Electronic Supplementary Material (ESI) for RSC Advances.

Facile synthesis of indole heterocyclic compounds based micellar nano anti-cancer drugs

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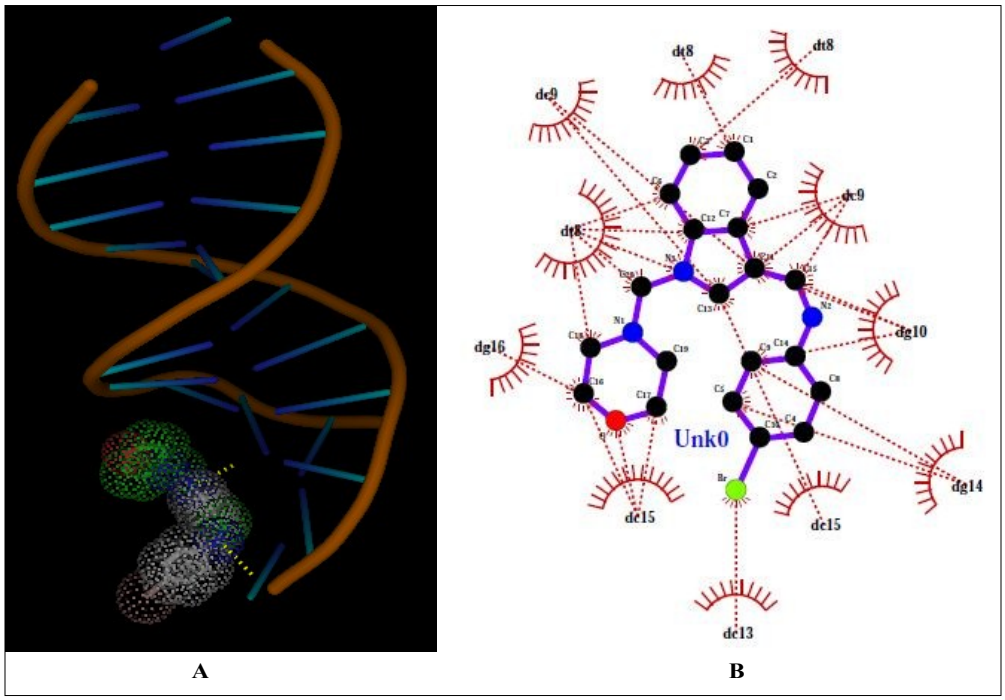
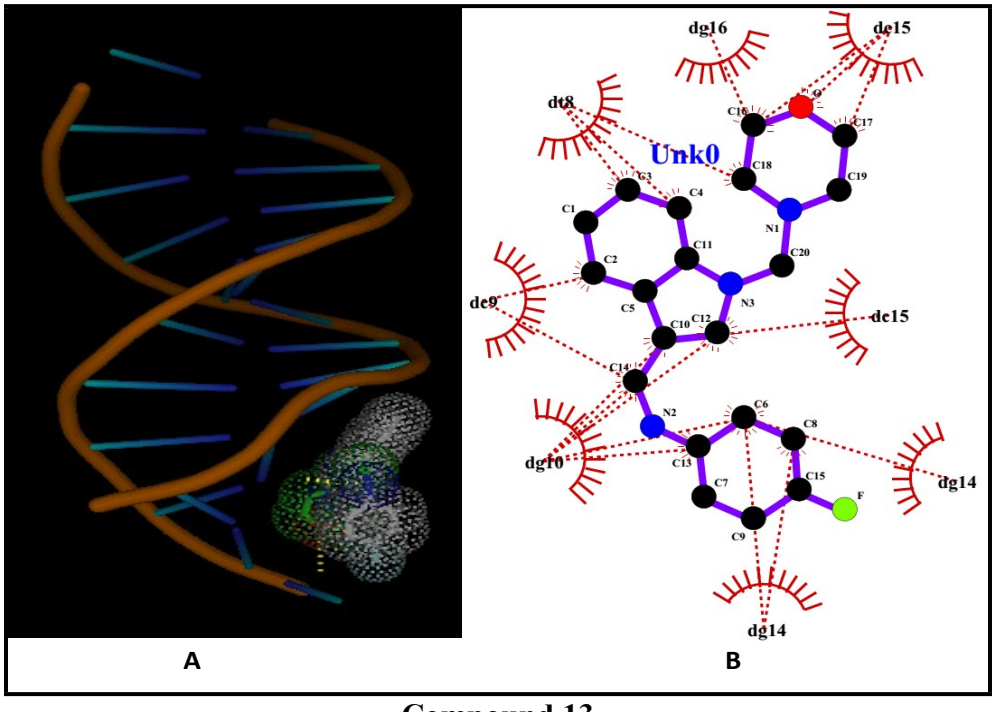
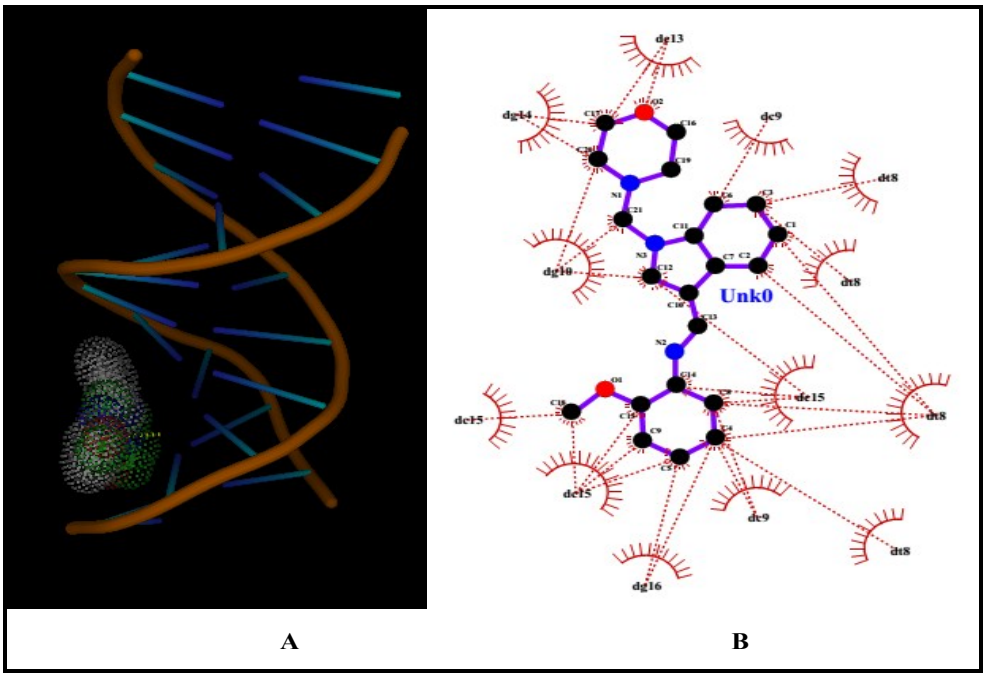
DNA DOCKING STUDIES



Compound 12



Compound 13



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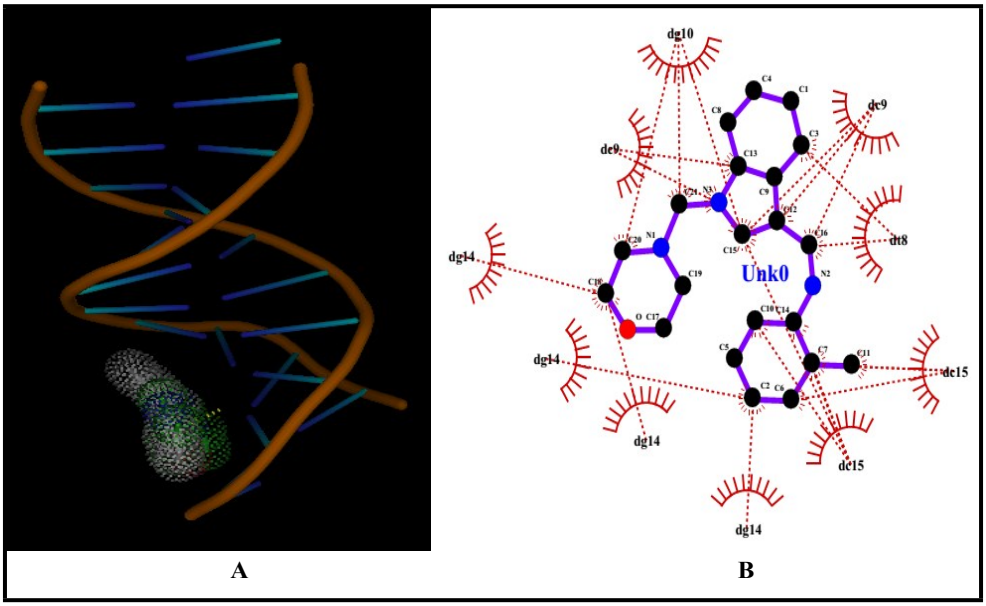

