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ORIGINAL RESEARCH

Synthesis of novel 4-hydroxycoumarin derivatives: evaluation of antimicrobial, antioxidant activities and its molecular docking studies

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Abstract A series of novel 4-hydroxycoumarin derivatives **4a–n** were synthesized by treating 2-(2-oxo-2H-chromen-4-yloxy)acetic acid **3** with various amines. Acid **3** was obtained from the hydrolysis of corresponding ester **2** which was prepared from 4-hydroxycoumarin **1** and ethyl bromoacetate. All synthesized compounds **4a–n** were characterized using spectral techniques. The synthesized compounds **4a–n** were evaluated for their antimicrobial and total antioxidant activity using in vitro well diffusion method and phosphomolybdenum method, respectively. Amongst all the compounds, **4c** has shown potential antimicrobial and antioxidant activity against the standard. All compounds have exhibited good binding energies from −4.46 to −5.70 kcal/mol against 24-kDa DNA gyrase B fragment from *E. coli* (PDB ID-1KZN) in molecular docking study and amongst them **4c** has shown maximum binding energy.

Keywords 4-Hydroxycoumarin derivatives · Antimicrobial · Total antioxidant · *E. coli* DNA gyrase B subunit · Molecular docking

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Introduction

In recent years the infectious diseases caused by the bacteria and fungi increased dramatically, resulting in serious threat to human health (Yoneyama and Katsumata, 2006). Even though several class of antibiotic drugs are available, multidrug resistance (MDR) in most of the pathogenic bacteria for these drugs have been emerging continuously (Bennett, 2008). To overcome these problems, new antibacterial drugs are postulated which have better activity than existing drugs against such bacteria. It emphasizes the exploitation of new antimicrobial and antioxidant drugs which can assist in treatment and prevent diseases in a better way.

In this present work we have reported the synthesis of novel 4-hydroxycoumarin derivatives with good antimicrobial and antioxidant activity. Coumarin (2-oxo-2H-chromene) is a naturally occurring heterocyclic compounds isolated from various plants, it has been found in the

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microorganisms, animals, essential oils and fruits (Egan *et al.*, 1990; Borges *et al.*, 2005). Many of coumarin derivatives have been synthesized and reported for its biological activities such as antibacterial (Kayser and Kolodziej, 1999; Al-Haizal *et al.*, 2003; Singh *et al.*, 2010), antifungal (Cristina *et al.*, 2008; Satyanaraya *et al.*, 2008), antioxidant (Parameswaran *et al.*, 2009; Patel Rajesh and Patel Natvar, 2011; Maja and Cacic, 2012) antiinflammatory (Shashwat *et al.*, 2008; Georgia *et al.*, 2009), antitumor (Nofal *et al.*, 2000; Nawrot *et al.*, 2006), antiviral (Kirkiacharian *et al.*, 2008) and CNS stimulant. 4-Hydroxy-coumarin is one of the important classes in coumarin family and has wide range of applications in organic synthesis. Substituted 4-hydroxycoumarins have been known for their broad range of pharmacological activities such as antimicrobial (She-Feng *et al.*, 2014; Diwakar *et al.*, 2015; Sined *et al.*, 2015), antioxidant (Mario *et al.*, 1996; Hamdi *et al.*, 2008; Abdul Amir *et al.*, 2011), anti-inflammatory (Nicolaides *et al.*, 1998; Rambabu *et al.*, 2012) and also proven to be anticoagulant rodenticide (Fig. 1).

Based on the reports and biological interests of 4-hydroxycoumarin, a series of novel 4-hydroxy-coumarin derivatives **4a–n** were designed, synthesized and their studies described in this article. All synthesized molecules **4a–n** were screened for their in vitro antimicrobial and antioxidant activity with an aim of obtaining more useful compounds with respect to multidrug resistance. Molecular docking studies have been executed against X-ray crystallographic structure of *E. coli* (PDB ID: 1KZN).

Experimental

Refer electronic supplementary material for materials and methods.

Synthesis of novel 4-hydroxycoumarin derivatives 4a-n

The reaction leading to novel derivatives of 4-hydroxycoumarin **4a–n** is outlined (Scheme 1; Table 1). 4-Hydroxycoumarin was heated with ethyl bromoacetate in the presence of potassium carbonate to obtain ethyl 2-(2-oxo-2H-chromen-4-yloxy)acetate **2** which on further hydrolysis gave (2-oxo-2H-chromen-4-yloxy)acetic acid **3**. Further this **3** was treated with various amines in the presence of carbodiimide (EDC), hydroxybenzotriazole (HOBt) and diisopropylethylamine (DIPEA) to obtain the targeted compounds **4a–n**.

The structure of all novel 4-hydroxycoumarin derivatives **4a–n** were elucidated by using spectral techniques such as IR, ^{1}H-NMR, ^{13}C-NMR, and MS as instanced for compound **4b**. In the IR spectrum (KBr) of **4b**, the broad band appear at 3290 cm^{-1} confirms the presence of amide N–H stretching, the short bands observe at 3087 and 2960 cm^{-1} are corresponds to aromatic and aliphatic C–H stretchings, respectively, the presence of carbonyl group of lactone and amide groups confirmed by the sharp bands present at 1734 and 1667 cm^{-1}, respectively, the band at 1625 cm^{-1} agrees to benzenoid band of phenyl rings, the short band at 1213 cm^{-1} indicated the presence of C–O function in the system, and the medium bands at 766 and 704 cm^{-1} are corresponds to the C–H out of plane bending of mono-substituted benzene ring of **4b**.

