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Egyptian Journal of Basic and Applied Sciences

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Full Length Article

Synthesis, antibacterial and molecular docking studies of new benzimidazole derivatives

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ARTICLE INFO

Article history:

Received 18 October 2016

Received in revised form 17 September 2017

Accepted 17 September 2017

Available online 28 September 2017

Keywords:

Benzimidazole

Triazinane & oxadiazinane 4-thiones

Antibacterial activity

Molecular docking

ABSTRACT

The new analogs of benzimidazole fused heterocyclic compounds such as triazinane and oxadiazinanes were synthesised by classical amino methylation with different aryl-*N,N'* unsymmetrical thioureas. The antibacterial activity of triazinane and oxadiazinane compounds have been assessed with zone of inhibition by well diffusion method using a panel of selected gram positive and gram negative bacterial strains and which have showed good activity. The synthesised molecules were subjected to molecular docking studies with two proteins, namely *topoisomerase II* (PDB ID: 1JII) and *DNA gyrase subunit b* (PDB ID: 1KZN). The molecular docking studies are supporting the antibacterial activity exhibiting high inhibition constant and binding energy.

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1. Introduction

The organic compounds specifically with N-heterocyclic ring systems exhibit a wide range of biological activities through effective binding to enzyme receptor site. As per the present global scenario, thousands of new heterocyclic compounds either isolated from natural sources or synthesized in the laboratories are added to the literature every year. Many of these compounds have drawn the attention of researchers based on their biological, therapeutic and industrial potential.

Benzimidazoles are found to be useful intermediates for the development of new molecules of biological or pharmaceutical interest. Substituted benzimidazole derivatives have been found to possess Biological activities such as antitumor [1], antimicrobial [2], anthelmintic [3], antibacterial [4], analgesic [5], anti inflammatory [6] etc. In recent times, new techniques have been adopted for the efficient synthesis of novel heterocycles by using heterogeneous, nano-catalysts and photocatalysis that are highly and eco-friendly [7–13]. Triazinane derivatives belonging to nitrogen heterocycles have greatest importance due to their potential applications. These have been identified as commercial products which are used as H₂S scavengers in the areas with relatively low concen-

trations of H₂S and it is inexpensive to use. The products of the scavenging reactions are believed to be biodegradable and water soluble [14]. Little work has been published in the area of 1,3,5-triazinane-4-thiones and 1,3,5-triazinane-2-ones showing antimicrobial activity [15]. These are also promising intermediates in the synthesis of tyrosine derivatives, which are well-known compounds used as Biocidal [16] and enantio-differentiating coupling reagents [17]. Heterocyclic structural unit has a significant place among pharmaceutically important synthetic and natural materials [18], showing powerful antiproliferative action [19]. For these reasons, 1,3,5-triazinane derivatives incorporating thiourea unit may be important in many fields [20].

2. Experimental section

2.1. Materials and methods

Melting points of the synthesized compounds were determined in open capillary tubes and were uncorrected. Reaction Progress was observed by TLC plates, Bruker 300 MHz instrument was used to record ¹H NMR spectra in DMSO/CDCl₃ using TMS as internal standard. Chemical shifts (δ) are expressed in ppm. Perkin Elmer BX series FT-IR was to record IR spectra, Elemental analysis were performed on a PerkinElmer 240 CHN analyzer (Scheme 1).