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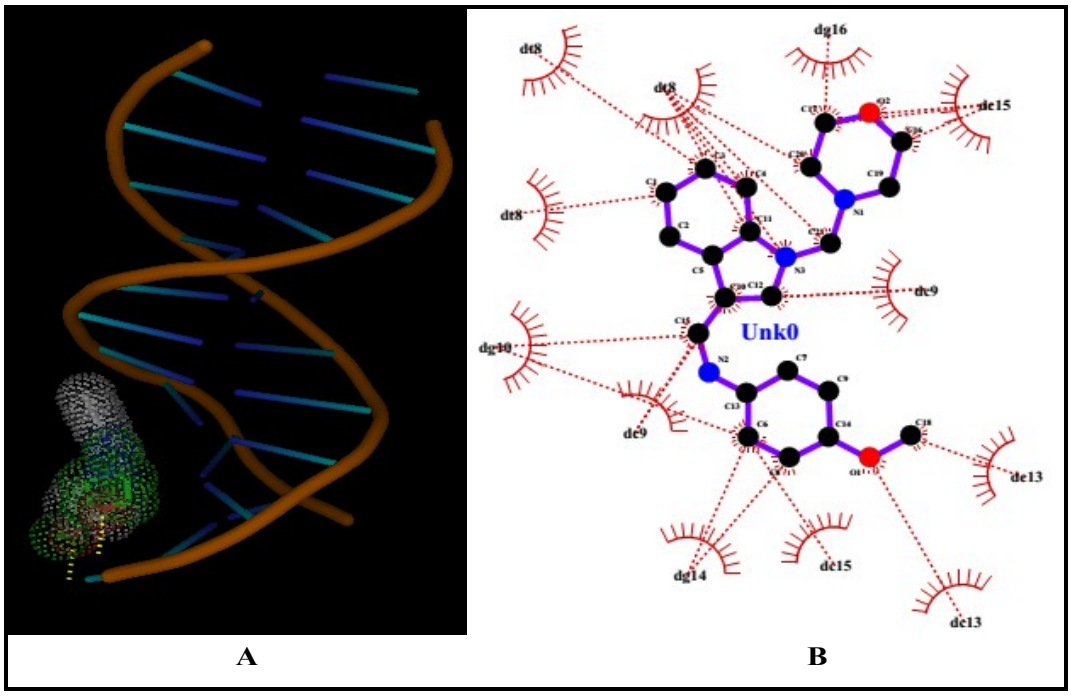
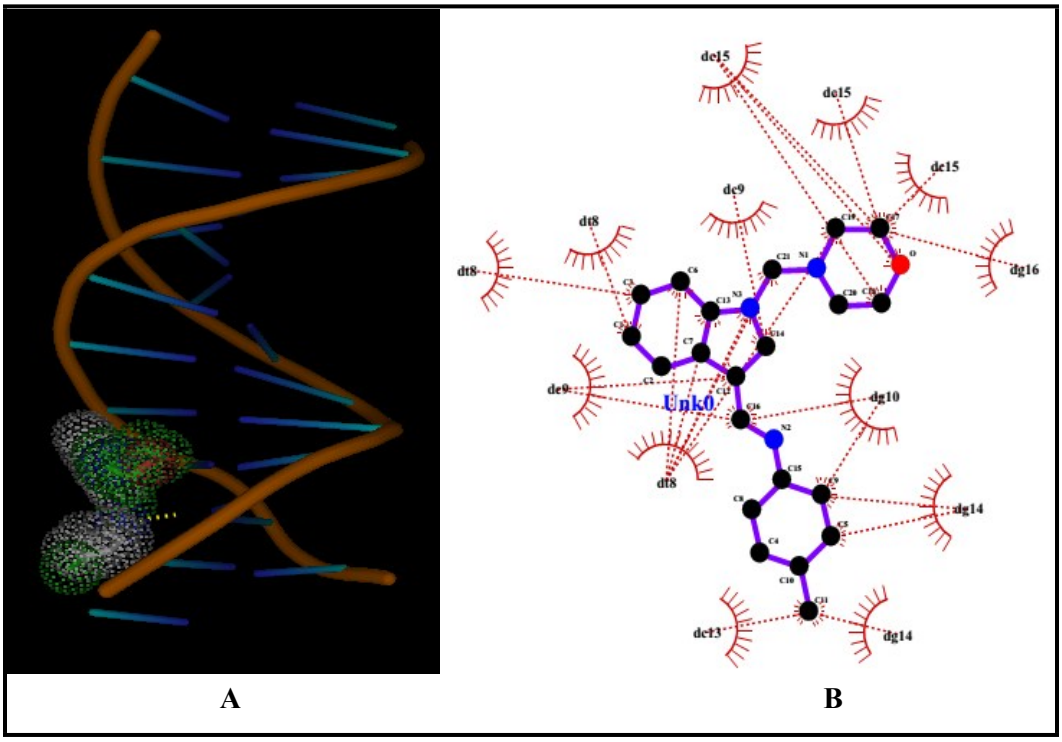


