Synthesis, Insilico and Antibacterial Activity Studies of Substituted Dihydro-1, 2-Oxazole Benzopyran-2-One Hybrids

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Authors’ contributions

This work was carried out in collaboration among all authors. Authors AK and PK designed the study, performed the statistical analysis, and wrote the protocol. Author PN helped in antimicrobial study. Author SMR managed the literature searches. Author AD helped in drafting the final manuscript. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2021/v33i35A31882
Editor(s):
(1) Dr. Farzaneh Mohamadpour, University of Sistan and Baluchestan, Iran.
(2) Partha Sarathi Bairy, Graphic Era Hill University, India.
Reviewers:
(1) Mina Golestani, Tabriz University of Medical Sciences, Iran.
(2) Partha Sarathi Bairy, Graphic Era Hill University, India.
Complete Peer review History: http://www.sdiarticle4.com/review-history/70413

Received 22 April 2021
Accepted 28 June 2021
Published 05 July 2021

Original Research Article

ABSTRACT

A series of substituted dihydro-1, 2-oxazole benzopyran-2-one (SR1-SR6) were synthesized through the intermediate substituted benzopyran-2-one chalcones and were characterized using spectral analysis. Compounds were docked with receptor DNA Gyrase B (PDB code: 5L3J) to know its interaction and binding energy; ranges -3.38 to -2.15 kcal/mol. Further these compounds were tested for antibacterial activity using tube dilution method and MIC values were observed; ranges 3.12 to 25 µg/ml. Compound 3-(5-(m-tolyl)-4,5-dihydroisoxazol-3-yl)-2H-chromen-2-one (SR3) showed the best interaction with binding energy -3.38 kcal/mol and antimicrobial activity having MIC 3.12 µg/ml.

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1. INTRODUCTION

Microbial infection from recent past has become a challenging problem for health care provider and scientists [1]. Finding a new antimicrobial agents and antimicrobial targets is in great demand to obviate the threat caused by life-threatening infections [2]. Since the resistance towards pathogenic bacteria is growing for present molecule. Therefore, it has become compulsory need for the scientist to develop the antimicrobial molecule which can treat various infection worsen the of quality life of the patient and eventually leads to normal life.

Oxazole is a significant class of the aromatic heterocyclic family. Due presence of heteroatom nitrogen and oxygen in the ring makes a privileged molecule. Many substituted oxazole precursor shows various biological activities such as brain-derived neurotropic factor inducers [3], analgesic [4], trypanocidal [5], anti-mitotic with pro-apoptotic [6], antifungal [7], anti-inflammatory [8], anti-depressant [9], antimicrobial [10], anti-diabetic [11] and antiobesity agents. Besides this, oxazole derivatives show antiproliferative activity for many cancer cells, especially human prostate cancer and human epidermoid carcinoma [12-13]. It has been even used as antimicrobial agent by preventing the bacterial protein synthesis. One the very frequently used molecule contains oxazole ring is linezolid; which is used in treatment of multidrug resistance infection. Apart from these cycloserine and furazolidone also contain oxazole ring and used as antimicrobial agent by preventing a bacterial cell wall synthesis and damaging bacterial DNA respectively. [14-15]

At the same time benzopyran derivatives have versatile biological properties such as anti-inflammatory [16-17], antioxidant [18], vasorelaxant [19], cytotoxic [20], anti-HIV [21], antitubercular [22] and antimicrobial [23]. Presently antimicrobial molecule containing benzopyran ring is novobiocinan acts by targeting bacterial DNA gyrase and topoisomerase IV and control the topological state of DNA during replication and acts as antimicrobial agent [24-26].

Therefore we plan to synthesize oxazole benzopyran-2-one hybrids and choose DNA gyrase receptor to dock with the synthesized compound and evaluate its binding pattern with the receptor.

