Green pathway for the Construction of Aryl-1,8-Naphthyridine-Thiazole Scaffolds And In Vitro-Antimicrobial Evaluation, DNA-Binding Interactions, Viscosity Measurements, Molecular modeling Studies And ADME Properties

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Abstract

Environmentally friendly research can be bringing cost-effective technology it is essential and desirable in the current state-of-the-art research. Eco-friendly green synthesis of substituted aryl-1,8-naphthyridine-thiazole-4-carboxamide derivatives and evaluation of their biological studies antibacterial and antifungal activity of all the synthesized compounds demonstrated remarkable *in-vitro* microbial activity as well as DNA binding studies Viscosity Measurements by electronic absorption spectroscopy. The intrinsic binding constants (K_b) values of **(5a-f)** molecules with Ct-DNA obtained from UV-Vis spectroscopy. Molecular docking studies results and ADME properties were well complemented to the DNA-binding intercalative studies.

Introduction

In the current research, the selective construction of value-added medicinal active molecules has driven important attention to Pharmaceutical Applications. These compounds are known to contribute to designing the new drug for the potential treatment of severe diseases (e.g., HIV, Cancer, and Hypertension) that could not be cured easily. Few of the potent drug molecules are shown in **Figure.1** these entire shown drugs molecule possess one of the main functional group is like an amide bond common. As per our knowledge is concerned the existence of an amide bond in the drug molecules has plays a significant role in binding with protein including the R and S configuration of the products. The classical formation of the amide bond is required azide and carbonyl functional group gives rise to amide and amine which is well known as the Schmidt reaction. However, intact functional groups (amine, amide, and carbonyl),) in a drug molecule for a specific properties, predominantly, anti-cancer drugs required special attention. In addition, so far available drugs are costly and also very less yielding during the synthesis.

Over the past decade finding, cost-effective alternative methods for new molecules design in the target application have become a significant challenge in the scientific community. Amide bond construction is a fundamentally significant reaction in organic synthesis and plays an important role in modern biology. DNA has a strong affinity for many heterocyclic compounds therefore studies of the interaction between DNA and new chemotherapeutic agents and plays a key role in the fight against cancer [1]. 1,8-Naphthyridine derivatives are significant class of heterocyclic compounds in medicinal chemistry. The 1,8-Naphthyridine ring system is a core structure in various synthetic pharmaceutical drugs and demonstrate interesting pharmacological activities [2] include that anti-inflammatory,[3] anti-tumor,[4] antibacterial, [5] and ant-malarial activity [6].

It has long held the ambition of the chemist to find the pathways via a green and sustainable approach to synthesized selective organic molecules. In continuation of our previous studies on the development of eco-friendly methodologies and biologically active compounds [7–9] In view of the great importance of amide bond we have synthesized compounds (**5a-f**) utilizing of 2-bromo-N-(3-phenyl-1,8-naphthyridin-2-yl)thiazole-4-carboxamide derivatives involving various substituted 3-phenyl-1,8-naphthyridin-2-amines with 2-bromothiazole-4-carboxylic acid at ambient temperature obtained corresponding compounds with good yields.

Experimental

All the solvents and reagents were obtained from commercial sources and used as such unless noted otherwise. Melting points were determined in open capillaries using Buchi melting point apparatus and are uncorrected. The progress of the reactions as well as purity of the compounds was monitored by thin layer chromatography with F_{254} silica-gel precoated aluminum sheets using hexane/ethyl acetate (7/3) as eluent. The absorption spectral studies were conceded out by Ultraviolet-visible spectrometer. IR spectra were recorded on Perkin-Elmer 100S spectrometer using KBr pellet. NMR spectra were recorded on Bruker 400 MHz spectrometer using DMSO-d_6 as solvent and TMS as an internal

standard. Mass spectra (ESI) were recorded on a Jeo1 JMSD-300 spectrometer. Elemental analyses were performed on a Carlo Erba EA 1108 automatic elemental analyzer.

General procedure for the synthesis of 3-phenyl-1,8-naphthyridin-2-amines (3a-f)

To take compound 2-amino-nicotinaldehyde 1 (1 mmol, 122.12 mg), Aryl acetonitrile 2 (1 mmol) and added catalytic amount of piperidine under reflux conditions 4–5 hours. After completion of the reaction (monitored by the TLC) the reaction mixture was cooled to room temperature and the reaction was poured into cold water. The solid obtained was filtered, washed with water, and dried under vacuum to obtain the corresponding pure amide products (3a-f).

General procedure for the synthesis of 2-bromo-N-(3-Aryl-1,8-naphthyridin-2-yl)thiazole-4-carboxamide derivatives (5a-f)

To take compound 3-phenyl-1,8-naphthyridin-2-amine 3 (1.1 mmol), 2-bromothiazole-4-carboxylic acid **4** (1 mmol, 208.03 mg), HATU (2 mmol, 760.40 mg) and added catalytic amount of DBU dissolved in DMF stirred at ambient temperature. After completion of the reaction (monitored by the TLC) the reaction mixture was poured into cold water. The solid found was filtered, washed with water and recrystallized from methanol obtained corresponding pure products (5a-f).

