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Anthracene and 1,8-napthalimide aminothiazole hybrids: Synthesis, Antimicrobial activity and Molecular Docking Studies

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ABSTRACT

With our efforts to develop potent antimicrobial agents, a series of anthracene and 1,8-napthalimide aminothiazole analogues were synthesized and characterized by using fundamental spectral analysis. All of the synthesized hybrids were screened for their anti-microbial activities against the bacterial strains *E. coli, B. subtillis* and *S. aureus*, and the fungal strains *A. niger* and *C. albicans*. Among the compounds investigated, compounds **4c, 4d**, and **6c** exhibited the most potent antimicrobial activity. Fluconazole and Norfloxacin were used as standard drugs for antifungal and antibacterial activity. The molecular docking investigation revealed that the compounds **4c, 4d** and **6c** displayed the lowest binding energy values within the promoter regions of the PDB ID (1JIJ, 4WMZ). The *in vitro* antimicrobial activity results are well corroborated with the molecular docking results.

Keywords: Anthracene, 1,8-Napthalimide, Aminothiazoles, Antimicrobial activity, Docking studies.

INTRODUCTION

In current history, epidemiological studies have established that infections produced by pathogenic bacteria and fungi have a considerable negative impact on human health. Drug resistance was found to be on the increase, posing a threat to the efficacy of antimicrobial therapy, according to large-scale surveillance. The rise of multidrug-resistant pathogenic microorganisms has prompted researchers to look into new drug treatments.[1] As a result, research is increasingly focused on developing new antimicrobial agents that increase the bioactivity of existing medications while simultaneously targeting other targets to address resistance.[2] Heterocyclic naphthalimides have developed as a promising molecular frameworks, because of their wide spectrum of medical applications, such as anti-inflammatory, anti-cancer, antiviral, antibacterial, antidepressant, and antifungal agents.[3,4] Thiazoles have been used in the development of drugs for HIV infections,[5] allergies,[6] pain,[7] inflammation,[8] hypertension,[9] schizophrenia,[10] bacterial infections[11] and hypnotics,[12] as well as new inhibitors of

fibrinogen receptor antagonists and bacterial DNA gyrase B10 with antithrombotic activity.[13] Nowadays a variety of commercial medicines used also contain the thiazole moiety, which includes epothilones, sulfathiazole, dasatinib, and tiazofurins.

Keeping the attributes mentioned above and in continuation of our research work in designing new bioactive heterocyclic frameworks, we developed anthracene and 1,8-napthalimide based aminothiazole hybrids as potential bioactive compounds and screened for their antimicrobial activity. Further, the molecular docking study was performed by using topoisomerase II and lanosterol alpha demethylase inhibitor. In this study, the molecular docking results of the compounds were correlated with their antimicrobial activity results.

EXPERIMENTAL

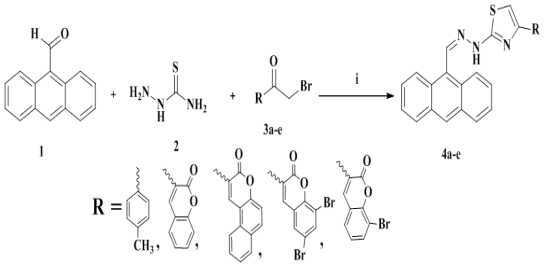
MATERIAL AND METHOD

All the solvents and reagents used for the synthesis were of analytical grade and used directly. The completion of the reaction was monitored by using RANKEM silica gel G and E-Merck precoated TLC plates and visualization was done by using a UV chamber. The melting points of the newly synthesized compounds were determined in open capillary tubes and incorporated accordingly. ^{1}H NMR spectra were recorded On a Bruker 400 MHz spectrometer. ^{13}C NMR spectra were recorded on a Bruker 100 MHz spectrometer. The mass spectra were recorded using the ESI–Mass spectrum.

Synthesis

Synthesis of anthracene aminothiazole derivatives (4a-e)

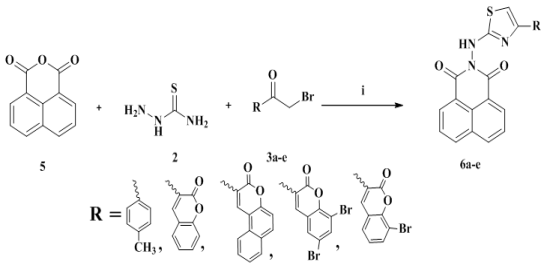
A mixture of 9-Anthraldehyde (1 mmol, 206 mg), thiosemicarbazide (1 mmol, 91 mg), and α-bromoketones (**3a-e**, 1 mmol) was taken in pure ethanol (10 mL) and a few drops of ACOH were added and the mixture was stirred for 3-5 h at 60-70ºC. TLC was used to observe the reaction progress. After the completion of reaction, the mixture was filtered, washed with fresh water and EtOH to produce the final compounds **(4a-e)** shown in Scheme 1.



