Nanotechnology Perceptions
ISSN 1660-6795
www.nano-*ntp.com*

A Convenient Synthesis Of Heterocyclic Oxazinyl Derivatives Of -4,5-Dihydro-1H-Pyrazole-5-Carbonyl-Naphthalen-2(1H)-One, -2-Mercaptopyrimidin-4-Yl-Naphthalen-2(1H)-One, 2-Hydroxypyrimidin-4-Yl-Naphthalen-2(1H)-One And Their Antimicrobial Activity

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A versatile and convenient synthesis of new cyclize derivatives derived from chalone. First synthesized the 3-acetyl-2H-chromenone-2 by the condensation of salicylaldehyde, ethyl acetoacetate and N-(unsubstituted/substituted-aryl)- di 3, 4-hydro- 2H-benzo [e,1,3] oxazine-carb-6-aldehyde formed by using p-hydroxy aldehyde and substituted aromatic amine to form (E)-3-(3-(N-(unsubstituted/substituted-aryl)-di-3, 4-hydro- 2H-benzo [e,1,3] oxazinyl-7)acryloyl)-3-acetylcoumarin which were than cyclized using hydrazine hydrates, thiourea and urea to furnish the pyrazole-carbonyl, hydroxy-pyrimidinyl and mercapto-pyrimidinyl. We characterized these derivatives with the help of IR, 1HNMR, and mass spectral studies, The antimicrobial activity was assessed in vitro by serial dilution method.

Keywords: thiourea, primary aroamtic amine, 1,4-dioxane, salicylaldehyde, ethyl acetoacetate, urea, pyridine.

Introduction:

The synthesis of Chalcone base cyclized derivatives as hydroxypyrimidin, mercaptopyrimidin and pyrazole all three with common two heterocyclic moieties acetylnaphthalen and Oxazines

to address the multiple infectious disease. However, individually all these three moieties are giving potential results to control various diseases. The Oxazines[1-2] as major component of these derivatives as the proven through wide spectrum of biological activities and in material sciences. They can be driven to alter their unique chemical properties. In present Oxazine six-membered heterocyclic ring nitrogen and oxygen atoms are positioned 1, 3 to each other. The prominent drugs having Oxazines as similar structure are shown in Figure 1. Linezolid[3] has an oxazine nucleus, while ciclopirox[4] and milrinone[5] have a 2-oxopyridine nucleus. Linezolid is used to control the bacterial infections, ciclopirox is used to treat fungal infections, and milrinone is work in heart failure. As a very effective material[6-7] in the various industries as organic photovoltaic cells, dyes, polymer building blocks, organic field-effect transistors, textile industry, photoelectronic materials and chemical sensors, Oxazole[8]-containing derivatives are uswed as II-stage diabetes treatment example platelets aleglitazar [9].

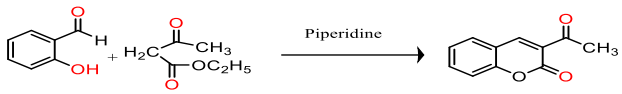
Pyrazole derivatives[10-22] are documented to possess antibacterial, antifungal, antitubercular, anti-inflammatory, analgesic, antidiabetic, antimalarial, antipyretic, anticonvulsant, antidepressant, anticancer, antiviral and antiangiogenetic activities. The Numerous uses in fields including technology, medicine, and agriculture result from the pyrazole nucleus's existence in various structures. They are described as inhibitors of protein glycation, as well as antiviral agent.

Mercapto pyrimidine moiety[23-29] is an essential core in the chemical structure showing crucial role to control in different biological activity because of its unique structure, with two N- atoms in hexagone ring and a -SH group connect to one of the ring's carbon atoms. The presence of S-atom in the mercapto group authorize to covalent bonds with additional molecules or atoms mercaptopyrimidinyl-4 vital to many different chemical reactions. It acts as a basic scaffold in the synthesis of various organic derivatives, working as a building block to create more complex derivatives specially in drug research . It exhibits antiviral against several DNA and RNA viruses such as Herpes simplex polio viruses.

As parts of nucleic acids, pyrimidines and their derivatives[30-37] hold a unique place in medicinal chemistry and possess a range of pharmacological traits, such as antiviral, antitumor, analgesic, and anticancer effects. Although several drugs are already approved to treat viral infections, and there are a number of candidates conducting clinical trials, nucleosides are the most popular and successful class of antiviral medication. As a result, the vigorous hunt for novel nucleoside derivatives attracted a lot of attention. Pyrimidines are crucial parts of biological macromolecules like DNA and RNA because they are bioactive chemicals. Therefore, adding pyrimidines to nucleoside derivatives may lead to the development of several new compounds with possible antiviral and anticancer properties.

The present research work, we report the synthesise structural properties and antimicrobial activities of (E)-3-(3-(N-(p-unsubstituted/substituted-aryl)-di-3, 4-hydro- 2H -benzo [e,1,3] oxazinyl-7)acryloyl)- 3-acetylcoumarin(Chalcone 3a-d), 3-(6-(N-(p-Cl-phenyl)-di 3,4-hydro-2H-benzo [e,1,3] oxazinyl-7)-2-mercaptopyrimidinyl-4)- acetylcoumarin (5a-d) and 3-(6-(N-(p-Cl-phenyl)-di-3, 4-hydro-2H-benzo [e,1,3] oxazinyl-7)-o-hydroxypyrimidinyl-4)-acetylcoumarin (6a-d) exhibits good to strong activity profiles.

