

Synthesis, Docking and Antimicrobial Activity of Some New Coumarin Incorporated Thiazole Derivatives

ABSTRACT

Exposure of resistance by fungal and bacterial strains with respect to already existing antimicrobial agents is one of the crucial problems and also a motive to synthesize a new class of antimicrobial agents having potential activity in comparison with the commonly used therapy. The structurally interesting compounds for synthesizing antimicrobial agents are coumarin derivatives. Synthesis and screening of a series of new coumarin derivatives coupled with thiazole are performed for their antimicrobial properties. A series of new thiazolyl coumarin derivatives was synthesized upon refluxing 3-bromoacetyl coumarin, substituted benzaldehyde and thiosemicarbazide in presence of glacial acetic acid. Substituted 3-acetyl coumarin undergoes bromination in presence of bromine and chloroform to form 3-Bromoacetyl coumarin. The docking studies have been carried out against the enzyme DNA gyrase (1KZN). The thiazolyl coumarin derivatives were characterized on the basis of IR, ^1H NMR and Mass spectral data. Compound SCT 2 showed the highest docking score -5.662 compared to other compounds. Screening of the final synthesized compounds were performed for their antibacterial activity by tube dilution method. Compound SCT 1 and SCT 2 showed significant antibacterial activity with minimum inhibitory concentration of 12.5 $\mu\text{g}/\text{ml}$ and 6.25 $\mu\text{g}/\text{ml}$ respectively compared to standard Cephalosporin. The MIC results suggest that compounds SCT 1 and SCT 2 showed promising antibacterial activity. So these compounds are found to be interesting lead molecules for further synthesis as antimicrobial agents.

Keywords: Coumarin, thiazole, docking, antibacterial

1. INTRODUCTION

Currently, resistance patterns of pathogenic bacteria to regularly used antibiotics and drugs have happened to be the mediocre incidence, causing irritations in clinics and chaos in health of public all over the world. The issue is more critical than that can be imagined because of the frequent genetic development of pathogenic bacterial strains by accomplishing resistance to antibiotics/ drugs that were not at all used for treatment often. Sadly, with any fresh generation of antibiotics or freshly launched drugs newer resistant bacteria develop continually. The inherent bacterial genetic exchange mechanisms ease bacterial consortia for obtaining characters from genetically alike as well as distant bacteria. Every year, around 17 million people are dying from infectious diseases and around 50,000 people are infected. [1] Therefore, the use of antibiotics swiftly loose usefulness thereby resulting in the creation of a vacuum in need of coveted antibacterial. As a result, the evolution of new antibacterial drug candidate remains as the future scope. Growing incidences of microbial infection by the evolution of microbial resistance of the most antibiotics are through either genome of microbial mutations or a developed mechanism of resistance of action which is a major health problem.

Numerous reports state that synthetic and natural Coumarin derivatives own antimicrobial activity. [2-6] Chlorobiocin and Novobiocin are acknowledged antimicrobials consisting of Coumarin (i.e. 2H-1-benzopyran-2-ones) skeleton. There are several Coumarin derivatives which have been reported for antiviral, antiproliferative, anticancer, antiallergic, antioxidant, antiHIV, antiinflammatory and anticoagulant activities. It was discovered that enhanced biological activity was produced when one biodynamic heterocyclic system was coupled with another heterocyclic system. The growing problem in the treatment of infectious diseases caused by fungi and bacteria is drug resistance. [7] The crucial medical issue of fungal and bacterial resistance and the rapid rate at which it evolves has resulted in soaring levels of resistance to classical antibiotics. The discovery and evolution of useful antifungal and antibacterial [8] drugs with novel mechanisms of action have therefore turned out to be serious duties for infectious disease research programs. [9] Coumarins present a variety of bioactivities, including estrogenic, dermal photosensitizing, antimicrobial, vasodilator, anticoagulant, molluscicidal, antihelminthic, sedative and hypnotic, analgesic and hypothermic actions. [10] Additionally, the pharmacological properties and also therapeutic applications of coumarins rely on the pattern of substitution. In the recent times, they are stated to have several pharmacological activities such as antimicrobial activity. Some of the coumarin drugs with antimicrobial activity are 2-quinoxalone-coumarin hydrazone, 3-acetylcoumarin-INH hybrid, coumarin fused with tetrahydroisoquinoline, 4-methyl 7-hydroxy coumarin thiosemicarbazone, 4-methyl coumarin bearing thiazolidinone, 3-aminoalkyl-4-hydroxy coumarin, thiazolyl hydrazonyl substituted coumarin, 3,4,7-trisubstituted coumarin, 4-amino alkylated coumarin etc.