Scheme 1. Synthesis of anthracene aminothiazole hybrids (4a-e): Reagents and conditions: (i) EtO, few drops AcOH at 60-70°C, 3-5 hours

Synthesis of naphthalimide aminothiazole derivatives (6a-e)

A mixture of 1,8-Naphthalic anhydride (5, 1 mmol), thiosemicarbazide (2, 1 mmol), and 3-α-bromoketones (3a-e, 1 mmol) was taken in 10 mL of DMF solvent, heated at 100ºC for 3–4 hours. The mixture was filtered and dried under vacuum to produce the final compounds (6a-e) displayed in Scheme 2.



Scheme 2. Synthesis of naphthalimide aminothiazole hybrids (6a-e): Reagents and conditions: (i) DMF at 100°C, 3-4 hours

2-(2-(anthracen-9-ylmethylene) hydrazinyl)-4-(p-tolyl)thiazole (4a)

Yellow solid; m.p: 258-260°C; proton-NMR values: δ 12.12 (N-NH), 9.20 (CH=N), 8.48-7.30(aromatic protons), 7.32 (thiazole C4-proton), 2.43 (-CH_3); ^{13}Carbon-NMR: δ 169.53, 152.35, 143.98, 138.54, 134.28, 130.39, 128.54, 127.98, 127.71, 127.16, 126.29, 110.06, 22.12; MS ($C_{25}H_{19}N_3S$) m/z: 394.1215 $[M+H]^+$.

3-(2-(2-(anthracen-9-ylmethylene) hydrazinyl) thiazol-4-yl) -2H-chromen-2-one (4b)

Yellow-solid; m.p: 302-304ºC; proton-NMR values: δ 12.10 (=N-NH), 8.89 (-CH=N), 8.53-7.36 (aromatic protons) 7.26 (thiazole C4-proton), 7.23-7.18 (Aromatic-proton); ^{13}Carbon-NMR values: δ 166.23, 159.83, 155.13, 153.58, 139.07, 132.87, 130.51, 130.28, 129.86, 129.56, 128.60, 127.94, 127.20, 126.32, 125.01, 121.15, 120.60, 117.14, 109.92; MS ($C_{27}H_{17}N_3O_2S$) m/z 448.1334 $[M+H]^+$.

2-(2-(2-(anthracen-9-ylmethylene) hydrazinyl) thiazol-4-yl)-3H-benzo[f]chromen-3-one (4c)

Yellow solid; m.p: 276-278ºC; proton-NMR values: δ 12.11 (-N=NH), 9.08 (-CH=N), 8.59-7.39 (aromatic protons), 7.35 (thiazole C4-Proton); ^{13}Carbon-NMR values: δ 168.19, 160.23, 154.54, 152.55, 139.12, 131.06, 130.36, 128.96, 128.03, 127.21, 126.25, 124.80, 122.39, 121.68, 118.51, 117.08, 109.94; MS ($C_{31}H_{19}N_3O_2S$) m/z 498.1154 $[M+H]^+$.

3-(2-(2-(anthracen-9-ylmethylene) hydrazinyl) thiazol-4-yl)-6,8-dibromo -2H-chromen-2-one (4d)

Orange-solid; m.p: 312-314ºC; proton-NMR values: δ 12.08 (-N=NH), 9.12 (,-CH=N), 8.62-7.41 (aromatic protons), 7.26 (thiazole C4-Proton); ^{13}Carbon-NMR values: δ 168.23, 159.24, 152.36, 151.34, 139.11, 137.54, 131.25, 130.82, 130.42, 129.38, 128.68, 128.06, 127.16, 126.39, 121.89, 121.10, 119.57, 113.72, 108.99; MS ($C_{27}H_{15}Br_2N_3O_2S$) m/z 604.5316 $[M+2]^+$.