1. **Synthesis of acetylnaphthalen-2(1H)-one:**



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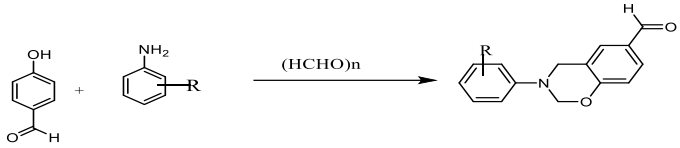
A 20 mmol. Salicylaldehyde (30 mmol), ethyl acetoacetate, absolute alcohol (10 mL), and diethylamine (1 mL) were refluxed with continuous stirring under for 4-5 h. The product was filtered and then washed with excess water, dried in air, and recrystallised from ethanol. Yield 81%; mp 120–121°C; Mol. Wt: 186.21 Anal. Calcd. for C12H10O2 ,C, 77.40; H, 5.41 found:C, 77.40; H, 5.41

2.The Synthesis of 3-(substituted-phenyl)-3,4-dihydro-2H-benzo[e][1,3]oxazine-6-carbaldehyde(2a-d):



For the synthesis of 3-(substituted-phenyl)-3,4-dihydro-2H-benzo[e][1,3]oxazine-6-carbaldehyde (2a-d): used three-necked flask with stirrer having 0.4mol aqueous formaldehyde solution and 50 ml toluene was added at room temperature And was cooled upto 5℃ by ice water with stirring and then add substituted aromatic amine 0.2mol and 15 ml toluene was dropped into flask under stirring and maintained the temperature below 5℃. After .5hr stirring at same temperature, 0.2mol of p-hydroxybenzaldehyde in 50 ml toluene was added into flask with contentious stirring. and kept under room temperature for one hour with continuous stirring. Then stirred with heating for 5 hr at 95 ℃. the residue was removed by under reduced pressure and more chloroform was added to dissolve the residues.The resulting solution was washed with 0.5 ml of aqueous NaOH solution and repeatedly wash with water to remove the impurities and unreacted reagents. After that, the solvent was evaporated by a rotary evaporator the crude, product was recrystallized from toluene. Characterization data of the derivatives thus synthesized, are given as:

2a. **3-(4-chlorophenyl)-3,4-dihydro-2H-benzo[e][1,3]oxazine-6-carbaldehyde:**

Yield 84%; mp 124°C; Mol. Wt: 273.72; Elemental Calculated for $C_{15}H_{12}ClNO_2$, C-65.82; Cl-12.95;N-5.12 Found: C-65.82;Cl-12.90; N-5.07.

IR (KBr) υ_{max}**/per-cm:** 2995 (C-H, str. arom.), 2830 (C-H, str. aradehyde), 1290 (C-N, oxazine), 1655 (C=O, str. aldehyde), 1560 (C=C,s tr. arom.), 710 (chloro-C); Nuclear Magnetic Resonance-$CDCl_3$-300 MHz, δ, ppm: 7.18-7.83 (m, 7H, arom-H), 1.83 (s, 1H, aldehyde), 3.86 (s,2H,CH_2-oxazine -N), 4.74 (s, 2H,CH_2-oxazine -O).

2b. 3-(4-bromophenyl)-3,4-dihydro-2H-benzo[e][1,3]oxazine-6-carbaldehyde:

Yield 87%; mp 112– 113°C; Mol. Wt: 318.17 Anal. Calcd. for $C_{15}H_{12}BrNO_2$, C, 56.63; H, 3.80; Br, 25.11; N, 4.40 found:C, 56.56; H, 3.874; Br, 25.09; N, 4.33.

IR (KBr) υ_{max}/per-cm: 2988 (C-H, str.,arom), 2842 (C-H, str.araldehyde), 1285 (C-N,oxazine), 1660 (C=O, str.), 1570 (C=C,str.,aroma), 1295 (C-N, oxazine), 815 (C-Br); Nuclear Magnetic Resonance-$CDCl_3$-300 MHz, δ, ppm: δ7.10-7.93 (m, 7H, Ar-H), 1.88 (s, 1H, aldehydde), 3.89 (s,2H,CH_2-N), 4.71 (s, 2H,CH_2-O).

2c. **3-(4-hydroxyphenyl)-3,4-dihydro-2H-benzo[e][1,3]Oxazine-6-carbaldehyde:**

Yield 78%; mp 111°C; Mol. Wt: 255.27 Anal. Calcd. for $C_{15}H_{13}NO_3$, C, 70.58; H, 5.13; N, 5.49 found:C, 70.52; H, 5.10; N, 5.44.

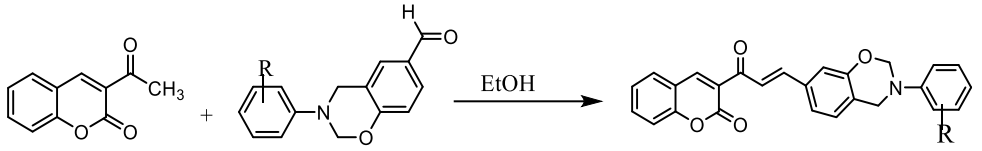
IR (KBr) **υ_{max}/per-cm**: 2996 (C-H, str., arom), 2855 (C-H, str. araldehyde), 1294 (C-N, oxazine), 1673 (C=O, str.), 1567 (C=C,str., arom), 1292 (C-N, oxazine.), 3340 (C-OH); Nuclear Magnetic Resonance-$CDCl_3$-300 MHz, δ, ppm: δ7.05-7.94 (m, 7H, Ar-H), 1.81 (s, 1H, aldehydde), 3.83 (s,2H,CH_2-N), 4.64 (s, 2H,CH_2-O).

2d. 3-(p-tolyl)-3,4-dihydro-2H-benzo[e][1,3]oxazine-6-carbaldehyde

Yield 74%; mp 113-132 °C, Mol. Wt:253.30 , Anal. Calcd. for $C_{16}H_{15}NO_2$, C, 75.87; H, 5.97; N, 5.53 found:C, 75.83; H, 5.94; N, 5.50.

IR (KBr) υ_{max}/per-cm: 2978 (C-H, str., arom), 2864 (C-H, str.araldehyde), 1290 (C-N,oxazine), 1665 (C=O, str.), 1572 (C=C,str., arom,),; Nuclear Magnetic Resonance-$CDCl_3$-300 MHz, δ, ppm: δ6.94-7.52 (m, 7H, Ar-H), 1.83 (s, 1H, aldehydde), 3.87 (s,2H,CH_2-N), 4.68 (s, 2H,CH_2-O).

