **6**, which exhibits the best anti-cancer activities over various cell lines, shows bathochromic shift of 60 nm on interacting with Fe^{+3} ions and a hypsochromic shift of 27 nm when mixed with $Cu(NO_3)_2$. This is followed by the change in λ_{max} of compounds **8**, **5** and **2** when mixed with the solution of $FeCl_3$. Compound **2** with minimum tumor inhibitory activities also does not show shift in absorption maxima when mixed with $FeCl_3$.

This systematic approach consisting of the design of appropriate molecules and their binding studies with different metal ions could be helpful towards the development of anti-cancer agents.

Conclusions

The reactions of 5-formyl-/5-benzoyl- and 5-(3-phenyl-acryloyl)-6-hydroxy-1*H*-pyrimidine-2,4-diones with phenylene diamine, ethylene diamine and hydrazine provided the corresponding enamines. The investigations for anti-cancer activities of molecules **2**, **5**, **6** and **8** at 59 human tumor cell lines identify compound **6** exhibiting considerable anti-cancer activity at various cell lines. The UV spectral studies of these molecules in solution with $Cu(OAc)_2$ and $FeCl_3$ show their interactions with Cu^{+2} and Fe^{+3} ions.

Experimental Section

General

Melting points were determined in capillaries and are uncorrected. ^1H and ^{13}C NMR spectra were run on JEOL 300 MHz and 75.4 MHz NMR respectively using $CDCl_3$ as solvent. Chemical shifts are given in δ with TMS as an internal reference. *J* values are given in Hertz. Chromatography was performed with silica 100-200 mesh and reactions were monitored by thin layer chromatography (TLC) with silica plates coated with silica gel HF-254.

General procedure

The solution of 5-substituted-6-hydroxy-1,3-dimethyl-pyrimidin-2,4-dione and the appropriate amine (phenylene diamine/ hydrazine /ethylene diamine) (1.2 equiv. for compounds **1-3** and 0.5 equiv. for compounds **5-9**) in methanol was stirred at 35°C for 3-5 hr. The solid suspension on filtration and washing with diethyl ether provided the pure compound.

5-[(2-Amino-phenylimino)-methylene]-1,3-dimethyl-pyrimidine-2,4,6-trione 1: Yellowish solid, yield 77%, m.p. 252°C, IR (KBr): 1630 (C=O), 1670 (C=O), 3420 (NH), 3480 (NH) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.36 (6H, s, CH_3), 6.84-7.41 (4H, m, Ph), 8.63 (1H, d, *J* = 10.5 Hz, =CH), 12.30 (2H, broad doublet, *J* = 11.7 Hz, NH_2, exchangeable with D_2O), 12.35 (1H, broad doublet, *J* =11.7 Hz, NH, exchangeable with D_2O); ^{13}C ($CDCl_3$): δ 27.28 (+ve, CH_3), 28.05 (+ve, CH_3), 93.07 (C_5), 118.17 (+ve, ArCH), 119.05 (+ve, ArCH), 120.54 (+ve, ArCH), 126.66 (ArC), 127.8 (+ve, ArCH), 137.84 (ArC), 151.89 (C_2), 153.65 (+ve, CH), 162.64 (C_6/C_4), 165.15 (C_6/C_4). Anal. Calcd for $C_{13}H_{14}N_4O_3$: C, 56.93; H, 5.14; N, 20.43. Found: C, 56.73; H, 5.44; N, 20.23%. MS (FAB mass): *m/z* 274 (M^++1).