3-(2-(2-(anthracen-9-ylmethylene)hydrazinyl) thiazol-4-yl)-8-bromo-2H -chromen-2-one (4e)

Orange-solid; m.p: 318-320ºC; proton-NMR values: δ 12.10 (-N=NH), 9.06 (-CH=N), 8.51-7.31 (aromatic protons), 7.22 (thiazole C4-Proton), 7.08 (Aromatic-proton); ^{13}Carbon-NMR values: δ 168.53, 159.10, 153.35, 151.52, 139.35, 135.35, 130.68, 130.68, 129.32, 128.58, 128.12, 127.55, 126.58, 121.98, 120.64, 111.28, 109.12; MS ($C_{27}H_{16}BrN_3O_2S$) m/z 604.5316 $[M + 2]^+$.

2-((4-(p-tolyl)thiazol-2-yl) amino)-1H-benzo[de] isoquinoline-1,3(2H)-dione (6a)

Pale yellow solid; m.p: 228-230ºC; proton-NMR values: δ 10.62 (-NH), 8.34-7.39 (aromatic protons), 7.21 (thiazole C4-Proton), 2.35 ($-CH_3$); ^{13}Carbon-NMR values: δ 168.74, 160.15, 143.89, 138.68, 134.56, 132.13, 131.64, 130.53, 129.99, 128.86, 127.82, 127.11, 126.34, 110.69, 22.78; MS ($C_{22}H_{15}N_3O_2S$) m/z 386.0912 $[M+H]^+$.

2-((4-(2-oxo-2H-chromen-3-yl) thiazol-2-yl)amino)-1H-benzo[de] isoquinoline-1,3(2H)-dione (6b)

Yellow solid; m.p: 282-284ºC; proton-NMR values: δ 10.84 (-NH), 8.38-7.53 (aromatic protons), 7.34 (thiazole C4-Proton), 7.20 (aromatic protons); ^{13}Carbon-NMR values: δ 168.36, 161.23, 160.19, 154.13, 139.24, 132.92, 132.06, 131.49, 129.92, 129.69, 128.81, 127.10, 126.39, 125.14, 121.20, 120.89, 117.20, 109.20; MS ($C_{24}H_{13}N_3O_4S$) m/z 440.3015 $[M+H]^+$.

2-((4-(3-oxo-3H-benzo[f] chromen-2-yl)thiazol-2-yl)amino)-1H-benzo[de] isoquinoline-1,3(2H)-dione (6c)

Yellow-solid; m.p: 244-246ºC; proton-NMR values: δ 10.85 (-NH), 8.36 (Ar-H), 8.25-7.32 (aromatic protons), 7.26 (thiazole C4-Proton); ^{13}Carbon-NMR values: δ 168.39, 161.12, 160.02, 154.54, 139.36, 132.10, 131.46, 130.87, 130.15, 128.96, 127.09, 126.44, 124.62, 122.29, 121.61, 118.43, 116.83, 108.99; MS ($C_{28}H_{15}N_3O_4S$) m/z 490.0915 $[M+H]^+$.

2-((4-(6,8-dibromo-2-oxo-2H-chromen-3-yl) thiazol-2-yl)amino)-1H-benzo[de] isoquinoline-1,3(2H)-dione (6d)

Orange solid; m.p: 294-296ºC; proton-NMR values: δ 10.79 (-NH), 8.36-7.53 (aromatic protons), 7.23 (thiazole C4-Proton); ^{13}Carbon-NMR values: δ 168.29, 161.25, 159.76, 151.34, 139.26, 137.63, 131.98, 131.36, 129.99, 129.39, 128.84, 127.12, 126.39, 121.63, 121.35, 119.73, 113.67, 108.96; MS ($C_{24}H_{11}Br_2N_3O_4S$) m/z 596.8832 $[M+2]^+$.

2-((4-(8-bromo-2-oxo-2H-chromen-3-yl) thiazol-2-yl)amino)-1H-benzo[de] isoquinoline-1,3(2H)-dione (6e)

Orange solid; m.p: 318-320ºC; proton-NMR values: δ 10.79 (-NH), 8.38-7.43 (aromatic protons), 7.23 (thiazole C4-Proton); ^{13}Carbon-NMR values: δ 168.34, 161.22, 160.04, 151.14, 139.21, 134.99, 131.98, 131.42, 130.16, 129.23, 128.79, 127.16, 126.39, 121.96, 120.42, 111.34, 109.05; MS ($C_{24}H_{12}BrN_3O_4S$): m/z 518.6302 $[M + H]^+$.