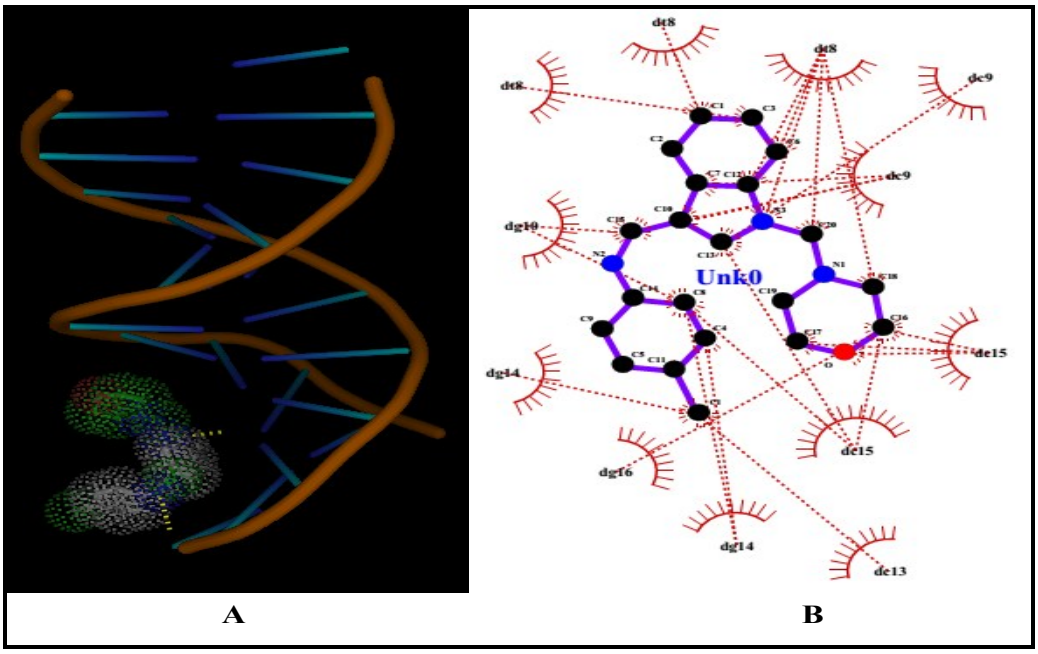
A B

Compound 16

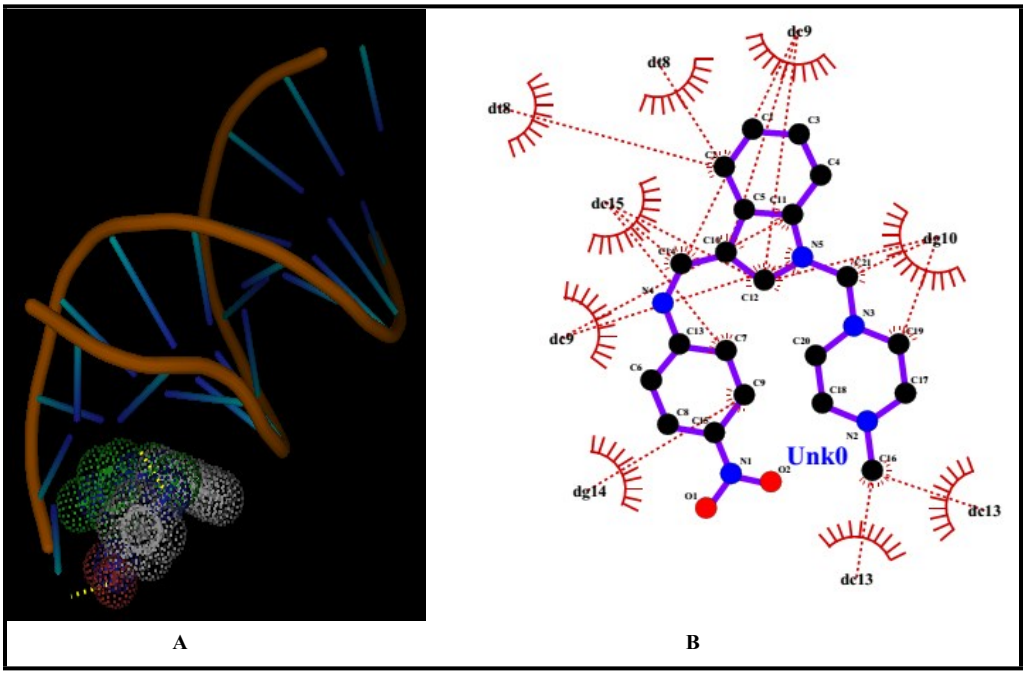


A B

Compound 17



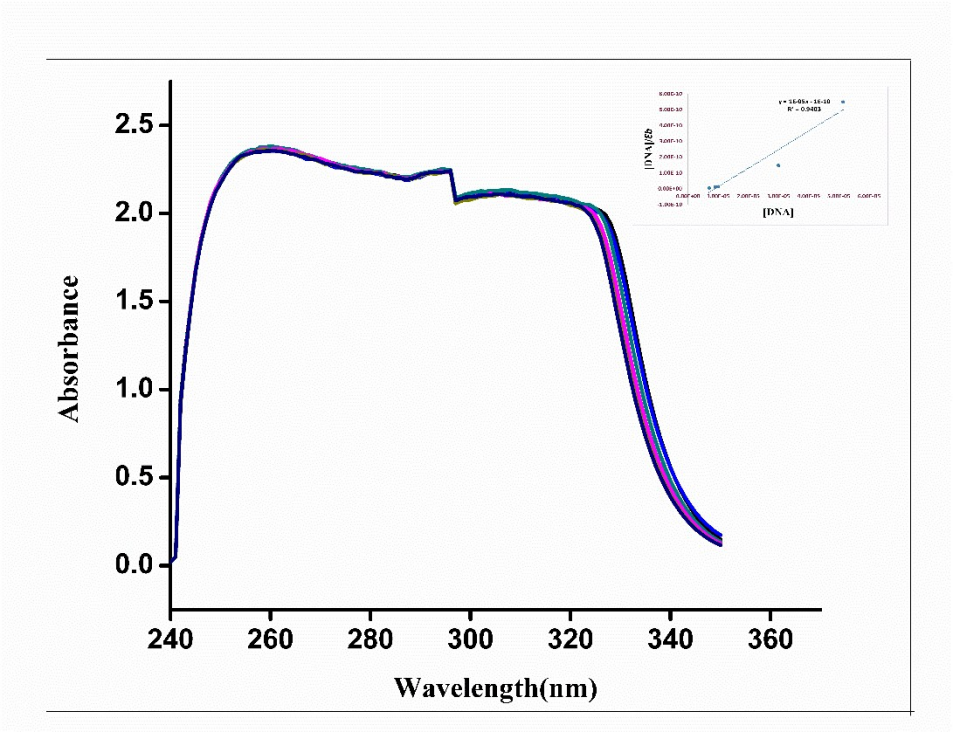
Compound 18



Compound 19

Fig. 2. Docking poses of 12,13,14, 15, 16, 17, 18, 19 with DNA (a) 3D-pose depicting vicinity and hydrogen bonding and (b) 2D-pose showing residues involved in hydrophobic interactions.

DNA Binding graph of compounds 12, 13,14, 15, 16, 17, 18, 19, 20 and 22



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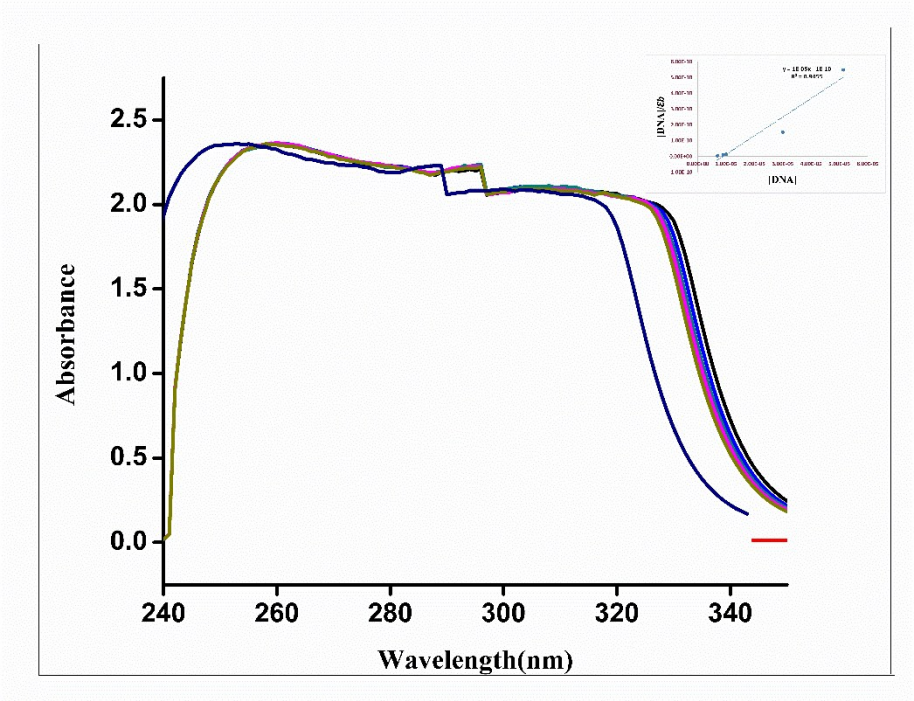

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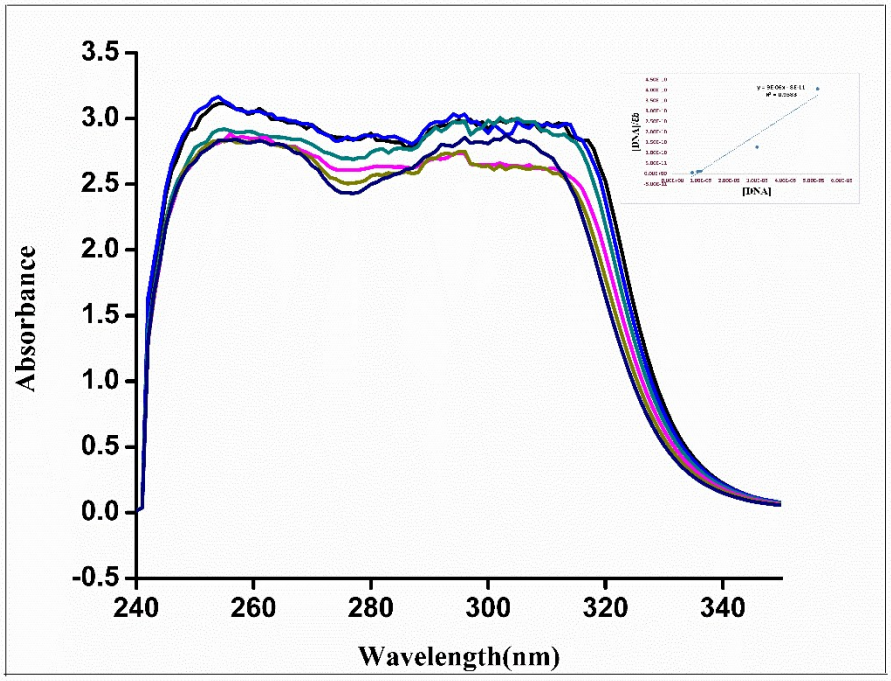
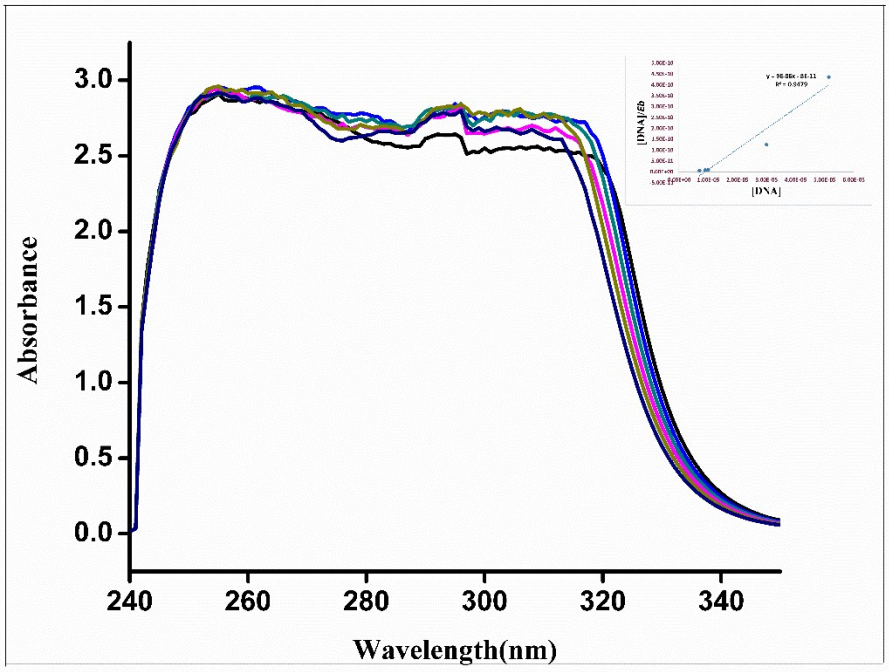


