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Solvatochromic absorption and fluorescence studies of adenine, thymine and uracil thio-derived acyclonucleosides

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ABSTRACT

Adenine, thymine and uracil thio-derived acyclonucleosides were synthesized and characterized by UV-Vis, FT-IR, ^{1}H and ^{13}C NMR spectroscopic techniques. The photophysical properties of the derivatives were evaluated in solvents with diverse polarities and at various pH values. The solvent dependent absorbance and emission spectral shifts were analysed using physical parameters of the selected solvents. The regression and correlation coefficients were calculated using multiple regression techniques. The fitting coefficients gave an estimate of the contribution of each interaction to the total spectral shift in various solutions. Multiple linear regression studies, Kamlet-Taft equation and stokes shift correlation with orientation polarizability provide valuable information concerning spectroscopic characteristics of the studied molecules.

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1. Introduction

Purines and pyrimidines are the fundamental building blocks of many biological systems mainly nucleic acids (DNA and RNA), coenzymes (NAD^+, $NADP^+$ and FAD), and signal transduction systems (cAMP and cGMP). Due to the importance of nucleosides in drug discovery and medicinal chemistry, chemists have considered their derivatives as an active field of increasing interest in synthesis and biological activity [1,2]. Acyclic nucleosides form a unique class of nucleoside analogues with wide range of activities against cancer and infections caused by viruses, microbes and other pathogenic microorganisms [3-5]. The most commonly known example is the antiviral drug (Acyclovir) which was discovered in 1988. Its activity and selectivity were the reason for synthesis of several derivatives such as ganciclovir and valganciclovir. Novel nucleosides with anticancer and/or antiviral activity, with modifications in the nucleobase and/or the sugar moiety have also increased considerably. Among sulfur and nitrogen containing nucleoside derivatives, thiosemicarbazide and thiourea derivatives demonstrate wide range of biological activities, including anticancer [6], anti-HIV [7], antibacterial [8], antiviral [9] and antifungal [10] owing to their ability of diffusion through semipermeable cell membrane [11,12].

UV-Visible spectrophotometry is the fundamental and most widely spread method for the qualitative and quantitative analysis of organic compounds, whereas spectrofluorometry involves the measurement of emitted light by a molecule following UV light excitation. The absorption or emission spectral curves are dependent on the solvent media [13]. Several intermolecular solute-solvent interactions (Ion-dipole, dipole-dipole, dipole-induced dipole and hydrogen bonding) may result in spectral changes (Position, intensity and shape) upon varying the solvent polarity which tend to modify the energy difference between ground and excited state of the chromophore [14]. Quantitative measures of these interactions were set by different scientists to understand the extent of contribution of these interactions towards the solvation phenomena.

After the discovery of DNA's structure by Watson and Crick, it was later suggested that its structure is formed as a result of electron cloud interactions (π-π interactions) between stacked base pairs and hydrogen bonding between

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neighboring nucleosides. In order to gain wider understanding of the mechanisms that control the photostability of DNA, Daniels and Hauswirth were the first to study the photophysical properties of nucleic acids in solutions [15]. However, it has been found that the photochemical properties of nucleobase derivatives are completely different from those of the natural group. Modification of the nucleobases by substitution increases the excited states lifetimes and sometimes can yield derivatives with more intense emission. For example, adenine (6-aminopurine) doesn't display as strong fluorescence emission as its close derivative 2-aminopurine and thus it is used as a substitute for adenine in DNA as a fluorescent probe to detect protein-induced local conformational changes [16]. This finding couldn't be labeled for all modified nucleobases since certain derivatives have been found to decompose rapidly in solution and this constitutes a real issue in the biological situation with several consequences. Literature survey revealed that several purine and pyrimidine derivatives as well as their metal complexes were studied for solvatochromism in different media, this included: purine derivatives [17] and pyrimidines derivatives [18-21], thiadiazolo and thiazolo pyrimidines [22,23], barbituric and thiobarbituric acid [24,25] and thiophene derivatives [26]. Concerning nucleosides synthesis, adenine and thymine ester derivatives had been prepared via N9 and N1 alkylation, respectively using ethylacrylate [27-29], where as the adenine hydrazide preparation was reported by Liu *et al*. [30].

Solvatochromism of nucleobase derivatives is of particular importance since their solvation in the aqueous medium and lipophilic membrane permeability is crucial for their functioning in biological systems. Therefore, studying the solvent effect of these derivatives is effective in modulating the solvent interactions in biological environments since various physiological processes such as transportation, signaling, metabolism are controlled by solvation [31]. Thus, much research is still needed regarding the photophysics of nucleobases and their derivatives. In recent years, experimental and theoretical studies have been made to understand and correlate the ultraviolet (UV) and emission spectra of purine and pyrimidine derivatives. This motivated us to carry out the present work, which involved the synthesis of a series of novel adenine, thymine and uracil thiosemicarbazide and thiourea derivatives. The structures were confirmed by UV-Vis, FT-IR, ^{1}H and ^{13}C NMR spectroscopy. The study the photophysics and photochemistry of the new acyclonucleosides in different solvents was performed in order to provide valuable information concerning reactivity and spectroscopic characteristics of the studied molecules and to assess the effects of polarity, hydrogen bonding formation, pH variation and related structural changes affect the absorption and fluorescence spectroscopic characteristics of the compounds.

2. Experimental

2.1. Chemicals and instruments

All chemicals, reagents and solvents were obtained from Sigma-Aldrich, Merck or Fluka Chemika and were used without further purification. The solvents used in synthesis and spectroscopic measurements were of analytical grade. Double distilled water was used for the preparation of aqueous solutions. The progress of reactions was monitored by TLC using aluminum silica gel plates 60 F_{254}. Melting points were measured with a Gallenkamp apparatus. IR spectra were recorded in KBr pellet, on a Nicolet™ iS™10 FT-IR Spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 300 MHz NMR spectrometer in DMSO, $CDCl_3$ and D_2O or D_2O/D_2SO_4, using TMS and DSS as references; chemical shifts are reported in ppm, and signals are expressed as s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). pH Measurements in the range 1-13, were made using a pH meter Eutech pH 700, previously calibrated with standard buffers pH = 4.00, 7.00 and 9.00. The electronic absorption spectra were recorded on a Jasco V-630 double beam UV-Visible spectrophotometer. The spectrofluorometric measurements were carried out on a Jasco FP-8300 spectrofluorometer. The electronic absorption and emission spectra of these compounds were recorded for dilute solutions (1×10^{-4} - 1×10^{-7} M), depending on the solubility of the studied compounds in various organic solvents of different polarities: hexane, dichloromethane (DCM), *N*,*N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), acetonitrile (CH_3CN), ethyl acetate, 1-butanol, ethanol (EtOH), methanol (MeOH) and water. The solutions were prepared just before taking measurements. The effect of pH change on the electronic absorption spectra was studied in 0.1 M HCl, 0.1 M NaOH and Britton-Robinson buffers of variable pH = 2, 3, 5, 7, 9 and 10. All measurements were carried out at room temperature.

2.2. Synthesis of the purine and pyrimidine derivatives

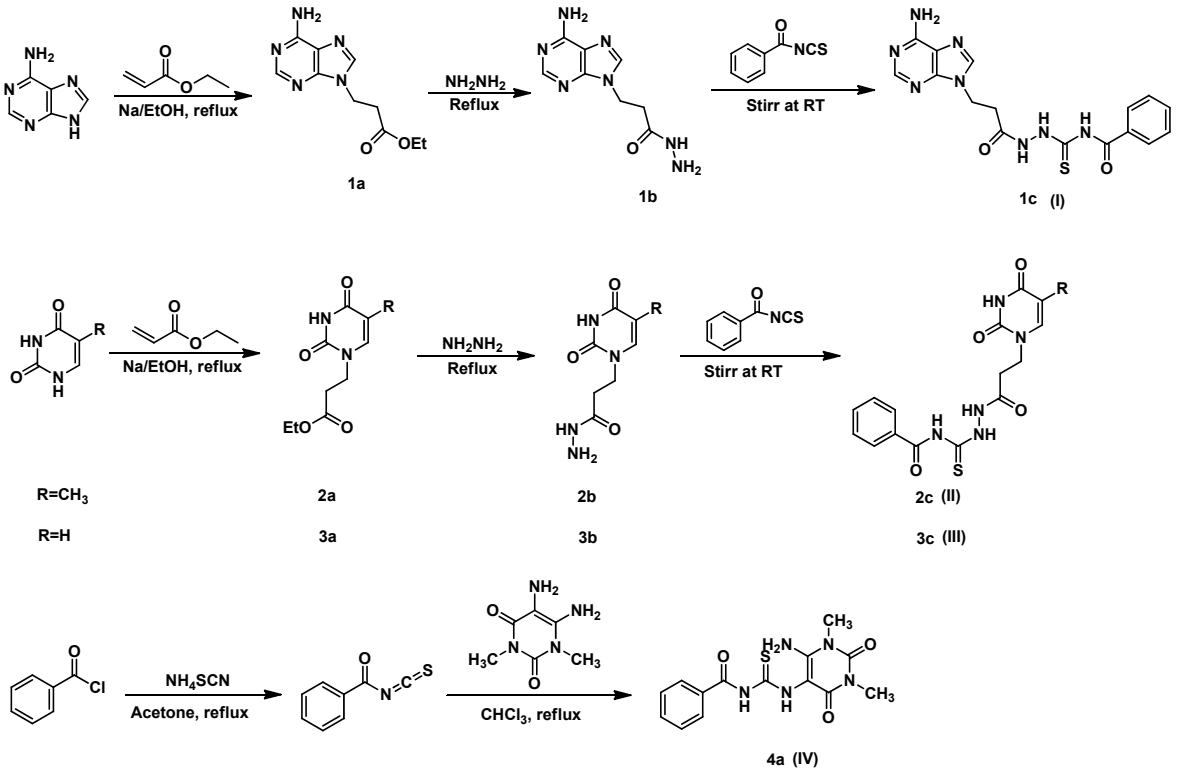
2.2.1. General procedure for the synthesis of the nucleobase ester derivatives 1a, 2a and 3a with the general formula, Nu-$(CH_2)_2COOCH_2CH_3$, via Michael addition, where NuH is adenine, uracil or thymine nucleobase