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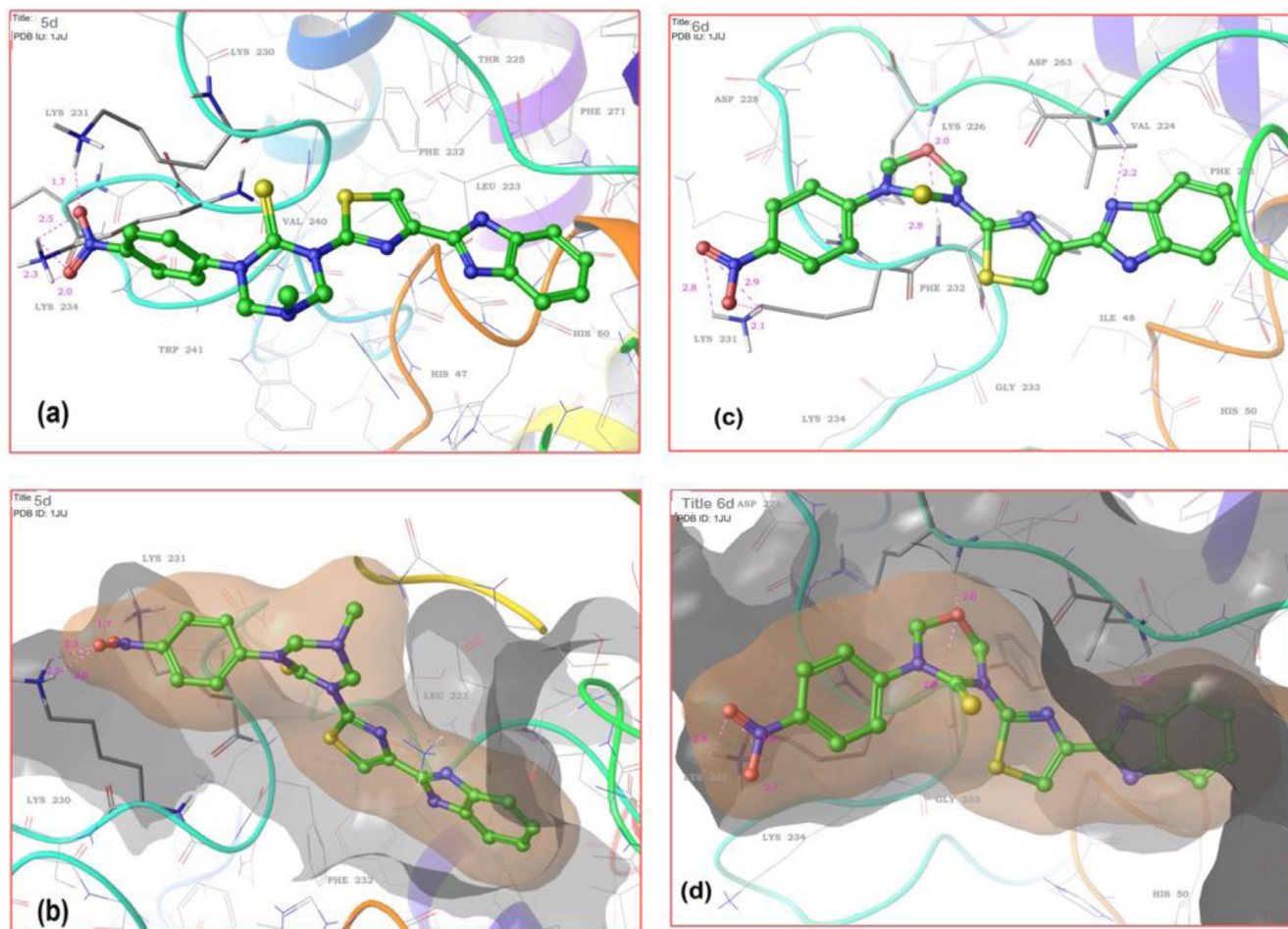


Fig. 2. Ligand-Protein 3D interaction on active site of PDB 1JJJ.

NMR (DMSO- d_6 , 300 MHz, δ ppm), 11.20 (s, 1H, NH), 6.38 (s, 1H, CH Ar), 4.64 (s, 4H, CH₂), 3.30 (s, 3H, CH₃), 7.71–7.86 (m, 4H, Ar H), 7.14–7.37 (m, 5H, Ar H), 6.78–6.94 (m, 2H, Ar H), MS, m/z (%), 407 (M^+); Anal. Calcd. For C₂₀H₁₈N₆S₂: C, 59.10; H, 4.46; N, 20.67%; Found: C, 58.78; H, 4.04; N, 19.98%.