Compound 14



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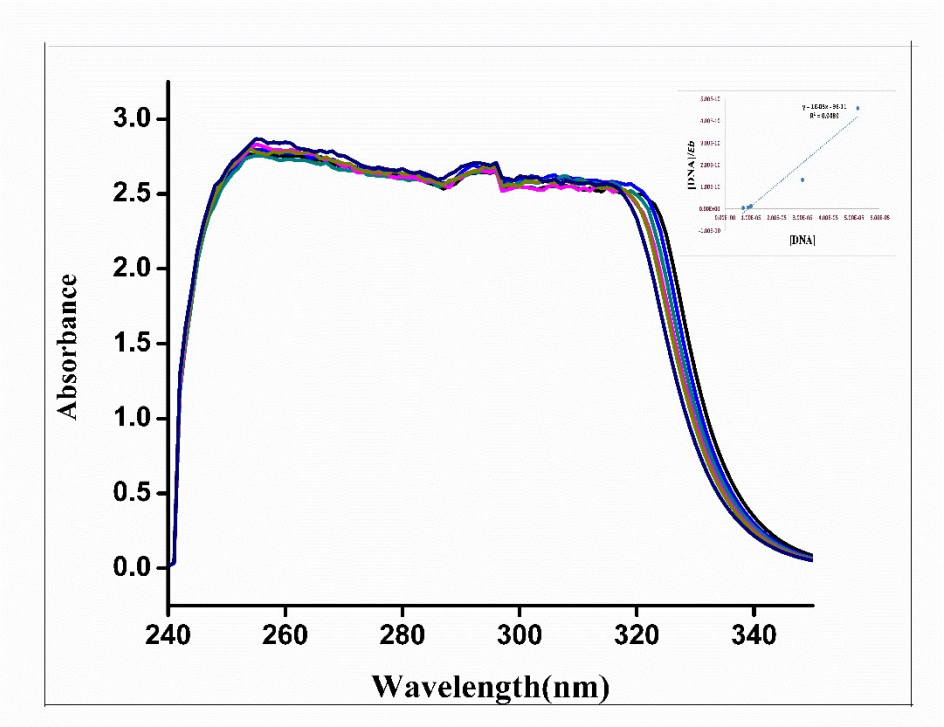

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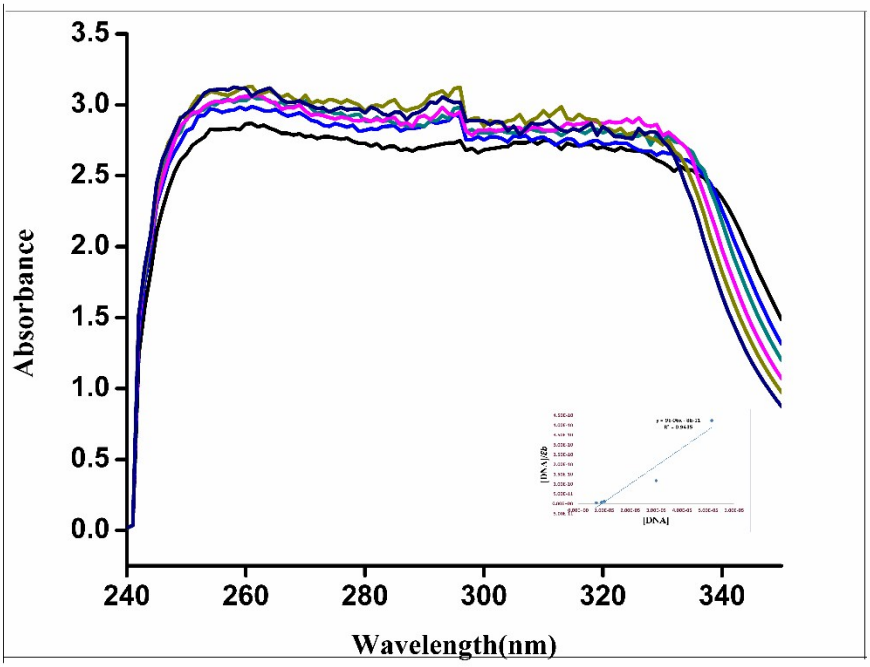