Results and discussion

The title compounds were synthesized by the condensation reaction of 3-phenyl-1,8-naphthyridin-2-amines with 2-bromothiazole-4-carboxylic acid at ambient temperature utilizing HATU catalyst furnished good yields. The representation is shown in **Scheme 1**. In the preliminary stage of investigation for optimizing the reaction condition we have screened to test their efficiency in presence of HATU with various types of organic bases such as Pyridine, Et_3N, DABCO, DBU and DMAP among them DBU is the most effective for this reaction giving 84% of yield. Remaining bases such as Pyridine, Et_3N, DABCO and DMAP were less effective gave 70%, 68%, 71% and 72% yields, respectively.

For increasing the yield of the reaction we have screened various solvents such as (CH_3OH, DCM, EtOH, DMF and DMA) to test their efficiency in the presence of HATU and DBU at RT among these DMF is giving better yields (87–92%). It is important to mention that the polar solvents afforded better yield than the non-polar ones and the best results was got in DMF solvent. On the basis of the above results during the optimization of base and solvent. Then we construction best optimized condition for this reaction HATU is a catalyst; DBU as a base and DMF solvent at room temperature. With this efficient transformation, we have successfully synthesized 1,8-naphthyridine-thiazole-4-carboxamide **(5a-f)** compounds The results are presented in Table 1. All the synthesized compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR, Mass spectral data and elemental analysis.

Spectral Data

2-Bromo- N -(3-phenyl-1,8-naphthyridin-2-yl)thiazole-4-carboxamide (5a)

Pale brown solid; IR (KBr, cm^{-1}) ν_{max}: 3352, 1720, 1524, 1194; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 11.47 (s, 1H), 8.79 (s, 1H), 8.41 (m, 3H) 8.38–7.98 (m, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 114.6, 118.7, 120.5, 126.2, 127.4, 128.6, 129.2, 130.5, 132.1, 135.3, 136.4, 143.8, 148.2, 149.3, 153.8, 160.3; MS (ESI) m/z: 411.28 $[M+1]^+$; Anal. calcd. For $C_{18}H_{11}BrN_4OS$: C, 52.57; H, 2.70; N, 13.62. Found: C, 52.53; H, 2.76; N, 13.67%.

2-Bromo- N -(3-(4-bromophenyl)-1,8-naphthyridin-2-yl)thiazole-4-carboxamide (5b)

Yellow solid; IR (KBr, cm^{-1}) ν_{max}: 3336, 1717, 1570, 1522, 1214; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 11.34 (s, 1H), 8.99 (s, 1H), 8.21–8.17 (m, 4H), 8.03–7.97 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 115.6, 117.7, 120.3, 124.6, 125.5, 127.9, 128.3, 129.9, 130.6, 136.1, 136.7, 148.5, 148.8, 149.2, 158.4, 160.9; MS (ESI) m/z: 490. $[M + H]^+$; Anal. calcd. for $C_{18}H_{10}Br_2N_4OS$: C, 44.11; H, 2.06; N, 11.43. Found: C, 44.16; H, 2.00; N, 11.44%.

2-Bromo- N -(3-(4-chlorophenyl)-1,8-naphthyridin-2-yl)thiazole-4-carboxamide (5c)

Pale brown solid; IR (KBr, cm^{-1}) ν_{max}: 3336, 1718, 1570, 1214; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 11.37 (s, 1H), 9.23 (s, 1H), 8.67 (m, 4H), 8.51 (s, 1H), 7.84–7.41 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 113.4, 119.6, 121.9, 122.5, 125.9, 127.8, 129.4, 130.4, 136.1, 137.8, 138.6, 140.3, 150.5, 153.0, 153.4, 160.1; MS (ESI) m/z: 445.94 $[M + H]^+$; Anal. calcd. for $C_{18}H_{10}BrClN_4OS$: C, 48.50; H, 2.26; N, 12.57. Found: C, 48.56; H, 2.21; N, 12.53%.

2-Bromo- N -(3-(4-nitrophenyl)-1,8-naphthyridin-2-yl)thiazole-4-carboxamide (5d)

Pale green solid: IR (KBr, cm^{-1}) ν_{max}: 3383, 1714, 1571, 1246; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 11.52 (s, 1H), 9.61 (s, 1H), 8.72 (s, 1H), 8.34 (d, 2H, J = 8.4 Hz) 8.14–7.817.49 (m, 5H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 112.4, 117.6, 119.5, 127.2, 127.9, 128.6, 129.8, 130.4, 137.1, 142.1, 152.2, 154.0, 155.2, 158.7, 161.9; MS (ESI) m/z: 456.27 $[M + H]^+$; Anal. calcd. for $C_{18}H_{10}BrN_5O_3S$: C, 47.38; H, 2.21; N, 15.35. Found: C, 47.42; H, 2.37; N, 15.47%.

2-Bromo- N -(3-(3-nitrophenyl)-1,8-naphthyridin-2-yl)thiazole-4-carboxamide (5e)

Pale green solid; IR (KBr, cm^{-1}) ν_{max}: 3381, 1653, 1579, 1240; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 11.43 (s, 1H), 8.69 (m, 4H), 8.41 (s, 1H), 7.61–7.39 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 112.3, 112.9, 113.7, 116.3, 117.9, 123.3, 125.8, 127.3, 137.6, 138.3, 142.6, 143.2, 148.4, 153.6, 155.2, 158.7, 161.5; MS (ESI) m/z: 456.97 (Should be 455.976) $[M + H]^+$; Anal. calcd. for $C_{18}H_{10}BrN_5O_3S$: C, 47.38; H, 2.21; N, 15.35. Found: C, 47.42; H, 2.27; N, 15.39%.