Small ring heterocycles including sulfur and nitrogen have been investigated since a long time because of their therapeutic relevance and synthetic diversity. Amongst the extensive range of heterocycles inspected by honoured prospects in the discovery of drugs, it is identified that thiazoles play a vital role in medical chemistry. [11] Thiazole ring is a structural fragment of natural compounds such as carboxylase,

epothilones, thiamine pyrophosphate (TPP, a coenzyme important in respiration in the Krebs cycle), thiamine (vitamin B1), and the large family of macrocyclic thiopeptide antibiotics, micrococcin P1 and thiostrepton. [12] Thiazole derivatives are related with a broad spectrum of biological properties, including hypnotics, HIV infections, schizophrenia, inflammation, hypertension, anticancer, antimalarial, antiviral, antituberculous, antimicrobial, anticonvulsant, bacteriostatic activities, and very recently for the treatment of pain, as fibrinogen receptor antagonists with anti-thrombotic activity, as new inhibitors of bacterial DNA gyrase B. [13–15] They are also used in drug development application for allergy treatment. [16] It is reported in the literature that when thiazole ring is coupled with coumarins, the biological activity gets enhanced many fold. The challenges of antibacterial research are significant and a good start towards the development of new class of hybrid antimicrobials along with the aid of computer aided drug design may deliver new antimicrobials to the clinic. Based on the above observation it is worthwhile to prepare newer compounds for their antimicrobial activity.

2. MATERIALS AND METHODS

2.1 Molecular docking study

Molecular docking study was done to understand the interconnections between receptor and ligand (synthesized compounds). In silico analysis was performed on Schrodinger 2018-3 suite device Maestro 11.7.012, (Ligprep, Glide XP docking, QikProp), this software package programmed on DELL Inc.27” workstation machine running on Intel Core i7-7700 CPU @ 3.60 GHz x8, processor with 8 GB RAM and 1 TB hard disk with Linux –X6_64 as the operating system. QikProp was used to predict the ADME properties of synthesized compounds. For docking calculation, the protein (PDB code: 1KZN) was downloaded from protein data bank and refined using protein preparation wizard. Assessment of binding affinity was done in terms of binding free energies (S-score, kcal/mol). The synthesized compounds were all docked in the groove of binding site present in DNA Gyrase 1KZN.

All chemicals that were used are of analytical grade: Salicylaldehyde, ethyl acetoacetate, piperidine, ammonium acetate, ethanol, substituted benzaldehyde and sodium hydroxide. Determination of melting points was done by open capillary method and are uncorrected. Purity of the final compounds and intermediates was checked by thin layer chromatography (TLC) using silica gel G plates. The spots were made visible under UV light. n-hexane: Ethylacetate (5:5) was used as solvent for running the TLC of these compounds. All IR spectra were registered using ATR method in Alpha Bruker. ¹H NMR spectra were recorded at 400 MHz Bruker Avance II NMR Spectrometer. Mass spectrum was recorded on GC-MS Perkin Elmer Clarus 680 Spectrometer obtained by electro impact ionization method.