2.1.3.2. 1-(4-(1H-benzo[d]imidazol-2-yl)thiazol-2-yl)-5-methyl-3-p-tolyl-1,3,5-triazinane-2-thione (5b). Yield 71% m.p 177–180 °C. IR (KBr) λ_{\max} in (cm⁻¹) 3360 (NH), 3086 (C–H), 3011 (C–H), 1569 (C=N), 1265 (C=S); ¹H NMR (DMSO- d_6 , 300 MHz, δ ppm), 7.78–7.89 (m, 4H, Ar H), 7.16–7.36 (m, 5H, Ar H), 6.72–6.90 (m, 2H, Ar H), 11.42 (s, 1H, NH), 6.56 (s, 1H, CH Ar), 4.54 (s, 4H, CH₂), 2.25 (s, 3H, CH₃); MS, m/z (%), 420 (M^+); Anal. Calcd. for C₂₁H₂₀N₆S₂: C, 59.97; H, 4.79; N, 19.98%; Found: C, 59.78; H, 4.64; N, 19.78%.

2.1.3.3. 1-(4-(1H-benzo[d]imidazol-2-yl)thiazol-2-yl)3-(4-methoxyphenyl)-5-methyl-1,3,5-triazinane-2-thione (5c). Yield 68% m.p 178–180 °C. IR (KBr) λ_{\max} in (cm⁻¹) 3363 (NH), 3080 (C–H), 1563 (C=N), 1275 (C=S); ¹H NMR (DMSO- d_6 , 300 MHz, δ ppm), 7.68–7.79 (m, 4H, Ar H), 7.12–7.26 (m, 5H, Ar H), 6.70–6.88 (m, 2H, Ar H), 11.48 (s, 1H, NH), 6.53 (s, 1H, CH Ar), 4.52 (s, 4H, CH₂), 2.27 (s, 3H, CH₃), 3.55 (s, 3H, CH₃); MS, m/z (%), 437 (M^+); Anal. Calcd. For C₂₁H₂₀N₆OS₂: C, 57.78; H, 4.62; N, 19.25 (%); Found: C, 56.98; H, 4.54; N, 18.78 (%).

2.1.3.4. 1-(4-(1H-benzo[d]imidazol-2-yl)thiazol-2-yl)5-methyl-3-(4-nitro phenyl)-1,3,5-triazinane-2-thione (5d). Yield 66% m.p 175–177 °C. IR (KBr) λ_{\max} in (cm⁻¹) 3358 (NH), 3076 (C–H), 1525

(–NO₂) 1569 (C=N), 1275 (C=S), 695 (C–S). ¹H NMR (DMSO- d_6 , 300 MHz, δ ppm), 7.65–7.76 (m, 4H, Ar H), 7.18–7.29 (m, 5H, Ar H), 6.72–6.89 (m, 2H, Ar H), 11.05 (s, 1H, NH), 6.64 (s, 1H, CH Ar), 4.51 (s, 4H, CH₂), 2.25 (s, 3H, CH₃); MS, m/z (%), 452 (M^+); Anal. Calcd. For C₂₀H₁₇N₇O₂S₂: C, 53.20; H, 3.79; N, 21.73 (%); Found: C, 52.78; H, 3.51; N, 20.85 (%).

2.1.3.5. 1-(4-(1H-benzo[d]imidazol-2-yl)thiazol-2-yl)3-(4-chloro phenyl)-5-methyl-1,3,5-triazinane-2-thione (5e). Yield 65% m.p 179–181 °C. IR (KBr) λ_{\max} in (cm⁻¹) 3371 (NH), 3084 (C–H), 1569 (C=N), 1270 (C=S), 783 (C–Cl) 690 (C–S). ¹H NMR (DMSO- d_6 , 300 MHz, δ ppm), 7.68–7.79 (m, 4H, Ar H), 7.16–7.28 (m, 5H, Ar H), 6.70–6.85 (m, 2H, Ar H), 10.52 (s, 1H, NH), 6.62 (s, 1H, CH Ar); MS, m/z (%), 442 (M^+), 443 (M^{++}). Anal. Calcd. For C₂₀H₁₇ClN₆S₂: C, 54.47; H, 3.89; N, 19.06%; Found: C, 53.86; H, 3.78; N, 18.85%.