2. MATERIALS AND METHODS

DNA gyrase by molecular docking studies and evaluate its anti-bacterial activity by tube dilution method. Melting points were determined by open capillary and are uncorrected. The IR spectra (in ATR technique) were recorded in Tensor 27 spectrophotometer, Bruker optic (Germany). 1H NMR spectra were recorded (CDCl3) on Bruker spectrometer (400Mz) using TMS as an internal standard. Chemical shift values are given in δ scales. The mass spectra were recorded using a Jeol-D-300 Mass spectrometer (70eV), Shimadzu (Japan) by FAB. Elemental analyses were performed using Vairo Elemental Model, C, H, N analyzer. The completion of the reaction was checked by thin layer chromatography (TLC) on silica gel-G coated plates by using suitable solvent system and observed in UV light. Commercial grade solvents and reagents obtained from Sigma-Aldrich with purity ≥ 98% were used.
2.1 General Procedure for the Synthesis of Substituted Dihydro-1, 2-Oxazole Benzopyran-2-One Hybrids

2.1.1 Step 1: synthesis of benzopyran-2-one

A mixture of substituted salicylaldehyde (0.05 mol) and ethyl acetoacetate was added to 250ml conical flask. It was then condensed by adding sufficient piperidine drop wise 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.

2.1.2 Step 2: Synthesis of substituted benzopyran-2-one Chalcone (SC1-SC6)

A mixture of substituted 3-acetyl coumarin (0.01 mol) and different substituted benzaldehyde (0.01 mol) in 20 ml absolute ethanol was stirred together at room temperature for 24 hours in the presence of 20% sodium hydroxide. The completion of the reaction was monitored by TLC. The reaction mixture was then poured into crushed ice and acidified with 2N hydrochloric acid with stirring. The product obtained was filtered, washed with water and recrystallized from ethanol.

2.1.3 Step 3: Substituted 3 Dihydro-1, 2-Oxazole Benzopyran-2-one (SR1-SR6)

A mixture of chalcones (0.01 mol), hydroxyl amine (0.01 mol) was dissolved in 10 ml of ethanolic NaOH and stirred for 5-6 hrs with a magnetic stirrer. The completion of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was poured into crushed ice. The precipitated solid was filtered, washed with cold water and recrystallized from ethanol [27].

2.2 Molecular Docking Study

Molecular docking study was performed to know the interactions between ligand (synthesized...
compounds) and receptor. All computational analysis was carried out on Schrodinger 2018-3 suite device Maestro 11.7.0.12, (ligprep, glide XP docking, grid generation). This software package programmed on DELL Inc.27" workstation machine running on Intel Core i7-7700 CPU@ 3.60 GHz x8, processor with 8GB RAM and 1000 GB hard disk with Linux–X6_64 as the operating system. For docking calculation, the protein Protein data bank PDB (code: 5L3J) was downloaded from protein data bank and refined using protein preparation wizard. Docking score were calculated using maestro (Schrodinger) software. The binding affinity was assessed in terms of binding free energies (S-score, kcal/mol) [28]. All synthesized compounds were docked in the groove of binding site present in DNA Gyrase B 5L3J.

2.3 Evaluation of Antibacterial Activity

2.3.1 Determination of minimum inhibitory concentration by tube dilution method

2.3.1.1 Control tests

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.

Procedure

Double concentration of the nutrient broth was prepared. Distribute each 2.5 ml into 9 test tubes and label them A1 to A9. Distribute 2.5 ml in to two test tubes and label them as positive control and negative control. Prepare drug stock solution of 2000 µg/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 µg/ml. Serial dilution of the same was performed to give 100 µg/ml, 50 µg/ml, 25 µg/ml, 12.5 µg/ml and 6.25 µg/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 µg/ml, 50 µg/ml, 25 µg/ml, 12.5 µg/ml, 6.25 µg/ml and 3.12 µg/ml and 1.56µg/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 non-absorbent 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 E.coli , except in the negative control tube. Incubate all the tube at 37°C for 48 hrs and observe the turbidity [29].