Antimicrobial assay

The tube dilution method was used to test the antimicrobial properties of the developed anthracene and 1,8-nathptalimide aminothiazole analogues against *Bacillus subtilis* and *Staphylococcus aureus* (*Gram-positive* bacteria) and *Escherichia coli* (*Gram-negative* bacteria) and two fungal species, *Candida albicans*, and *Aspergillus niger*. The stock solutions were prepared for the synthesized hybrids (**4a-e** and **6a-e**) as well as the standard drugs (fluconazole and norfloxacin) were taken in acetone to a conc. of 100 g/mL, and then serially tube diluted.[14] Double strength sabouraud dextrose broth-I.P (antifungal) and strength nutrient broth-I.P (antibacterial) were used to dilution test.[15] The samples have been incubated at 25±1ºC for seven days (fungal), 37±1ºC for 24 h (bacteria), and findings were recorded in terms of Methyl Isocyanate (MIC).

Molecular Docking

The molecular docking, a computer aided experimental approach was used to demonstrate the interacting mechanism of anthracene, and 1,8-napthalimide aminothiazole derivatives with receptor active sites. Chem Bio Design Ultra 12.0 (www.cambridgesoft.com) was used to draw all of the compounds 2D structures, and energy-minimized 3D structures. These were produced by using Gaussian 09[16] and also by using a small basic set hf/3-21g*.[17] Crystallography 3D structures of topoisomerase II for (bacterial), and lanosterol alpha demethylase for (fungal) proteins were retrieved from RSC PDB (www.rscb.org) PDB ID: 1JIJ, 4WMZ.[18,19] The proteins were cleaned and prepared for docking by using the UCSF-chimera 1.10.1 protein preparation wizard program, which removes any existing ligand and water molecules. For docking, such low-energy compounds and receptors are utilized. Auto-Dock 4.2 package suite and Auto-Dock Tools (ADT) version 1.5.6 were utilized for the molecular docking study.[20] The docking procedure involves stiff protein receptors topoisomerase II and lanosterol alpha demethylase as well as flexible anthracene and 1,8-napthalimide aminothiazole analogues. ADT was utilized to remove the water molecules. Gasteiger charges were applied to verity atom, and integrated non-polar H atoms in protein structures. The distance between both the acceptor and donor atoms in an H-bond was determined to be 1.9 Å. The structure was saved in PDBQT format for further ADT research. For each analogue, ten docked conformations were created during docking. A genetic algorithm was utilized to calculate the energy. Rotatable bonds, gasteiger partial charges, non-polar hydrogen atoms and grid box with dimensions 72 × 72 × 72 $Å^3$ were created on the topoisomerase II, lanosterol alpha demethylase protein receptor was allocated with aid of spacing (Angstrom): 0.3750 Å and Auto Dock Tools 1.5.6.[21] The maximum number of examinations and the population size were 2,500,000 and 150, respectively. Using Discovery studio 4.1.0, the output results were graphically evaluated.

RESULTS AND DISCUSSION

Chemistry

All the synthesized compounds are stable at room temperature, the structural assignments were determined by using ^{1}HNMR, ^{13}C NMR, and ESI mass spectroscopic data. Spectral analysis for compound **4a** reveals: ^{1}H-NMR spectrum displayed hydrazinyl proton (-C=N-NH) at δ 12.12 ppm, imine proton (CH=N) at δ 9.20 ppm, and thiazole **C4** proton at δ 7.32 ppm as singlet signals. The ^{13}C NMR spectrum reveals major signals at δ 169.53 ppm for thiazole-C2 carbon, δ 143.98 ppm for imine carbon, δ 110.06 ppm for thiazole-C4 carbon, and δ 22.12 ppm for the methyl group. The ESI mass spectrum reveals $[M+H]^+$ ion peak at m/z: 394.1215 which corresponds to the molecular weight of the compound **4a**. As a result, the structure of compound **4a** has been confirmed. Compound 6a reveals: Singlet signals were found in ^{1}H NMR spectra for the –N-NH proton at 10.62 ppm and the thiazole-C4 proton at 7.21 ppm. The ^{13}C NMR spectra have appeared signals at δ 168.74 ppm for thiazole-C2 carbon, δ 160.15 ppm for carbonyl carbon of 1,8-napthalimide, δ 110.69 ppm for thiazole-C4 carbon and δ 22.78 ppm for the methyl group. Similarly, the ESI mass spectrum of $[M+H]^+$ ion peak at m/z: 386.0912 also further supports the formation of compound **6a**.