In ^{1}H-NMR spectrum of **4b**, the broad signal at δ: 7.73–7.71 ppm confirmed the presence of –NH proton, the signals in the range of δ: 7.62–5.70 ppm shows ten aromatic protons, the quintet signal at δ: 5.29–5.25 ppm shows the presence of one –CH proton, a triplet signal at δ: 4.68–4.60 ppm confirms the presence of two methylene protons, and a singlet signal at δ: 1.59 shows the presence of three protons of methyl group. In ^{13}C-NMR spectrum of

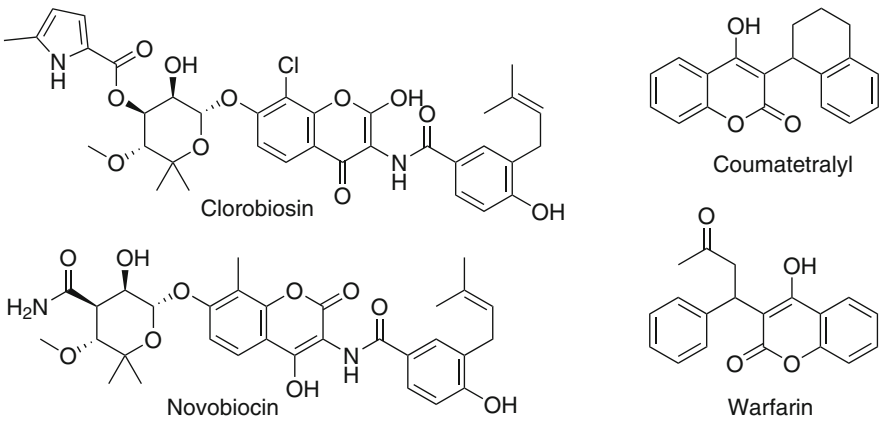
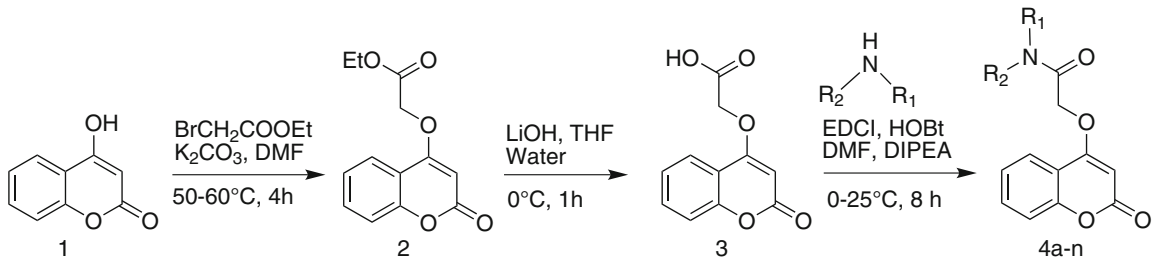


Fig. 1 Structures of some 4-hydroxycoumarin derivatives used as drugs



Scheme 1 Synthesis of novel derivatives of 4-hydroxycoumarin **4a–n**

Table 1 Novel 4-hydroxycoumarin derivatives **4a–n**

Entry	R^1	R^2	HPLC (area %)	Melting point (°C)	Yield (%)
4a	Phenyl	Phenyl	93.0	246–248	92.8
4b	Hydrogen	*R*-(+)-1-phenylethyl	99.1	158–161	94.8
4c	Hydrogen	2,4-Dimethoxybenzyl	97.9	172–174	94.0
4d	Hydrogen	Cycloheptyl	97.8	149–152	91.0
4e	Hydrogen	((1r,3s,5R,7S)-3-Hydroxyadamantan-1-yl)	98.4	226–229	82.0
4f	Hydrogen	(2-Thienyl)ethyl	98.7	150–152	94.0
4g	Hydrogen	*R*-(+)-1-(1-naphthyl)ethyl	99.0	180–183	95.4
4h	Hydrogen	2-(2-Pyridyl)ethyl	99.7	159–162	91.2
4i	Methyl	(Ethoxycarbonyl)methyl	98.7	97–100	92.3
4j	Hydrogen	2-Propynyl-	99.2	170–173	92.7
4k	–	5,6,7,8-Tetrahydrotetrazolo[1,5-a]-pyrazinyl	90.0	200–202	88.5
4l	Hydrogen	(4-Fluorophenyl)methyl	99.2	196–198	95.6
4m	Hydrogen	(4-Methylphenyl)methyl	99.3	172–174	96.0
4n	–	1-(1,4-Piperazinyl)	99.4	192–195	84.0

4b, the signals appear in the region between δ: 164.6 to 91.94 show the presence of aromatic carbons, the signal at δ: 67.61 shows the presence of one $-CH_2$ carbon, the signal at δ: 48.84 shows the presence of –CH carbon and a signal present at δ: 21.66 confirmed the presence of one $-CH_3$ group. An identifying peak observed at *m/z*: 324.2 in the mass spectrum (EI-MS) for $[M + H]^+$ ion further conforms the compound **4b**. Apart from above data, the structure of compound **4b** was demonstrated unambiguously with the help of single-crystal X-ray diffraction (Table 2; crystal data deposited at CCDC, and the CCDC No. 1037062).

Synthetic procedures

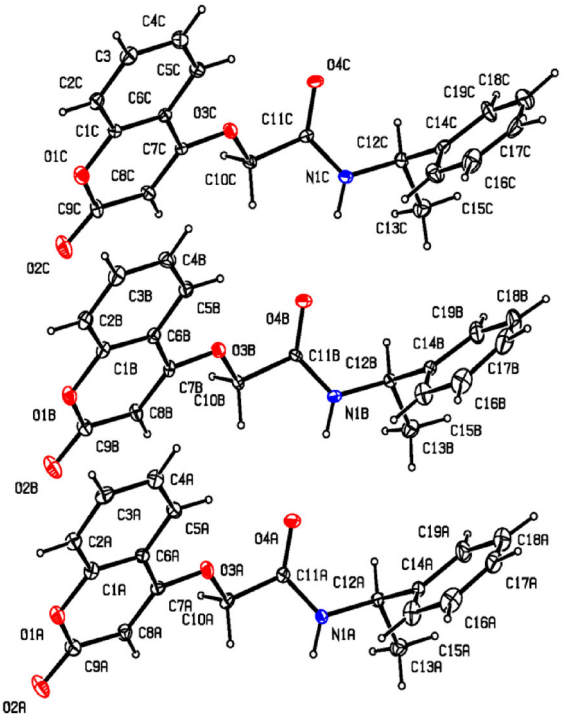
*Procedure for synthesis of Ethyl 2-(2-oxo-2H-chromen-4-yloxy)acetate (**2**)* Ethyl bromoacetate(1.2 mol eq) was added to a solution of 4-hydroxycoumarin **1** (1.0 mol eq.), potassium carbonate (1.5 mol Eq) in DMF (10 mL) and heated to 50–60 °C for 4 h. The progress of the reaction was monitored by TLC (mobile phase: ethyl acetate/hexane). After completion of reaction, the mixture was poured into the ice-cold water, filtered and dried u/vacuum to obtain **2** as a white solid, yield 84 %, mp 100–103 °C and purity by HPLC 98 %. IR (KBr, cm^{-1}): 3079 (C–H, aromatic), 2988 (C–H, aliphatic), 1716 (C=O, lactone), 1704 (C=O, ester), 1622 (C=C, alkene); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.82–7.29 (m, 4H, Ar–H), 5.68 (s, 1H, –C=CH–), 4.57–4.54 (t, 2H, $-OCH_2$), 4.34–4.31 (t, 2H, $-O-CH_2-CH_3$), 2.13 (s, 3H, $-O-CH_2-CH_3$), ^{13}C NMR (100 MHz, $CDCl_3$); δ_C 168.57 (ring lactone –O–C=O), 164.35 (ester O–C=O), 161.5 to 115.0 (8 Ar–C), 91.3 ($-OCH_2$), 65.52 ($-CH_2-CH_3$), 54.7 ($-CH_2-CH_3$); EI-MS: *m/z* 249.0 $[M + H]^+$, 100 %).