3. RESULTS AND DISCUSSION

In the present study the oxazole benzopyran-2-one hybrid derivatives were synthesized by infusing benzopyran ring and oxazole ring and were studied for molecular docking study and antibacterial activity.

In the process of synthesis, the starting material substituted salicylaldehyde and ethyl acetoacetate were reacted as the mentioned procedure and lead to formation of intermediates as substituted benzopyran-2-one chalcone. (SC1-SC6). These intermediates were characterized using N.M.R, I.R and Mass spectroscopy. The observed peak value and chemical shift value of IR and N.M.R were 1760 cm⁻¹, 1480 cm⁻¹, 6.89 (1H, d, J = 16.5 Hz), which shows the presence C=O, C=C functional group and eneone proton thus confirm the formation of intermediates. These intermediates were further reacted with hydroxyl amine as the procedure leads to the formation of final compounds substituted 3 dihydro-1,2-oxazole benzopyran-2-one (SR1-SR6). The conformation of these compounds was done based on the spectral studies. The peak value 1256 cm⁻¹ (C=O-N str) and 1610 cm⁻¹ (C=N str) and chemical shift value 6.19 (1H, dd, J = 7.9, 6.8 Hz) O-C-H of isoxazol confirm the formation of final compounds. The physicochemical parameter these intermediates and final compounds are reported in Table 1 and 2.

Final compounds interaction pattern with DNA Gyrase B (PDB code: 5L3J) were studied and was compared with standard drug ciprofloxacin. Compound SR3 shows the best interaction pattern with best binding energy -3.38 kcal/mol. This form hydrogen bond, hydrophobic interaction, charged negatives and polar interaction with respective amino acids VAL, ALA, VAL, ILE, LEU, 98, PRO, ARG, LYS and THR. Apart from the SR3 the compound shows hydrogen bond is SR1&SR6-forms one hydrogen bonds. The other interaction patterns and dockings core for all other compounds are shown in the Table 3, 4 and Figs 1, 2, 3.
SR1-SR6 was evaluated for antibacterial activity by using tube dilution method and a result is mentioned in Table 5 and figure 4. 3-(5-(m-toly)-4, 5-dihydroisoxazol-3-yl)-2H-chromen-2-one (SR3) have shown the best antibacterial activity having MIC value 3.12 µg/ml. The effect of the substitution in the phenyl ring region as R1 and substitution in the-acetyl-2H-chromen-2-one region as R. Substituted 3 Dihydro-1,2-oxazole Benzopyran-2-one were considered to summarize the structural activity relationship, when the R1 substituent is electron pumping group like methyl it increases antibacterial activity; at the same time electron withdrawing group like nitro and chloro decreases. Similarly, when the R hydrogen was replaced with methoxy group there was decrease in the antibacterial activity.

3.1 Spectral Data

3.1.1 3-acetyl-7-methoxy-2H-chromen-2-one

It was obtained as yellow crystals (EtOH). mp 143-145°C; UV (EtOH) $\lambda_{\text{max}}$ (log $\epsilon$) 294 (4.26) nm; Rf= 0.52 (n-hexane: ethyl acetate, 8:2)IR $\nu_{\text{max}}$ 3000(C-H aromatic), 1510 (C=O str), 1670(C=O str), 1220(C-O-C str) cm$^{-1}$; HNMR (CDCl$_3$, 400 MHz): $^1$H NMR: Μ 5.24, δ (3H, s), 3.80 (3H, s), 5.30 (1H, d), 5.53 (1H, d), 6.42-6.46 (2H, 6.44 (dd), 6.42 (dd),), 7.71 (1H, s), 8.08 (1H, dd,),...MS: m/z = 219(M$^+$); Anal. Calcd for C$_{18}$H$_{17}$NO$_6$: C, 66.05; H, 4.62, O 29.33. Found: C, 66.09; H, 4.57; O, 29.32.