2-Bromo- N -(3-(3-bromophenyl)-1,8-naphthyridin-2-yl)thiazole-4-carboxamide (5f)

Yellow solid; IR (KBr, cm^{-1}) ν_{max}: 3466, 1740, 1528, 1218; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 11.51 (s, 1H), 8.99 (d, 2H, J = 8.4 Hz), 8.23 (s, 1H), 7.97 (s,1H), 7.81–7.52 (m, 5H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 112.6, 112.9, 116.2, 119.7, 126.3, 127.5, 128.2, 133.6, 137.8, 141.3, 142.3, 148.9, 152.3, 153.6,159.4, 161.2; MS (ESI) m/z: 489.89 (Should be 488.9015) $[M + H]^+$; Anal. calcd. for $C_{18}H_{10}Br_2N_4OS$: C, 44.11; H, 2.06; N, 11.43. Found: C, 44.27; H, 2.25; N, 11.57%.

Pharmacology:

Anti-bacterial activity

The synthesized compounds **(5a-f)** were screened for their *in-vitro* antibacterial activity against gram-positive bacteria *Staphylococcus aureus* and gram-negative bacteria *Escherichia coli* using Ampicillin as standard drug. Activity was determined by the disc diffusion method [10] by measuring the zone of inhibition at three different concentrations 10, 20 and 30µg mL^{-1}. All the compounds showed good activity against the tested microorganisms is shown in Table 2. Among them, compounds **5b** and **5c** showed maximal zones of inhibition against the tested bacterial strains.

Anti-fungal activity

All synthesized compounds **(5a-f)** were tested for *in-vitro* antifungal activity against the pathogenic fungal strains *Aspergillusniger* and *Aspergillusflavus* by Agar Well Diffusion Method [11]. Zone of inhibition (in mm) was compared with standard drug grieseofulvin is shown in Table 2. All products displayed moderate to high inhibition activity against the tested fungal strains.

Table 2
Antimicrobial activity screening data of the synthesized compounds.

C	B.S						F.S					
	S.aureus (Conc.in µg/mL)			*E.coli* (Conc.in µg/mL)			*A.niger* (Conc.in µg/mL)			*A.flavus* (Conc.in µg/mL)		
	10	**20**	**30**	**10**	**20**	**30**	**10**	**20**	**30**	**10**	**20**	**30**
5a	6	13	22	5	14	21	6	19	23	6	13	24
5b	**9**	**18**	**27**	**8**	**17**	**28**	**9**	**16**	**26**	**8**	**17**	**28**
5c	**7**	**16**	**23**	**8**	**15**	**24**	**7**	**15**	**24**	**7**	**16**	**25**
5d	5	14	19	6	12	19	6	12	19	6	11	18
5e	6	15	20	7	13	17	5	11	20	7	13	20
5f	5	14	19	6	14	16	6	12	19	5	12	19
Ampicillin	9	19	29	9	20	29	-	-	-	-	-	-
Grieseofulvin	-	-	-	-	-	-	9	19	29	9	20	29
C = Compounds, BS = Bacterial strains, F.S = Fungal strains,												

DNA Binding experiments

Absorption Titrations

Absorbance spectroscopy is an optical method and valuable in examining the interaction between molecules and nucleic acids. The relative binding assessment of compounds with calf thymus DNA was performed in tris–HCl buffer (0.01 M, pH 7.2). The ratio of absorbance of Ct-DNA in buffer at 260 and 280 nm is concerning 1.9:1 representing that Deoxyribonucleic acid was apparently free from protein contamination [12]. The concentration of DNA in the stock solution was predictable from its absorption intensity at 260 nm using a molar absorption coefficient ε260 = 6600 L mol-1 cm^{-1} [13]. Absorption titration measurements were carrying out by maintaining the concentration of the complex constant (20µM) and varying concentration from 0 to 100 µM of DNA. The data were substituted into the following Eq. (1) to calculate intrinsic binding constant Kb were determined from the following Eq. [14]

$$[DNA] / (\varepsilon_a - \varepsilon_f) = [DNA] / (\varepsilon_b - \varepsilon_f) + 1 / K_b [(\varepsilon_b - \varepsilon_f)] \text{ ---------- (1)}$$

Where, [DNA] represents the concentration of DNA, εa, εf and εb are the apparent extinction coefficients Aobs/[M], the extinction coefficient for free compound and the extinction coefficient for compound in the fully bound form, respectively. In the plots of [DNA] / εa–εf versus [DNA], Kb is given by the ratio of the slope to the intercept.

DNA Binding studies

Since DNA is a significant cellular receptor, development of small molecules that are capable of binding and cleaving DNA at specific sites is a fascinating subject for the chemists. DNA targeting anticancer drugs primarily interact with DNA through the following two modes: covalent binding and non-covalent binding. We have studied the DNA binding properties of the synthesized **(5a-f)** compounds by absorption spectroscopy in absence as well as in the presence of Ct-DNA. Upon the addition of increasing amount of Ct-DNA to the fixed amount of complex the band position of the compounds were altered resulting in the notable hypo chromic shift with slight blue shift was observed. The absorption bands of the molecules at about 270 nm exhibited hypochromic. The hyper chromic shift indicates the binding of (5a-f) molecules to Calf thymus-DNA via intercalation mode. The intrinsic binding constants of these compounds were found to be **5b** ($2.06 \times 10^5\ M^{-1}$) > **5c** ($1.08 \times 10^5\ M^{-1}$) > **5a** ($0.8 \times 10^5\ M^{-1}$) > **5d** ($0.7 \times 10^5\ M^{-1}$) **5f** ($0.6 \times 10^5\ M^{-1}$) > **5e** ($0.4 \times 10^5\ M^{-1}$) respectively. The obtain results are revealed that compound **5b** binds more strongly with Ct-DNA as compared to the remaining compounds. The intrinsic binding K_b value of compound 5b is higher in magnitude which may be due to the additional interaction bonding with DNA base pair shown in Fig. 2.