*2-(2-Oxo-2H-chromen-4-yloxy)acetic acid (**3**)* Solution of lithium hydroxide (1.2 mol eq.) in water (2 mL) was added to ethyl 2-(2-oxo-2H-chromen-4-yloxy)acetate **2** (1.0 mol eq.) in THF (5 mL) at 0 °C and stirred at 0 °C for 1 h. Completion of the reaction was confirmed by TLC (mobile phase: ethyl acetate/hexane) and THF was distilled off in Rota vapor. The obtained solution was washed with ethyl acetate (20 mL). The aqueous layer was acidified with 2 N HCl (pH 1.0–2.0), and the obtained solid was

Table 2 Crystal data, refinement and ORTEP diagram of **4b**

Parameters	Values
Empirical formula	$C_{19}H_{17}NO_4$
Formula weight	323.34
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system, space group	Orthorhombic, P 2_1 2_1 2_1
Unit cell dimensions	$a = 11.329(5)$ Å, $\alpha = 90°$
	$b = 14.675(5)$ Å, $\beta = 90°$
	$c = 29.182(5)$ Å, $\gamma = 90°$
Volume	4852(3) A^3
Z, Calculated density	12, 1.328 Mg/m^3
Absorption coefficient	0.094 mm^{-1}
$F(000)$	2040
Crystal size	0.20 × 0.15 × 0.10 mm
Theta range for data collection	1.40° to 28.33°
Limiting indices	$-15 \leq h \leq 15$, $-19 \leq k \leq 19$, $-38 \leq l \leq 38$
Reflections collected/unique	47,774/11,952 [R(int) = 0.0672]
Completeness to theta	99.6 %
Max. and min. transmission	0.9907 and 0.9815
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	11,952/0/652
Goodness-of-fit on F^2	0.902
Final R indices [$I > 2$sigma(I)]	$R1 = 0.0466$, w$R2 = 0.1080$
R indices (all data)	$R1 = 0.1970$, w$R2 = 0.1684$
Largest diff. peak and hole	0.137 and −0.129 e A^{-3}

ORTEP diagram of 4b



filtered, washed with hexane and dried under vacuum to give **3** as white solid, yield 78 %; mp 227–230 °C and purity by HPLC 99 %. IR (KBr, cm^1); 3080 (C–H, aromatic), 2926 (C–H, aliphatic),1770 (C=O, lactone), 1720 (C=O, acid), 1629 (C=C, alkene); ^{1}H NMR (400 MHz, DMSO): δ_H 7.81–7.35 (m, 4H, Ar–H), 5.86 (s, 1H, –C=CH–), 4.92 (s, 2H, –OCH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 168.57 (C=O, lactone), 164.3 (C=O, acid), 161.5–115.0 (8 Ar–C), 91.37 (–CH_2),; EI-MS: *m/z* 221.0 $[M + H]^+$, 100 %).

General procedure for the synthesis of 4a–4n

DIPEA (3.1 mol eq.) was added to a mixture of 2-(2-oxo-2H-chromen-4-yloxy)acetic acid **3** (1.0 mol eq.) EDCI (1.2 mol eq.), HOBt (1.0 mol eq.), amine (1.0 mol eq.) and DMF (5 mL) at 0–5 °C and allowed the mass to ambient temperature and stirred for 8 h. Progress of the reaction was monitored by TLC (mobile phase: ethyl acetate/hexane). After completion of the reaction, mixture was poured into ice/water and the obtained solid **(4a–n)** was filtered, washed with hexane and dried under vacuum.

N-benzhydryl-2-(2-oxo-2H-chromen-4-yloxy)acetamide (**4a**) White powder, yield 92.8 %, mp 246–248 °C, purity by HPLC 93 %. IR (KBr, cm^{-1}): 3257 (N–H, amide), 3087 (C–H, aromatic), 2969 (C–H, aliphatic), 1716 (C=O, lactone), 1655 (C=O, amide), 1629 (C=C, alkene); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.7–7.68 (d, 1H), 7.62–6.88 (m, 15H, Ar–H), 6.38 (d, 1H, –NH), 5.70 (s, 1H, –CH)), 4.72 (s, 2H, –CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 165 (C=O, lactone), 164.12 (C=O, amide), 162–92.2 (11 Ar–C), 67.77 (–CH_2), 56.9 (–CH); EI-MS: *m/z* 386.1 $[M + H]^+$, 100 %). Anal. Calcd. for $C_{24}H_{19}NO_4$: C, 74.79; H, 4.97; N, 3.63. Found C, 74.82; H, 5.01; N, 3.65.