2.1.4. Synthesis of 3-(4-(1H-benzo[d]imidazol-2-yl)thiazol-2-yl)-5-substituted phenyl-1,3,5-oxadiazinane-4-thione (6)

A mixture of compound (4) in (1 mmol), 30% formaldehyde (2 mmol) was taken in ethanol (30 ml) and added 1 ml concentrated HCl and refluxed for about 5–6 h at 100–110 °C. The progress of the reaction was monitored by TLC. After completion of the reaction, it was cooled and neutralized with 10% NaOH. The product was passed through silica gel by column and it was eluted from 60% ethyl acetate and hexane. These compounds were purified by recrystallisation from suitable solvents. The structures of these compounds have been confirmed on the basis of analysis and spectral (IR, ¹H NMR and Mass) data. Compounds 6(b–e) were

prepared by similar procedure with minor changes in reaction conditions.

2.1.4.1. 3-(4-(1H-benzo[d]imidazol-2-yl)thiazol-2-yl)-5-phenyl-1,3,5-oxadiazinane-4-thione (6a). Yield 70% m.p 175–177 °C. IR (KBr) λ_{\max} in (cm⁻¹) 3368 (NH), 1569 (C=N), 1260 (C=S), ¹H NMR (DMSO-*d*₆, 300 MHz, δ ppm), 11.20 (s, 1H, NH), 7.14–7.32 (m, 4H, Ar H), 6.65–6.85 (m, 5H, Ar H), 5.52 (s, 4H, CH₂); MS *m/z* (%), 394 (M⁺) Anal. Calcd. For C₁₉H₁₅N₅O₂S₂: C, 58.00; H, 3.84; N, 17.80%; Found: C, 57.86; H, 3.78; N, 17.25%.

2.1.4.2. 3-(4-(1H-benzo[d]imidazol-2-yl)thiazol-2-yl)-5-*p*-tolyl-1,3,5-oxadiazinane-4-thione (6b). Yield 65% m.p 175–178 °C. IR (KBr) λ_{\max} in (cm⁻¹) 3362 (NH), 1569 (C=N), 1265 (C=S); ¹H NMR (DMSO-*d*₆, 300 MHz, δ ppm), 11.25 (s, 1H, NH), 7.18–7.36 (m, 4H, Ar H), 6.69–6.88 (m, 5H, Ar H), 5.55 (s, 4H, CH₂), 2.25 (s, 3H, CH₃); MS, *m/z* (%), 407 (M⁺); Anal. Calcd. For C₂₀H₁₇N₅O₂S₂: C, 58.90; H, 4.20; N, 17.19 (%); Found: C, 57.86; H, 4.12; N, 17.02 (%).

2.1.4.3. 3-(4-(1H-benzo[d]imidazol-2-yl)thiazol-2-yl)-5-(4-methoxyphenyl)-1,3,5-oxadiazinane-4-thione (6c). Yield 68% m.p 174–176 °C. IR (KBr) λ_{\max} in (cm⁻¹) 3368 (NH), 1569 (C=N), 1260 (C=S); ¹H NMR (DMSO-*d*₆, 300 MHz, δ ppm), 7.18–7.36 (m, 4H, Ar H), 6.69–6.88 (m, 5H, Ar H), 11.14 (s, 1H, NH), 5.53 (s, 4H, CH₂), 3.77 (s, 3H, OCH₃); MS, *m/z* (%), 423 (M⁺); Anal. Calcd. For C₂₀H₁₇N₅O₃S₂: C, 58.90; H, 4.20; N, 17.19 (%); Found: C, 57.86; H, 4.12; N, 17.02 (%).