5-[1-(2-Amino-phenylamino)-3-phenyl-allylidine]-1,3-dimethyl-pyrimidine-2,4,6-trione 2: Yellowish solid, yield 73%, m.p. 165°C, IR (KBr): 1630 (C=O), 1690 (C=O), 3600 (NH), 3670 (NH) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.32 (3H, s, CH_3), 3.48 (3H, s, CH_3), 4.49 (1H, d, *J* = 8.7 Hz, CH), 5.27 (1H, d, *J* = 8.7 Hz, CH), 6.89-7.42 (9H, m, 2XPh); ^{13}C ($CDCl_3$): δ 27.83 (+ve, CH_3), 28.02 (+ve, CH_3), 94.56 (C_5), 115.87 (+ve, ArCH), 118.18 (+ve, ArCH), 123.06 (ArC), 126.6 (+ve, ArCH), 127.5 (+ve, ArCH), 128.09 (+ve, ArCH), 133.68 (+ve, CH), 136.97 (ArC), 141.77 (C_2), 151.55 (C-N), 174.01 (C_6/C_4); Anal. Calcd for $C_{21}H_{20}N_4O_3$: C, 67.01; H, 5.36; N, 14.88. Found: C, 67.34; H, 5.25; N, 14.95%. MS (FAB mass): *m/z* 376 (M^+).

5-[(2-Amino-phenylamino)-phenyl-methylene]-1,3-dimethyl-pyrimidin-2,4,6-trione 3: Yellowish solid, yield 79%, m.p.182°C, IR (KBr): 1658 (C=O), 1697 (C=O), 3400 (NH) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.20 (3H, s, CH_3), 3.42 (3H, s, CH_3), 6.40 (1H, t, *J* = 7.5 Hz, ArH), 6.45 (1H, d, *J* = 7.5 Hz, ArH), 6.64 (1H, d, *J* = 7.8 Hz, ArH), 6.90 (1H, t, *J* = 7.5 Hz, ArH), 7.14-7.30 (5H, m, Ph); ^{13}C ($CDCl_3$): δ 27.83 (+ve, CH_3), 28.02 (+ve, CH_3), 93.0 (C_5), 115.87 (+ve, ArCH), 118.18 (+ve, ArCH), 123.06 (ArC), 126.6

(+ve, ArCH), 127.5 (+ve, ArCH), 128.09 (+ve, ArCH), 133.68 (ArC), 141.77 (C_2), 151.55 (C-N), 174.01 (C_4/C_6); Anal. Calcd for $C_{19}H_{18}N_4O_3$: C, 68.66; H, 4.85; N, 16.86. Found: C, 68.91; H, 5.15; N, 16.63%. MS (FAB mass): *m/z* 350 (M^++1).

Compound 5: White solid, yield 73%, m.p. 218 ^oC, IR(KBr): 1510 (C=O), 1650 (C=O), 3610 (NH) cm^{-1}; ^1H NMR ($CDCl_3$+TFA): δ 3.32 (6H, s, CH_3), 3.35 (6H, s, CH_3), 3.95 (4H, m, 2XCH_2), 8.52 (2H, d, *J* = 14.7 Hz, CH), 10.55 (1H, broad doublet, NH, exchanges with D_2O); ^{13}C ($CDCl_3$): δ 27.66 (+ve, CH_3), 28.48 (+ve, CH_3), 50.29 (-ve, CH_2), 91.34 (C_5), 151.76 (C_2), 161.74 (+ve, CH), 164.37 (C_6/C_4), 164.95 (C_6/C_4); Anal. Calcd. For $C_{16}H_{20}N_6O_6$: C, 48.98; H, 5.14; N, 21.42. Found: C, 49.12; H, 5.05; N, 21.58%. MS (FAB mass): *m/z* 393 (M^++1).