3. Synthesis of (E)-3-(3-(3-(substituted-phenyl)-3,4-dihydro-2H-benzo[e][1,3]oxazin-7-yl)acryloyl)naphthalen-2(1H)-one (Chalcone 3a-d):



A 0.01 mol of each acetylnaphthalen-2(1H)-one and 3-(substituted-phenyl)-3,4-dihydro-2H-benzo[e][1,3]oxazine-6-carbaldehyde (2a-d) were mixed in 30 ml ethanol as solvent in a round bottom flask placed on ice bath and add 10 ml NaOH solution dropwise with continuous stirring for .30 hr. The process was continued for 4-6 hr. at room temperature. The reaction was kept in a refrigerator for overnight. Then it was diluted with 50ml ice-cold distilled water and washed well with cold water and recrystallized from rectified methanol.Characterization data of the derivatives thus synthesized, are given as:

3a. (E)-3-(3-(3-(4-chlorophenyl)-3,4-dihydro-2H-benzo[e][1,3]oxazin

-7-yl)acryloyl)naphthalen-2(1H)-one:

Yield 67%; mp 141 °C; Mol. Wt: 441.91, Anal. Calcd. for $C_{27}H_{20}ClNO_3$, C, 73.39; H, 4.56;

Cl, 8.02; N, 3.17found:C, 73.34; H, 4.52; Cl, 8.0; N, 3.12.

IR (KBr) υ_{max}/per-cm:2910 (C-H, str., Sub Aryl), 2835(CH_2-O), 1730 (coumarin C=O), 1600 (CH=CHC=O, str.), 1535 (C=C,str., Sub Aryl), 1145 (C-N), 1035 (C-O), 716 (C-Cl, str.); Nuclear Magnetic Resonance-$CDCl_3$-300 MHz, δ, ppm: δ7.05-7.12 (m, 12H, Ar-H), 2.20(d, 1H,CH=CH), 2.49(s,2H, CH_2-N,oxazine), 3.3(s,2H,-O-CH_2-N,oxazine), 4.8(s,2H,-CH-C=O).

3b. (E)-3-(3-(3-(4-bromophenyl)-3,4-dihydro-2H-benzo[e] 1,3]oxazin

-7-yl)acryloyl)naphthalen-2(1H)-one:

Yield 81%; mp 1118 – 119°C; Mol. Wt: 486.37 Anal. Calcd. for $C_{27}H_{20}BrNO_3$, C, 66.68; H, 4.15; Br, 16.43; N, 2.88 found:C, 66.61; H, 4.12; Br, 16.37; N, 2.82.

IR (KBr) υ_{max}/per-cm: 2916 (C-H, str., Sub Aryl), 2830(CH_2-O), 1740 (coumarin C=O), 1615 (CH=CHC=O, str.), 1528 (C=C,str., Sub Aryl), 1160 (C-N), 1044 (C-O), 790 (C-Br str.); Nuclear Magnetic Resonance-$CDCl_3$-300 MHz, δ, ppm: δ6.92-7.18 (m, 12H, Ar-H), 2.28(d, 1H,CH=CH), 2.53(s,2H, CH_2-N,oxazine), 3.27(s,2H,-O-CH_2-N,oxazine), 4.79(s,2H,-CH-C=O).

3c. (E)-3-(3-(3-(4-hydroxyphenyl)-3,4-dihydro-2H-benzo[e][1,3]

oxazin-7-yl)acryloyl)naphthalen-2(1H)-one:

Yield 77%; mp 127 – 128°C; Mol. Wt: 423.47 Anal. Calcd. for$C_{27}H_{21}NO_4$,C, 76.58; H, 5.00; N, 3.31 found:C, 76.53; H, 4.096; N, 3.28.

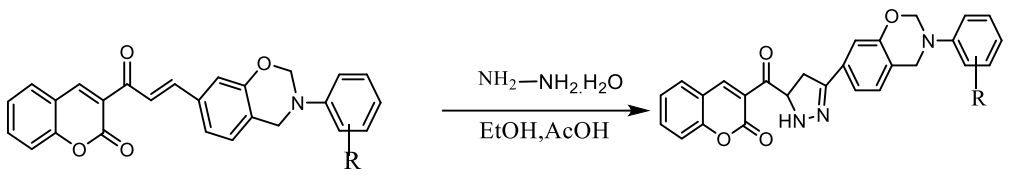
IR (KBr) υ_{max}/per-cm: 2925 (C-H, str., Sub Aryl), 2820(CH_2-O), 1742 (coumarin C=O), 1618 (CH=CHC=O, str.), 1542 (C=C,str., Sub Aryl), 1132 (C-N), 1025 (C-O), 3315(C-OH, str.); Nuclear Magnetic Resonance-$CDCl_3$-300 MHz, δ, ppm: δ6.84 -7.34 (m, 12H, Ar-H), 5.16(s,1H,-OH) , 2.31(d, 1H,CH=CH), 2.52(s,2H, CH_2-N,oxazine), 3.62(s,2H,-O-CH_2-N,oxazine), 4.76(s,2H,-CH-C=O).

3d.(E)-3-(3-(3-(p-tolyl)-3,4-dihydro-2H-benzo[e][1,3]oxazin-7-yl)acryloyl)naphthalen-2(1H)-one:

Yield 76%; mp 112 – 113°C; Mol. Wt: 421.50 Anal. Calcd. for $C_{28}H_{23}NO_3$,C, 79.79; H, 5.50; N, 3.32 found:C, 79.75; H, 5.46; N, 3.26.