2.1.4.4. 3-(4-(1H-benzo[d]imidazol-2-yl)thiazol-2-yl)-5-(4-nitrophenyl)-1,3,5-oxadiazinane-4-thione (6d). Yield 66% m.p 176–178 °C. IR (KBr) λ_{\max} in (cm⁻¹) 3353 (NH), 1566 (C=N), 1523 (NO₂), 1262 (C=S), ¹H NMR (DMSO-*d*₆, 300 MHz, δ ppm), 11.22 (s, 1H, NH), 7.20–7.36 (m, 4H, Ar H), 6.70–6.85 (m, 5H, Ar H), 5.53 (s, 4H, CH₂); MS, *m/z* (%), 423 (M⁺); Anal. Calcd. For C₁₉H₁₄N₆O₃S₂: C, 52.04; H, 3.20; N, 19.18 (%); Found: C, 51.86; H, 3.02; N, 18.82 (%).

2.1.4.5. 3-(4-(1H-benzo[d]imidazol-2-yl)thiazol-2-yl)-5-(4-chlorophenyl)-1,3,5-oxadiazinane-4-thione (6e). Yield 65% m.p 175–

178 °C. IR (KBr) λ_{\max} in (cm⁻¹) 3358 (NH), 1563 (C=N), 1260 (C=S), 780 (C–Cl); ¹H NMR (DMSO-*d*₆, 300 MHz, δ ppm), 11.26 (s, 1H, NH), 7.18–7.36 (m, 4H, Ar H), 6.72–6.86 (m, 5H, Ar H), 5.55 (s, 4H, CH₂); MS, *m/z* (%), 423 (M⁺); Anal. Calcd. For C₁₉H₁₄N₆ClO₂S₂: C, 53.34; H, 3.30; N, 16.35 (%); Found: C, 52.85; H, 3.22; N, 16.25 (%).

3. Anti bacterial activity

The antibacterial activity of synthesized compounds was evaluated against six bacteria by using the well diffusion method. *Gentamycin* was employed as standard drug to compare the results. Strains of *Bacillus subtilis* MTCC 441, *Bacillus cereus* ATCC 9372, *Staphylococcus aureus* ATCC 96, *E. coli* ATCC 8739, *Klebsiella pneumoniae* MTCC 109, *Salmonella typhi* ATCC 4420 were taken from the department of microbiology, Kakatiya University Warangal. The bacterial cultures were developed by selective nutrient broth at 37 °C and stored at 4 °C for further use. Nutrient broth was used for the preparation of inoculums of the bacteria and nutrient agar was used for the screening method [21] and their results were tabulated in Table 1.

3.1. Molecular docking

Auto Dock 4.2 (MGL tools-1.5.6) was used to perform all docking simulations. A set of new triazinane–benzimidazole derivatives were subjected to docking with *topoisomerase II* (PDB ID: 1JJJ) and *DNA gyrase subunit b* (PDB ID:1KZN). From the Protein Data Bank (RCSB) (<http://www.rcsb.org/pdb>). The *DNA gyrase subunit b* and crystal structure of target enzyme *topoisomerase II* was retrieved. To carry out in silico studies, the 2D structures of the synthesized ligands **5(a–e)**, **6(a–e)** were drawn and converted to energy minimized 3D structures in the pdb file format using Marvin Sketch (Chem Axon). By removing the hetero atoms, water molecule and cofactors, the target protein file was prepared by leaving the associated residue with protein by using Auto Dock 4.2 (MGL tools-1.5.6). Preparation of target protein file Auto Dock 4.2 (MGL

Table 1
Antibacterial activity of compounds **5** and **6 (a–e)**.