To a suspension of the corresponding nucleobase (for compound **1a** 1.0 g, 7.4 mmol; for compound **2a** 1.0 g, 7.93 mmol; for compound **3a** 1.0 g, 8.9 mmol) in absolute ethanol:benzene mixture (8:1, *v*:*v*) (for compound **1a** 25.6 mL/3.2 mL; for compound **2a** 24 mL/3 mL; for compound **3a** 36 mL/4.5 mL), a piece of sodium metal (16.7 mg, 0.4 mmol) was added carefully at room temperature, followed by addition of ethyl acrylate (1.0 g, 9.98 mmol, 1.1 mL) till the evolution of hydrogen gas ceases. The resultant mixture was then refluxed overnight. The solution was reduced to minimal volume and the obtained solid was recrystallized from ethanol. In case of uracil, oil is obtained upon solvent evaporation, which solidifies when left to cool and dry in air for sufficient time (Scheme 1).

3-(6-Aminopurine-9-yl)-propionic acid ethyl ester (**1a**): Color: White. Yield: 90%. M.p.: 167-168 °C. FT-IR (KBr, ν, cm^{-1}): 1733 ν(C=O) (ester), 1204 ν(C-O) (ester), 1609, 3315 ν(N-H) (amine), 1481 ν(C=N)(Ar-imine). ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 1.20-1.25 (t, 3H, CH_3, CH_3-CH_2-O), 2.91-2.93 (t, 2H, CH_2, N-CH_2-CH_2-CO), 4.09-4.17 (q, 2H, CH_2, CH_3-CH_2-O), 4.48-4.50 (t, 2H, CH_2, N-CH_2-CH_2-CO), 5.69 (s, 2H, NH_2, C-NH_2), 7.91 (s, 1H, Ar-CH), 8.36 (s, 1H, Ar-CH). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm) 14.1 (1C, CH_3, C*H*$_3$-CH_2-O), 34.16, 39.44, 61.55 (3C, 3CH_2, N-CH_2-CH_2-COO-CH_2-CH_3), 141.28, 153.00, 155.37 (3C, purine ring), 170.92 (1C, C=O, -CH_2-COO-CH_2-CH_3). The spectroscopic data are in agreement with the literature [27,28,32].

3-(5-Methylpyrimidine-2,4(3H)-dione-1-yl)-propionic acid ethyl ester (**2a**): Color: White. Yield: 88%. M.p.: 167-168 °C. FT-IR (KBr, ν, cm^{-1}): 1707 ν(C=O) (ester), 1198 ν(C-O) (ester), 3037 ν(=C-H) (pyrimidine ring). ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 1.2-1.3 (t, 3H, CH_3, -COO-CH_2-CH_3), 1.9 (s, 3H, CH_3, C-CH_3), 2.7-2.8 (t, 2H, CH_2, N-CH_2-CH_2-COO), 3.9-4.0 (t, 2H, CH_2, N-CH_2-CH_2-COO), 4.1-4.2 (q, 2H, CH_2, -COO-CH_2-CH_3), 7.2 (s, 1H, Ar-CH), 8.9 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm) 12.2, 14.1 (2C, 2CH_3), 33.1, 45.0, 61.1 (3C, 3CH_2, N-CH_2-CH_2-COO-CH_2-CH_3), 110.2, 141.6, 150.6, 164.1 (4C, Ar-C), 171.4 (1C, C=O). The spectroscopic data are in agreement with the literature [29].

3-(Pyrimidine-2,4(3H)-dione-1-yl)-propionic acid ethyl ester (**3a**): Color: White. Yield: 98%. M.p.: 167-168 °C. FT-IR (KBr, ν, cm^{-1}): 1711 ν(C=O) (ester), 1201 ν(C-O) (ester), 3050 ν(=C-H) (pyrimidine ring). ^{1}H NMR (300 MHz, D_2O, δ, ppm): 1.1-1.2 (t, 3H, CH_3, -COO-CH_2-CH_3), 2.5-2.6 (t, 2H, CH_2, N-CH_2-CH_2-COO), 3.6-3.7 (q, 2H, CH_2, -COO-CH_2-CH_3), 4.0-4.1 (t, 2H, CH_2, N-CH_2-



Scheme 1

CH_2-COO), 5.8 (d, 1H, CH, pyrimidine HC=CH), 7.5 (d, 1H, CH, pyrimidine HC=CH), 9.6 (s, 1H, NH). ^{13}C NMR (75 MHz, D_2O, δ, ppm): 14.1 (1C, CH_3, COO-CH_2-CH_3), 33.0, 47.1, 61.3 (3C, CH_2, N-CH_2-CH_2-COO-CH_2-CH_3) 105.4, 142.1, 150.6, 163.5 (4C, Ar-C), 171.1 (1C, C=O).

2.2.2. General procedure for the synthesis of the nucleobase-hydrazide derivatives 1b, 2b and 3b

The nucleobase hydrazides were prepared by refluxing the corresponding ester (for compound **1b**, 1.0 g, 4.24 mmol; for compound **2b** 1.0 g, 4.4 mmol; for compound **3b** 1.0 g, 4.7 mmol) with hydrazine monohydrate (for compound **1b** 0.64 g, 12.72 mmol, 0.58 mL; for compound **2b** 0.70 g, 13.98 mmol, 0.7 mL; for compound **3b**, 0.66 g, 13.18 mmol, 0.6 mL) in ethanol for 24 hrs. The solution was reduced in volume and the solid was filtered and recrystallized from ethanol. Oil is obtained in the case of uracil, which solidifies when dried under reduced pressure (Scheme 1).

3-(6-Amino-9H-purin-9-yl)propanehydrazide (**1b**): Color: White. Yield: 98.38 %. M.p.: 269-271 °C. FT-IR (KBr, ν, cm^{-1}): 1679 ν(C=O) (amide), 1647, 3325 ν(N-H) (amine), 1422 ν(C-N) (amide), 1480 ν(C=N) (Ar-imine). ^{1}H NMR (300 MHz, D_2O-D_2SO_4, δ, ppm) 3.02-3.03 (t, 2H, CH_2, N-CH_2-CH_2-CO), 4.63-4.66 (t, 2H, CH_2, N-CH_2-CH_2-CO), 8.39 (s, 1H, Ar-CH), 8.48 (s, 1H, Ar-CH). ^{13}C NMR (75 MHz, D_2O-D_2SO_4, δ, ppm): 35.3, 42.5 (2CH_2, N-CH_2-CH_2-CO), 120.5, 147.0, 147.5, 151.1, 152.3 (5C, purine ring), 172.9 (1C, C=O). The spectroscopic data are in agreement with the literature [30].

3-(5-Methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl) propanehydrazide (**2b**): Color: White. Yield: 90.65 %. M.p.: 189-190 °C. FT-IR (KBr, ν, cm^{-1}): 1692 ν(C=O) (amide), 1639, 3346 ν(N-H) (amine), 1423 ν(C-N)(amide), 3094 ν(=C-H) (pyrimidine ring). ^{1}H NMR (300 MHz, D_2O, δ, ppm): 1.85 (s, 3H, CH_3, C-CH_3), 2.57-2.61 (t, 2H, CH_2, N-CH_2-CH_2-CO), 3.99-4.03 (t, 2H, CH_2, N-CH_2-CH_2-CO), 7.42 (s, 1H, Ar-CH). ^{13}C NMR (75 MHz, D_2O, δ, ppm): 14.08 (1C, CH_3, C-CH_3), 35.61, 48.16 (2C, 2CH_2, N-CH_2-CH_2-CO), 113.58, 145.87, 154.9, 169.88 (4C, pyrimidine ring), 174.64 (1C, C=O).