2.2 General procedure for the synthesis of 3-Acetyl Coumarin

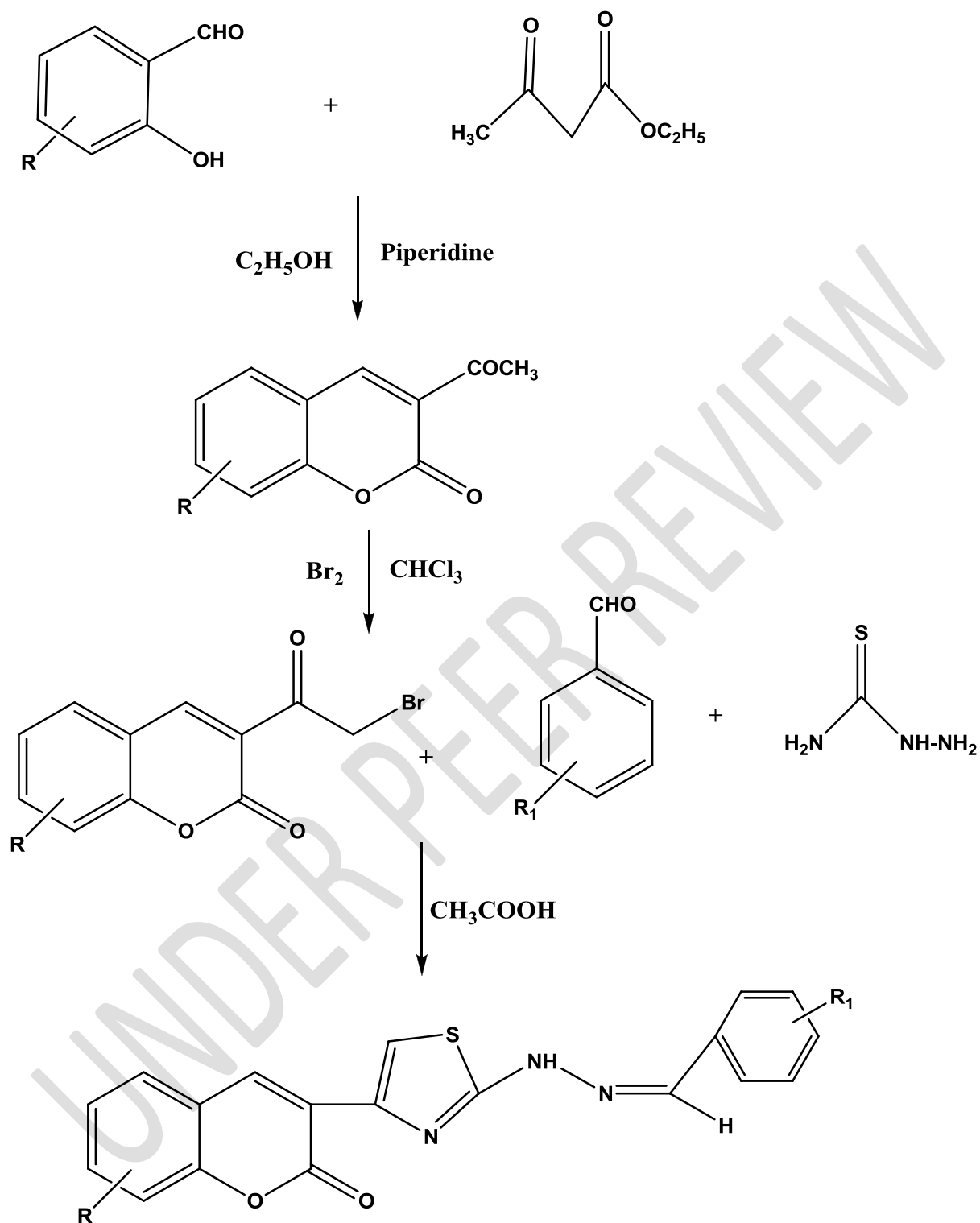
A mixture of salicylaldehyde (0.05 mol) and ethylacetoacetate was added to 250ml conical flask. It was then condensed by adding sufficient piperidine dropwise with stirring in ice cold condition. The reaction mixture was then kept overnight in refrigerator. The solid lumps were broken in cold ethanol. The resulting yellow colored solid mass was then filtered and washed with cold ethanol to remove the excess piperidine. It was then recrystallized from ethanol to give white needle shaped crystals.

2.3 General procedure for the synthesis of 3-Bromo Acetyl Coumarin

3-acetyl-2*H*-chromene-2-one (0.01 mol) was dissolved in chloroform (0.1mol) and a solution of Bromine (0.01 mol) in chloroform was added drop wise with continuous stirring and mixture was kept in water bath at 70°C. The progression of reaction was observed by thin layer chromatography. After the completion of reaction, judged by TLC, the reaction mixture was washed with diethyl ether and recrystallized using ethanol to provide 3-(2-bromoacetyl)-2*H*-chromen-2-one. .