Compound	Conc.	Zone of inhibition in mm					
		<i>E. coli</i>	<i>S. typhi</i>	<i>K. pneumoniae</i>	<i>S. aureus</i>	<i>B. subtilis</i>	<i>B.cereus</i>
5a	10	5	7	5	4	4	5
	20	6	8	5	5	6	7
5b	10	8	9	9	8	7	8
	20	10	11	10	10	9	11
5c	10	13	12	12	11	10	12
	20	15	13	14	12	11	14
5d	10	7	8	7	6	6	7
	20	9	9	8	8	7	9
5e	10	11	11	10	9	9	10
	20	12	13	12	11	11	12
6a	10	5	4	4	3	4	3
	20	7	6	5	5	4	6
6b	10	10	9	9	8	7	10
	20	14	10	12	9	7	12
6c	10	12	10	11	10	9	13
	20	16	11	13	11	10	15
6d	10	9	8	7	6	5	8
	20	10	10	9	8	8	11
6e	10	8	7	5	6	5	6
	20	9	7	6	6	7	7
Standard	10	17	14	16	13	14	15
	20	18	15	18	15	16	18

Table 2Molecular docking reports for compounds **3** and **4** (a–e) against protein 1JJ and 1KZN.

Sl. No.	PDB code	Compounds	Binding energy (kcal/mol)	Inhibition constant (Ki)	Residue involved H-bond
1	1JJ	5a	−8.96	270.77 nM	Gly193, Gly38
2	1JJ	5b	−8.92	287.57 nM	Gly193, Gly38
3	1JJ	5c	−8.65	454.52 nM	His50
4	1JJ	5d	−9.05	232.69 nM	Lys234, Lys231, Val224
5	1JJ	5e	−8.75	388.00 nM	Val224, His47
6	1JJ	6a	−8.73	253.86 nM	Phe232, Lys231, Lys226, Val224
7	1JJ	6b	−8.47	620.88 nM	Phe232, Lys226, Lys231, Val224
8	1JJ	6c	−8.61	487.21 nM	Gly193, Gly196, Val224, Phe232
9	1JJ	6d	−9.10	212.52 nM	Phe232, Lys226, Lys231, Val224
10	1JJ	6e	−8.18	1.01 μ M	Phe232, Val224, Lys226, Lys231
11	1KZN	5a	−9.30	151.92 nM	Asn46, Val120
12	1KZN	5b	−9.50	108.08 nM	Asn46, Val120
13	1KZN	5c	−8.90	301.70 nM	Asn46, Arg139, Arg76
14	1KZN	5d	−10.04	43.89 nM	Arg139, Arg76, Asn46,
15	1KZN	5e	−9.21	178.27 nM	Asn46, Val120
16	1KZN	6a	−8.13	254.36 nM	Asn46
17	1KZN	6b	−8.85	324.18 nM	Asn46
18	1KZN	6c	−8.44	655.89 nM	Asn46, Thr165, Ser121, Val120
19	1KZN	6d	−9.37	135.75 nM	Arg76, Arg136, Glu50, Asn46, Ser121, Val120
20	1KZN	6e	−8.84	331.59 nM	Asn46

tools-1.5.6) tool has been done, which involves the assign of Gas-teiger charges for all the atoms of molecules converting into AD4 type. Docking simulations for the compounds **5(a–e)**, **6(a–e)** were performed against the active site of *topoisomerase II* and *DNA gyrase* subunit b, finally Maestro elements tutorial 1.8 was used to visualize docking results tabulated in Table 2.

4. Results and discussion

In the present study, it has been discussed that the synthesis of various benzimidazole fused triazinane 4-thione heterocyclic moieties by cyclic condensation based on classical Mannich amino methylation of *N,N'* unsymmetrical thio ureas (**4**) with 30% HCHO and methyl amine in ethanol. An aliphatic amine has been yielded in the condensation between methyl amine and formaldehyde, it cyclizes immediately to produce corresponding 1,3,5-triazinane since imine is unstable. With respect to biological activity, benzimidazole fused heterocyclic compounds such as triazinane derivatives are of very important than the cyclic compounds. Here the efforts are more focused on the synthesis of compound (**1**) by using $\text{NaHSO}_4\text{--SiO}_2$ catalyst and high yield of derived product is achieved by refluxing in ethanol. $\text{NaHSO}_4\text{--SiO}_2$ is a heterogeneous and eco friendly catalyst [22].