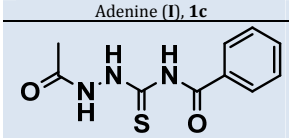
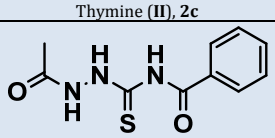
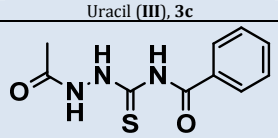
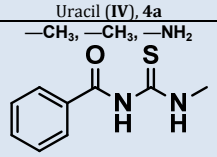
3-(2, 4-Dioxo-3, 4-dihydropyrimidin-1(2H)-yl)propane hydrazide (**3b**): Color: White. Yield: 80%. M.p.: >300 °C. FT-IR (KBr, ν, cm^{-1}): 1675 ν(C=O) (amide), 1613, 3328 ν(N-H) (amine), 1425 ν(C-N) (amide), 3080 ν(=C-H) (pyrimidine ring). ^{1}H NMR (300 MHz, D_2O-D_2SO_4, δ, ppm): 2.5-2.6 (t, 2H, CH_2, N-CH_2-CH_2-CO), 4.0-4.1 (t, 2H, CH_2, N-CH_2-CH_2-CO), 5.7-5.8 (d, 1H, pyrimidine HC=CH), 7.5-7.6 (d, 1H, pyrimidine HC=CH). ^{13}C NMR (75 MHz, D_2O-D_2SO_4, δ, ppm): 33.3, 40.5 (2C, CH_2, N-CH_2-CH_2-CO), 129.5, 146.0, 147.5, 150.1 (4C, Ar-C), 174.9 (1C, C=O).

2.2.3. General procedure for synthesis of purine and pyrimidine thiosemicarbazide derivatives 1c, 2c and 3c

A suspension of the prepared nucleobase hydrazide (for compound **1c** 0.66 g, 3.0 mmol; for compound **2c** 0.64 g, 3.0 mmol; for compound **3c** 0.59 g, 3.0 mmol) in DMSO (20 mL) was mixed with a solution of benzoylisothiocyanate in acetone (20 mL) (3.0 mmol), prepared as described in literature [33], and left to stir overnight at room temperature. The obtained yellow solution was poured onto crushed ice, and the product was obtained by salting out with brine. The product was filtered by suction filtration, washed with water several times and then recrystallized using water:ethanol mixture (1:1, *v*:*v*). The reaction steps involved in the synthesis of compound **1c**, **2c** and **3c** derivatives is presented in Scheme 1.

N-(2-(3-(6-amino-9H-purin-9-yl)propanoyl)hydrazine carbonothioyl)benzamide (**1c**) (**I**): Color: White. Yield: 80%. M.p.: 200-202 °C. FT-IR (KBr, ν, cm^{-1}): 3409, 3102 ν(N-H) (amine), 1701 ν(C=O) (amide), 1667 ν(C=N) (purine ring), 1598 ν(C=C) (purine ring), 1242 ν(C=S) (thiourea).

Table 1. Purine and pyrimidine derivatives with their functional groups studied in solvent effect.

Adenine (**I**), **1c**	Thymine (**II**), **2c**	Uracil (**III**), **3c**	Uracil (**IV**), **4a**
			

^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.95 (t, 2H, CH_2, N-CH_2-CH_2-CO), 4.45 (t, 2H, CH_2, N-CH_2-CH_2-CO), 7.25 (s, 2H, NH_2), 7.46 (m, 2H, benzene ring), 7.65 (m, 1H, benzene ring), 7.74 (d, 2H, benzene ring), 8.08 (s, 1H, purine ring CH), 8.17 (s, 1H, purine ring CH), 11.01 (s, 1H, NH, CO-NH-NH-CS-NH), 11.72 (s, 1H, NH, CO-NH-NH-CS-NH), 12.56 (s, 1H, NH, CO-NH-NH-CS-NH). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 35.6, 50.1(2C, CH_2, N-CH_2-CH_2-CO), 127.8, 128.9, 132.2 (6C, Ar-C, benzene ring C), 119.8, 143.7, 150.9, 152.2, 156.8 (5C, Ar-C, purine ring C), 165.6, 176.1 (2C, C=O), 182.4 (1C, C=S).

3-Benzoyl-1-[3-(thymine-1-yl)propamido]thiourea (**2c**) (**II**): Color: White. Yield: 76%. M.p.: 199-201 °C. FT-IR (KBr, ν, cm^{-1}): 3344, 3110 ν(N-H) (amine), 1697 ν(C=O) (amide), 1670 ν(C=N) (pyrimidine ring), 1595 ν(C=C) (pyrimidine ring), 1217 ν(C=S) (thiourea). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.7 (s, 3H, CH_3, pyrimidine ring), 2.7-2.8 (t, 2H, CH_2, N-CH_2-CH_2-CO), 3.9-4.0 (t, 2H, CH_2, N-CH_2-CH_2-CO), 7.4-7.6 (m, 5H, benzene ring), 7.7-7.8 (s, 1H, CH, pyrimidine ring), 10.9 (s, 1H, NH, CO-NH-NH-CS-NH), 11.0 (s, 1H, NH, CO-NH-NH-CS-NH), 11.3 (s, 1H, NH, CO-NH-NH-CS-NH), 11.8 (s, 1H, NH pyrimidine ring). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 12.1 (1C, CH_3), 34.8, 50.1 (2C, CH_2), 110.6, 127.8, 128.9, 132.6, 139.3 (Ar-C), 150.8, 163.7, 164.6 (3C, C=O), 181.4 (1C, C=S).

3-Benzoyl-1-[3-(uracil-1-yl)propamido]thiourea (**3c**) (**III**): Color: White. Yield: 65%. M.p.: 247-249 °C. FT-IR (KBr, ν, cm^{-1}): 3434, 3168 ν(N-H) (amino), 1706 ν(C=O) (amide), 1674 ν(C=N) (pyrimidine ring), 1593 ν(C=C) (pyrimidine ring), 1271(νC=S) (thiourea). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.7-2.8 (t, 2H, N-CH_2-CH_2-CO), 3.8-3.9 (t, 2H, N-CH_2-CH_2-CO), 5.45 (d, 1H, CH), 7.5-7.8 (m, 5H, benzene ring), 7.8, 7.9 (d, 1H, CH), 9.80 (s, 1H, NH, CO-NH-NH-CS-NH), 10.00 (s, 1H, NH, CO-NH-NH-CS-NH), 11.00 (s, 1H, NH, CO-NH-NH-CS-NH), 11.40 (s, 1H, NH pyrimidine ring). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 34.8, 49.9 (2C, CH_2), 102.2, 127.3, 128.6, 132.1, 146.1, 150.6, 163.6 (Ar-C), 153.4. 162.3, 165.5, 166.7 (4C, C=O), 184.9 (1C, C=S).

2.2.4. Synthesis and characterization of N-[[(6-amino-1,2,3, 4-tetrahydro-1,3-dimethyl-2,4-dioxo-5-pyrimidinyl)amino] thioxomethyl]-benzamide (4a) (IV)

Benzoylisothiocyanate (3.0 mmol) in acetone (20 mL), was mixed with a solution of 5,6-diamino-1,3-dimethyluracil (1.0 g, 3.0 mmol) in 30 mL chloroform, and refluxed for 3 h. The mixture was allowed to cool down to room temperature, and the separated solid was filtered under suction, washed with ethanol and recrystallized from a mixture of ethanol:water (1:1, *v*:*v*) to yield 1.76 g of light yellow product. The synthesis of uracil-thiosemicarbazide derivative is shown in Scheme 1. Color: Light yellow. Yield: 90%. M.p.: 256-258 °C. FT-IR (KBr, ν, cm^{-1}): 3441, 3355, 3114 ν(N-H), 2860 ν(C-H), 1693 ν(C=O) (amide), 1628 ν(C=N) (pyrimidine ring), 1599 ν(C=C) (pyrimidine ring), 1180 ν(C=S) (thiourea). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.5 (s, 3H, CH_3, N-CH_3), 3.1 (s, 3H, CH_3, N-CH_3), 6.9 (s, 2H, NH_2, C-NH_2), 7.5-7.9 (m, 5H, Ar-H), 11.3 (s, 1H, NH, CO-NH), 11.5 (s, 1H, NH, CS-NH). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 20.83 (1C, CH_3), 30.13 (1C, CH_3), 80.96, 128.41, 132.1, 132.19, 151.2, 153.4, 158.7 (Ar-C), 168.5 (1C, C=O), 183.3 (1C, C=S). The spectroscopic data are in agreement with the literature [34].