2.4 General procedure for the synthesis of Thiazolyl Coumarin Derivatives (SCT1-SCT12)

Equimolar mixture of 3-Bromo Acetyl Coumarin (0.05 mol), thiosemicarbazide (0.05 mol) and various substituted benzaldehyde (0.05 mol) was refluxed in the presence of glacial acetic acid (2 ml) for 4-5 hours. The reaction mixture was transferred into crushed ice and stirred well until the product was formed. It was filtered, dried and recrystallized using ethanol.



Thiazolyl Coumarin Derivatives (SCT1-SCT12)

Figure 1: Scheme for the synthesis of Thiazolyl Coumarin Derivatives

2.5 Minimum Inhibitory Concentration

The broth dilution test is one of the standard method for determining the level of resistance to an antibiotic. Serial dilutions of the antibiotic are made in a liquid medium which is inoculated with a standardized number of organisms and incubated for a prescribed time. The lowest concentration of antibiotic preventing appearance of turbidity is considered to be the minimal inhibitory concentration (MIC). After preparation of different concentrations of the test compound in nutrient broth (by using the broth dilution method), we inoculate them with the test organism. The MIC is determined after incubation by choosing the lowest concentration in which no growth occurs. The MIC and the zone of inhibition are inversely correlated. In other words, the more susceptible the microorganism is to the antimicrobial agent, the lower the MIC and the larger the zone of inhibition. Conversely, the more resistant the microorganism, the higher the MIC and the smaller the zone of inhibition. The method gives information on the storage of standard antibiotic powder, preparation of stock antibiotic solution, media, preparation of inocula, incubation condition and reading and interpretation of results. [17]

Procedure:

Double concentration of the nutrient broth were prepared. Distribute each 2.5 ml into 8 test tubes and label them A1 to A8. Distribute 2.5 ml in two test tubes and label them as positive control and negative control. Prepare drug stock solution of 2000 $\mu\text{g/ml}$ by dissolving the drug in water. From this stock solution the following dilutions were prepared; 2.5 ml of the stock solution diluted to 25 ml with water to give 200 $\mu\text{g/ml}$. Serial dilution of the same was performed to give 100 $\mu\text{g/ml}$, 50 $\mu\text{g/ml}$, 25 $\mu\text{g/ml}$, 12.5 $\mu\text{g/ml}$ and 6.25 $\mu\text{g/ml}$ respectively. Add 2.5 ml each double concentration nutrient broth to 2.5 ml of the above dilutions so that the concentration further gets halved. i.e., 100 $\mu\text{g/ml}$, 50 $\mu\text{g/ml}$, 25 $\mu\text{g/ml}$, 12.5 $\mu\text{g/ml}$, 6.25 $\mu\text{g/ml}$ and 3.12 $\mu\text{g/ml}$ respectively. Add 2.5 ml of water to positive control and negative control tube and mix well. Mix all the tubes well close with nonabsorbent cotton plugs and sterilize by autoclaving 15 lbs./sq. in (121°C) for 15 min. Cool the tubes to room temperature and inoculate all the tubes with one loopful of the test organism *Escherichia coli*, except in the negative control tube. Incubate all the tube at 37°C for 48 hrs and observe the turbidity.

Negative control: In this no growth is expected. It confirms that the medium is sterile.

Positive control: In this the growth of the inoculated organism is expected. This indicates that (a) The nutrient of medium supports the growth of organism that has been inoculated. (b) Inoculation of live organisms.