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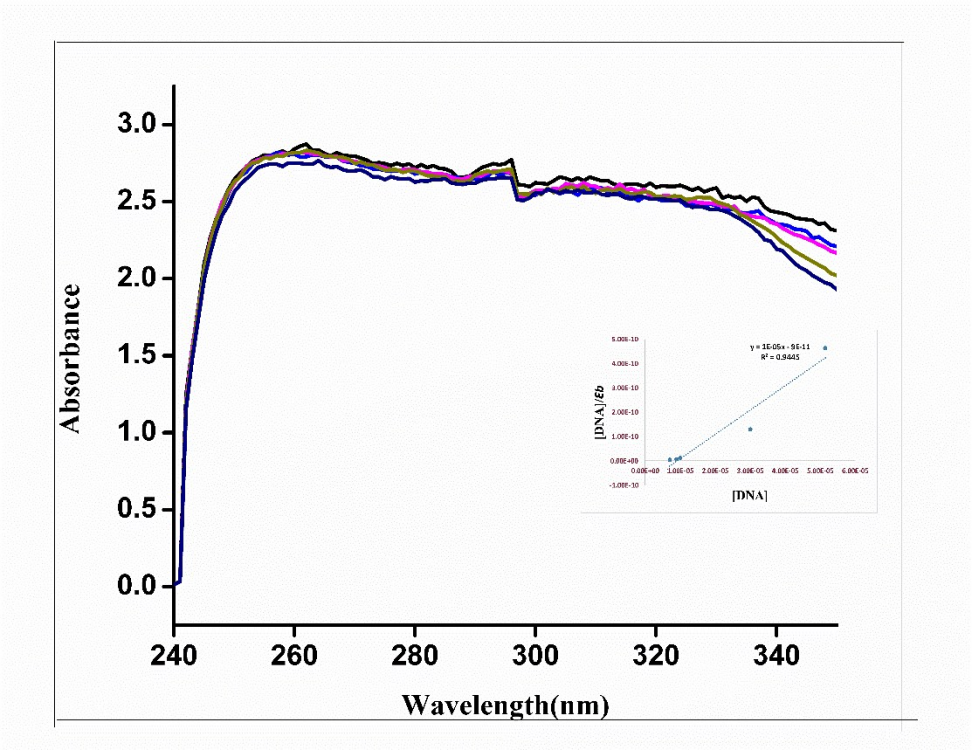
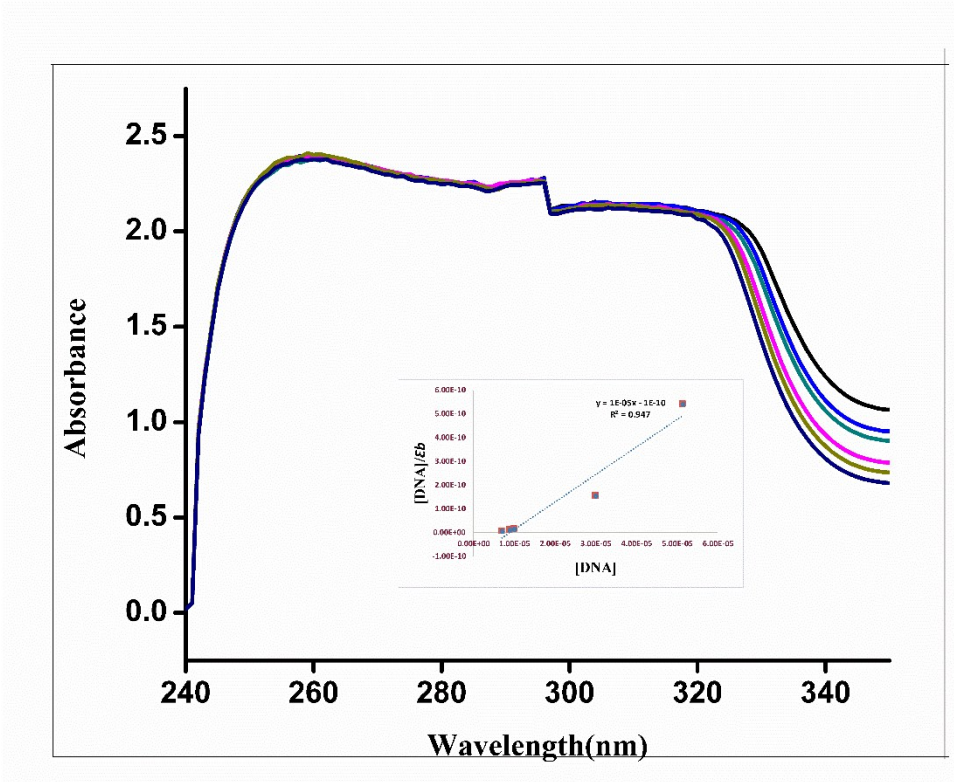
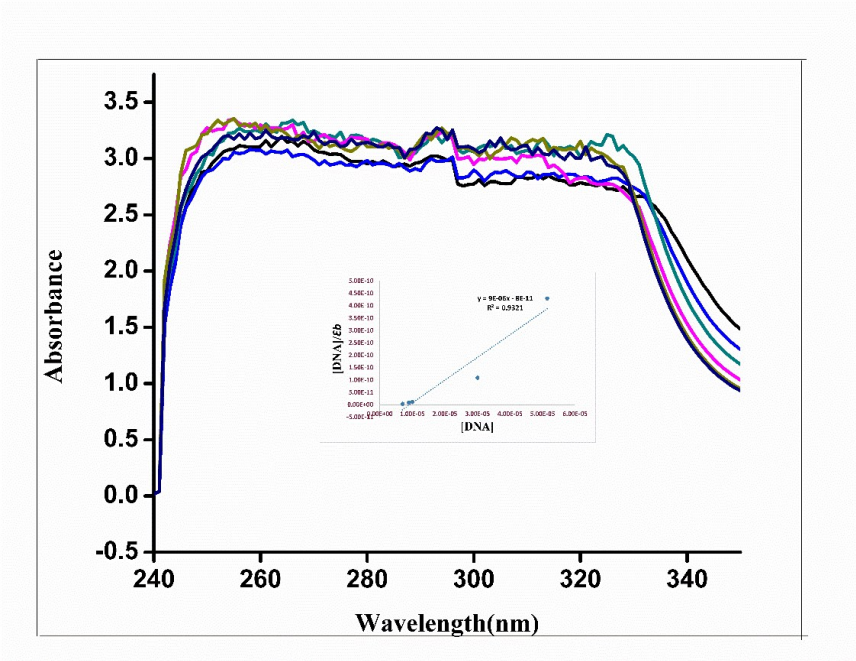


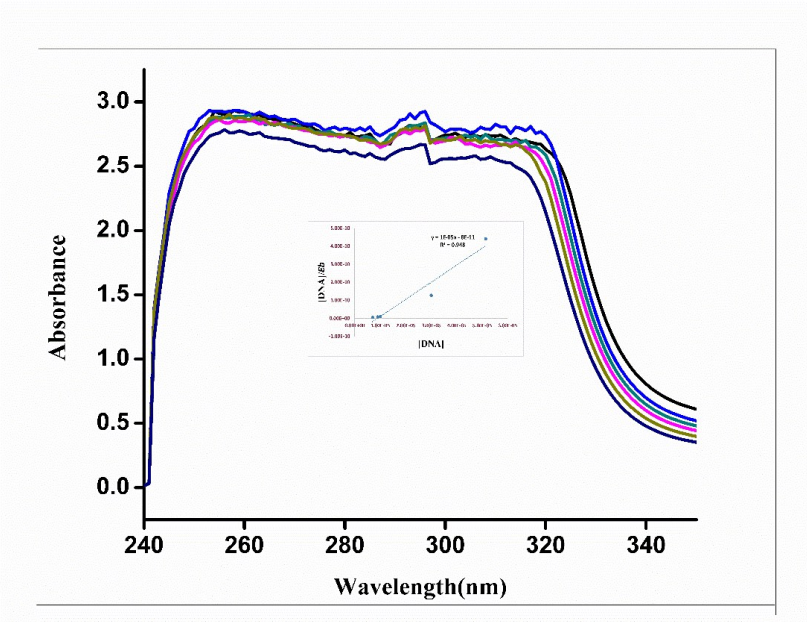
Compound 18



Compound 19



Compound 20



Compound 22

Fig. 1: Absorption spectra of 12,13,14,15,16,17,18,19,20 and 22 in the absence and presence of different Ct-DNA concentrations. Inset: plots of [DNA]/εb vs [DNA] for the absorption titration of Ct-DNA with compounds. The concentrations of DNA are 1) 5.15 x 10^{-5} 2) 3.0 x 10^{-5} 3)1.00 x 10^{-5} 4) 0.9 x 10^{-5} and5) 0.7 x 10^{-5}.

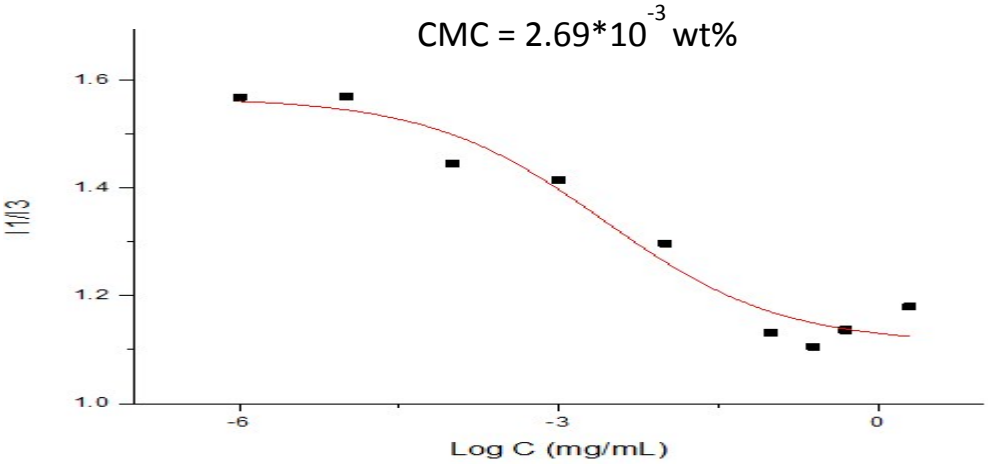


Fig 3:- Critical Micelle Concentration by pyrene 1:3 method

These were characterized by UV-Vis., FT-IR, Mass, NMR spectroscopy. The structural data is described in supplementary material.

3.1 1-[1-(morpholin-4-ylmethyl)-1H-indol-3-yl]-N-(4-nitrophenyl)methanimine (11)

Yellowish creamish powder; yield: 72%; Melting point:210-213^{0}C, IR (cm^{-1}): 1381.70 (-NO_2 sym), 1443.23 (-CH_2- bending), 1736.61 (C=N strec.), 1033.61 (-CH_2- ring strec.), 1590.32 (C=C skeleton), 3037.74 (CH aromatic stretching), 1092.88 (O-C-O), 3171.48 (N[CH_2]$_3$); ^{1}H NMR (300 MHz DMSO-d_6):7.2(s,1H,=CH), 8.33 (s, 1H, -CH=N), 7.32(dd, 2H, aromatic),

7.91(d, 2H, aromatic), 7.11(d, 2H, aromatic), 8.20(d, 2H, aromatic), 4.91(s, 2H, >CH_2), 2.51(t, 2H, >CH_2), 3.62 (t, 2H, >CH_2);ESI-MS (m/z) Calcd for $C_{20}H_{20}N_40_3$ $[M+2Na+5H]^+$: 363.4, found: 365.0.