3. Results and discussion

The biological relevance of UV light absorption by nucleobases explains the strong scientific interest in the excited state dynamics of their derivatives. In the present paper, we report the synthesis and photophysical characterization of several acyclonucleosides.

3.1. Synthesis of organic compounds

In this study, the coupling reaction at one nitrogen atom in the heterocyclic nucleic bases is a useful method for introducing certain substituents into the heterocyclic base [35]. Adenine or uracil or thymine was refluxed with ethylacrylate and sodium metal in ethanol for 18 h to produce 3-(adenine-9-yl)propionic acid ethylester, 3-(uracil-1-yl)propionic acid ethylester and 3-(thymine-1-yl)propionic acid ethylester, respectively [27-29,36,37]; then the synthesized ester derivatives were converted to hydrazides upon reflux with hydrazine hydrate. The hydrazide was finally coupled to benzoylisothiocyanate to give the thioureido-propionohydrazide nucleobases. *N*-[[(6-Amino-1, 2, 3, 4-tetra hydro-1,3-dimethyl-2, 4-dioxo-5-pyrimidinyl)amino]thioxo methyl]-benzamide was synthesized in 90% yield by condensing 5,6-diamino-1,3-dimethyluracil and benzoyl isothiocyanate following a reported procedure [34]. Table 1 shows the different substituents that are linked to the parent nucleobases: adenine, thymine and uracil.

All the synthesized compounds were characterized by IR, ^{1}H and ^{13}C NMR techniques. ^{1}H NMR spectra of the nucleobase-ester derivatives revealed the presence of characteristic three triplets and one quartet corresponding to the 3 × CH_2 and 1 × CH_3 group of the *N*-alkyl group. The IR spectra showed characteristic ester stretching peaks at 1196 and 1725 cm^{-1} due to νC-O and νC=O groups.

The nucleobase-ester derivative was then converted to nucleobase-hydrazide via overnight reflux with hydrazine. ^{1}H NMR characterization (in D_2O) showed the two methylene group-protons in adenine, thymine and uracil hydrazide derivative resonate at compound **1b** 3.02-3.03 (t, 2H), 4.63-4.66 (t, 2H); compound **2b** 2.5-2.6 (t, 2H), 3.9-4.3 (t, 2H) and compound **3b** 2.5-2.6 (t, 2H), 4.0-4.1 (t, 2H), respectively, while the $NHNH_2$ group-protons did not appear due to exchange with solvent protons. The FT-IR spectra revealed peaks at 1679 (C=O), 1647, 3325 (NH), 1422 cm^{-1} (C-N amide) for hydrazide derivative, **1b**.

In ^{1}H NMR spectra of the adenine, thymine and uracil thiourea derivatives (**I**, **II** and **III**), the chemical shifts in the regions 9.80-12.56 ppm and 5.40-8.17 ppm are assigned to protons of -NH in thiourea derivatives and aromatic protons in the compounds, respectively. ^{13}C NMR spectra gave signals in the regions 150.8-176.1 and 181.4-184.9 ppm for –C=O and –C=S, respectively. From the FT-IR spectra of all thiosemi carbazides, the NH-stretching bands in the region 3100-3434 cm^{-1}, along with the strong bands observed at 1690 and 1665 cm^{-1} in free ligand are assigned to ν(C-O) and 1180 cm^{-1} due to ν(C=S) suggests that ligand exists in thioketo form. Absence of any band in the range 2500-2800 cm^{-1} points towards the lack of -SH stretching absorptions in the molecule. It reveals the presence of the thione group in all compounds.

Table 2. Electronic absorption λ_{max} (nm) values for purine and pyrimidine derivatives (**I-IV**) in different solvents.

Solvents	I	II	III	IV
Water	258	204, 271	261	243
DMSO	263	266	264	271
Acetonitrile	258	263	261	239
DMF	270	270	269	270
Methanol	259	267	263	239
Ethanol	258	266	262	241
1-butanol	259	263	260	241
DCM	260	263	261	241
Ethylacetate	259	263	260	268
Hexane	257	229, 262	228, 263	236, 264

Table 3. Electronic absorption λ_{max} (nm) values for purine and pyrimidine derivatives (**I-IV**) in acidic, basic solutions and Britton-Robinson buffers with different pH.

Solvents	I	II	III	IV
0.1 N NaOH	261	263	223, 260	237, 270
0.1 N HCl	258	252, 271	267	241, 270
pH = 2	258	271	266	244, 270
pH = 3	258	271	266	244, 270
pH = 5	257	271	266	247, 269
pH = 7	230	226, 267	227, 262	228, 270
pH = 9	257	255	257	242, 270
pH = 10	256	252	253	237, 270

Table 4. Emission λ_{max} (nm) values for purine and pyrimidine derivatives (**I-IV**) in different solvents.

Solvents	I	II	III	IV
Water	363, 387	388	315, 356	408
DMSO	358	359	358	356
Acetonitrile	278, 316	359	308	364
DMF	312	358	414	358
Methanol	320	292	320	383
Ethanol	329	335, 358	327	397
1-butanol	312, 347	329	360	309, 389
DCM	308	339	353	314
Ethylacetate	308, 352	317, 356	312, 355	315
Hexane	281, 313	283, 312	284, 312	293, 309

Compound **4a** was characterized by FT-IR, ^{1}H and ^{13}C NMR. ^{1}H and ^{13}C NMR spectra confirmed the structure of the compound. The most characteristic signals in the ^{1}H NMR spectrum of the compound were those corresponding to the aromatic protons (7.5-7.9 ppm) and thiourea-NH protons (11.3-11.5 ppm). Further characterization by FT-IR, the spectrum showed the appearance of the NH-stretching bands at 3441, 3355 and 3114 cm^{-1}. The strong bands observed at 1693 and 1599 cm^{-1} correspond to C=O and C=C stretching vibrations, respectively. The band at 1180 cm^{-1} indicated the presence of C=S suggesting that the ligand exists in the thioketo form.

3.2. Solvatochromism influence on spectra

The shift in the peak maximum position in absorption or emission spectra of the compounds in solvents of various polarities is expressed as solvatochromism. The difference in solvation stability of a compound between its excited and ground state upon UV light excitation can result in solvato-chromism. Thus, when using polar solvents, the derivative stability in the ground state is usually greater than the excited state and a negative solvatochromism will result. When studying the solvation stability of compounds in electronic transitions of the molecules upon excitation, only those which take part in solvatochromism are to be spotlighted in this study since they depend on both solvent used and the chromophore e.g. π-π* and n-π*, as well as intramolecular charge transfer on excitation.

3.3. UV/Vis absorption and fluorescence study of the nucleobase derivatives I-IV

To study the solvatochromism/solvatofluorochromism of the synthesized compounds, UV-Vis absorption and fluorescence spectroscopic data were collected at room temperature in various organic solvents and as well as in buffer solutions of different pH (Figure 1-3). Most of the absorption bands are >250 nm, making the compounds efficient chromophores. The spectral data are listed in Tables 2-4. As expected, the absorption maxima of the studied compounds in hexane appear in the following order **I** < **II** < **III** < **IV**, revealing a smaller HOMO-LUMO gap due to substituent effects. The absorption maxima of compounds **I**, **II** and **III** are red shifted when going from hexane to water. The highest shift in water, DMSO and DMF was observed with thymine derivative **II** (~271 nm) in comparison with adenine and uracil having the same substituent (thiosemicarbazide group). This shift to longer wavelength may be assigned to π-π* transitions (longer wavelength due to intramolecular charge transfer). Compound **IV** absorption spectrum showed two distinctive bands in all studied solvents, except in DMSO and DMF. The first band in the range 232-255 nm is labeled as π-π* due to transition of conjugated multiple bonds. The other band in the range 270-290 nm is labeled as n-π* due to transition of the C=O groups and are expected to take place from non-bonding orbitals to different π* molecular orbitals. This suggested that the compound in non-polarized ground state is more polarized in the excited state than in the ground state in protic solvents since the high energy polar structure of excitation state is stabilized. The red shift can also be explained by the hydrogen donor ability of the compound that occurs between the NH_2 group and C=O in the molecule.

λ_{em} of compounds **I-IV** in polar solvents water or DMSO have higher values when compared to the non-polar solvents hexane and DCM. Compounds **II** and **III** also showed intense emission peaks in DMSO, however compound **IV** showed intense peak in ethanol. Gradual red shift is generally observed in emission spectra with increasing solvent polarity. This is explained by the fact that the excited state of the compound is more stabilized in highly polar solvents when compared to that in less polar solvents.

Table 5. Solvent polarity and refractive index parameters used in regression equations.