Viscosity measurements

The interaction of compounds (5a-f) with Ct-DNA was also studied with the aid of viscosity measurements to find further clues about binding mode. The application of viscosity measurements of solution in DNA binding studies is one of the most useful techniques carried out in the absence of crystallographic structural data. Viscosity measurements are measured as most critical test of DNA binding studies. The viscosity of Ct-DNA in the absence and presence of the target compounds in the 5 Mmtris–HCl/ 50 mMNaCl buffer solution (pH = 7.2) was measured with Ostwald capillary viscometer maintained at 28 ± 0.1°C. Viscosity experiments were performed by using constant concentration of DNA while slowly increasing the concentration of test samples. Data were existing as (η/ηo)1/3 versus the ratio of the concentration of the compound to Ct-DNA, where η is the viscosity of Ct-DNA in the attendance of the compound and ηo is the viscosity of Ct-DNA alone. Comparative viscosity values were calculated from the practical flow time of DNA solution (t) corrected for the flow time of buffer alone (t0), with the expression ηo=(t − t0)/t0.[15] As a support of the above testimonial, viscosity measurements were carried out. The effect of compound (5a–f) on the viscosity of DNA at 28 ^{O}C is shown in Fig. 3

Molecular Docking Studies

In correlation to DNA binding studies, it was thought worthwhile to carryout in silico studies to support the DNA intercalation. The 3D structure of DNA dodecamerd (CGCGAATTCGCG) 2, with PDB ID as 1BNA, was regained from RCSB protein data bank (www.rcsb.org) [16]. An interaction of the docked DNA with ligands was analyzed to identify their hypothetical binding mode. Molecules were built using Maestro build panel and prepared by LigPrep OPLS_2005 force field. The DNA was equipped using protein preparation module applying the default parameters. Gridwas generated around the active site of the DNA. Receptor Vander Waals scaling for the non polar atoms was kept 0.9.[17] GLIDE 5.6[18] was used for molecular docking. Low energy conformation of the ligands was designated and docked into the grid using extra precision (XP) docking mode. [19–21] the binding energies of all the compounds are represented in Table 3. Conformation inhabiting the position between the base pairs indicates a sign of good intercalation. Hydrogen bonding is an important factor to understand the binding with hetero atoms. All these compounds exhibited deep binding interaction with the DNA receptor, compounds sits in the major groove of DNA and forms hydrogen bonds with the both DNA chains. The binding mode of compound **5b** with DNA (glide score: -5.60), showed one hydrogen bond between H of **5b** compound and O atom of DT (20) of one strand of DNA, where H of the **5b** acts as hydrogen bond donor and the O atom of DT (20) acts as hydrogen bond acceptor (**5b** H — O of DT (20): 2.189 Å). Other compounds **5a** (-4.61), 5c (-4.71) and 5d(-4.17) showed one hydrogen bond with N atom of DA(6) of

other strand of DNA (H … No fDA(6): 2.125, 2.201 and 2.177 Å respectively). Dock pose conformations of **5a**, **5b**, **5c** and **5d** with DNA receptor are illustrated in Fig. 4.

A regression analysis between dock score (binding affinity) and experimental DNA binding values of the synthesized compounds were carried out and given a correlation coefficient r is 0.89 representing important correlation between molecular docking (dock score) and DNA binding activity. The scatter plot of dock score versus experimental DNA binding showed in Fig. 5.

Predicted ADME properties

The premeditated molecules were also constructed, minimized and docked into the protein active site. ADME (absorption, distribution, metabolism and excretion) properties of designed molecules were evaluated computationally using QikProp module of Schrodinger.[22] The physically considerable descriptors and pharmaceutically relevant properties of organic molecules with observance to Lipinski's rule of five are calculated by QikProp. Newly synthesized products were analyzed for drug-likeness by assessing their physiochemical properties and by applying Lipinski's rule of five (Table 3).

Table 3
Glide score and ADME properties of the synthesized molecules

Comp	Glidescore (k.cal/mol)	MWt	QPlogPo/w[a]	QPlogS[b]	QPPCaco[c]	QPlogBB[d]	QPPMDCK[e]	%Human Oral Absorption[f]
5a	-4.61	411.27	3.842	-5.463	1323.319	-0.2	3686.585	100
5b	-5.60	490.17	4.405	-6.296	1338.013	-0.029	9907.415	100
5c	-4.71	445.72	4.329	-6.183	1337.968	-0.039	9214.055	100
5d	-4.17	456.27	3.125	-5.581	160.052	-1.279	375.855	84.697
5e	-2.62	456.27	3.127	-5.585	160.664	-1.278	377.409	84.736
5f	-3.70	490.17	4.405	-6.299	1336.848	-0.03	9887.761	100

Conclusions

In summary, The adopted method is believed to be effective and can contribute to the design of the new molecule for potential drug applications we have prepared green and environmentally benign method for the bioactive 1,8-Naphthyridine-thiazole-4-carboxamide scaffolds. These compounds were evaluated for their *in vitro* anti antimicrobial activity against pathogenic bacterial and fungal strains. The absorption and fluorescence studies reveal the stabilization of the energy levels of the compounds in presence of DNA. The DNA cleavage and molecular modeling studies undertaken in the present work are in total agreement with the primary intercalative mode of binding. Molecular docking studies results were well complemented to the DNA-binding intercalative studies.