Compound 6: White solid, yield 70%, m.p. 155^oC, IR(KBr): 1520 (C=O), 1600 (C=O), 3600 (NH) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.81 (1H, dd, ^2J = 10.8 Hz, ^3J = 5.6 Hz, 1H of CH_2), 2.95 (1H, dd, ^2J = 10.8 Hz, ^3J = 5.8 Hz, 1H of CH_2), 3.24 (6H, s, CH_3), 3.27 (1H, m, 1H of CH_2), 3.33 (6H, s, CH_3), 3.68 (1H, m, 1H of CH_2), 4.10 (2H, d, *J* = 8.7 Hz, CH), 5.01 (2H, d, *J* = 8.7 Hz, CH), 7.25-7.40 (10H, m, 2XPh); ^{13}C ($CDCl_3$): δ 28.25 (+ve, CH_3), 28.55 (+ve, CH_3), 37.07 (-ve, CH_2), 68.76 (-ve, CH_2), 91.19 (C_5), 116.8 (+ve, CH), 122.10 (+ve, ArCH), 122.34 (+ve, ArCH), 124.96 (+ve, ArCH), 126.26 (+ve, ArCH), 127.53 (+ve, ArCH), 128.58 (+ve, ArCH), 128.8 (+ve, ArCH), 129.4 (ArC), 140.72 (ArC), 145.32 (+ve, CH), 155.32 (C-N), 163.37 (C_2), 166.7 (C_6/C_4), 171.5 (C_6/C_4); Anal. Calcd for $C_{32}H_{32}N_6O_6$: C, 64.42; H, 5.41; N, 14.09. Found: C, 64.60; H, 5.81; N, 14.35%. MS (FAB mass): *m/z* 596 (M^++1).

Compound 7: White solid, yield 72%, m.p. 155^oC, IR(KBr): 1650 (C=O), 1700 (C=O), 3620 (NH) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.84 (2H, t, *J* = 5.4 Hz, CH_2), 3.08 (2H, t, *J* = 5.4 Hz, CH_2), 3.18 (3H, s, CH_3), 3.38 (3H, s, CH_3), 6.23 (2H, broad, NH_2, exchangeable with D_2O), 7.0-7.49 (5H, m, ArH), 12.58 (1H, broad doublet, NH, exchangeable with D_2O); ^{13}C ($CDCl_3$): δ 27.64 (+ve CH_3), 27.83 (+ve CH_3), 41.11 (-ve CH_2), 44.14 (-ve, CH_2), 90.39 (C_5), 125.55 (+ve, ArCH), 128.76 (+ve, ArCH), 129.02 (+ve, ArCH), 130.12 (ArC), 134.61 (+ve, ArCH), 151.68 (C-N), 155.16 (C_2), 160.38 (C_6/C_4); Anal. Calcd. for $C_{15}H_{18}N_4O_3$: C, 59.59; H, 6.0; N, 18.53. Found: C, 59.42; H, 6.28; N, 18.75%. MS (FAB mass): *m/z* 303 (M^++1).

Compound 8: White solid, yield 64%, m.p. 170^oC, IR (KBr): 1610 (C=O), 1660 (C=O), 3300-3350 (NH) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.24 (12H, s, CH_3), 4.17 (2H, d, *J* = 9 Hz, CH), 4.42 (2H, d, *J* = 9 Hz, CH), 7.38-7.49 (10H, m, Ph); ^{13}C ($CDCl_3$): δ 25.85 (+ve, CH_3), 83.74 (C_5), 114.78 (+ve, CH), 124.76 (+ve, ArCH), 126.22 (ArC), 127.08 (+ve, ArCH), 126.20 (+ve, ArCH), 127.38 (+ve, ArCH), 138.92 (C_2), 146.90 (+ve, CH), 150.27 (C-N), 161.54 (C_6/C_4). Anal. Calcd. for $C_{30}H_{28}N_6O_6$: C, 63.37; H, 4.96; N, 14.78. Found: C, 63.58; H, 5.23, N, 14.58%. MS (FAB mass): *m/z* 568, (M^++1).

Compound 9: White solid, yield 65%, m.p. 204^oC, IR(KBr): 1645 (C=O), 1705 (C=O), 3340 (NH) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.24 (12H, s, CH_3), 7.24-7.60 (10H, m, ArH); ^{13}C ($CDCl_3$): δ 27.21 (+ve, CH_3), 87.17 (C_5), 125.98 (+ve, ArCH), 127.9 (+ve, ArCH), 128.55 (+ve, ArCH), 131.78 (ArC), 140.7 (C_2), 152.32 (C-N), 166.29 (C_6/C_4); Anal Calcd. for $C_{26}H_{24}N_6O_6$: C, 60.46; H, 4.68; N, 16.27. Found: C, 60.01; H, 5.01; N, 16.51%. MS (FAB mass): *m/z* 517 (M^++1).

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