Empirical solvent polarity (E)	Kirkwood dielectric function (K)	Dispersion parameter (J)	Dipolar effects parameter (H)	Solvent permanent dipole-solvent induced dipole interactions (M)	Solute permanent dipole-solvent permanent dipole interactions (N)
2.859 x 10^{-3} υ_{max}	(D-1)/(2D+1)	(D – 1)/(D + 2)	(n^2– 1)/(n^2+ 2)	(n^2– 1)/(2n^2+ 1)	J-H

Table 6. Physical parameters for used solvents.

Solvents	*D*	*n*	*E*	*K*	*M*	*N*	*π**	*α*	*β*
Water	78.5	1.330	63.1	0.491	0.171	0.757	1.09	1.17	0.18
Methanol	32.6	1.329	55.5	0.477	0.169	0.710	0.60	0.93	0.62
Ethanol	24.3	1.361	51.9	0.470	0.181	0.710	0.54	0.83	0.77
1-butanol	17.1	1.400	50.2	0.457	0.195	0.601	0.47	0.79	0.88
Ethylacetate	6.02	1.372	38.1	0.385	1.852	0.3986	0.55	0.00	0.45
Acetonitrile	37.5	1.344	46.0	0.480	0.175	0.712	0.75	0.19	0.31
DMF	36.7	1.427	43.8	0.480	0.204	0.666	0.88	0.00	0.69
DMSO	48.9	1.478	45.0	0.485	0.221	0.658	1.00	0.00	0.76
Hexane	1.88	1.3727	31.0	0.185	0.1854	0.00086	-0.04	0.00	0.00
DCM	9.10	1.4242	40.7	0.422	0.2034	0.4744	0.82	0.13	0.10

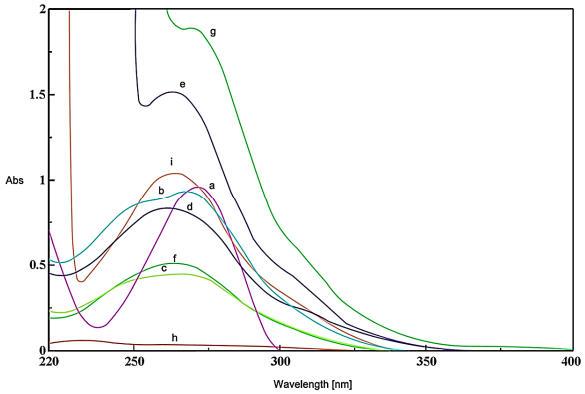


Figure 1. Electronic absorption spectra of compound **II** in different solvents: (a) water, (b) methanol, (c) ethanol, (d) 1-butanol, (e) ethyl acetate, (f) acetonitrile, (g) dimethylformamide, (h) dimethyl sulfoxide, (i) hexane, (j) DCM.

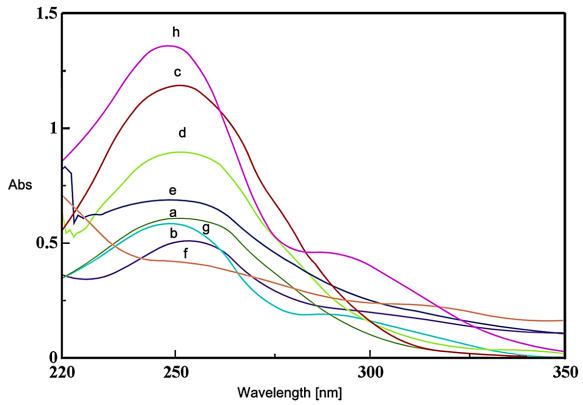


Figure 2. Electronic absorption spectra of compound **I** in different aqueous solvents: (a) 0.1 N HCl, (b) 0.1 N NaOH and Britton-Robinson buffers: (c) pH = 2, (d) pH = 3, (e) pH = 5, (f) pH = 7, (g) pH = 9, (h) pH = 10.

The electronic absorption spectra of compounds **I-IV** have been also measured in aqueous buffer solutions of varying pH values ranging from 1-13. The electronic absorption spectra of compounds **II-IV** in solutions of varying pH (1-13) undergo a bathochromic shift in the absorption band in acid medium and a hypsochromic shift in an alkaline one. The highest Δλ (11 nm in 0.1 M HCl, relative to 0.1 M NaOH) was observed with compound **II**. Thus, these compounds with an increased electronegativity of the oxygen of the carbonyl group in the aliphatic side chain forms hydrogen bonds at a low pH (acid medium). This leads to a criterion of positive oxonium ion on carbonyl group causing a new charge transfer (CT) band in absorption spectra due to the charge transfer from adjacent nitrogen atom to a positive oxonium ion. On increasing the pH of the media, the absorption band is hypsochromically shifted due to inhibition of the new CT band formed in acidic media. The spectra of compounds **I-III** in the pH range 1-5, showed one band in the UV region, representing the absorption of the protonated form of these compounds. Protonation in these derivatives occur in the primary or secondary amino groups. With increasing the pH of the medium above 5.0, deprotonation of the primary or secondary nitrogen atom and consequently decreases in the CT band intensity is observed.

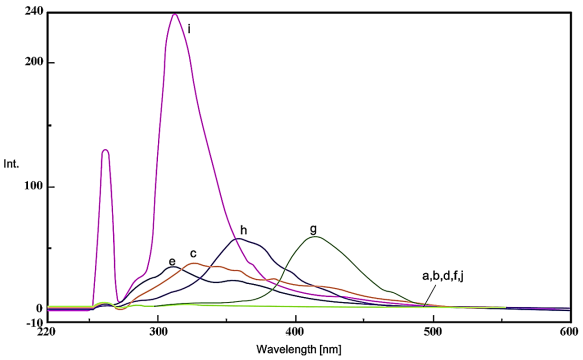


Figure 3. Electronic emission spectra of compound **III** in different solvents: (a) water, (b) methanol, (c) ethanol, (d) 1-butanol, (e) ethyl acetate, (f) acetonitrile, (g) dimethylformamide, (h) dimethyl sulfoxide, (i) hexane, (j) chloroform.

3.4. Methods of calculations and results

The UV absorption spectra (200-400 nm) as well as emission spectra (220-600 nm) were recorded at a concentration approximately 1×10^{-4}-1×10^{-7} M in ten solvents of different polarities. The relationships between solvent parameters and experimental electronic spectral values ν_{max} was studied by linear regression analysis. To understand the behavior of a solvent involved in a process, it is important to understand the solute-solvent interactions.

3.4.1. Multiple regression analysis of spectroscopic data

Several solvent parameters were used in multiple linear regression equations either each parameter alone or in combination with another as two, three or four components and were presented in Table 5 [38-43]. The solvent parameters values are presented in Table 6; where n is refractive index, *D* is dielectric constant and α, π* and β are solvatochromic parameters.

Table 7. Regression analysis values for the compounds at different λ_{max} in different solvents with significance or p-values.

Parameter	I	II	III	IV
D	0.178 (0.622)	0.418 (0.230)	0.455 (0.186)	0.129 (0.722)
		0.805 (0.005)	0.181 (0.617)	0.438 (0.206)
n	0.619 (0.057)	0.414 (0.235)	0.177 (0.625)	0.621 (0.055)
		0.089 (0.808)	0.405 (0.246)	0.273 (0.446)
E	0.102 (0.779)	0.238 (0.507)	0.558 (0.093)	0.217 (0.547)
		0.676 (0.032)	0.134 (0.713)	0.651 (0.041)
K	0.330 (0.351)	0.322 (0.364)	0.945 (0.0001)	0.229 (0.524)
		0.556 (0.095)	0.081 (0.823)	0.899 (0.001)
M	0.081 (0.823)	0.137 (0.705)	0.040 (0.913)	0.485 (0.156)
		0.270 (0.451)	0.303 (0.394)	0.219 (0.544)
N	0.251 (0.484)	0.229 (0.525)	0.881 (0.010)	0.119 (0.744)
		0.612 (0.060)	0.085 (0.815)	0.838 (0.002)
D, n	0.672 (0.123)	0.553 (0.279)	0.514 (0.342)	0.657 (0.139)
		0.805 (0.026)	0.468 (0.42)	0.550 (0.284)
D, E	0.412 (0.522)	0.436 (0.477)	0.560 (0.268)	0.509 (0.351)
		0.810 (0.024)	0.460 (0.435)	0.658 (0.137)
n, E	0.642 (0.156)	0.420 (0.507)	0.717 (0.08)	0.623 (0.179)
		0.708 (0.087)	0.406 (0.532)	0.884 (0.005)
D, n, E	0.674 (0.272)	0.656 (0.306)	0.725 (0.187)	0.686 (0.251)
		0.813 (0.073)	0.527 (0.553)	0.934 (0.004)
E,K	0.619 (0.184)	0.787 (0.034)	0.970 (0.0001)	0.627 (0.174)
		0.680 (0.114)	0.303 (0.714)	0.900 (0.003)
E, M	0.160 (0.913)	0.246 (0.804)	0.609 (0.198)	0.488 (0.386)
		0.677 (0.117)	0.394 (0.555)	0.651 (0.145)
E, N	0.601 (0.208)	0.788 (0.034)	0.929 (0.001)	0.569 (0.255)
		0.683 (0.111)	0.370 (0.598)	0.841 (0.014)
K, M	0.331 (0.666)	0.378 (0.582)	0.969 (0.0001)	0.582 (0.235)
		0.582 (0.235)	0.305 (0.711)	0.901 (0.003)
K, N	0.501 (0.364)	0.553 (0.279)	0.975 (0.0001)	0.595 (0.216)
		0.654 (0.142)	0.086 (0.974)	0.928 (0.001)
M,N	0.252 (0.795)	0.307 (0.707)	0.925 (0.01)	0.548 (0.287)
		0.622 (0.18)	0.303 (0.713)	0.838 (0.014)
E, K, M	0.649 (0.318)	0.788 (0.101)	0.982 (0.0001)	0.729 (0.181)
		0.682 (0.258)	0.505 (0.594)	0.902 (0.013)
E, K,N	0.619 (0.374)	0.793 (0.095)	0.977 (0.0001)	0.655 (0.307)
		0.686 (0.251)	0.455 (0.689)	0.947 (0.02)
E, M, N	0.617 (0.378)	0.789 (0.1)	0.955 (0.01)	0.709 (0.213)
		0.684 (0.254)	0.530 (0.546)	0.841 (0.049)
K, M, N	0.546 (0.515)	0.553 (0.502)	0.982 (0.0001)	0.676 (0.269)
		0.654 (0.308)	0.327 (0.866)	0.945 (0.003)
E, M, N, K	0.653 (0.515)	0.793 (0.216)	0.985 (0.001)	0.732 (0.344)
		0.687 (0.442)	0.547 (0.719)	0.965 (0.004)