Declarations

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Ethical approval

This article does not encompass any studies with human participants or animals performed by any of the authors.

Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author's contributions

BS=Design and synthesis and drafted the manuscript's first author, DR= Wrote the manuscript, PS= Microbial activity and docking studies, KK= Analysis data, BS= reviewed the manuscript

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Availability of data and materials

We attached a supporting file

Conflict of interest

There are no conflicts of interest to declare.

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Table

Table 1 is available in the Supplementary Files section.

Scheme

Scheme 1 is available in the Supplementary Files section.

Figures

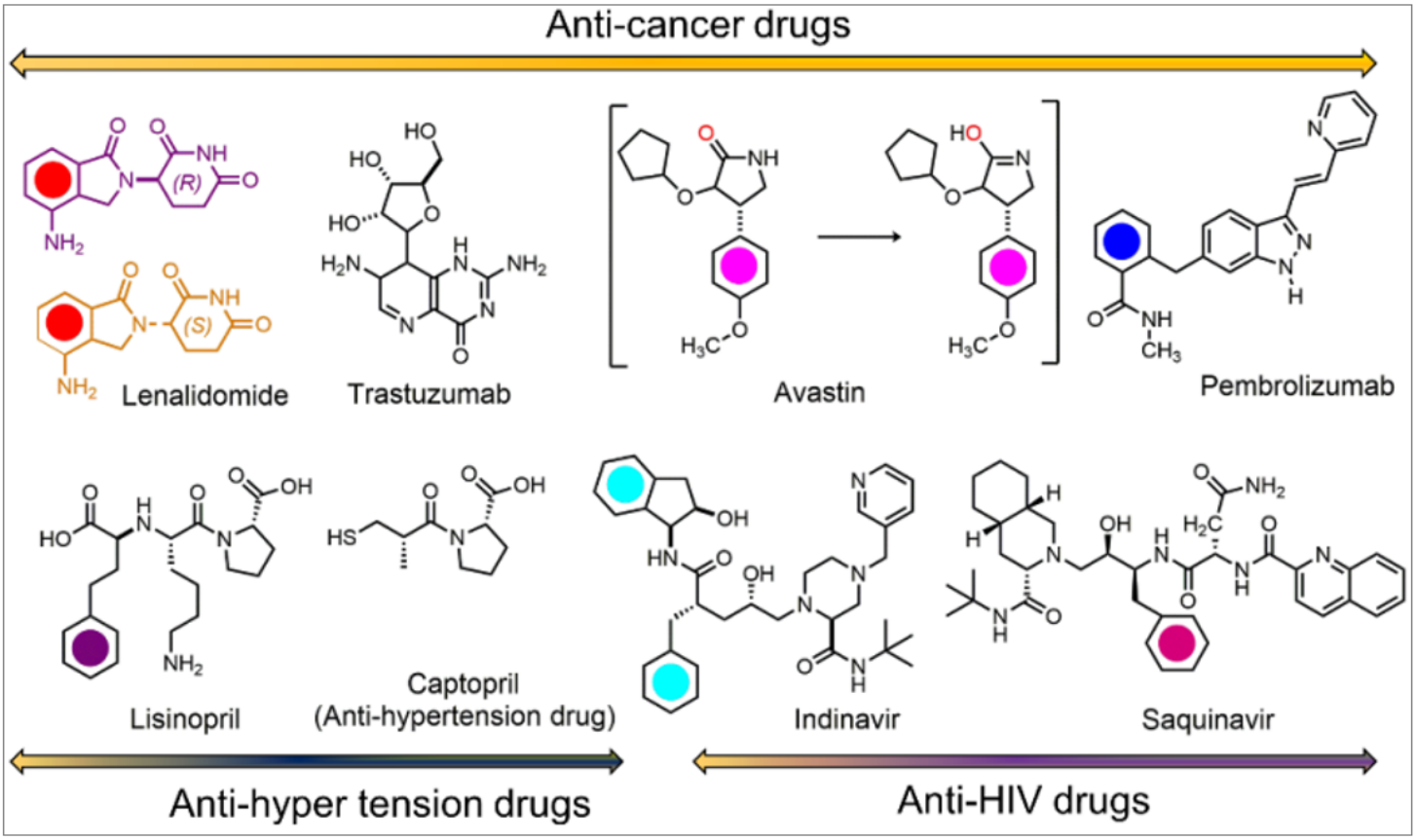

Figure 1

The active drug molecules for the anti-cancer, anti-hypertension, and Anti-HIV

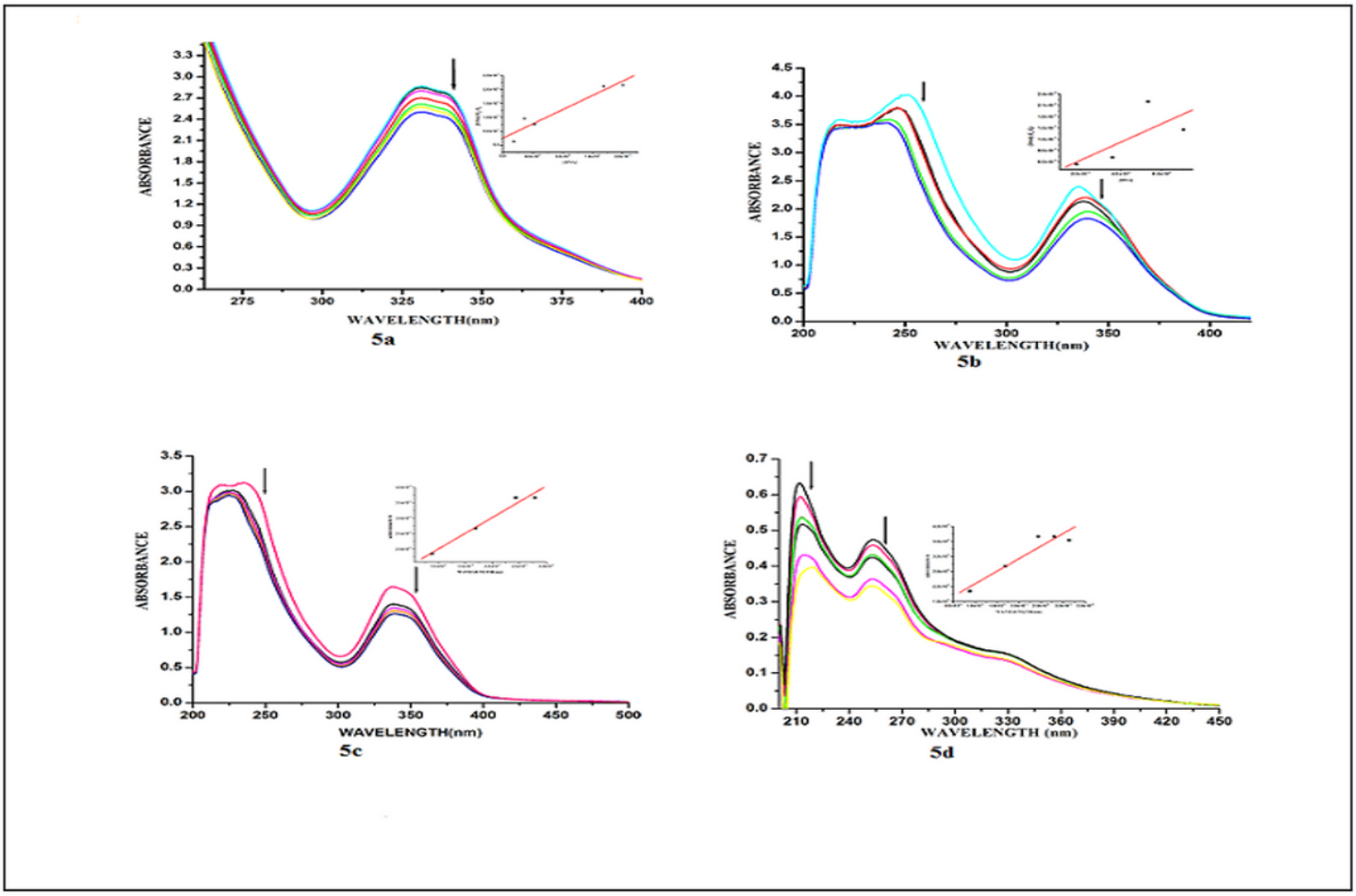

Figure 2

Changes in the electronic absorption spectra of **(5a-f)** (Tris-HCl/NaCl buffer by addition of Ct-DNA.