(R)-2-(2-oxo-2H-chromen-4-yloxy)-N-(1-phenylethyl)acetamide (**4b**) White powder, yield 94.8 %, mp 158–161 °C, purity by HPLC 99.1 %, specific optical rotation +24° (c = 1 %, $CHCl_3$). IR (KBr, cm^{-1}): 3290 (N–H, amide), 3087 (C–H, aromatic), 2960 (C–H, aliphatic), 1734 (C=O, lactone), 1667 (C=O, amide), 1625 (C=C, alkene); ^{1}H NMR

(400 MHz, $CDCl_3$): δ_H 7.73–6.4 (m, 10H, Ar–H), 5.70 (bs, 1H, –NH), 5.29–5.25 (q, 1H, –CH–CH_3), 4.68 (s, 2H, –CH_2), 1.59 (d, 3H, –CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 164.6 (C=O, lactone), 164.0 (C=O, amide), 162.0 to 91.94 (12 Ar–C), 67.61 (–CH_2), 48.84 (–CH), 21.66 (–CH_3); EI-MS: *m/z* 324.2 $[M + H]^+$, 100 %). Anal. Calcd. for $C_{19}H_{17}NO_4$: C, 70.58; H, 5.30; N, 4.33. Found C, 70.55; H, 5.35; N, 4.35.

*N-(2,4-dimethoxybenzyl)-2-(2-oxo-2H-chromen-4-yloxy)acetamide (**4c**)* White powder, yield 94 %, mp 172–174 °C, purity by HPLC 97.9 %. IR (KBr, cm^{-1}): 3288 (N–H, amide), 3084 (C–H, aromatic), 2960 (C–H, aliphatic), 1731 (C=O, lactone), 1655 (C=O, amide), 1624 (C=C, alkene); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.78–6.44 (m, 8H, Ar–H), 5.67 (bs, 1H, –NH), 4.61 (s, 2H, –NH–CH_2), 4.50 (d, 2H, –CH_2), 3.80 (s, 6H, (–OCH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 165.0 (C=O, lactone), 163.8 (C=O, amide), 162.0–92.14 (14 Ar–C), 67.64 (–CH_2), 55.62, (–CH_2), 39.43 (–OCH_3); EI-MS: *m/z* 370.2 $[M + H]^+$, 100 %. Anal. Calcd. for $C_{20}H_{19}NO_6$: C, 65.03; H, 5.18; N, 3.79. Found C, 65.23; H, 5.21; N, 3.77.

*N-Cycloheptyl-2-(2-oxo-2H-chromen-4-yloxy)acetamide (**4d**)* White powder, Yield 91 %, mp 149–152 °C, purity by HPLC 97.8 %. IR (KBr, cm^{-1}): 3290 (N–H, amide), 3075 (C–H, aromatic), 2930 (C–H, aliphatic), 1743 (C=O, lactone), 1696 (C=O, amide), 1620 (C=C, alkene); ^{1}H NMR (400 MHz,$CDCl_3$): δ_H 7.79–6.23 5H, Ar–H), 5.71 (bs, 1H, NH), 4.62 (s, 2H, –OCH_2), 4.0 (s, 1H, CH), 1.68–1.49 (m, 12H, ring –CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 164.35 (C=O, lactone), 164.06 (C=O, amide), 162.1–92.22 (8, Ar–C), 67.79 (–OCH_2), 50.6–24.14 (4 aliphatic ring carbons); EI-MS: *m/z* 316.1 $[M + H]^+$ 100 %. Anal. Calcd. for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found C, 68.50; H, 6.75; N, 4.49.

*(1r,3s,5R,7S)-N-(3-Hdroxyadamant-1-yl)-2-(2-oxo-2H-chromen-4-yloxy)acetamide (**4e**)* White solid, yield 82 %, mp 226–229 °C, purity by HPLC 98.4 %, specific optical rotation −35° (c = 1 %, $CHCl_3$). IR (KBr, cm^{-1}): 3336 (NH, amide), 3071 (C–H, aromatic), 2918 (C–H, aliphatic), 1724 (C = O, lactone), 1682 (C = O, amide), 1624 (C = C, alkene); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.72–6.05 (m, 4H, Ar–H), 5.71 (bs, 1H, -NH), 4.53 (s, 2H, –OCH_2), 2.33–0.86 (m, 15H, adamantyl ring protons); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 164.5 (C = O, lactone), 164.10 (C = O, amide), 162.2-91.97 (8, Ar–C), 68.91 (–OCH_2), 67.7, −30.6 (11, adamantyl carbons); EI-MS: *m/z* 370.2 $[M + H]^+$, 100 %). Anal. Calcd. for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79. Found C, 68.38; H, 6.32; N, 3.82.

*2-(2-Oxo-2H-chromen-4-lyoxy)-N-(2-(thiophen-2-yl)ethyl)acetamide (**4f**)* Brown solid, yield 94 %, mp 150-152 °C, purity by HPLC 98.7 %. IR (KBr, cm^{-1}): 3289 (N–H, amide), 3083 (C–H, aromatic), 2934 (C–H, aliphatic), 1728 (C=O, lactone), 1663 (C=O, amide), 1625 (C=C, alkene); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.62–6.40 (m, 8H, Ar–H), 5.71 (bs, 1H, –NH), 4.61 (s, 2H, –CH_2), 3.72–3.68 (t, 2H, NH–CH_2), 3.14–3.11 (t, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 165.8 (C=O, lactone), 164.3 (C=O, amide), 161.47–91.4 (11, Ar–C) 67.6 (–OCH_2), 39.8 (–NHCH_2) 38.8 (–CH_2); EI-MS: *m/z* 330.1 $[M + H]^+$, 100 %. Anal. Calcd. for $C_{17}H_{15}NO_4S$: C, 61.99; H, 4.59; N, 4.25. Found C, 62.03; H, 4.64; N, 4.28.