3.2 N-(4-bromophenyl)-1-[1-(morpholin-4-ylmethyl)-1H-indol-3-yl]methanimine (12)

Light yellowish creamish powder; yield: 69%; Melting point:170-173^{0}C, IR (cm^{-1}): 676.88 (C-Br), 1449.14 (-CH_2- bending), 1648.15 (C=N strec.), 1004.19 (-CH_2- ring strec.), 1522.21 (C=C skeleton), 3092.36 (CH aromatic stretching), 1106.76 (O-C-O), 3018.83 (N[CH_2]$_3$); ^{1}H NMR (300 MHz $CHCl_3$-d_6): 7.03(s,1H,=CH), 8.23 (s, 1H, -CH=N), 7.27(dd, 2H, aromatic), 7.89(d, 2H, aromatic), 7.21(d, 2H, aromatic), 8.11(d, 2H, aromatic), 4.82(s, 2H, >CH_2), 2.62(t, 2H, >CH_2), 3.57 (t, 2H, >CH_2);ESI-MS (m/z) Calcd for $C_{20}H_{20}BrN_30$ [M -6H]$^+$: 397.3, found: 390.9.

3.3 N-(4-fluorophenyl)-1-[1-(morpholin-4-ylmethyl)-1H-indol-3-yl]methanimine (13)

Brown coloured powder; yield: 71%; Melting point:179-184^{0}C, IR (cm^{-1}): 1105.72 (C-F), 1446.65 (-CH_2- bending), 1650.54 (C=N strec.), 1006.23 (-CH_2- ring strec.), 1526.61 (C=C skeleton), 3015.48 (CH aromatic stretching), 1217.09 (O-C-O), 2867.71 (N[CH_2]$_3$); ^{1}H NMR (300 MHz $CHCl_3$-d_6): 7.17(s,1H,=CH), 8.43 (s, 1H, -CH=N), 7.44(dd, 2H, aromatic), 7.90(d, 2H, aromatic), 7.29(d, 2H, aromatic), 8.00(d, 2H, aromatic), 4.73(s, 2H, >CH_2), 2.58(t, 2H, >CH_2), 3.55 (t, 2H, >CH_2);ESI-MS (m/z) Calcd for $C_{20}H_{20}FN_30$ [M + Na-2H]$^+$: 336.4, found: 357.0.

3.4 N-(2-methoxyphenyl)-1-[1-(morpholin-4-ylmethyl)-1H-indol-3-yl]methanimine (14)

Light yellowish cream powder; yield: 73%; Melting point:112-115^{0}C, IR (cm^{-1}): 1302.18 (C-0CH_3), 1445.12 (-CH_2- bending), 1647.89 (C=N strec.), 1003.72 (-CH_2- ring strec.), 1525.10 (C=C skeleton), 3091.50 (CH aromatic stretching), 1103.93 (O-C-O), 3015.94(N[CH_2]$_3$); ^{1}H

NMR (300 MHz $CHCl_3$-d_6): 7.31(s,1H,=CH), 8.62(s, 1H, -CH=N), 3.89(s,3H,-OCH_3), 7.63(dd, 2H, aromatic), 7.87(d, 2H, aromatic), 7.32(d, 2H, aromatic), 7.16(dd, 2H, aromatic), 4.89(s, 2H, >CH_2), 3.28(t, 2H, >CH_2), 4.43 (t, 2H, >CH_2);ESI-MS (m/z) Calcd for $C_{21}H_{23}N_30_2$ [M +3K+4H]$^+$: 348.4, found: 352.0.

3.5 N-(2-methylphenyl)-1-[1-(morpholin-4-ylmethyl)-1H-indol-3-yl]methanimine (15)

Orange coloured cream powder; yield: 76%; Melting point:102-105^{0}C, IR (cm^{-1}): 2866.94 (C-CH_3), 1446.52 (-CH_2- bending), 1650.23 (C=N strec.), 1005.43 (-CH_2- ring strec.), 1526.20 (C=C skeleton), 3015.79 (CH aromatic stretching), 1217.42 (O-C-O), 2866.94(N[CH_2]$_3$); ^{1}H NMR (300 MHz $CHCl_3$-d_6): 7.32(s,1H,=CH), 8.26(s, 1H, -CH=N), 2.28(s,3H,-CH_3), 7.42(dd, 2H, aromatic), 7.91(d, 2H, aromatic), 7.21(d, 2H, aromatic), 7.27(dd, 2H, aromatic), 4.73(s, 2H, >CH_2), 3.28(t, 2H, >CH_2), 4.35 (t, 2H, >CH_2);ESI-MS (m/z) Calcd for $C_{21}H_{23}N_30$ [M + H]$^+$: 332.4, found: 332.1.

3.6 N-(4-methoxyphenyl)-1-[1-(morpholin-4-ylmethyl)-1H-indol-3-yl]methanimine (16)

Dark cream coloured powder; yield: 70%; Melting point:125-129^{0}C, IR (cm^{-1}): 1304.57 (C-OCH_3), 1447.72 (-CH_2- bending), 1651.38 (C=N strec.), 1007.55 (-CH_2- ring strec.), 1525.20 (C=C skeleton), 3015.54 (CH aromatic stretching), 1217.56 (O-C-O), 3093.58 (N[CH_2]$_3$); ^{1}H NMR (300 MHz $CHCl_3$-d_6): 7.00(s,1H,=CH), 3.71(s,3H,-OCH_3), 8.28(s, 1H, -CH=N), 7.38(dd, 2H, aromatic), 7.68(d, 2H, aromatic), 7.29(d, 2H, aromatic), 7.9(d, 2H, aromatic), 4.66(s, 2H, >CH_2), 3.18(t, 2H, >CH_2), 2.92(t, 2H, >CH_2);ESI-MS (m/z) Calcd for $C_{21}H_{23}N_30_2$ [M +3K+Na+5H]$^+$:348.4, found: 353.0.

3.7 N-(4-methylphenyl)-1-[1-(morpholin-4-ylmethyl)-1H-indol-3-yl]methanimine (17)

Orange coloured powder; yield: 61%; Melting point:161-164^{0}C, IR (cm^{-1}): 2864.32 (C-CH_3), 1445.57 (-CH_2- bending), 1649.22 (C=N strec.), 1027.93 (-CH_2- ring strec.), 1518.65

(C=C skeleton), 3016.48 (CH aromatic stretching), 1217.88 (O-C-O), 2968.13 ($N[CH_2]_3$); ^1H NMR (300 MHz $CHCl_3$-d_6): 7.21(s,1H,=CH), 2.41(s,3H,-CH_3), 8.11(s, 1H, -CH=N), 7.46(dd, 2H, aromatic), 7.78(d, 2H, aromatic), 7.41(d, 2H, aromatic), 7.90(d, 2H, aromatic), 4.46(s, 2H, >CH_2), 2.56(t, 2H, >CH_2), 2.77(t, 2H, >CH_2);ESI-MS (m/z) Calcd for $C_{21}H_{23}N_30$ [M +K+Na+5H]$^+$:332.4, found: 398.1.

3.8 N-(4-chlorophenyl)-1-[1-(morpholin-4-ylmethyl)-1H-indol-3-yl]methanimine (18)

Dark yellow coloured powder; yield: 74%; Melting point:120-123^{0}C, IR (cm^{-1}): 745.22 (C-Cl), 1449.05 (-CH_2- bending), 1646.57 (C=N strec.), 1005.73 (-CH_2- ring strec.), 1525.02 (C=C skeleton), 3016.48 (CH aromatic stretching), 1217.90 (O-C-O), 2967.84 ($N[CH_2]_3$); ^1H NMR (300 MHz $CHCl_3$-d_6): 7.35(s,1H,=CH), 8.19(s, 1H, -CH=N), 7.62(dd, 2H, aromatic), 7.96(d, 2H, aromatic), 7.22(d, 2H, aromatic), 7.96(d, 2H, aromatic), 5.00(s, 2H, >CH_2), 2.44(t, 2H, >CH_2), 4.08(t, 2H, >CH_2); ESI-MS (m/z) Calcd for $C_{20}H_{20}ClN_30$ [M +K+Na+3H]$^+$:352.86, found: 354.0.

3.9 1-{1-[(4-methylpiperazin-1-yl)methyl]-1H-indol-3-yl}-N-(4nitrophenyl)methanimine (19)

Dark yellowish creamish powder; yield: 65%; Melting point:212-220^{0}C, IR (cm^{-1}): 1371.92 (-NO_2 sym), 1450.50 (-CH_2- bending), 1643.55 (C=N strec.), 1006.21 (-CH_2- ring strec.), 1519.67 (C=C skeleton), 3021.39 (CH aromatic stretching), 2944.51 ($N[CH_2]_3$); ^1H NMR (300 MHz DMSO-d_6): 7.31(s,1H,=CH), 8.39 (s, 1H, -CH=N), 7.42(dd, 2H, aromatic), 8.00(d, 2H, aromatic), 7.11(d, 2H, aromatic), 8.10(d, 2H, aromatic), 4.91(s, 2H, >CH_2), 2.62(t, 2H, >CH_2), 4.12 (t, 2H, >CH_2);ESI-MS (m/z) Calcd for $C_{21}H_{23}N_50_2$ [M +2K+Na-4H]$^+$:362.4, found: 459.1.