3.1.2 3-(3-(4-nitrophenyl) acryloyl)-2H-chromen-2-one (SC1)

It was obtained as yellow crystals (EtOH). mp 167-169°C; UV (EtOH) $\lambda_{\text{max}}$ (log $\epsilon$) 282 (4.21) nm; Rf= 0.47 (n-hexane: ethyl acetate, 8:2)IR $\nu_{\text{max}}$3010(C-H aromatic), 1490 (C=Cstr), 1710(C=O str), 1250(C-O-C str) 1040(44Ar-C-NO$_2$str) cm$^{-1}$; HNMR (CDCl$_3$, 400 MHz): $^1$H NMR: δ 6.63 (1H, s), 6.89 (1H, d), 7.35-7.50 (4H, 7.43 (dd), 7.47 (dd), 7.39 (dd),), 7.50 (1H, dd), 7.72 (1H, ddd), 7.93-8.07 (3H, 8.04 (dd),), 7.97 (dd),).MS: m/z = 321(M$^+$); Anal. Calcd for C$_{19}$H$_{14}$NO$_6$: C, 67.29; H, 3.45; N, 4.36; Found: C, 67.26; H, 3.42; N, 4.31.

3.1.3 3-(5-(m-toly) acryloyl)-2H-chromen-2-one (SC3)

It was obtained as yellow crystals (EtOH). mp 174-176°C; UV (EtOH) $\lambda_{\text{max}}$ (log $\epsilon$) 286 (4.24) nm; Rf= 0.39 (n-hexane: ethyl acetate, 8:2)IR $\nu_{\text{max}}$ 3010(C-H aromatic), 1480 (C=C str), 1710(C=O str), 1250(C-O-C str); $^1$HNMR (CDCl$_3$, 400 MHz): $^1$H NMR: δ 2.42 (3H, s), 6.67 (1H, s), 6.79 (1H, d ,), 7.18 (1H, ddd,), 7.30 (1H, ddd), 7.36-7.53 (4H, 7.43 (ddd),), 7.45 (ddd),, 7.50 (ddd),, 7.40 (ddd (+)), 7.49 (1H, ddd +), 7.67-7.83 (2H, 7.72 (ddd),, 7.79 (d),MS: m/z = 291(M$^+$); Anal. Calcd for C$_{19}$H$_{14}$NO$_6$: C, 78.61; H, 4.86; O, 16.53; Found: C, 78.58; H, 4.87; O, 16.56.

3.1.4 3-(3-(4-nitrophenyl) acryloyl)-2H-chromen-2-one (SC4)

This compound was obtained as yellow crystals (EtOH); mp 188-190°C; UV (EtOH) $\lambda_{\text{max}}$ (log $\epsilon$) 296 (4.26) nm; Rf= 0.51 (n-hexane: ethyl acetate, 7:3)IR $\nu_{\text{max}}$3010(C-H aromatic), 1480 (C=C str), 1710(C=O str),1380 (C-H aliphatic bending), 1250(C-O-C str),$^1$HNMR (CDCl$_3$, 400 MHz): δ 3.82 (3H, s), 6.49 (1H, s), 6.58 (1H, ddd,,), 6.96 (1H, d),, 7.27 (1H, ddd,), 7.35-7.50 (3H, 7.39 (dd),, 7.46 (ddd),, 7.94 (1H, d),, 8.04 (2H, ddd,),MS: m/z = 351 (M$^+$); Anal. Calcd for C$_{19}$H$_{21}$NO$_6$: C, 64.96; H, 3.73; N, 3.99; Found: C, 64.93; H, 3.77; N, 4.01.