*(R)-N-(1-(1-Naphthalen-1-yl)ethyl)-2-((2-oxo-2H-chromen-4yl) oxy) acetamide (**4g**)* White solid, yield 95.4 %, mp 180–183 °C, purity by HPLC 99 %, specific optical rotation +6° (c = 1 %, $CHCl_3$). IR (KBr, cm^{-1}): 3283 (N–H, amide), 3088 (C–H, aromatic), 2975 (C–H, aliphatic), 1734 (C=O, lactone), 1668 (C=O, amide), 1625 (C=C, alkene); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.10–7.22 (m, 12H, Ar–H), 5.64 (bs, 1H, –NH), 4.68 (s, 2H, –OCH_2), 4.64–4.59 (q, 1H, CH), 1.76 (d, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.70 (C=O, lactone), 164.06 (C=O, amide), 162–92.12, (18C, Ar–C) 67.72 (–OCH_2), 45.29 (CH), 20.93 (CH_3); EI-MS: *m/z* 374.2 $[M + H]^+$, 100 %). Anal. Calcd. for $C_{23}H_{19}NO_4$: C, 73.98; H, 5.18; N, 3.75. Found C, 74.15; H, 4.64; N, 3.78.

*2-(2-Oxo-2H-chromen-4-loxy)-N-(2-(pyridin-2-yl)ethyl)acetamide (**4h**)* Light brown solid, mp 159–162 °C, yield 91.2 %, purity by HPLC 99.7 %. IR (KBr, cm^{-1}): 3254 (N–H, amide), 3063 (C–H, aromatic), 2966 (C–H, aliphatic), 1731 (C=O, lactone), 1668 (C=O, amide), 1628 (C=C, alkene); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.29–7.10 (m, 10H, Ar–H), 5.67 (bs, 1H, –NH), 4.63 (s, 2H, –OCH_2), 3.82–3.80 (t, 2H, CH_2), 3.06 (t, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 165.25 (C=O, lactone), 163.91 (C=O, amide), 162–91.7 (13, Ar–C), 67.44 (–OCH_2), 38.09 (–NH–CH_2–CH_2), 35.89 (–NH–CH_2–CH_2); EI-MS: *m/z* 325.2 $[M + H]^+$, 100 %). Anal. Calcd. for $C_{18}H_{16}N_2O_4$: C, 66.66; H, 4.97; N, 8.64. Found C, 66.55; H, 5.00; N, 8.69.

*Ethyl 2-(N-methyl-2-(2-oxo-2H-chromen-4-yloxy)-acetamido) acetate (**4i**)* White solid, mp 97–100 °C, yield: 92.7 %, purity by HPLC 98.7 %. IR (KBr, cm^{-1}): 3078 (C–H, aromatic), 2968 (C–H, aliphatic), 1736 (C=O, lactone), 1717, (C=O, ester), 1665 (C=O, amide), 1626 (C=C, alkene); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.94–7.31 (m, 4H, Ar–H), 5.64 (bs, 1H, –NH), 4.95 (s, 2H, –OCH_2), 4.25–4.20 (q, 2H, –OCH_2CH_3), 4.17 (s, 2H, –NCH_2), 3.15 (s, 3H, –NCH_3), 1.3–1.25 (t, 3H, –OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 165.95 (C=O, lactone), 165.0 (C=O, amide), 162–91.6 (9, Ar–C), 66.87 (–OCH_2), 61.71 (–OCH_2CH_3), 49.83 (–NCH_2), 35.66 (–NCH_3), 14.28 (–OCH_2CH_3); EI-MS: *m/z* 320.1 $[M + H]^+$, 100 %. Anal.

Calcd. for $C_{16}H_{17}NO_6$: C, 60.18; H, 5.37; N, 4.39. Found C, 60.55; H, 5.40; N, 4.35.

2-(2-Oxo-2H-chromen-4-yloxy)-N-(prop-2-ynyl)acetamide (**4j**) White solid, mp 170–173 °C, yield 92.7 %, purity by HPLC 99.2 %. IR (KBr, cm^{-1}): 3232 (N–H, amide), 3075 (C–H, aromatic), 2932 (C–H, aliphatic), 1725 (C=O, lactone), 1655 (C=O, amide), 1624 (C=C, alkene); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.82–6.50 (m, 5H, Ar–H), 5.71 (bs, 1H, –NH), 4.68 (s, 2H, –OCH_2), 4.21 (s, 2H, –NH–CH_2), 2.31 (s, 1H, alkyne –CH); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 165.44 (C=O, lactone), 165.02 (C=O, amide), 162.63–92.31 (8, Ar–C), 78.68 (–NH–CH_2), 72.55 (–OCH_2), 67.57 (–C≡CH), 29.25 (–C≡CH); EI-MS: *m/z* 258.2 $[M + H]^+$, 100 %). Anal. Calcd. for $C_{14}H_{11}NO_4$: C, 65.37; H, 4.31; N, 5.44. Found C, 65.67; H, 4.35; N, 5.49.

4-2-(5,6-Dihydrotetrazolo[1,5-a]pyrazin-7(8H)-yl-2-oxoethoxy)-2H-chromen-2-one (**4k**) Brown solid, mp: 200–202 °C, yield 88.5 %, purity by HPLC 90 %. IR (KBr, cm^{-1}): 3080 (C–H, aromatic), 2968 (C–H, aliphatic), 1716 (C=O, lactone), 1666 (C=O, amide), 1624 (C=C, alkene); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 7.85–6.06 (m, 5H, Ar–H), 5.35 (t, 2H), 5.07 (t, 2H), 4.61 and 4.44 (2s, 2H, N–CH_2–), 4.03 (s, 2H, –OCH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 165.2 (C=O, lactone), 164.5 (C=O, amide), 161.7–91.6 (9, Ar–C), 66.67 (–OCH_2), 66.52 and 45.0 (–NCH_2–CH_2N–), 44.7 (–NCH_2); EI-MS: *m/z* 328.2 $[M + H]^+$ 100 %. Anal. Calcd. for $C_{16}H_{13}N_5O_4$: C, 65.37; H, 4.31; N, 5.44. Found C, 65.67; H, 4.35; N, 5.49.