3. RESULTS

Table 1: Physical Data of Thiazolyl Coumarin Derivatives

Comp code	R	R ¹	Mol. Formula	Mol. Wt	m.p (°C)	% Yield
SCT 1	H	4-OH	C ₁₉ H ₁₃ N ₃ O ₃ S	363	182	89%
SCT 2	H	4-Cl	C ₁₉ H ₁₂ ClN ₃ O ₃ S	382	180	81%
SCT 3	6-NO ₂	4-Br	C ₁₉ H ₁₁ BrN ₃ O ₄ S	471	161	78%
SCT 4	6-NO ₂	3,4-OCH ₃	C ₂₁ H ₁₆ N ₃ O ₆ S	452	169	69%
SCT 5	6-NO ₂	4-OH	C ₁₉ H ₁₂ N ₃ O ₅ S	408	153	87%
SCT 6	6-Br	4-OH	C ₁₉ H ₁₂ BrN ₃ O ₃ S	442	177	74%
SCT 7	6-Br	3,4-OCH ₃	C ₂₁ H ₁₆ BrN ₃ O ₄ S	486	134	83%
SCT 8	6-Br	4-N(C ₂ H ₅) ₂	C ₂₃ H ₂₁ BrN ₃ O ₃ S	490	182	77%
SCT 9	6-Cl	3,4-OCH ₃	C ₂₁ H ₁₆ ClN ₃ O ₄ S	442	178	80.6%
SCT 10	6-Cl	4-N(C ₂ H ₅) ₂	C ₂₃ H ₂₁ ClN ₃ O ₃ S	453	166	78%
SCT 11	6-Cl	4-OH	C ₁₉ H ₁₂ ClN ₃ O ₃ S	398	164	89%
SCT 12	6-Cl	4-Br	C ₁₉ H ₁₁ BrClN ₃ O ₃ S	461	121	84%

Spectral Data

3-(2-(2-(4-hydroxybenzylidene)hydrazinyl)thiazol-4-yl)-2H-chromen-2-one (SCT1)

IR (cm⁻¹): 1571 (Ar C=C str), 1709 (C=O str of δ lactone), 1600 (C=N str), 3314 (NH str), 3650 (OH-phenolic str).

¹H NMR (400 MHz, DMSO-d₆): δ 11.493 (s, NH, 1H), 10.012 (s, 1H, OH), 7.120-8.627 (m, 10H, Ar-H)

Mass (m/z): 363 (M⁺)

3-(2-(2-(4-chlorobenzylidene)hydrazinyl)thiazol-4-yl)-2H-chromen-2-one (SCT2)

IR (cm⁻¹): 1483 (C=C str), 1725 (C=O str of δ lactone), 1601 (C=N str), 3486 (NH str), 749 (C-Cl str).

¹H NMR (400 MHz, DMSO-d₆): δ 11.482 (s, NH, 1H), 7.160-8.727 (m, Ar-H, 10H), 7.405-8.727 (m, 1H, thiazole).

Mass (m/z): 382 (M⁺)

3-(2-(2-(4-bromobenzylidene)hydrazinyl)thiazol-4-yl)-6-nitro-2H-chromen-2-one (SCT3)

IR (cm⁻¹): 1592 (Ar C=C str), 1704 (C=O str of δ lactone), 1517 (C=N str), 3467 (NH str), 1362 (NO₂ str), 627 (C-Br str).

¹H NMR (400 MHz, DMSO-d₆): δ 11.487 (s, NH, 1H), 7.609-8.713 (m, 1H, thiazole), 7.591-8.713 (m, Ar-H, 9H).

Mass (m/z): 472 (M+1)

6-bromo-3-(2-(2-(4-hydroxybenzylidene)hydrazinyl)thiazol-4-yl)-2H-chromen-2-one (SCT6)

IR in cm⁻¹: 1464 (Ar C=C str), 1678 (C=O str of δ lactone), 1507 (C=N str), 3125 (NH str), 644 (C-Br str), 3511 (OH-phenolic str).

¹H NMR (400 MHz, DMSO-d₆): δ 7.002-8.611 (m, Ar-H, 9H), 11.420 (s, NH, 1H), 9.875 (s, OH, 1H), 7.419-8.611 (m, 1H, thiazole).

Mass (m/z): 443 (M+1)

6-chloro-3-(2-(2-(3,4-dimethoxybenzylidene)hydrazinyl)thiazol-4-yl)-2H-chromen-2-one (SCT9)

IR in cm⁻¹: 1510 (C=C str), 1685 (C=O str of δ lactone), 1540 (C=N str), 3328 (NH str), 806 (C-Cl str), 1229 (C-O str).

¹H NMR (400 MHz, DMSO-d₆): δ 7.009-8.643 (m, Ar-H, 8H), 11.318 (s, NH, 1H), 3.511 (s, 6H, OCH₃), 7.398-8.643 (m, 1H, thiazole).