Antimicrobial studies of compounds

Using the tube dilution method, researchers focus on one *Gram-negative* bacteria, *Escherichia coli*, and two *Gram positive*-bacteria, *Bacillus subtilis* and *Staphylococcus aureus*, and also on antifungal species *Candida albicans*, and *Aspergillus niger*. Fluconazole and Norfloxacin were used as standard references for fungi and bacteria, respectively. The MIC findings of the investigated compounds and reference medicines were reported in μM. The findings are summarized in Table 1. From the findings, compound **4c** displayed excellent bacterial activity against the tested strains, exhibiting MIC values of 7.63 μM, 9.13 μM and 8.39 μM, respectively. The compounds **4d** and **6c** have displayed good activity against tested strains. The other compounds have moderate to poor activity against the three tested strains. These findings were compared to those obtained with the reference drug norfloxacin. The antifungal activity of compound **4d** has exhibited promising activity against species *A. niger* and *C. albicans*, with MIC values of 7.31 μM and 8.64 μM, respectively. The compounds **4c** and **6c** have displayed good activity against the examined strains. The reaming compounds have moderate to poor activity compared with the reference drug fluconazole.

Table 1: Antimicrobial activity of the synthesized hybrids (4a-e and 6a-e)

Compounds	Minimum inhibitory concentration (μM)				
	Bacterial			**Fungal**	
	S. aureus	*B. subtilis*	*E. coli*	*A. niger*	*C. albicans*
4a	63.12	45.89	89.12	67.03	52.47
4b	21.30	36.42	31.21	41.12	31.61
4c	7.63	9.13	8.39	11.09	8.11
4d	10.01	12.19	17.12	7.31	8.64
4e	21.25	28.13	45.03	32.12	29.08
6a	69.12	>100	48.74	>100	39.46
6b	39.12	53.12	43.86	23.74	32.18
6c	16.42	20.76	17.51	14.5	12.45
6d	65.08	41.36	39.02	42.89	25.12
6e	>100	75.23	29.67	36.45	63.69
Norfloxacin	3.42	4.27	3.15	-	-
Fluconazole	-	-	-	3.85	4.56

Molecular docking

The binding mechanism of the synthesized anthracene and 1,8-napthalimide aminothiazole hybrids with their respective receptors was investigated by using molecular docking analysis. Most potent antibacterial hybrids (**4c, 4d,** and **6c**), as well as a reference drug (norfloxacin), were studied using molecular docking as in receptor of topoisomerase-II (PDB ID: 1JIJ) as from the PDB file. The binding energies, interacting amino acids, and interacting groups were displayed in Table 2. One of the most potent hybrids in these studies, i.e compound **4c** is with a binding affinity of -12.56 kcal/mole, exhibited three H-bonding interactions with His 50, Asp 40, and the 75 amino acids, as well as with other hydrophobic interactions, π-π stacking with amino acid aromatic rings. The compounds **4d** and **6c** have the lowest binding energy values, with one hydrogen bond interaction with key amino acid Gly 193 by **4d** and two hydrogen bond interactions with Asp 40 and Gly 193 key amino acid by **6c**, as well as remaining hydrophobic interactions with aromatic rings of key amino acids. The best structural conformations of **4c, 4d** and **6c** with receptor-binding pockets are shown in Figures 1.

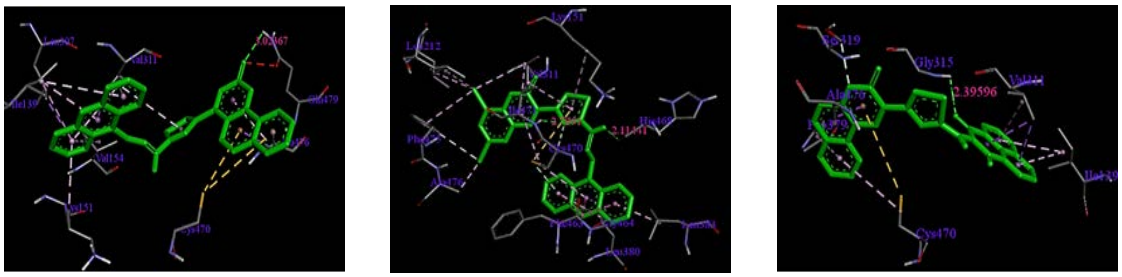
The most potent antifungal scaffolds **(4c, 4d,** and **6c)** of the reference drug (fluconazole) were compared to the lanosterol-α-demethylase binding poses from the PDB file 4WMZ. The binding energies, interacting amino acids, and interacting groups were displayed in Table 3. The compounds **4c, 4d** and **6c** exhibited the lowest binding energies of -13.23 kcal/mol, -13.28 kcal/mol, and -12.93 kcal/mol. The molecule **4c** has one H-bond interaction with the O atom of the carbonyl functional group on the coumarin moiety with Gln 479 amino acid residue, and the remaining interactions are all hydrophobic through amino acids. The compound **4d** and **6c** are with also lowest bonding energy values with two hydrogen-bonding interactions with amino acids His 468 by N atom of –NH group, and Ile 47 by N atom of thiazole ring by **4d** and one H-bond interaction with key amino acid Gly 315 by O atom of carbonyl functional group on the naphthalimide ring by **6c** and the remaining all the other hydrophobic interactions with amino acids. The best structural conformations of **4c, 4d,** and **6c** with receptor-binding pockets are shown in Figure 2.