3.10 N-(4-fluorophenyl)-1-{1-[(4-methylpiperazin-1-yl)methyl]-1H-indol-3-yl}methanimine (20)

Light yellow coloured powder; yield: 75%; Melting point:186-187^{0}C, IR (cm^{-1}): 1093.83 (C-F), 1450.36 (-CH_2- bending), 1647.71 (C=N strec.), 1032.10 (-CH_2- ring strec.), 1505.54 (C=C skeleton), 3016.34 (CH aromatic stretching), 2968.95 (N[CH_2]$_3$); ^{1}H NMR (300 MHz DMSO-d_6): 7.22s,1H,=CH), 8.31 (s, 1H, -CH=N), 7.43(dd, 2H, aromatic), 8.12(d, 2H, aromatic), 7.31(d, 2H, aromatic), 8.24(d, 2H, aromatic), 4.72(s, 2H, >CH_2), 2.74(t, 2H, >CH_2), 3.61 (t, 2H, >CH_2); ESI-MS (m/z) Calcd for $C_{21}H_{23}FN_4$ [M +7H]$^+$:349.5, found: 356.0.

3.11 N-(2-methoxyphenyl)-1-{1-[(4-methylpiperazin-1-yl)methyl]-1H-indol-3yl}methanimine (21)

Dark yellow coloured powder; yield: 62%; Melting point:108-110^{0}C, IR (cm^{-1}): 1366.43 (C-OCH_3), 1445.02 (-CH_2- bending), 1656.32 (C=N strec.), 1010.70 (-CH_2- ring strec.), 1527.29 (C=C skeleton), 3015.24 (CH aromatic stretching), 2951.62 (N[CH_2]$_3$); ^{1}H NMR (300 MHz $CHCl_3$-d_6): 7.25(s,1H,=CH), 8.42(s, 1H, -CH=N), 3.81(s,3H,-OCH_3), 7.53(dd, 2H, aromatic), 7.91(d, 2H, aromatic), 7.29(d, 2H, aromatic), 7.11(dd, 2H, aromatic), 4.89(s, 2H, >CH_2), 3.28(t, 2H, >CH_2), 3.45 (t, 2H, >CH_2);ESI-MS (m/z) Calcd for $C_{22}H_{26}N_40$ [M -4H]$^+$:361.5, found: 356.0

3.12 N-(4-methylphenyl)-1-{1-[(4-methylpiperazin-1-yl)methyl]-1H-indol-3-yl}methanimine (22)

Whitish coloured powder; yield: 60%; Melting point:157-159^{0}C, IR (cm^{-1}): 2942.18 (C-CH_3), 1450.93 (-CH_2- bending), 1655.04 (C=N strec.), 1011.20 (-CH_2- ring strec.), 1519.55 (C=C skeleton), 3092.96 (CH aromatic stretching), 3017.74 (N[CH_2]$_3$); ^{1}H NMR (300 MHz DMSO-d_6): 7.21(s,1H,=CH), 2.32(s,3H,-CH_3), 8.11(s, 1H, -CH=N), 7.16(dd, 2H, aromatic),

7.82(d, 2H, aromatic), 7.25(d, 2H, aromatic), 7.80(d, 2H, aromatic), 4.36(s, 2H, $>CH_2$), 2.56(t, 2H, $>CH_2$), 2.77(t, 2H, $>CH_2$); ESI-MS (m/z) Calcd for $C_{22}H_{26}N_4$ $[M+Na+2H]^+$:345.5, found: 347.0.

3.13 N-(4-chlorophenyl)-1-{1-[(4-methylpiperazin-1-yl)methyl]-1H-indol-3-yl}methanimine (23)

Yellow coloured powder; yield: 67%; Melting point:136-138^{0}C, IR (cm^{-1}): 745.22 (C-Cl), 1446.92 (-CH_2- bending), 1642.52 (C=N strec.), 1034.60 (-CH_2- ring strec.), 1591.44 (C=C skeleton), 3016.02 (CH aromatic stretching), 2922.00 (N[CH_2]$_3$); ^{1}H NMR (300 MHz $CHCl_3$-d_6): 7.51(s,1H,=CH), 8.45(s, 1H, -CH=N), 7.55(dd, 2H, aromatic), 7.78(d, 2H, aromatic), 7.32(d, 2H, aromatic), 7.85(d, 2H, aromatic), 5.33(s, 2H, $>CH_2$), 2.33(t, 2H, $>CH_2$), 4.17(t, 2H, $>CH_2$);ESI-MS (m/z) Calcd for $C_{21}H_{23}ClN_4$ $[M+K-H]^+$:366.0, found: 405.1.

Docking studies

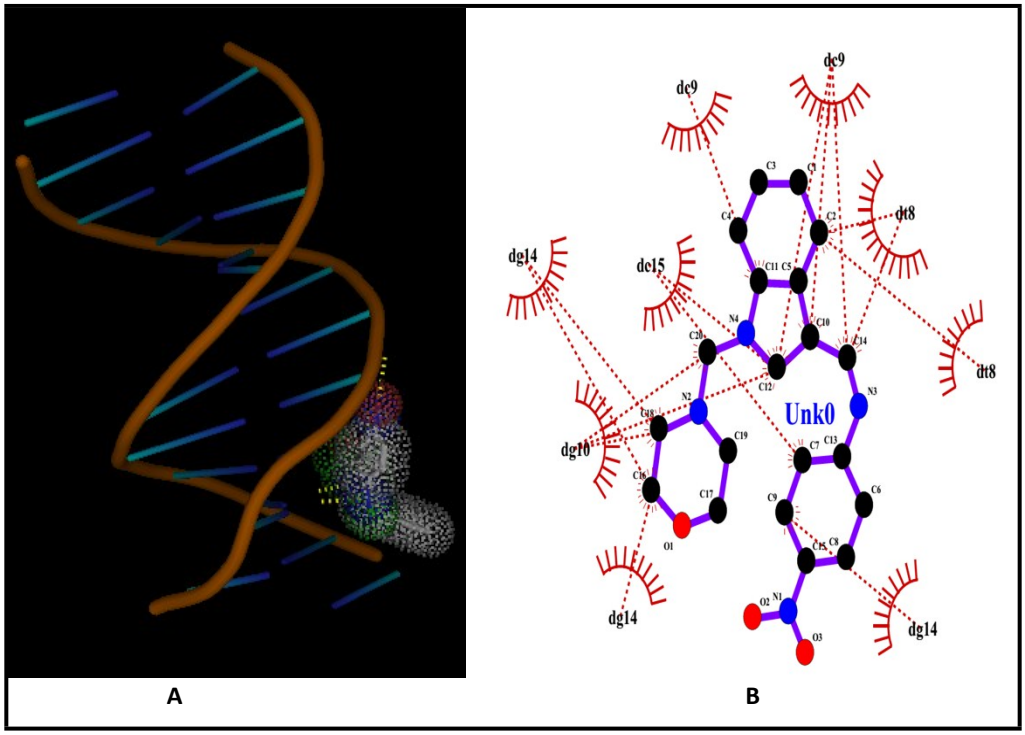


Fig. SI 1. Docking poses of **11** with DNA (a) 3D-pose depicting vicinity and hydrogen bonding and (**b**) 2D-pose showing residues involved in hydrophobic interactions.