IR (KBr) υ_{max}/per-cm: 2916 (C-H, str., Sub Aryl), 2840(CH_2-O), 1735 (coumarin C=O), 1636 (CH=CHC=O, str.), 1565 (C=C,str., Sub Aryl), 1152 (C-N), 1012 (C-O); Nuclear Magnetic Resonance-$CDCl_3$-300 MHz, δ, ppm: δ 6.83-7.41 (m, 12H, Ar-H), 2.34(d, 1H,CH=CH), 2.51(s,2H, CH_2-N,oxazine), 3.23(s,2H,-O-CH_2-N,oxazine), 4.54(s,2H,-CH-C=O), 2.26 (3H, s, CH_3).

4. Synthesis of 3-(3-(3-(substituted-phenyl)-3,4-dihydro-2H-benzo[e][1,3]oxazin-7-yl)-4,5-dihydro-1H-pyrazole-5-carbonyl)naphthalen-2(1H)-one (4a-d):



A 0.01 mole of (E)-3-(3-(3-(substituted-phenyl)-3,4-dihydro-2H-benzo[e][1,3]oxazin-7-yl)acryloyl)naphthalen-2(1H)-one (Chalcone 3a-d) in 20ml 1.4-dioxane and 0.01 mole hydrazine hydrate was refluxed on heating mental for 12-14 hr. the reaction mixture was cooled, poured into crushed ice and used acid HCl for the neutralizetion. The precipitate was filtered, dried and recrystallized from methanol. The characterization data of the derivatives thus synthesized, are given as:

4a. 3-(3-(3-(4-chlorophenyl)-3,4-dihydro-2H-benzo[e][1,3]oxazin-7-yl)-4,5-dihydro-1H-pyrazole-5-carbonyl)naphthalen-2(1H)-one:

Yield 63% mp 124 – 125°C; Mol. Wt: 483.95 Anal. Calcd. for $C_{28}H_{22}ClN3O_3$,C, 69.49; H, 4.58; Cl, 7.33; N, 8.68 found:C, 69.42; H, 4.53; Cl, 7.29; N, 8.63.

IR (KBr) **υ_{max}/per-cm**: 1132 (C-N), 1115 (C=N), 2924 (C-H, str., Sub Aryl), 1610 (coumarin C=O), 1636 (-CH_2-O, str.), 1565 (C=C,str., Sub Aryl), 1152 (C-N), 995 (C-O), 716 per cm (C-Cl, str.); Nuclear Magnetic Resonance-$CDCl_3$-300 MHz, δ, ppm: δ6.82-7.42 (m, 13H, Ar-H), 6.14 (s, CH_2, coumarin), 4.2(s,2H,O-CH_2-N,oxazine), 2.9(s,2H-CH_2,oxazine), 2.40(s,1H,N-H).

4b. 3-(3-(3-(4-bromophenyl)-3,4-dihydro-2H-benzo[e][1,3]oxazin-7-yl)-4,5-dihydro-1H-pyrazole-5-carbonyl)naphthalen-2(1H)-one:

Yield 77%; mp 110 – 111°C; Mol. Wt: 528.41 Anal. Calcd. for $C_{28}H_{22}BrN_3O_3$, C, 63.65; H, 4.20; Br, 15.12; N, 7.95 found:C, 63.60; H, 4.14; Br, 15.07; N, 7.91.

IR (KBr) υ_{max}/per-cm: 1124(C-N), 1110 (C=N), 2928 (C-H, str., Sub Aryl), 1618 (coumarin C=O), 1630 (-CH_2-O, str.), 1570 (C=C,str., Sub Aryl), 1146 (C-N), 992 (C-O), 670 cm −1 (C-Br,str.) ; Nuclear Magnetic Resonance-$CDCl_3$-300 MHz, δ, ppm: δ6.91-7.52 (m, 13H, Ar-H), 6.18 (s, CH_2, coumarin), 4.7(s,2H,O-CH_2-N,oxazine), 2.11(s,2H-CH_2, oxazine), 2.37(s,1H,N-H).

4c. 3-(3-(3-(4-hydroxyphenyl)-3,4-dihydro-2H-benzo[e][1,3]oxazin-7-yl)-4,5-dihydro-1H-pyrazole-5-carbonyl)naphthalen-2(1H)-one:

Yield 58%; mp 129 – 130°C; Mol. Wt: 465.51 Anal. Calcd. for $C_{28}H_{23}N_3O_4$, C, 72.25; H, 4.98; N, 9.03 found:C, 72.20; H, 4.94; N, 9.01.

IR (KBr) υ_{max}/per-cm: 1136(C-N), 1130 (C=N), 2960 (C-H, str., Sub Aryl), 2845(CH_2-O), 1630 (coumarin C=O), 1582 (C=C,str., Sub Aryl), 1135 (C-N), 985 (C-O), 3280 (C-OH) ; Nuclear Magnetic Resonance-$CDCl_3$-300 MHz, δ, ppm: δ6.83-7.69 (m, 13H, Ar-H), 6.23 (s, CH_2, coumarin), 4.11(s,2H,O-CH_2-N, oxazine), 2.17(s,2H-CH_2, oxazine), 2.32(s,1H,N-H), 4.63(s,1H,-OH).

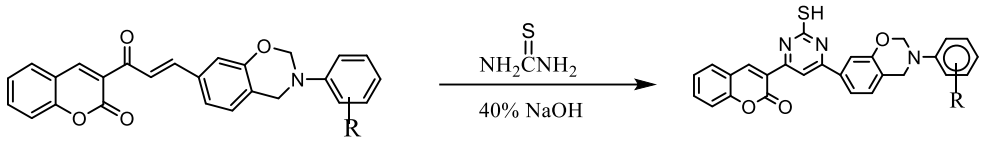
4d. 3-(3-(3-(p-tolyl)-3,4-dihydro-2H-benzo[e][1,3]oxazin-7-yl)-4,5-dihydro-1H-pyrazole-

5-carbonyl)naphthalen-2(1H)-one:

Yield 63%; mp 105 – 106°C; Mol. Wt: 463.54 Anal. Calcd. for $C_{29}H_{25}N_3O_3$, C, 75.14; H, 5.44; N, 9.07 found:C, 75.09; H, 5.41; N, 9.02.