The chemical structure of title compounds **5** and **6** were established on the basis of spectroscopic analysis. The IR spectrum showed absorption bands in the range from 3355 to 3373 cm^{-1} for (NH) functions, 1562 to 1590 cm^{-1} for (C=N) function and C=S absorptions in the range from 1231 to 1277 cm^{-1} . The ^1H NMR spectra of test compounds revealed the presence of singlet signals at 6.38 ppm for thiazole protons (CH), 11.20 ppm for NH proton, 4.64 ppm for CH_2 (triazinane) and 5.53 ppm CH_2 (oxadiazinane) respectively in addition to the aromatic protons as a multiplet (H) in the range 6.78–8.40 ppm. The mass spectrum showed a

corresponding molecular ion peak at *m/z* with respect to their molecular weights (Table 3).

4.1. Biological study and structure activity relationship

The newly synthesized title compounds **5a–e** and **6a–e** were evaluated for their antibacterial activity against *Bacillus subtilis*, *Bacillus cereus*, *Staphylococcus aureus*, *E. coli*, *Klebsiella pneumoniae*, and *Salmonella typhi*. The antibacterial activity of the tested compounds was assessed by zone of inhibition using well diffusion method. *Gentamycin* was used as standard drug for comparison. Structure activity relationship (SAR) studies for the antibacterial activity of compounds **5a–e** and **6a–e** mentioned in Table 1. The results of antibacterial screening (Table 1) reveal that the compounds **5a–e** and **6a–e** displayed a better activity as compared to the standard drug. The electronic property of the compounds has close relationship to their biological activity. The substitution of the electron withdrawing groups such as chloro (**5e** and **6e**), and nitro (**5d** and **6d**) on the benzene ring exhibited more activity, whereas the introduction of electron donating groups such as methyl (**5b** and **6b**) and methoxy (**5c** and **6c**) groups on the benzene ring did not exhibit much activity. Compound **5a** and **6a** showed least activity because it has no substituent on the benzene ring. This evidence confirmed that suitable functional groups on benzene ring were necessary for better antibacterial activities in drug design [23]. Hence these results implied that electron withdrawing groups play important roles in the antibacterial activities of these tested compounds.

Molecular docking based on the fact that Vosaroxin is a benzimidazole derivative which is an antibacterial drug and it is proved to exert its action by the inhibition of *topoisomerase II*, in clinical trails. On the basis of drug action, it has been performed docking simulation of the newly synthesized benzimidazole derivatives **5a–e** and **6a–e** binding the active site of the *topoisomerase II crystal structure* (PDB ID: 1JJ) and *DNA gyrase subunit b* (PDB ID: 1KZN). The docking result of the tested compounds **5d** and **6d** showed high binding energy with *topoisomerase II* and *DNA gyrase subunit b*. Compound **5d** and **6d** showed very good binding energy with −9.05, −9.10 kcal/mol respectively for *topoisomerase II*. Compound **5d** and **6d** showed very good binding energy with −10.04, −9.37 respectively for *DNA gyrase subunit b*. The binding energies, inhibition constants and residues involved in H-bonding are tabulated in Table 2.

Table 3Substituents for compounds **5** and **6**.

5 and 6	Ar
a	C_6H_5
b	$4\text{-CH}_3\text{C}_6\text{H}_4$
c	$4\text{-OCH}_3\text{C}_6\text{H}_4$
d	$4\text{-NO}_2\text{C}_6\text{H}_4$
e	$4\text{-ClC}_6\text{H}_4$

5. Conclusions

The research study reported efficient synthesis of new analogs of triazinane and oxadiazinane by classical amino methylation with different aryl-*N,N'* unsymmetrical thioureas. All compounds were characterized by standard spectroscopic techniques and evaluation of the antibacterial activity of all new compounds was carried out and proved significant to moderate activity also the compounds showed good inhibitory activity against molecular docking.

Acknowledgements

The authors gratefully acknowledge the Department of Chemistry, Kakatiya University, Warangal for constant support during this research work.

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