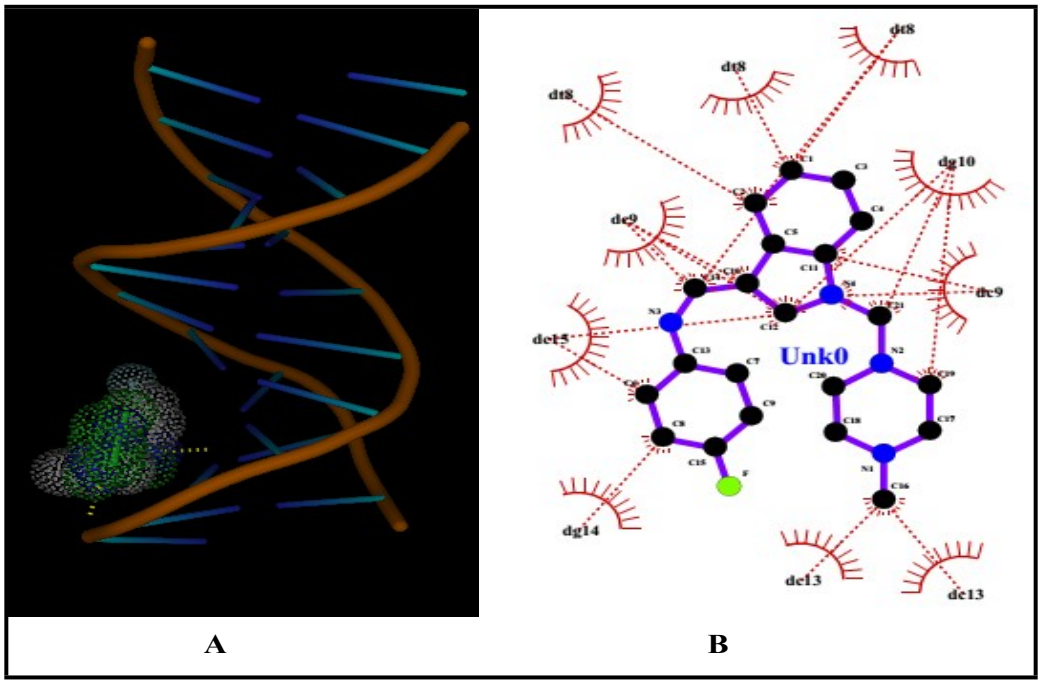


Fig. SI 2. Docking poses of **20** with DNA (a) 3D-pose depicting vicinity and hydrogen bonding and (**b**) 2D-pose showing residues involved in hydrophobic interactions.

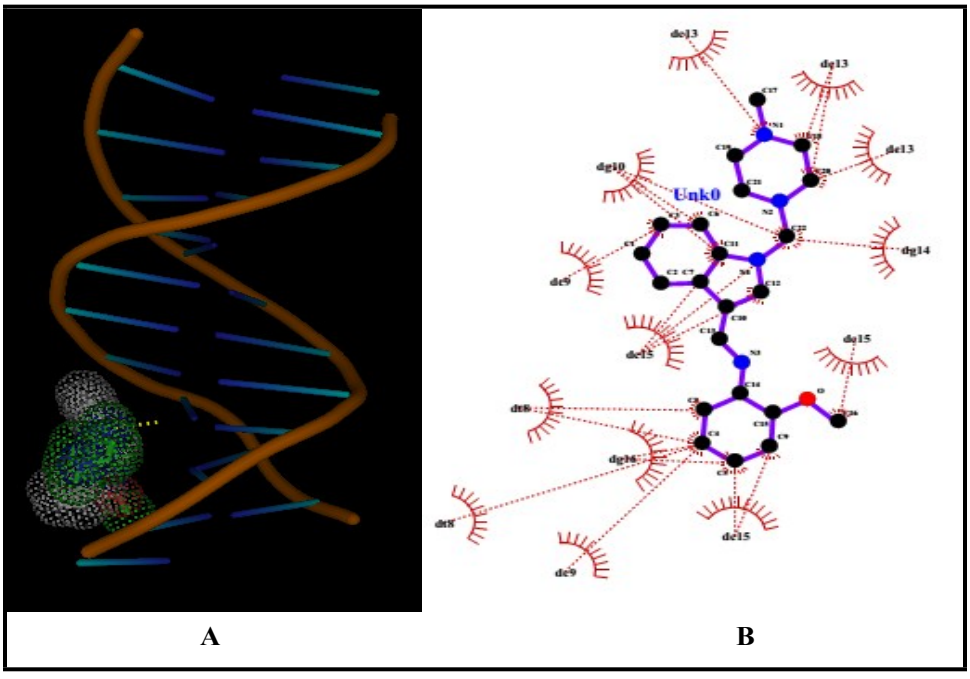


Fig. SI 3. Docking poses of **21** with DNA (a) 3D-pose depicting vicinity and hydrogen bonding and (**b**) 2D-pose showing residues involved in hydrophobic interactions.

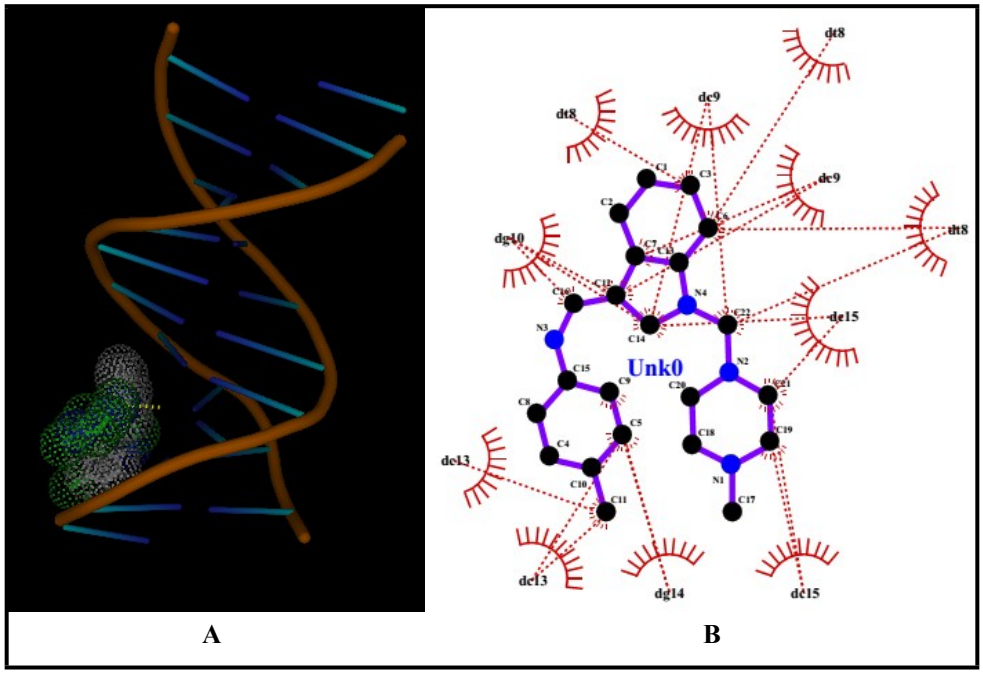


Fig. SI 4. Docking poses of **22** with DNA (a) 3D-pose depicting vicinity and hydrogen bonding and (**b**) 2D-pose showing residues involved in hydrophobic interactions.

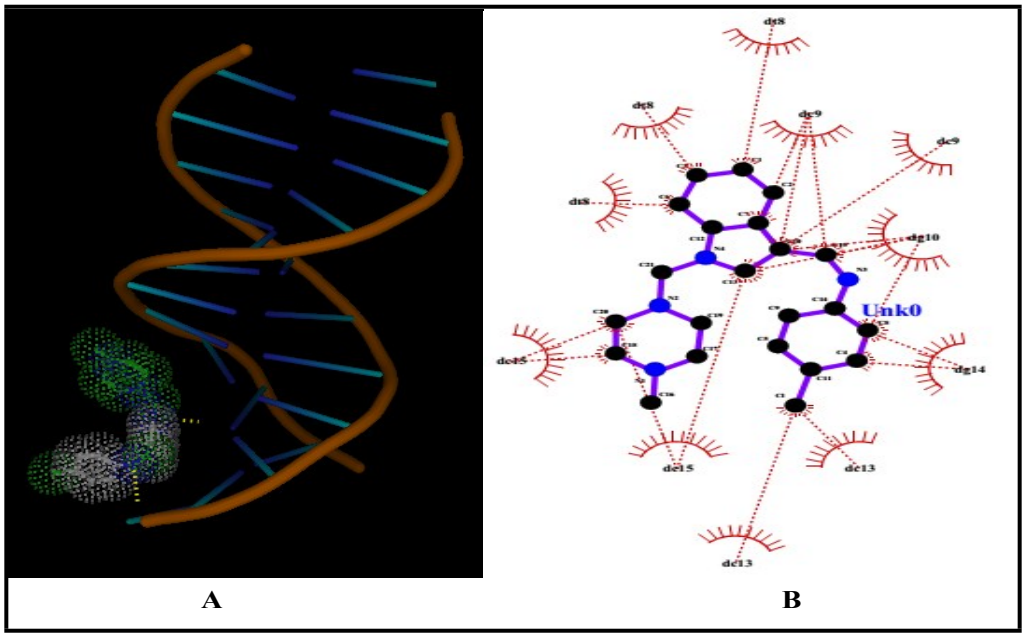


Fig. SI 5. Docking poses of **23** with DNA (a) 3D-pose depicting vicinity and hydrogen bonding and (**b**) 2D-pose showing residues involved in hydrophobic interactions.