Mass (m/z): 443 (M+1)

3-(2-(2-(4-bromobenzylidene)hydrazinyl)thiazol-4-yl)-6-chloro-2H-chromen-2-one (SCT12)

IR in cm⁻¹: 1463 (C=C str), 1714 (C=O str of δ lactone), 1602 (C=N str), 2921 (NH str), 731 (C-Cl str), 612 (C-Br str).

¹H NMR (400 MHz, DMSO-d₆): δ 11.326 (s, NH, 1H), 7.112-8.608 (m, 9H, Ar-H)

Mass (m/z): 462 (M+1)

Table 2: Docking score of thiazolyl coumarin derivatives with 1KZN

Comp code	Docking score
SCT1	-5.482
SCT2	-5.662
SCT3	-4.913
SCT4	-4.968
SCT5	-4.511
SCT6	-4.442
SCT7	-4.883
SCT8	-3.806
SCT9	-4.662
SCT10	-4.416
SCT11	-4.633
SCT12	-4.668
Ciprofloxacin	-5.746

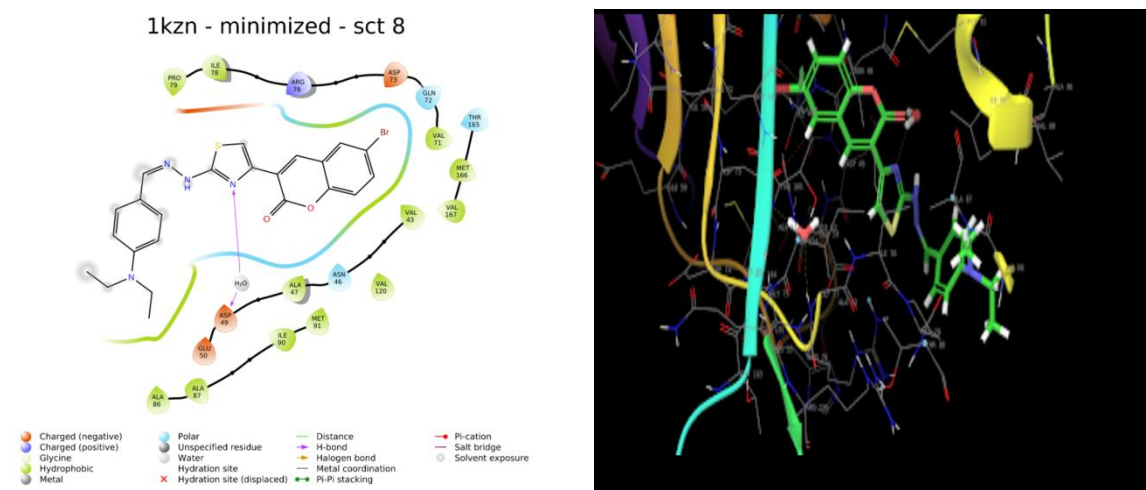


Fig 2: 2D and 3D ligand interaction of compound SCT 8 with 1KZN

Table 3: Antibacterial activity of thiazolyl coumarin derivatives (SCT 1-SCT 12)

Comp code	100 µg/ml	50 µg/ml	25 µg/ml	12.5 µg/ml	6.25 µg/ml	3.12 µg/ml	1.2 µg/ml
SCT 1	-	-	-	-	+	+	+
SCT 2	-	-	-	-	-	+	+
SCT 3	-	-	-	+	+	+	+
SCT 4	-	-	+	+	+	+	+
SCT 5	-	-	+	+	+	+	+
SCT 6	-	-	+	+	+	+	+
SCT 7	-	-	-	+	+	+	+
SCT 8	-	-	-	+	+	+	+
SCT 9	-	-	+	+	+	+	+

SCT 10	-	-	+	+	+	+	+
SCT 11	-	-	-	+	+	+	+
SCT 12	-	-	-	+	+	+	+

+: Growth, -: No growth

Table 4: Antimicrobial activity of thiazolyl coumarin derivatives (SCT 1-SCT 12) by tube dilution method