IR (KBr) υ_{max}/per-cm: 1122(C-N), 1140 (C=N), 2972 (C-H, str., Sub Aryl), 1642 (coumarin C=O), 1636 (-CH_2-O, str.), 1590 (C=C,str., Sub Aryl), 1147 (C-N), 977 (C-O), 2980 (C-CH_3) ; Nuclear Magnetic Resonance-$CDCl_3$-300 MHz, δ, ppm: δ 6.92-7.76 (m, 13H, Ar-H), 6.30 (s, CH_2, coumarin), 4.16(s,2H,O-CH_2-N, oxazine), 2.15(s,2H-CH_2, oxazine), 2.44(s,1H,N-H), 4.71(s,1H,-OH), 2.28 (3H, s, CH_3).

5. Synthesis of 3-(6-(3-(substituted-phenyl)-3,4-dihydro-2H-benzo[e][1,3]oxazin-7-yl)-2-mercaptopyrimidin-4-yl)naphthalen-2(1H)-one (5a-d):



A 0.01 mole of (E)-3-(3-(3-(substituted-phenyl)-3,4-dihydro-2H-benzo[e][1,3]oxazin-7-yl)acryloyl)naphthalen-2(1H)-one (Chalcone 3a-d) in 20 1,4-dioxane and 0.01 mole thiourea was refluxed for22-23 hr. The reaction mixture was cooled at room temperature, and then poured into ice cooled water with contentious stirring. The solid was filtered, washed and recrystallized from 1,4-dioxane. The characterization data of the derivatives thus synthesized, are given as:

5a.3-(6-(3-(4-chlorophenyl)-3,4-dihydro-2H-benzo[e][1,3]oxazin-7-yl)-2-mercaptopyrimidin-4-yl)naphthalen-2(1H)-one:

Yield 73%; mp 119°C; Mol. Wt: 498.00 Anal. Calcd. for $C_{28}H_{20}ClN_3O_2S$, C, 67.53; H, 4.05; Cl, 7.12; N, 8.44 found:C, 67.46; H, 4.02; Cl, 7.07; N, 8.38.

IR (KBr) υ_{max}/per-cm: 2495 (S-H), 1445 (C=N), 3050 (C-H, str., Sub Aryl), 1772 (coumarin C=O), 1590 (C=C,str., Sub Aryl), 1145 (C-N), 972(C-O),; Nuclear Magnetic Resonance-$CDCl_3$-300 MHz, δ, ppm: δ6.83-7.49 (m, 13H, Ar-H), 6.14 (s, CH_2, coumarin), 2.9(s,2H,O-CH_2-N, oxazine), 1.5 (s, SH).

5b.3-(6-(3-(4-bromophenyl)-3,4-dihydro-2H-benzo[e][1,3]oxazin-7-yl)-2-mercaptopyrimidin-4-yl)naphthalen-2(1H)-one:

Yield 77%; mp 133 – 134°C; Mol. Wt: 542.45 Anal. Calcd. for $C_{28}H_{20}BrN_3O_2S$, C, 62.00; H, 3.72; Br, 14.73; N, 7.75 found:C, 61.96; H, 3.67; Br, 14.70; N, 7.72.

IR (KBr) υ_{max}/per-cm: 2482 (S-H), 1440 (C=N), 3065 (C-H, str., Sub Aryl), 1766 (coumarin C=O), 1576 (C=C,str., Sub Aryl), 1152 (C-N), 970(C-O),; Nuclear Magnetic Resonance-$CDCl_3$-300 MHz, δ, ppm: δ6.94-7.61 (m, 13H, Ar-H), 6.23 (s, CH_2, coumarin), 2.81(s,2H,O-CH_2-N, oxazine), 1.39 (s, SH).

5c.3-(6-(3-(4-hydroxyphenyl)-3,4-dihydro-2H-benzo[e][1,3]oxazin-7-yl)-2-mercaptopyrimidin-4-yl)naphthalen-2(1H)-one:

Yield 68%; mp 116 – 117°C; Mol. Wt: 479.55 Anal. Calcd. for $C_{28}H_{21}N_3O_3S$, C, 70.13; H, 4.41; N, 8.76 found:C, 70.09; H, 4.36; N, 8.72.

IR (KBr) υ_{max}/per-cm: 2485(S-H), 1450 (C=N), 3068 (C-H, str., Sub Aryl), 1775(coumarin C=O), 1582 (C=C,str., Sub Aryl), 1160 (C-N), 980(C-O), 3290 (C-OH) ; Nuclear Magnetic Resonance-$CDCl_3$-300 MHz, δ, ppm: δ7.04-7.79 (m, 13H, Ar-H), 6.31 (s, CH_2, coumarin), 2.89(s,2H,O-CH_2-N, oxazine), 1.45 (s, SH), 4.817(s,1H,-OH) .

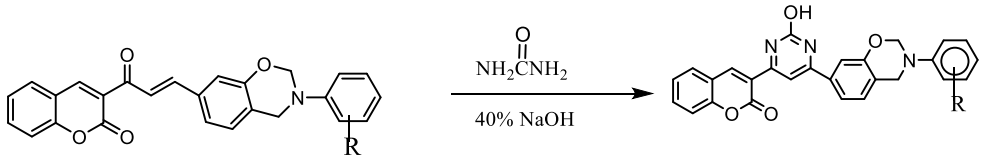
5d.3-(2-mercapto-6-(3-(p-tolyl)-3,4-dihydro-2H-benzo[e][1,3]oxazin-7-yl)pyrimidin-4-yl)naphthalen-2(1H)-one:

Yield 71%; mp 105 – 106°C; Mol. Wt: 477.58 Anal. Calcd. for $C_{29}H_{23}N_3O_2S$, C, 72.93; H, 4.85; N, 8.80 found: C, 72.88; H, 4.81; N, 8.76.