N-(4-Fluorobenzyl)-2-(2-oxo-2H-chromen-4-yloxy)-acetamide (**4l**) White solid, mp 196–198 °C, yield 95.6 %, purity by HPLC 99.2 %;. IR (KBr, cm^{-1}): 3297 (N–H, amide), 3099 (C–H, aromatic), 2975 (C–H, aliphatic), 1716 (C=O, lactone), 1667 (C=O, amide), 1621 (C=C, alkene); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 8.81 (s, 1H), 8. 06–7.15 (m, 9H, Ar–H), 5.86 (bs, 1H, –NH)), 4.8 (s, 2H, OCH_2), 4.38 (s, 2H, –NCH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ_H 165.9 (C=O, lactone), 164.3 (C=O, amide), 162.4–91.4 (12 Ar–C), 67.6 (–OCH_2), 41.3 (–NHCH_2); EI-MS: *m/z* 328.2 $[M + H]^+$, 100 %. Anal. Calcd. for $C_{18}H_{14}FNO_4$: C, 66.05; H, 4.31; N, 4.28. Found C, 65.67; H, 4.34; N, 4.31.

N-(4-Methylbenzyl)-2-(2-oxo-2H-chromen-4-yloxy)acetamide (**4m**) White solid, mp 172–174 °C, yield 96 %, purity by HPLC 99.3 %. IR (KBr, cm^{-1}): 3288 (N–H, amide), 3083 (C–H, aromatic), 2922 (C–H, aliphatic), 1721 (C=O, lactone), 1651 (C=O, amide), 1621 (C=C, alkene); ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H: 7.74–6.60 (m, 9H, Ar–H), 5.71 (bs, 1H, –NH), 4.69 (s, 2H, –OCH_2), 4.55 (s, 2H, –NCH_2), 2.34 (s, 3H, –CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C:165.7 (C=O, lactone), 164.3 (C=O, amide), 161.3–91.34 (12 Ar–C), 67.65(–OCH_2), 41.7 (–NCH_2), 20.6 (–CH_3); EI-MS: *m/z* 324.2 $[M + H]^+$, 100 %. Anal. Calcd. for $C_{19}H_{17}NO_4$: C, 70.58; H, 5.30; N, 4.33. Found C, 71.00; H, 5.35; N, 4.30.

4-(2-(Piperazine-1-yl)ethoxy)-2H-chromen-2-one (**4n**) Brown solid, mp 192–195 °C, yield 84 %, purity by HPLC 99.4 %. IR (KBr, cm^{-1}): 3070 (C–H, aromatic), 2962 (C–H, aliphatic), 1716 (C=O, lactone), 1669 (C=O, amide), 1624 (C=C, alkene); ^{1}H NMR (400 MHz, $CDCl_3$):δ_H 7.87–5.68 (m, 5H, Ar–H), 4.89 (s, 2H, –OCH_2), 3.65–3.49 (t, 8H, piperazine ring protons); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 164.8 (C=O, lactone), 163.9 (C=O, amide), 162.5–80.8 (8 Ar–C), 67.0 (–OCH_2), 45.0 (2 –NCH_2), 42.12 (2 –NHCH_2); EI-MS: *m/z* 289.1 $[M + H]^+$, 100 %). Anal. Calcd. for $C_{15}H_{16}N_2O_4$: C, 62.49; H, 5.59; N, 9.72. Found C, 62.31; H, 5.62; N, 9.70.

Biological evaluation

Antimicrobial activity

The synthesized compounds **4a–n** were examined for their antibacterial and antifungal activities by agar diffusion method. *Bacillus subtilis* ATCC 10876, *Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853 were used for testing the antibacterial activity. *Candida albicans* ATCC 66027 was used for testing antifungal activity.

The bacterial strains were grown for 16 h on trypticase soy agar (TSA) plates by incubating at 37 ± 0.5 °C in ambient air. The fungal strain was grown on Potato dextrose agar (PDA) at 37 ± 0.5 °C in ambient air for 40 h. The suspension of each culture was prepared in sterile normal saline. For testing antibacterial activity, Muller Hinton Agar (MHA) plates inoculated with bacterial culture suspension were prepared. Similarly, PDA plates inoculated with fungal culture suspension were prepared for testing antifungal activity.

The stock solution of test compounds (1000 µg/ml) was prepared in DMSO and a volume of 50 µl of each test compound was added into the wells (6 mm diameter) cut in the microbial culture inoculated agar medium; thus, the concentration of each tested compound was 50 µg/well. The filter paper disks of amikacin and ketoconazole at concentration of 10 and 30 µg, respectively, were tested. The agar plates were incubated at 37 ± 0.5 °C for 24 h (testing antibacterial activity) or 36 h (testing antifungal activity). The activity of compounds **4a–n** and the standards were measured by zone of inhibition around the well or disk (Table 3).

Compounds **4a–d**, **4g** showed activity against both the Gram-negative strains. Against Gram-positive strains **4c** and **4m** only showed activity. All the compounds were

Table 3 Antimicrobial activity of compounds **4a–n**: Zone of inhibition (MMS)

Entry	*E. coli* ATCC 25922	*P. eruginosa* ATCC 27853	*B. subtilis* ATCC 10876	*S. aureus* ATCC 25923	*C. albicans* ATCC 66027
4a	10	12	–	–	10
4b	12	10	–	–	9
4c	13	12	–	10	11
4d	11	10	–	–	–
4e	–	–	–	–	10
4f	–	–	–	–	12
4g	12	14	–	–	10
4h	–	–	–	–	13
4i	–	–	–	–	12
4j	–	–	–	–	13
4k	–	–	–	–	–
4l	–	–	–	–	10
4m	–	–	–	10	10
4n	–	–	–	–	10
Amikacin	17	17	20	18	–
Ketoconazole	–	–	–	–	21

–: No zone of inhibition

active against the fungal strain except **4d, 4k** and **4o**. Amongst compound **4c** has shown broad spectrum activity, i.e., anti-Gram-positive, anti-Gram-negative and antifungal activity. The reason for this may be the presence of dimethoxy substitution which enhances the in vitro activity against Gram-negative results in the potential antimicrobial activity when compared with other compounds (Takei *et al.*, 2002).