The maximum wavelength of absorption and emission spectra (λ_{max} and λ_{em}) was used in the following equation of multiple linear regression technique [44,45]:

$$y = a_o + a_1x_1 + a_2x_2 + a_3x_3 + ... + a_nx_n \quad (1)$$

where Y is the peak maximum located on the absorption or emission spectra in a given solvent; x_1, x_2, x_3, ..., are the solvent polarity parameters. a_o is the regression intercept, a_1, a_2, a_3, ..., a_n are the regression coefficients. SPSS (program of statistical package of social sciences) version 17 has been used to determine the multiple correlation coefficients (MCC) values which are considered as a measure of the goodness of fit. Correlation of a certain solvent parameter to the spectral shifts can be estimated from the value of MCC and the significance parameter (P). Thus, a high value (near one) of MCC together with the small value (near zero) of the significance parameter (P) means that the correlation is good.

Thus, spectral shifts in the investigated compounds were correlated to solvent parameters using one-parameter equation (Table 7) showed that the best MCC values for compounds **III** (0.945) and **IV** (0.899) were obtained for the K parameter, indicating significant contribution of dielectric constant on absorption peak location. However, in case of compound **II**, high correlation values (0.805) were obtained using parameter D indicating significant contribution of solvent dielectric constant. On the other hand, compound **I** showed best MCC values (0.619) with parameter n, indicating relatively moderate contribution of solvent refractive index and that only one parameter couldn't explain spectral shifts. From the results obtained, it can be concluded that combination of different solvent parameters can give better understanding of spectral shifts over single parameter correlation. The parameter E (denoting the solvent ability to form hydrogen bonds with the solute molecules) when combined with another parameter, either N or K, gave higher MCC values: 0.601 and 0.619; 0.787 and 0.788; 0.929 and 0.9; 0.841 and 0.9, respectively for compounds **I-IV**. Again, combining parameter E with two parameters K, M or N, better correlations (higher MCC values) were obtained. For example, when combining parameter E with the parameters M and N, the obtained MCC values were 0.617, 0.789, 0.955 and 0.841 for compounds **I-IV**, respectively (Table 7). Combining E, K, M and N parameters together gave the following MCC values: 0.653, 0.793, 0.985 and 0.965, for compounds **I-IV**, respectively.

In the study of solvent effect on fluorescence, one-parameter equation, Table 8, demonstrated the high MCC values of compounds **I**, **II** and **IV** (0.72, 0.763 and 0.81, respectively) were obtained using parameter D, indicated significant contribution of solvent dielectric constant. On the other hand, compound **III** showed best MCC values (0.669) with parameter n, indicating significant contribution of solvent refractive index. In addition, when combining E and D parameters, better correlation coefficient was observed except for compound **III**, and when combining E with N or K, the MCC values were higher than 0.7 in all compounds. The best MCC values were obtained with parameter E combined to M, N; N, K; and M, K. Table 8 also indicates higher MCC when combining three-parameter over two or one parameter equations. Tables 9 and 10 list the regression coefficients for E, K, M or K, M, N in combination.

Table 8. Regression analysis values for the compounds at different emission λ_{max} in different solvents with significance or p-values.

Parameter	I	II	III	IV
D	0.720 (0.029)	0.763 (0.028)	0.141 (0.697)	0.810 (0.027)
	0.677 (0.045)	0.559 (0.15)	0.205 (0.569)	0.701 (0.079)
n	0.226 (0.559)	0.219 (0.603)	0.669 (0.035)	0.321 (0.482)
	0.030 (0.939)	0.126 (0.766)	0.565 (0.088)	0.309 (0.501)
E	0.650 (0.058)	0.563 (0.146)	0.075 (0.837)	0.831 (0.020)
	0.527 (0.145)	0.316 (0.445)	0.042 (0.907)	0.929 (0.020)
K	0.562 (0.115)	0.639 (0.088)	0.506 (0.136)	0.661 (0.106)
	0.380 (0.313)	0.388 (0.342)	0.343 (0.332)	0.697 (0.082)
M	0.113 (0.771)	0.151 (0.722)	0.199 (0.581)	0.267 (0.563)
	0.221 (0.567)	0.196 (0.642)	0.116 (0.750)	0.424 (0.343)
N	0.556 (0.120)	0.619 (0.102)	0.404 (0.247)	0.776 (0.040)
	0.374 (0.322)	0.373 (0.362)	0.237 (0.510)	0.806 (0.028)
D, n	0.804 (0.044)	0.832 (0.052)	0.707 (0.088)	0.841 (0.086)
	0.694 (0.140)	0.597 (0.332)	0.632 (0.168)	0.736 (0.209)
D, E	0.733 (0.099)	0.767 (0.109)	0.151 (0.932)	0.861 (0.067)
	0.677 (0.159)	0.600 (0.328)	0.272 (0.764)	0.936 (0.015)
n, E	0.842 (0.025)	0.760 (0.116)	0.773 (0.041)	0.833 (0.094)
	0.591 (0.276)	0.430 (0.600)	0.643 (0.155)	0.929 (0.019)
D, n, E	0.868 (0.056)	0.840 (0.145)	0.783 (0.107)	0.868 (0.191)
	0.697 (0.307)	0.610 (0.559)	0.646 (0.323)	0.937 (0.070)
E, K	0.656 (0.185)	0.645 (0.261)	0.680 (0.114)	0.831 (0.095)
	0.530 (0.372)	0.388 (0.665)	0.470 (0.418)	0.932 (0.017)
E, M	0.661 (0.178)	0.566 (0.381)	0.199 (0.868)	0.831 (0.095)
	0.683 (0.152)	0.459 (0.554)	0.145 (0.929)	0.938 (0.015)
E, N	0.650 (0.193)	0.620 (0.298)	0.609 (0.197)	0.837 (0.090)
	0.547 (0.344)	0.375 (0.685)	0.359 (0.617)	0.930 (0.018)
K, M	0.562 (0.320)	0.642 (0.265)	0.518 (0.336)	0.689 (0.276)
	0.477 (0.461)	0.464 (0.545)	0.388 (0.565)	0.778 (0.155)
K, N	0.562 (0.32)	0.641 (0.267)	0.694 (0.100)	0.936 (0.015)
	0.380 (0.627)	0.390 (0.662)	0.619 (0.184)	0.945 (0.011)
M, N	0.556 (0.329)	0.619 (0.299)	0.415 (0.515)	0.785 (0.147)
	0.496 (0.428)	0.473 (0.532)	0.301 (0.718)	0.851 (0.076)
E, K, M	0.665 (0.366)	0.645 (0.496)	0.729 (0.181)	0.831 (0.263)
	0.696 (0.308)	0.480 (0.761)	0.478 (0.643)	0.938 (0.067)
E, K, N	0.730 (0.247)	0.680 (0.431)	0.713 (0.206)	0.942 (0.061)
	0.650 (0.393)	0.397 (0.858)	0.623 (0.366)	0.957 (0.041)
E, M, N	0.662 (0.372)	0.620 (0.542)	0.642 (0.331)	0.837 (0.252)
	0.709 (0.284)	0.478 (0.764)	0.382 (0.797)	0.938 (0.069)
K, M, N	0.562 (0.558)	0.647 (0.493)	0.785 (0.104)	0.943 (0.060)
	0.503 (0.661)	0.473 (0.771)	0.622 (0.368)	0.948 (0.053)
E, M, N, K	0.730 (0.450)	0.685 (0.659)	0.800 (0.202)	0.949 (0.191)
	0.738 (0.434)	0.481 (0.908)	0.626 (0.571)	0.920 (0.154)

Table 9. Regression analysis coefficients for the compounds at different λ_{max} using three-parameter *E, K, M* or (*K, M, N*).