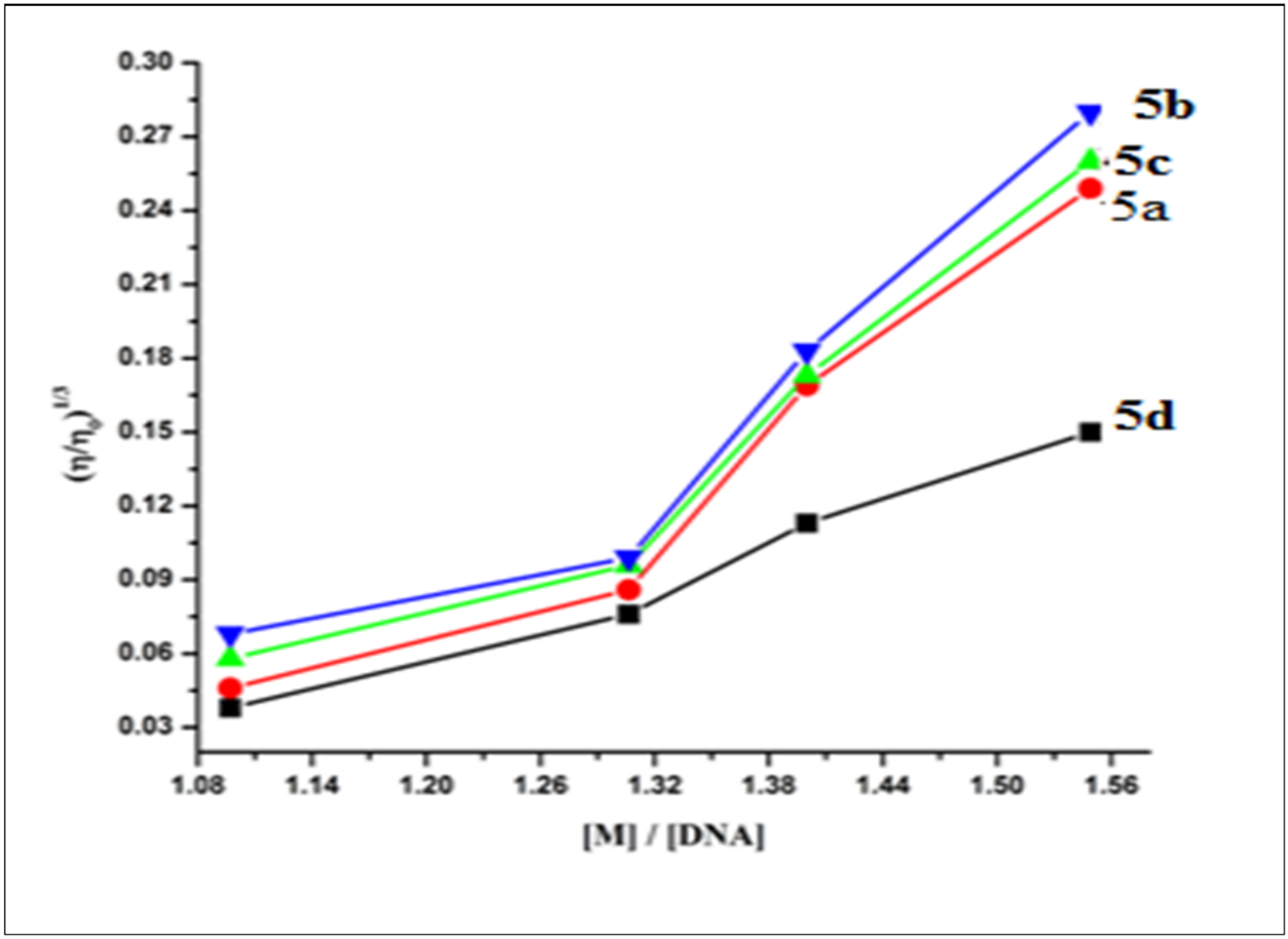

Figure 3

Effect of increasing concentration of active compounds (5a-d) on the relative viscosity of Ct-DNA at 28 ± 0.1 ^{O}C