IR (KBr) per cm: 2478(S-H), 1445 (C=N), 3082 (C-H, str., Sub Aryl), 1760(coumarin C=O), 1590 (C=C,str., Sub Aryl), 1164 (C-N), 986(C-O),; Nuclear Magnetic Resonance-$CDCl_3$-300 MHz, δ, ppm: δ6.96-7.72 (m, 13H, Ar-H), 6.39 (s, CH_2, coumarin), 2.78(s,2H,O-CH_2-N, oxazine), 2.23 (3H, s, CH_3),

1.41 (s, SH).

6. Synthesis of 3-(6-(3-(substituted-phenyl)-3,4-dihydro-2H-benzo[e][1,3]oxazin-7-yl)-2-hydroxypyrimidin-4-yl)naphthalen-2(1H)-one (6a-d):



A 0.01 mole of (E)-3-(3-(3-(substituted-phenyl)-3,4-dihydro-2H-benzo[e][1,3]oxazin-7-yl)acryloyl)naphthalen-2(1H)-one (Chalcone 3a-d) in 20 1,4-dioxane and urea 0.01 mole was refluxed for 18-20 hr. The reaction mixture was cooled at room temperature and, then poured into crushed ice with constant contentious stirring. The solid was obtained and recrystallized from 1,4-dioxane. The characterization data of the derivatives thus synthesized, are given as:

6a.3-(6-(3-(4-chlorophenyl)-3,4-dihydro-2H-benzo[e][1,3]oxazin-7-yl)-2-hydroxypyrimidin-4-yl)naphthalen-2(1H)-one:

Yield 63%; mp 1116°C; Mol. Wt: 481.94 Anal. Calcd. for $C_{28}H_{20}ClN_3O_3$

C, 69.78; H, 4.18; Cl, 7.36; N, 8.72 found:C, 69.73; H, 4.14; Cl, 7.31; N, 8.67.

IR (KBr) υ_{max}/per-cm: 3310 (O-H), 1730 (C=N, pyrimidin ring), 3082 (C-H, str., Sub Aryl), 1705 (coumarin C=O), 1590 (C=C, str., Sub Aryl), 1135 (C-N), 965(CH_2-O); Nuclear Magnetic Resonance-$CDCl_3$-300 MHz, δ, ppm: δ 7.05. -7.71 (m, 13H, Ar-H), 4.263 (s, CH_2,

coumarin), 4.2(s,2H,O-CH_2-N, oxazine), 2.9(s,2H,CH_2-N, oxazine), 2.40(s,IH,O-H).

6b. 3-(6-(3-(4-bromophenyl)-3,4-dihydro-2H-benzo[e][1,3]oxazin-7-yl)-2-hydroxypyrimidin-4-yl)naphthalen-2(1H)-one:

Yield 66%; mp 118 – 119°C; Mol. Wt: 526.39 Anal. Calcd. for $C_{28}H_{20}BrN_3O_3$, C, 63.89; H, 3.83; Br, 15.18; N, 7.98 found:C, 63.83; H, 3.77; Br, 15.12; N, 7.94.

IR (KBr) υ_{max}/per-cm: 3322 (O-H), 1720 (C=N, pyrimidin ring), 3095 (C-H, str., Sub Aryl), 1720 (coumarin C=O), 1578 (C=C,str., Sub Aryl), 1140 (C-N), 960(CH_2-O); Nuclear Magnetic Resonance-$CDCl_3$-300 MHz, δ, ppm: δ 6.97. -7.753 (m, 13H, Ar-H), 4.33 (s, CH_2, coumarin), 4.14(s,2H,O-CH_2-N, oxazine), 2.86(s,2H,CH_2-N, oxazine), 2.37(s,IH,O-H).

6c. 3-(2-hydroxy-6-(3-(4-hydroxyphenyl)-3,4-dihydro-2H-benzo[e][1,3]oxazin-7-yl)pyrimidin-4-yl)naphthalen-2(1H)-one:

Yield 73 %; mp 108 – 109°C; Mol. Wt: 463.49 Anal. Calcd. for $C_{28}H_{21}N_3O_4$, C, 72.56; H, 4.57; N, 9.07 found:C, 72.51; H, 4.53; N, 9.03.

IR (KBr) υ_{max}/per-cm: 3340 (O-H), 1725 (C=N, pyrimidin ring), 3084 (C-H, str., Sub Aryl), 1733 (coumarin C=O), 1583 (C=C,str., Sub Aryl), 1147 (C-N), 972(CH_2-O); Nuclear Magnetic Resonance-$CDCl_3$-300 MHz, δ, ppm: δ 7.11. -7.58 (m, 13H, Ar-H), 4.27 (s, CH_2, coumarin), 4.18(s,2H,O-CH_2-N, oxazine), 2.79(s,2H,CH_2-N, oxazine), 4.97(s,1H,-OH), 2.43(s,IH,O-H), 2.31 (3H, s, CH_3).

6d. **3-(2-hydroxy-6-(3-(p-tolyl)-3,4-dihydro-2H-benzo[e][1,3]oxazin-7-yl)pyrimidin-4-yl)naphthalen-2(1H)-one:**

Yield 58 %; mp 122 – 123°C; Mol. Wt: 461.52 Anal. Calcd. for $C_{29}H_{23}N_3O_3$, C, 75.47; H, 5.02; N, 9.10 found:C, 75.43; H, 5.00; N, 9.06.

IR (KBr) υ_{max}/per-cm: 3324 (O-H), 1718 (C=N, pyrimidin ring), 3075 (C-H, str., Aryl), 1742 (coumarin C=O), 1572 (C=C,str., Aryl), 1152 (C-N), 980(CH_2-O); Nuclear Magnetic Resonance-$CDCl_3$-300 MHz, δ, ppm: δ 7.04. -7.61 (m, 13H, Ar-H), 4.31 (s, CH_2, coumarin), 4.26(s,2H,O-CH_2-N, oxazine), 2.74(s,2H,CH_2-N, oxazine), 2.48(s,IH,O-H).