Compound	a_0	a_1	a_2	a_3
I	260.906 (235.551)	-1.512 (-42.164)	-0.37 (-1.815)	39.122 (113.533)
II	262.225 (119.466)	-1.09 (-218.426)	-2.559 (-0.314)	260.039 (600.906)
	254.602 (268.702)	0.195 (23.885)	4.29 (-0.117)	-0.342 (-38.892)
III	211.724 (186.061)	-0.312 (-45.158)	139.576 (2.863)	3.494 (225.11)
	265.898 (259.036)	-2.195 (-8.001)	-0.186 (-1.831)	13.677 (19.775)
IV	241.055 (165.693)	10.953 (-125.443)	-1.097 (10.038)	126.911 (348.578)
	260.865 (253.546)	-0.019 (-15.685)	21.956 (-0.854)	-0.307 (57.899)

Table 10. Regression analysis coefficients for the compounds at different emission λ_{max} using three-parameter *E, K, M* or (*K, M, N*).

Compound	a_0	a_1	a_2	a_3
I	214.301 (250.262)	32.123 (10.481)	6.289 (-0.674)	1.859 (143.910)
	242.604 (328.162)	23.162 (102.252)	2.361 (17.892)	-58.728 (-129.024)
II	236.711 (215.417)	0.384 (-61.622)	180.879 (-5.851)	-1.796 (356.767)
	272.384 (311.264)	0.676 (63.162)	73.777 (15.699)	16.216 (-23.497)
III	312.775 (9.420)	-19.750 (-550.425)	-3.273 (-29.376)	419.320 (1498.794)
	314.414 (116.235)	5.468 (-384.787)	-1.506 (-4.114)	230.863 (1039.800)
IV	175.110 (526.429)	0.633 (662.034)	3.647 (9.422)	-0.980 (-1279.869)
	193.187 (486.700)	-8.271 (522.415)	-26.327 (-5.348)	3.865 (-961.628)

Therefore, the multiple-parameter equations gave high MCC values, indicating that the evaluation of solvent effects on the electronic absorption and emission spectra of the studied compounds was useful.

3.4.2. Solvent induced spectral data analysis by two-parameter equation

Two-parameter equation was applied to further estimate the solvent induced spectral shifts [45,46].

$$\nu_{solution} = \nu_{vapor} + K_1 \frac{2D-2}{2D+1} + K_2 \frac{2n^2-2}{2n^2+1} \quad (2)$$

where $\nu_{solution}$ is the wavenumber of the peak maximum in presence of solvent, ν_{vapour} is the wavenumber of the peak maximum in absence of solvent, and K_1, K_2 and ν_{vapor} are the coefficients calculated using multiple regression technique. K_1, K_2, ν_{vapor}, r^2 *(ν, D)*, r^2 *(ν, n)* and MCC for the compounds **I-IV** are calculated (Table 11 and 12). The data indicate that both D and n of solvents affect the electronic spectral properties of these compounds but with varying degree.

Table 11. Values of K_1, K_2, ν_{vapor} and correlation analysis data for the compounds using the frequency of the absorption maximum in the presence of solvent.

Compound	ν_{vap} (cm^{-1})	K_1	K_2	MCC	R^2 (ν, D)	R^2 (ν, n)
I	43014.861	-872.530	-10133.774	0.703	0.032	0.391
II	38159.427	-1268.891	1563.774	0.591	0.647	0.007
III	39961.588	-4521.662	-167.176	0.409	0.033	0.163
IV	39032.99	-2133.973	-1315.273	0.926	0.193	0.073

Table 12. Values of K_1, K_2, ν_{vapor} and correlation analysis data for the compounds using the frequency of the emission maximum in the presence of solvent.

Compound	ν_{vap} (cm^{-1})	K_1	K_2	MCC	R^2 (ν, D)	R^2 (ν, n)
I	45831.059	-8016.610	-19900.629	0.623	0.452	0.053
II	46369.571	-9389.214	-21646.939	0.713	0.504	0.071
III	60302.631	-8463.984	-61000.525	0.868	0.026	0.445
IV	22195.918	-12548.354	45648.685	0.825	0.657	0.069

Table 13. Results of the correlations with Kamlet and Taft model for for the compounds using the frequency of the absorption maximum in the presence of solvent

Compound	*vo*	*s*	*a*	*b*	*R*	*S*
I	39068.338	-779.384	665.694	-764.917	0.774	0.429
II	38389.083	-811.117	-324.534	-71.411	0.735	0.371
III	38292.840	-222.238	345.545	-359.582	0.493	0.408
IV	37778.460	-528.060	-141.679	-520.680	0.920	0.146

R: correlation coefficient, *S*: standard error.

Table 14. Results of the correlations with Kamlet and Taft model for the compounds using the frequency of the emission maximum in the presence of solvent.

Compound	*vo*	*s*	*a*	*b*	*R*	*S*
I	36752.584	-5063.865	-1655.588	-2246.8	0.787	0.227
II	35437.196	-7559.419	-286.179	34.272	0.862	0.216
III	35176.213	-4724.932	2095.740	-5726.849	0.798	0.231
IV	34710.566	-4945.657	3706.393	-754.174	0.820	0.305

R: correlation coefficient, *S*: standard error.

Table 15. Percentage contribution of the solvatochromic parameters

Compound	Absorption			Emission		
	Pπ (%)	Pα (%)	Pβ (%)	Pπ (%)	Pα (%)	Pβ (%)
I	35.266	30.122	34.612	56.48	18.46	25.06
II	67.198	26.886	5.916	95.93	3.63	0.435
III	23.964	37.261	38.774	37.65	16.70	45.64
IV	44.359	11.902	43.739	52.58	39.40	8.02

The negative values of K_1 and K_2 indicate the decrease in energy of electronic transition due to the occurrence of strong solute-solvent interaction.

3.4.3. Kamlet and Taft method

In this method, the solvent polarity and hydrogen bonding can be correlated to spectral shifts using the linear solvation energy relationship developed by Kamlet and Taft method [47]. Spectroscopic solvent polarity parameters (π*, α and β) are given in Table 6. With this analysis, UV-Vis absorption and emission spectra are correlated with different solvent properties using Equation 3.

$$\nu_{max} = \nu_o + s.\pi^* + b.\beta + a.\alpha \quad (3)$$

where ν_{max} is the wavenumber in the maximum absorption band of nucleobase derivatives; ν_o is the regression intercept; π*, α and β are solvatochromic parameters. In these equations, π* represents the solvent dipolarity/polarizability and is considered as the solvent's ability to stabilize a charge or a dipole by its own dielectric effects. The variable α represents the solvent hydrogen-bond donor (HBD) acidity and is considered as the solvent's ability to donate a proton in a solvent-to-solute hydrogen bond. The variable β represents solvent hydrogen-bond acceptor (HBA) basicity and is considered as the solvent's ability to accept a proton in a solute-to-solvent hydrogen bond [48,49]. The correlation coefficients, MCCs, are greater than 0.5 in absorption and emission spectra (except for compound **IV** in absorption spectra), revealing the applicability of Kamlet-Taft equation. The influence of solute-solvent interactions on the absorption or emission maximum can be estimated from the sign and value of the regression coefficients (s, b & a) and their values are presented in Tables 13 and 14. From the results of the regression coefficients, it summarized that bathochromic shift increases with increasing the solvent hydrogen bond acceptor basicities and the solvent dipolarity/polarizability and is indicated by the negative value of b and s coefficients. This means that the electronic excited state is more stabilized relative to the ground state. The positive sign of coefficient (a) for compounds **I** and **III** in absorption spectra and compounds **III** and **IV** in emission spectra indicates a hypsochromic shifts with increasing solvent hydrogen bond donor acidities. This indicates the stabilization of the ground state relative to the electronic excited state.

In addition, from the values of the regression coefficients, one can calculate the percentage contribution of each solvatochromic parameters. The results are given in Table 15 which shows that the solvatochromism of the compounds is mainly due to the basicity and dipolarity/polarizability.