3.1.5 3-(5-(4-nitrophenyl)-4,5-dihydroisoxazol-3-yl)-2H-chromen-2-one (SR1)

It was obtained as yellowish green crystals (EtOH); mp 196-198°C; UV (EtOH) $\lambda_{\text{max}}$ (log $\epsilon$) 296 (4.26) nm; Rf= 0.62 (n-hexane: ethyl acetate, 6:4) IR $\nu_{\text{max}}$3130(C-H aromatic), 1530 (C=C str), 1720(C=O str),1380 (C-H aliphatic bending), 1250(C-O-C str),1256 (C-O-N str) $^1$HNMR (CDCl$_3$, 400 MHz): δ 3.05-3.22 (2H, 3.11 (dd),,), 3.17 (dd), 6.28 (1H, ddd,), 7.34 (1H, ddd), J = 7.7, 7.5, 1.1 Hz), 7.42 (1H, ddd,), 7.62-7.73 (3H, 7.66 (ddd),,), 7.69 (ddd),, 7.98-8.07 (4H, 8.02 (ddd),,), 8.04 (dd),,), 8.02 (s),MS: m/z = 336.07 (M$^+$); Anal. Calcd for C$_{19}$H$_{16}$NO$_6$: C, 64.29; H, 3.60; N, 8.33; Found: C, 64.27; H, 3.64; N, 8.31.

3.1.6 3-(5-(m-toly)-4,5-dihydroisoxazol-3-yl)-2H-chromen-2-one (SR3)

It was obtained as yellow solid (EtOH); mp175-175°C; UV (EtOH) $\lambda_{\text{max}}$ (log $\epsilon$) 304 (4.26) nm; Rf= 0.67 (n-hexane: ethyl acetate, 6:4)IR $\nu_{\text{max}}$3140(C-H aromatic), 1540 (C=C str), 1720(C=O str),1380 (C-H aliphatic bending), 1250(C-O-C str),1256 (C-O-N str) and 1610 (C=N str) $^1$HNMR (CDCl$_3$, 400 MHz): δ 2.25 (3H, s), 3.03 (1H, dd,), 3.20 (1H, dd,), 6.19 (1H, dd,), 7.14-7.23 (4H, 7.17 (ddd),,), 7.20 (ddd,),, 7.34 (1H, ddd,), 7.42 (1H, ddd,), 7.69 (1H, ddd,), 8.01-
Ciprofloxacin

Table 1. Physicochemical data of substituted benzopyran-2-one Chalcones (SC1-SC6)

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<th>Com. Code</th>
<th>R</th>
<th>R1</th>
<th>Mol. Formula</th>
<th>Mol.Wt</th>
<th>Physical State</th>
<th>M.P°C</th>
<th>%Yield</th>
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<td>H</td>
<td>NO₂</td>
<td>C₁₆H₁₁NO₂</td>
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<td>yellow crystals</td>
<td>167-169</td>
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<td>SC2</td>
<td>H</td>
<td>Cl</td>
<td>C₁₆H₁₂ClO₃</td>
<td>311</td>
<td>yellow crystals</td>
<td>181-183</td>
<td>62</td>
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<tr>
<td>SC3</td>
<td>H</td>
<td>CH₃</td>
<td>C₁₆H₁₂O₃</td>
<td>291</td>
<td>yellow crystals</td>
<td>174-176</td>
<td>68</td>
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<tr>
<td>SC4</td>
<td>4-OCH₃</td>
<td>NO₂</td>
<td>C₁₆H₁₃NO₄</td>
<td>351</td>
<td>yellow crystals</td>
<td>188-190</td>
<td>72</td>
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<td>SC5</td>
<td>4-OCH₃</td>
<td>Cl</td>
<td>C₁₆H₁₃ClO₄</td>
<td>341</td>
<td>yellow crystals</td>
<td>202-204</td>
<td>74</td>
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<td>CH₃</td>
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<td>190-192</td>
<td>75</td>
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Table 2. Physicochemical data of 3 dihydro-1,2-oxazole benzopyran-2-one (SR1-SR6)