Chemistry:

A three-step procedure was used for the preparation of the derivatives 4,5-dihydro-1H-pyrazole-5-carbonyl, 2-mercaptopyrimidin-4-yl, and pyrimidin-4-yl)naphthalen-2(1H)-one. The initial stage involved the synthesis of acetylnaphthalen-2(1H)-one-1 by the reaction salicylaldehyde and ethyl acetoacetate. FTIR spectra of the synthesized compound-1 exhibit absorption bands of naphthalen-2(1H)-one 1720(-$COCH_3$) and 1015(C-O) respectively. The singlet at δ ~9.2 ppm is because of H_3C-C=O proton, which is consistent with the suggested structure.. The oxazine-6-carbaldehyde(2a-d) obtained by the reaction of formaldehyde, toluene and p-hydroxy benzaldehyde. The spectral data 2710(Aldehyde),1035(C-O),1115(C-N) the condensation of compound-1 and compound-2 furnish the chalcone with various R groups charactrization data proven its prapoesd structure IR

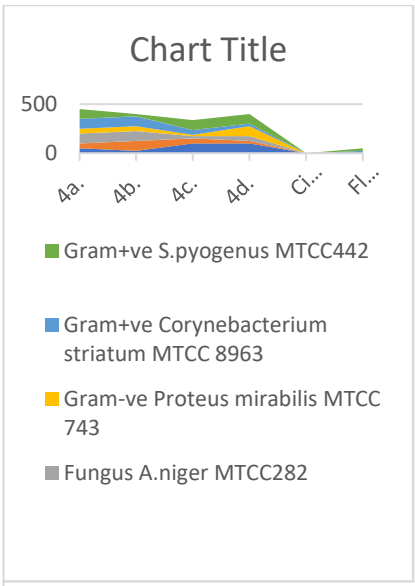
1600(CH=CHC=O),2.20(d,CH=CH), NMR . The final derivatives 4(a-d), 5(a-d), 6(a-d) yields

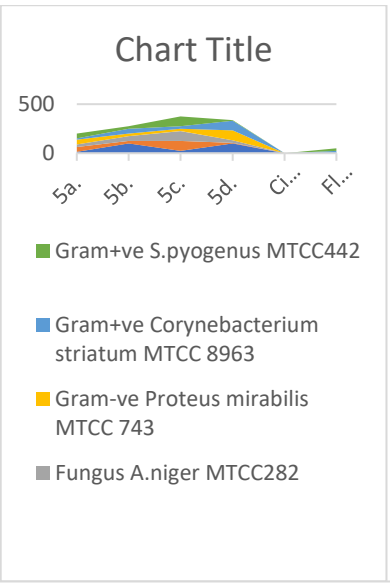
by the cyclization of chalcone derivatives using hydrazine hydrates, thiourea and urea. The Ir 1115(C=N),2495(S-H),3310(O-H)and Nmr 2.40(N-H),1.5(S-H),2.40(OH),value suggest the formation of ring in various derivatives.

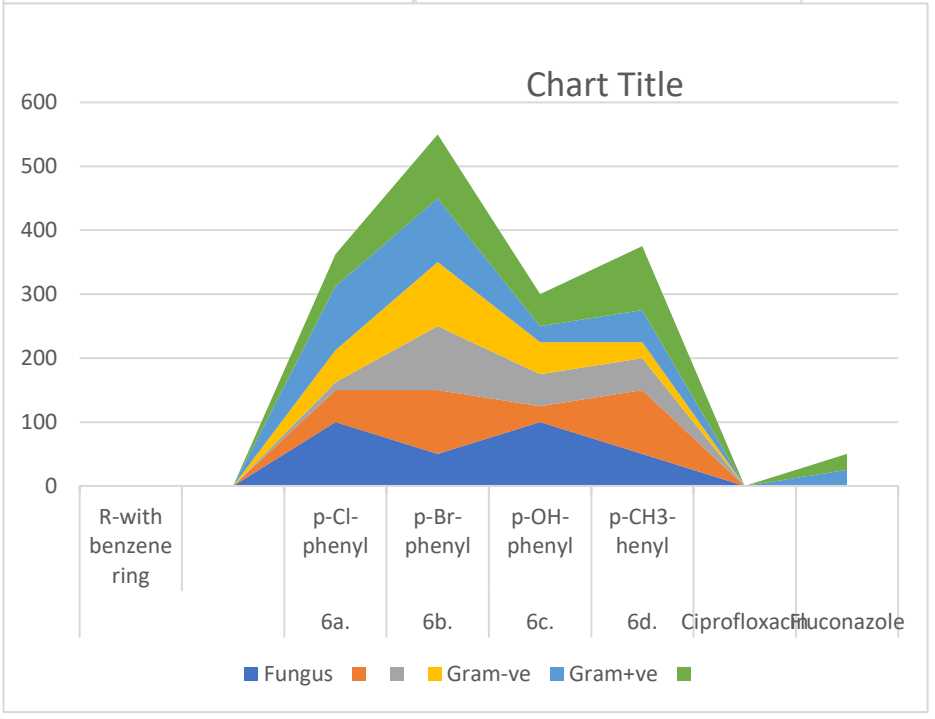
Antimicrobial activity:(MIC μg/mL) of compounds 4a-d, 5a-d and 6a-d:

S.No.		Fungus			Gram-ve	Gram+ve	
	R-with benzene ring	A.clavatus MTCC1323	C.albicans MTCC227	A.niger MTCC282	Proteus mirabilis MTCC 743	Corynebacterium striatum MTCC 8963	S.pyogenus MTCC442
4a.	p-Cl-aryl	50	50	100	100	100	100
4b.	p-Br-aryl	25	100	100	50	100	25
4c.	p-OH-aryl	100	100	25	12.5	100	100
4d.	p-CH_3-aryl	100	25	50	100	25	100
5a.	p-Cl-aryl	12.5	50	25	50	12.5	50
5b.	p-Br-aryl	100	25	50	25	50	25
5c.	p-OH-aryl	25	100	100	25	25	100
5d.	p-CH_3-aryl	100	6.25	25	100	100	6.25
6a.	p-Cl-aryl	100	50	12.5	50	100	50
6b.	p-Br-aryl	100	100	100	50	50	100
6c.	p-OH-aryl	100	25	50	50	25	50
6d.	p-CH_3-aryl	50	100	50	25	50	100
	Ciproflox acin	50	50		25		
	Fluconaz ole					25	25