Comp code	MIC ($\mu\text{g/ml}$)
SCT 1	12.5
SCT 2	6.25
SCT 3	25
SCT 4	50
SCT 5	50
SCT 6	50
SCT 7	25
SCT 8	25
SCT 9	50
SCT 10	50
SCT 11	25
SCT 12	25
Positive control	+
Negative control	-

4. DISCUSSION

4.1 Chemistry

The conventional method has been used for the synthesis of new series of thiazolyl coumarin derivatives using substituted benzaldehyde and thiosemicarbazide as given in Figure 1. Structure of all the synthesized compounds was confirmed on the basis of IR, ¹H NMR and Mass Spectroscopy. Molecular docking was performed for target protein 1KZN.

The yield of the synthesized thiazolyl coumarin derivatives were obtained in the range of 74-89%. IR spectra showed characteristic absorption band 1678-1725 (C=O str of δ lactone) coumarin. The IR spectra of final compounds showed characteristic absorption band at 1517 (C=N str), 3467 (NH str) which was absent in the intermediate 3-Bromoacetyl coumarin. Similarly the ¹H NMR of the synthesized thiazolyl coumarin derivatives showed characteristic signal at 11.420 (s, NH, 1H), 7.419-8.611 (m, 1H, thiazole) which was absent in the ¹H NMR spectra of 3-Bromoacetyl coumarin. Hence the formation of the thiazolyl coumarin derivatives was confirmed and further established by ¹H NMR and mass spectra which are in accordance with molecular formula.

Final compounds interaction pattern with DNA Gyrase (PDB code: 1KZN) were studied and was compared with standard drug ciprofloxacin as given in Table 2. Compound SCT 2 shows the best interaction pattern with best binding energy -5.662 kcal/mol. This form hydrogen bond, hydrophobic interaction, charged negatives and polar interaction with respective amino acids VAL-43, ALA-47, ILE-78, PRO-79, ARG-76, LYS-21, MET-166, ASP-73 and THR-165.

4.2 Antibacterial activity

The different thiazolyl coumarin derivatives were evaluated for their antibacterial activity by Tube dilution method. Compound SCT1 and SCT2 showed significant antibacterial activity with MIC of 12.5µg/ml and 6.25µg/ml respectively compared to standard Cephalosporin as given in Table 3 and 4. The presence of electron donating group like hydroxyl and electron withdrawing group like chloro resulted in increased antibacterial activity. The unsubstituted coumarin moiety in SCT1 and SCT2 resulted in increased antibacterial activity.

5. CONCLUSION

The study reports the successful synthesis of thiazolyl coumarin derivatives from cyclisation of 3-Bromoacetyl coumarin with moderate yields and few compounds have shown significant antibacterial activity. Compounds SCT1 and SCT2 might be useful as a lead molecule for pharmaceutical industries. So the current work requires further structural modification to get better antimicrobial actions.