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<th>Mol.Wt</th>
<th>Physical State</th>
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<td>H</td>
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<td>C₁₈H₁₂N₂O₅</td>
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<td>yellowish green crystals</td>
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<td>SR2</td>
<td>H</td>
<td>Cl</td>
<td>C₁₈H₁₃ClNO₃</td>
<td>325</td>
<td>yellow crystals</td>
<td>202-204</td>
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<td>H</td>
<td>CH₃</td>
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<td>173-175</td>
<td>75</td>
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<td>SR5</td>
<td>4-OCH₃</td>
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<td>C₁₈H₁₄ClNO₄</td>
<td>355</td>
<td>yellow crystals</td>
<td>205-207</td>
<td>72</td>
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<tr>
<td>SR6</td>
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Table 3. Data of docking score of SR1-SR6

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<th>SR2</th>
<th>SR3</th>
<th>SR4</th>
<th>SR5</th>
<th>SR6</th>
<th>Ciprofloxacin</th>
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<td>-4.94</td>
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Table 4. List of major interaction between amino acid and receptors5L3J

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<th>Hydrophobic bond</th>
<th>Charged negatives</th>
<th>Polar interaction</th>
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<td>ASP-73</td>
<td>ALA-47, VAL-71,97,120 ILE 78,PRO-79</td>
<td>ASP-73, GLU-50</td>
<td>HID55, THR-165, ASN-46</td>
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<tr>
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<td>-</td>
<td>ALA-47,53, VAL43,120,147, ILE-78, PRO-79</td>
<td>ARG-76,136</td>
<td>THR165, ASN-46</td>
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<tr>
<td>SR 3</td>
<td>VAL -19</td>
<td>ALA-18, VAL-19, ILE-23, LEU 126, 16, 98, PRO-23</td>
<td>ARG-20,22 LYS-21</td>
<td>THR-165</td>
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<tr>
<td>SR 4</td>
<td>-</td>
<td>ALA-47, VAL 43, 71, 120, 167, ILE-74,98, PRO-79</td>
<td>ASP-49,73 GLU-50</td>
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<tr>
<td>SR 5</td>
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<td>ALA-47, VAL 43, 71, 120,167, ILE-78,94, MET-95,166</td>
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<td>THR165, ASN-46</td>
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Table 5. Antimicrobial activity 3 Dihydro-1,2-Oxazole Benzopyran-2-one Derivatives (SR1-SR6)

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<th>Comd Code</th>
<th>100 µg/ml</th>
<th>50 µg/ml</th>
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+: Growth, -: No growth; Negative control: No growth observed, Positive control: growth observed

<table>
<thead>
<tr>
<th>Compound</th>
<th>SR1</th>
<th>SR2</th>
<th>SR3</th>
<th>SR4</th>
<th>SR5</th>
<th>SR6</th>
<th>SR7</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIC (µg/ml)</td>
<td>6.25</td>
<td>6.25</td>
<td>3.12</td>
<td>25</td>
<td>12.5</td>
<td>12.5</td>
<td>1.56</td>
</tr>
</tbody>
</table>

5L3J - minimized - SR2

Fig. 1. 2-D and 3-D Ligand interaction compound SR2 with 5L3J receptor
Fig. 2. 2-D and 3-D Ligand interaction compound SR3 with 5L3J receptor

Fig. 3. 2-D and 3-D Ligand interaction compound ciprofloxacin with 5L3J receptor

Fig. 4. MIC value of compounds SR1-SR6 by tube dilution method
Department of Chemistry, St. Philomena’s College (Autonomous) Mysuru and NGSM Institute of Pharmaceutical Sciences, Paneer Deralakatte Mangaluru, for providing all the necessary facilities. This work could not have been done without the excellent and valuable technical assistance of the following colleagues: Rector Dr. Bernard Prakash, Dr. Alphonse D’Souza. This work was supported by St. Philomenas college (Autonomous) Mysuru.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sdiarticle4.com/review-history/70413