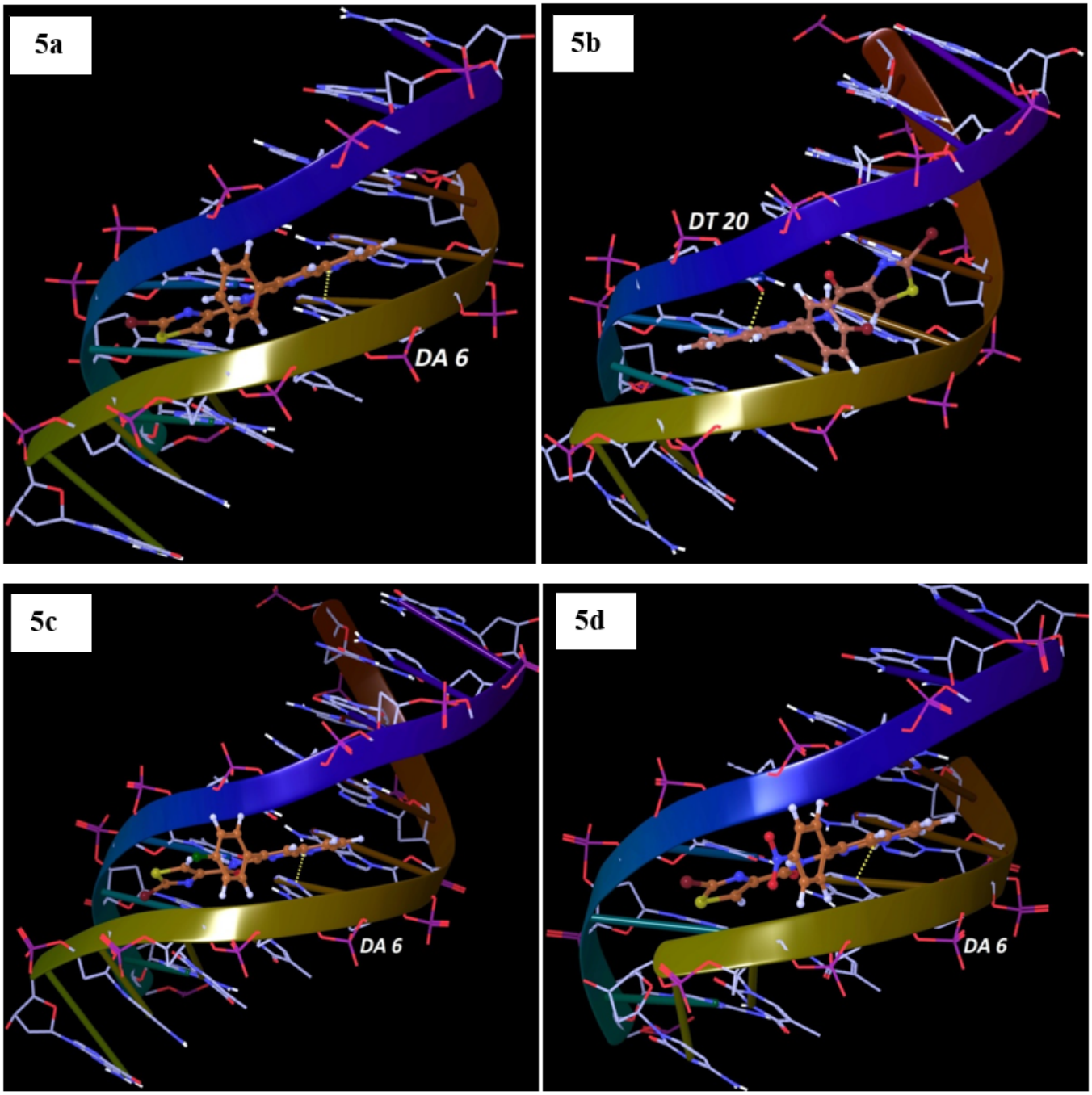

Figure 4

Docked pose conformations of active molecule **5a, 5b, 5c** and **5d** with DNA receptor

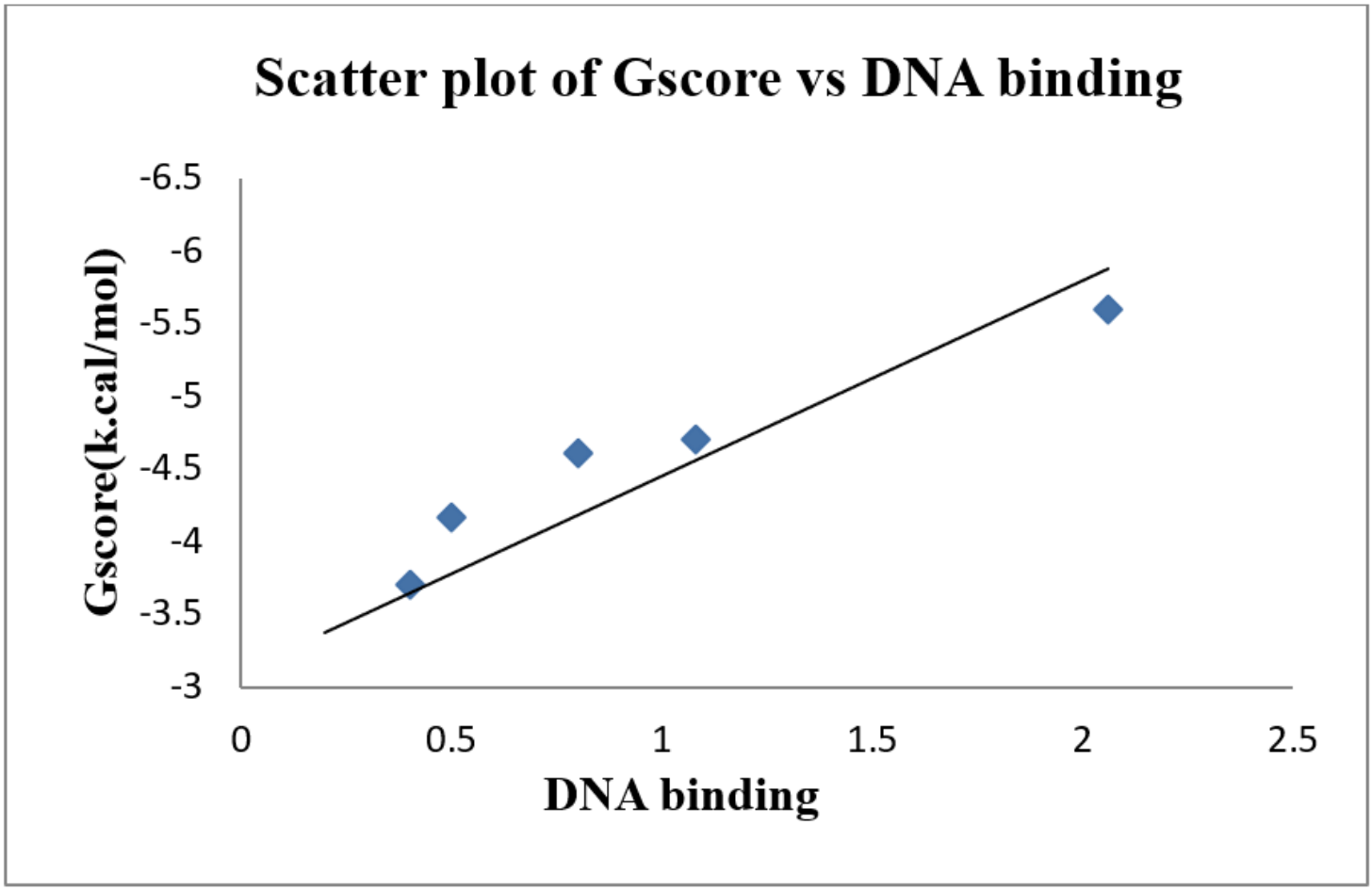

Figure 5

Scatter plot of dock score versus experimental DNA binding

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- supportingfile31.docx
- Scheme1.png
- Table1.docx