Total antioxidant activity

The total antioxidant capacity of the compounds **4a–n** was determined with phosphomolybdenum using ascorbic acid as the standard (Aliyu *et al.*, 2013; Prabakaran and Sendhil, 2011). An aliquot of 0.1 ml of compound (10, 100, 500, 1000, 2000 μg) solution was combined with 2.0 ml of reagent (0.6 M sulfuric acid, 28 mM sodium phosphate and 4 mM ammonium molybdate). The tubes were capped and incubated in a boiling water bath at 95 °C for 90 min. After the samples had cooled to room temperature, the absorbance was measured at 695 nm against blank in UV spectrophotometer. Increased absorbance of the reaction mixture indicated increased in antioxidant capacity.

According to the results (Fig. 2), all the compounds exhibited moderate-to-good antioxidant activity when compared with standard ascorbic acid. Amongst compound **4c** and **4e** shows the good antioxidant properties due to the presence of dimethoxy and hydroxyl group, respectively.

Molecular docking study

For the molecular docking study, protein structure of 24-kDa DNA gyrase B fragment from *E. coli* (PDB ID-1KZN) was obtained from the Protein Data Bank (Lafitte *et al.*, 2002). The co-crystallized ligand (clorobiocin) in the 24-kDa DNA gyrase B fragment from *E. coli* structure was removed. For the protein structure, all hydrogen atoms were added, lower occupancy residue structures were deleted, and any incomplete side chains were replaced using the ADT version 1.5.4. Further ADT was used to remove crystal water, added Gagteiger charges to each atom, and merged the non-polar hydrogen atoms to the protein structure. The distance between donor and acceptor atoms that form a hydrogen bond was defined as 1.9 Å with a tolerance of 0.5 Å, and the acceptor–hydrogen–donor angle was not less than 120°. The structures were then saved in PDBQT file format, for input into AutoDock version 1.5.4. A grid box with dimension of $40 \times 40 \times 40$ Å^3 and was centered on 18.113, 33.227, 33.307 was created around the binding site of clorobiocin on *E. coli* protein using AutoDock tools. The center of the box was set at clorobiocin, and grid energy calculations were carried out. For the AutoDock docking calculation, default parameters were used and 50 docked conformations were generated for each compound. In order to verify reproducibility of the docking calculations, the bound ligand (clorobiocin) was extracted from the complexes and submitted for one-ligand run calculation. This reproduced

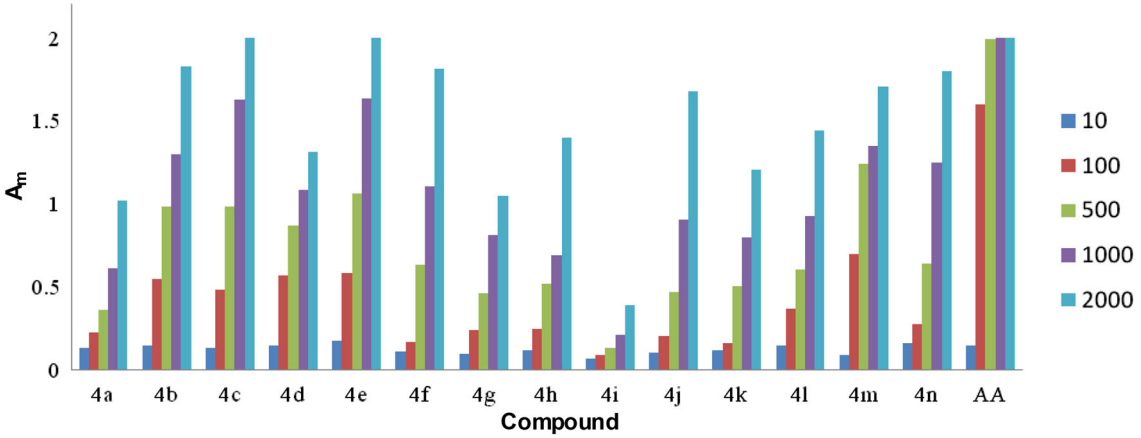


Fig. 2 Antioxidant activity of compounds **4a–n** against standard Ascorbic acid (A_m—activity relative to Ascorbic acid (AA)on molar basis)

top scoring conformations of 10 falling within root-mean-square deviation values of 0.905–1.585 Å from bound X-ray conformation for 1-KZN, suggesting this method is valid enough to be used for docking studies of other compounds. The outputs were exported to VMD and Pymol for visual inspection of the binding modes and interactions of the compounds with amino acid residues in the active sites (Fig. 3).

Docking of different ligands to protein was performed using AutoDock, same protocols used in as that of validation study. All docking were taken into 2.5 million energy evaluations were performed for each of the test molecules. Docked ligand conformations were analyzed in terms of energy, hydrogen bonding, and hydrophobic interaction between ligand and receptor protein 1-KZN. The detailed analysis of the ligand–receptor interactions was carried out, and final coordinates of the ligand and receptor were saved as pdb files. For display of the receptor with the ligand binding site, VMD software was used. From the docking scores, the free energy of binding (FEB) of all compounds were calculated (Table 4). The results of which revealed that compound **4c** as the most active with a binding energy of −5.70 kcal/mol. The least binding energy was exhibited by compound **4j** with a binding energy of −4.46 kcal/mol. The intermediary active compound **4a** showed −5.14 kcal/mol of binding energy. The binding interactions of these compounds were shown, respectively, in the diagram (Figs. 4, 5, 6).

When the designed 4-hydroxycoumarin derivatives **4a–n** was docked against the same receptor (1-KZN), the free binding energy values are greater than the standard for some derivatives and it was shown in the Table 4. This result shows that all the docked compounds bind efficiently with the receptor and exhibited free energy of binding

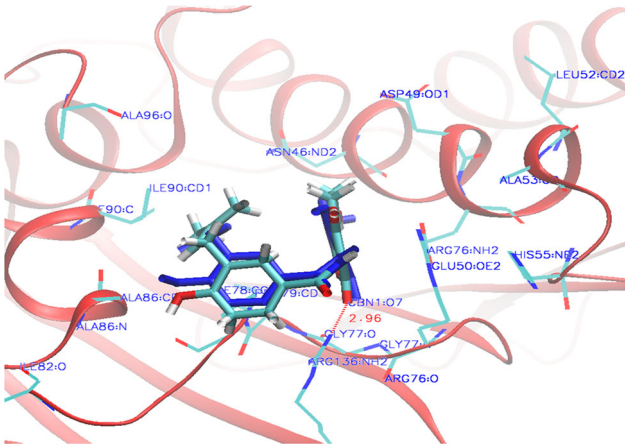


Fig. 3 Molecular docking of bound and docked clorobiocin in 24-kDa DNA gyrase B fragment of *E. coli*, (1KZN) where the docked ligand was discriminated by showing two hydrogen bond interactions. *Note*: *Dotted lines* in the above figure shows hydrogen bonding interactions