The sign of absorption solvatochromism for each compound can be obtained by subtracting the ν_{max} in the most polar solvent from that determined in the most nonpolar solvent and it is considered as a spectral shift, Δν (Table 16). Red or blue spectral shifts can be indicated from the positive and negative signs of Δν, respectively [50,51]. All investigated compounds exhibited a positive absorption solvatochromism on increasing the solvent polarity (Table 16). This was attributed to hydrogen bonding between electron pair of nitrogen atom and the polar solvents in the investigated compounds.

Correlation was made between the predicted absorbance maxima (ν_{max}) calculated from the Kamlet and Taft equation and the experimental ν_{max} values in order to assure the quality and applicability of the equation.

Table 16. Solvatochromism of the absorption spectra of compounds **I-IV**.

Compound	(ν_{max}) most non-polar solvent (cm^{-1})	(ν_{max}) most polar solvent (cm^{-1})	Δν (cm^{-1})	Solvatochromism
I	38910.50584	38759.68992	150.8159141	+
II	38167.93893	36900.36900	1267.569928	+
III	38314.17625	38022.81369	291.362557	+
IV	37878.78788	37037.03704	841.7508418	+

Table 17. λ_{max} (abs), λ_{max} (em) and Δν (cm^{-1}) for compounds **I-IV** and Δ*f* values in different solvents.

Solvent	Compound	λ (abs)	λ (em)	Δν	Δ*f*
Water	I	258	363	11211.4806	0.320
	II	271	388	11127.1731	
	III	261	315	6568.1445	
	IV	270	408	12527.2331	
methanol	I	259	320	7360.03861	0.308
	II	267	292	3206.60818	
	III	263	320	6772.81369	
	IV	270			
Ethanol	I	258	329	8364.55314	0.288
	II	266	335	7743.23869	
	III	262	327	7586.89918	
	IV	270	397	11848.1202	
1-butanol	I	259	312	6558.75656	0.263
	II	263	329	7627.67691	
	III	260	360	10683.7607	
	IV	272	309	4402.24634	
Ethylacetate	I	259	308	6142.50614	0.199
	II	263	317	6477.07236	
	III	260	312	6410.25641	
	IV	268	315	5567.40109	
Acetonitrile	I	258	278	2788.4669	0.305
	II	263			
	III	261	308	5846.64378	
	IV	269			
DMF	I	270			0.274
	II	270			
	III	269	414	13020.1318	
	IV	270			
DMSO	I	263	358	10089.8528	0.263
	II	266	359	9738.83176	
	III	264	358	9945.82698	
	IV	271	356	8810.48136	
Hexane	I	257	281	3323.31722	-0.003
	II	262	283	2832.24989	
	III	263	284	2811.54608	
	IV	264	293	3749.09505	
DCM	I	260	308	5994.00599	0.205
	II	263	339	8524.28861	
	III	261	353	9985.56435	
	IV	270	314	5189.90328	

This is proved by the results of R^2 values of compound **I** (0.9204); compound **II** (0.6118); compound **III** (0.6586); compound **IV** (0.8456) (Figure 4).

Therefore, it was observed that the transitions of the electronic absorption spectra are sensitive to the solvent polarity and the transition (π-π*) is shifted bathochromically as the solvent polarity increases. These changes were attributed to hydrogen-bonding interaction between the solute molecule and the solvent molecule which is a clear indication that most of the solavochromism of the compounds is due to the basicity and dipolarity/polarizability i.e. β and π, respectively, rather than acidity.

3.4.4. Stokes Shift

The Stokes shift is considered as one of the parameters that can be used to estimate the spectral shift in organic solvents. Increase in the dipole moment occurring upon excitation is attributed to charge redistribution in the excited state with respect to the ground state and this leads to increase in the Stokes shift (Table 17). To verify solvent polarity effect, the Stokes shift (Δν) was plotted versus the solvent orientation polarizability Δf (function of dielectric constant and refractive index) for the compounds in various solvents by using the Lippert-Mataga equation given below [52-54]:

$$\Delta\nu = \nu_{abs} - \nu_{em} = K + \left[\frac{2(\mu_e - \mu_g)^2}{hca^3}\right]\Delta f \quad (4)$$

$$\Delta f = f(D) - f\left(n^2\right) = \frac{(D-1)}{(2D+1)} - \frac{(n^2-1)}{(2n^2+1)} \quad (5)$$

where ν_{ab} and ν_{em} are the peak absorption and emission frequencies in cm^{-1}; μ_e and μ_g are the dipole moments of each compound in their excited and ground states; *h* is Plank's constant, c is the velocity of light, a is the Onsager cavity radius for each molecule, and *K* is a constant.

The stokes shift, solvent orientation polarizability, electronic absorption and emission spectral data of the compounds **I-IV** in different media are summarized in Table 17. The large Stokes shift in polar and non-polar solvents would indicate a primarily dipolar interaction between the solute and the solvent molecules.

For compound **III**, a linear dependence of Δν on Δf was obtained with r^2 = 0.6853, which validates the Lippert-Mataga equation while excluding water, methanol, acetonitrile and ethylacetate solvents. A value of R^2 = 0.7089 was obtained in case of compound **IV** in different solvents excluding methanol, 1-butanol, acetonitrile and DMF.

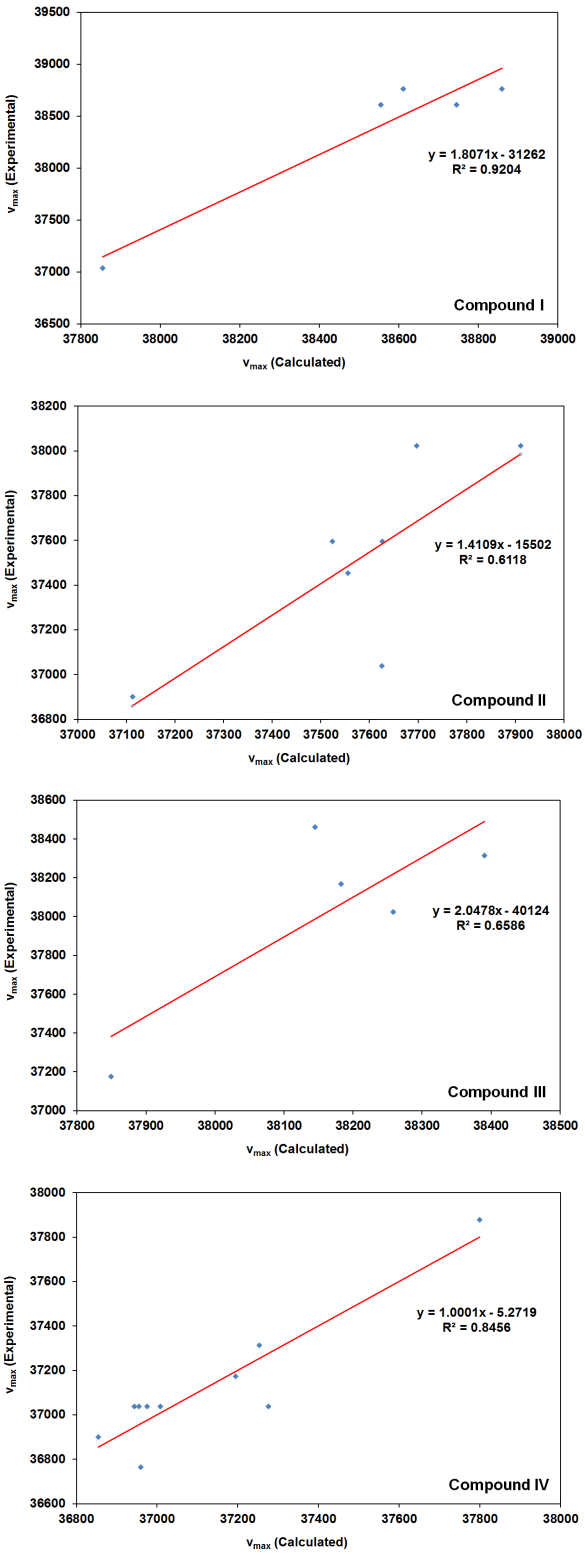


Figure 4. Linear relationship between the experimental and the calculated absorption maxima ν_{max} (in cm^{-1}) for compounds **I-IV**.

4. Conclusion

Several purine and pyrimidine acyclonucleoside derivatives have been synthesized and characterized. Measurements of absorption and fluorescence spectra in various organic solvents and in aqueous solvents at different pH were undertaken, and showed moderate to high solvatochromism. Multiple linear regression techniques were used to evaluate the effects of solvent polarity and hydrogen bonding on the spectra. Kamlet-Taft equation with the parameters π*, β and α were useful to demonstrate the effects of both types of hydrogen bonding and solvent dipolarity/polarizability. Positive solvatochromism is observed in all compounds with increasing solvent polarity. This study can provide valuable information concerning reactivity and spectroscopic characteristics of studied molecules.

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