Table 2: Molecular docking findings of most potent (antibacterial) analogues and standard drugs

Compounds	Binding energy (kcal/mol)	Interacting amino acids	Interacting groups
4c	-12.56	His 50	N of –N=CH group
		Asp 40	N of thiazole ring
		Thr 75	O of carbonyl group on coumarin ring
4d	-11.77	Gly 193	O of carbonyl group on coumarin ring
6c	-11.71	Asp 40	O of carbonyl group on naphthalimide ring
		Gly 193	O of carbonyl group on coumarin ring
Norfloxacin	-6.66	Gln190	N of piperazin ring
		Lys 84	O of carbonyl group on carboxylic acid
		Arg 88, Asp 40	O of OH group on carboxylic acid
		Asp 80	O of OH group

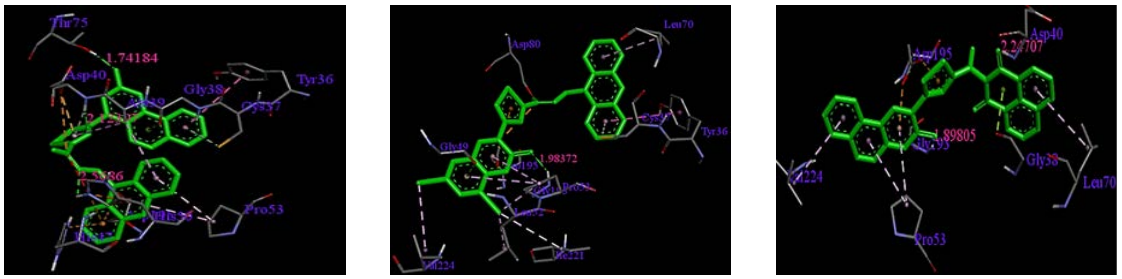
Table 3: Molecular docking findings of most potent (fungal) analogues and standard drugs

Compounds	Binding energy (kcal/mol)	Interacting amino acids	Interacting groups
4a	-13.23	Gln 479	O of carbonyl group on coumarin
4c	-13.28	His 468	N of –NH group
		Ile 47	N of thiazole ring
6c	-12.93	Gly 315	O of carbonyl group on naphthalimide ring
Fluconazole	-5.74	Ile 471	N of triazole ring
		Arg 385	Another N of triazole ring
		His 468	O of OH group



4c **4d** **6c**

Fig. 1. The best docking poses of the lead compounds (4c, 4d and 6c) with topoisomerase II (PDB ID: 1JIJ)



4c **4d** **6c**

Fig. 2. The best docking poses of the lead compounds (4c, 4d and 6c) with lanosterol alpha demethylase (PDB: 4WMZ)

CONCLUSION

In this study, anthracene and 1,8-napthalimide aminothiazole hybrids **(4a-e** and **6a-e)** were synthesized, characterized and evaluated for antimicrobial activity and molecular docking studies were also performed. Among the synthesized analogues, **4c, 4d** and **6c** showed significant antimicrobial efficacy towards the bacterial and fungal strains. The molecular docking analysis of the potent analogues displayed the lowest binding energies. The *in vitro* antibacterial potency findings are well supported by the molecular docking results. Overall, current research shows that anthracene and 1,8-napthalimide aminothiazoles such as **4c, 4d** and **6c** have the potential for development as lead compounds, so further structural modifications could lead to promising new antimicrobial treatments.

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Conflict of interest

The authors declare that they have no known competing financial interests.

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