Table 4 Docking scores of compounds **4a–n**

Entry	FEB[1] (kcal/mol) against 24-kDa DNA gyrase B fragment of *E. coli* (PDB ID-1KZN)
4a	−5.14
4b	−5.29
4c	−5.70
4d	−5.25
4e	−4.84
4f	−4.66
4g	−5.11
4h	−4.54
4i	−4.56
4j	−4.46
4k	−4.67
4l	−5.17
4m	−5.12
4n	−4.60
Clorobiocin[2]	−3.89

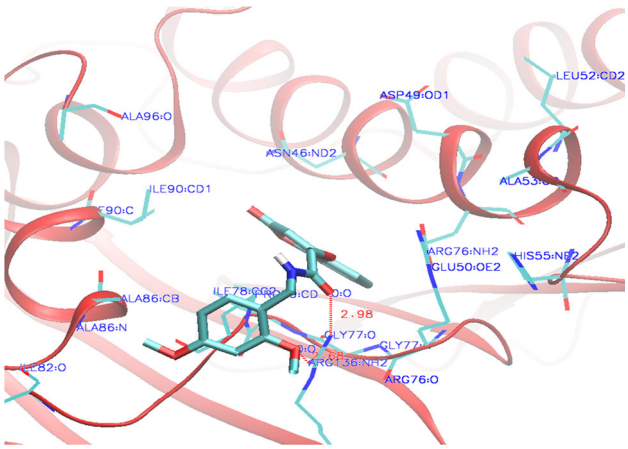


Fig. 4 Docking of most active compound **4c** (FEB = −5.70 kcal/mol) in 1 KZN. *Note*: *Dotted lines* in the above figure shows hydrogen bonding interactions

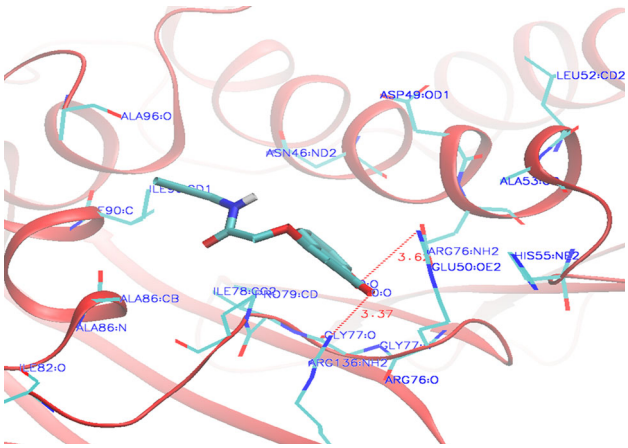


Fig. 5 Docking of least active compound **4j** (FEB = −4.46 kcal/mol) in 1KZN. *Note*: *Dotted lines* in the above figure shows hydrogen bonding interactions

value in the range of −4.46 to −5.70 kcal/mol. The binding model of compound **4c** and 1-KZN is depicted in Figs. 3 and 4, respectively, in that there are two hydrogen bond interactions observed. GLY77:O forms hydrogen bond with oxygen atom of the amide group present in the compound **4c,** and ARG136:NH_2 forms hydrogen bond with methoxy group present in the second position of the benzene ring. These molecular docking results along with the invitro antimicrobial data, suggesting that **4c** is most active compound.

Conclusion

In summary, a series of novel 4-hydroxycoumarin derivatives **4a–n** were disclosed and well characterized by using spectral techniques such as IR, ^{1}H-NMR, ^{13}C-NMR and

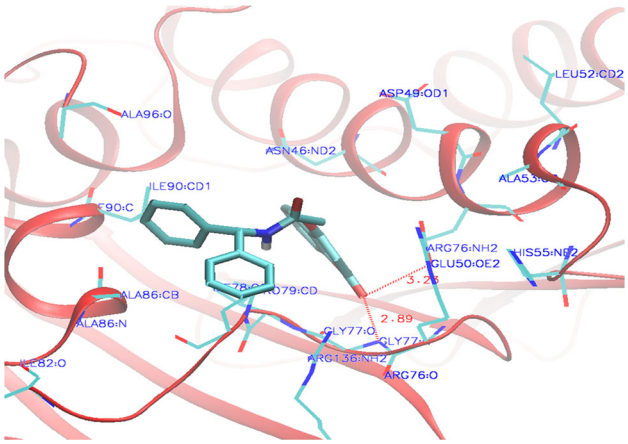


Fig. 6 Docking of moderate active compound **4a**(FEB = −5.14 kcal/mol) in 1KZN. *Note*: *Dotted lines* in the above figure shows hydrogen bonding interactions

MS. All the synthesized compounds **4a–n** were screened for their antimicrobial and antioxidant activities. Antifungal activity revealed that all compounds except **4d, 4k** and **4o** have showed good-to-moderate activity against *candida albicans*. Amongst them, compound **4a–d** and **4g** have shown good antibacterial activity when compared with others against standard drugs. The total antioxidant capacity of the synthesized compounds **4a–n** was determined with phosphomolybdenum using ascorbic acid as the standard. Amongst them, **4c** and **4e** have shown good antioxidant capacity. The binding energies range from −4.46 to −5.70 kcal/mol were found for all synthesized compounds when subjected to molecular docking study against 24-kDa DNA gyrase B fragment of *E. coli* (PDB ID-1KZN). Compound **4c** has exhibited maximum binding energy −5.70 kcal/mol when compared with others. Interestingly compound **4c** was found to have good antimicrobial and as well as antioxidant activity due to the presence of dimethoxy substitution in the phenyl ring which also showed maximum binding energy when compared with standard clorobiocin.

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