ETHICAL APPROVAL

Nil

REFERENCES

1. Holmes KK, Bertozzi S, Bloom BR, Jha P, Gelband H, DeMaria LM et al. Major Infectious Diseases: Key Messages from Disease Control Priorities. Arab J Chem. 2017;3(6):1-54. DOI: https://doi.org/10.1596/978-1-4648-0524-0_ch1
2. Amarnath A, Lenin V, Archunan G. Evaluation of the hypolipidemic activity of 6,7-dimethoxycoumarin on placental tissue factor mRNA expression in experimental anti-phospholipid syndrome. Pharmacogn Mag. 2013;9(35):264-70. doi: 10.4103/0973-1296.113287
3. Wangboonskul J, Tunsirikongkon A, Sasithornwetchakun W. Simultaneous determination of nine analytes in *Clausena harmandiana* Pierre. by new developed high-performance liquid chromatography method and the influence of locations in Thailand on level of nordentatin and dentatin. Pharmacogn Mag. 2015;11(41):1-7. doi: 10.4103/0973-1296.149666
4. Ranasinghe P, Perera S, Gunatilake M, Abeywardene E, Gunapala N, Premakumara S et al. Effects of *Cinnamomum zeylanicum* (Ceylon cinnamon) on blood glucose and lipids in a diabetic and healthy rat model. Phcog Res. 2012;4(2):73-79. <https://doi.org/10.4103/0974-8490.94719>
5. Patel PB, Patel TK, Baxi SN, Acharya HR, Tripathi C. Antitubercular effect of 8-[(4-Chloro phenyl) sulfonyl]-7-Hydroxy-4-Methyl-2*H*-chromen-2-One in guinea pigs. J Pharmacol Pharmacother. 2011;2:253-60. doi: 10.4103/0976-500X.85951
6. Kokanova-Nedialkova Z, Nedialkov PT, Nikolov SD. The genus *Chenopodium*: Phytochemistry, ethnopharmacology and pharmacology. Phcog Rev. 2009;3(6):280-306.
7. Raman N, Sakthivel A, Rajasekaran K. Synthesis and spectral characterization of antifungal sensitive Schiff base transition metal complexes. Mycobiology. 2007;35(3):150-53. <https://doi.org/10.4489/MYCO.2007.35.3.150>
8. Ironmonger A, Whittaker B, Baron AJ, Clique B, Adams CJ, Ashcroft AE et al. Scanning conformational space with a library of stereo- and regiochemically diverse aminoglycoside derivatives: The discovery of new ligands for RNA hairpin sequences. Org Biomol Chem. 2007;5:1081-86. <https://doi.org/10.1039/b618683a>
9. Kumar G, Kumar D, Devi S, Verma R, Johari R. Synthesis, spectral characterization of biologically active compounds derived from oxalyldihydrazide and 5-tertbutyl-2-hydroxy-3-(3-phenylpent-3-yl)benzaldehyde and their Cu(II), Ni(II) and Co(II) Complexes. Int J Eng Sci Technol. 2011;1(3):1630-35.
10. Parmer S, Kumar R. Substituted quinazolone hydrazides as possible antituberculous agents. J Med Chem. 1968;11:635-36. <https://doi.org/10.1021/jm00309a064>
11. Parekh NM, Juddhawala KV, Rawal BM. Antimicrobial activity of thiazolyl benzenesulfonamide-condensed 2, 4-thiazolidinediones derivatives. Med Chem Res. 2013;6(22):2737-45. <http://dx.doi.org/10.1007%2Fs00044-012-0273-x>
12. Yadlapalli RK, Chourasia OP, Jogi MP, Podile AR, Perali RS. Design, synthesis and in vitro antimicrobial activity of novel phenylbenzamido-aminothiazole-based azasterol mimics. Med Chem Res. 2013;6(22):2975-83.

13. Banothu J, Vaarla K, Bavantula R, Crooks PA. Sodium fluoride as an efficient catalyst for the synthesis of 2,4-disubstituted-1,3-thiazoles and selenazoles at ambient temperature. *Chin Chem Lett.* 2014;1(25):172-75. <https://doi.org/10.1016/j.ccllet.2013.10.001>
14. Gouda MA, Berghot MA, Abd El-Ghani GE, Khalil AM. Synthesis and antimicrobial activities of some new thiazole and pyrazole derivatives based on 4,5,6,7-tetrahydrobenzothiophene moiety. *Eur J Med Chem.* 2010;4(45):1338-45. <https://doi.org/10.1016/j.ejmech.2009.12.020>
15. Lv PC, Wang KR, Yang Y, Mao WJ, Chen J, Xiong J et al. Design, synthesis and biological evaluation of novel thiazole derivatives as potent FabH inhibitors. *Bioorg Med Chem Lett.* 2009;23(19):6750-54. doi: 10.1016/j.bmcl.2009.09.111
16. Zablotskaya A, Segal I, Geronikaki A, Eremkina T, Belyakov S, Petrova M et al. Synthesis, physicochemical characterization, cytotoxicity, antimicrobial, anti-inflammatory and psychotropic activity of new N-[1,3-(benzo)thiazol-2-yl]- ω -[3,4-dihydroisoquinolin-2(1*H*)-yl]al-Kanamides. *Eur J Med Chem.* 2013;23(70):846-56. doi: 10.1016/j.ejmech.2013.10.008
17. Andrews JM. Determination of minimum inhibitory concentrations. *J Antimicrob Chemother.* 2001;48(S1):5-16. doi: 10.1093/jac/48.suppl_1.5