Graphical representation of 4(a-d),5(a-d) and 6(a-d):







In- vitro anti-fungal and anti-bacterial assay [42-43]:

The newly synthesize the cyclization of chalcone derivatives as hydroxy pyrimidin, mercapto

pyrimidin and pyrazole compounds were evaluated in vitro for their anti-fungal and bacterial activity for various species viz., Proteus mirabilis,MTCC 743 , Corynebacterium striatum MTCC 8963, S.pyogenus MTCC442, A. clavatusMTCC1323, C.albicansMTCC227 and, A.niger MTCC282,

The serial dilution approach was used to assess the synthetic compounds' antifungal and antibacterial properties. The concentration of the test chemical in dimethyl sulfoxide (DMSO-d6) was determined to be 1 mg/mL. The culture was made by combining 20 mL of plane luria-bertani medium with 1 mL of broth that contained antibacterial growth in order to measure the antibacterial potency. Additionally, a control without antibiotic sample. Finally, control tubes having fluconazole and ciprofloxacin were made. For antimicrobial examination, all tube samples were incubated for 24 hours at 37°C; however anti fungal testing tube was incubated for 96 hours at 28°C. The absorbance value at 600 nm was calculated to verify growth for each conical tube. The MIC of the specific derivative was determined by plotting the compound concentration against the absorbance value.

The table presents the effectiveness of various compounds against different fungal and bacterial

strains. The columns represent the following categories:

1. Fungus/Pathogen: This refers to the microbial organisms under study, which include both Gram-ve and Gram+ve species.

2. R-with phenyl ring: These represent different compounds with a benzene ring, denoted by their chemical group variations, such as p-Cl-phenyl, p-Br-phenyl, etc.

3. Gram-ve and Gram+ve specie: These represent the two major

categories of bacteria, with Gram-negative bacteria listed first and Gram-positive ones second.

The table provides values (presumably in micromolar concentrations or percentages) that represent the efficacy of the different compounds against the listed organisms. These values range from 6.25 to 100, indicating varying degrees of inhibition or effectiveness. Compounds 4a. p-Cl-phenyl shows effectiveness ranging from 50% to 100% against various strains. Compound 4b p-Br-phenyl shows effectiveness ranging from 25% to 100%. Compound 4c p-OH-phenyl shows effectiveness ranging from 12.5% to 100% and compound 4d p-CH3-phenyl shows effectiveness ranging from 25% to 100%.

For Aspergillus clavatus (MTCC 1323), the best-performing compound is p-Cl-phenyl at 12.5

µg/mL (from 5a). Other compounds include p-OH-phenyl and p-CH3-phenyl (both 25 µg/mL from 5c and 5d respectively) also exhibit reasonable potency, but not as low as p-Cl-phenyl. The chlorine group (Cl) is an electron-withdrawing group that tends to make the aromatic ring more electrophilic.

This can enhance the compound reactivity, enabling it to more easily interact with bacterial cell membranes, proteins, or enzymes. The low MIC of p-Cl-phenyl (12.5 µg/mL) indicates that this increased reactivity is beneficial in inhibiting fungal growth at a lower concentration.

Chlorine is a moderately lipophilic group. This increases the compounds ability to cross fungal cell membranes, which is a critical step for antifungal activity. Since Aspergillus clavatus is a filamentous fungus, compounds that are lipophilic can penetrate its cell wall and membrane more easily, leading to higher efficacy at lower concentrations. The bromine group (Br), like chlorine, is an electron-withdrawing group but is slightly larger in size. While p-Br-phenyl is still potent (with a MIC of 25 µg/mL), the slightly larger size of the bromine atom compared to chlorine may decrease the overall interaction with the fungal cell, as its steric effect might not allow as much interaction with the target site.

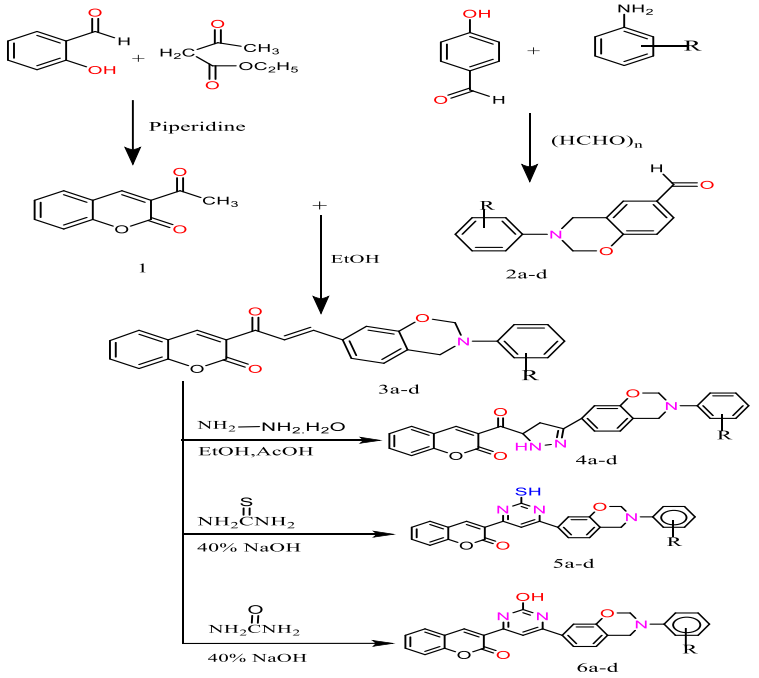
The hydroxyl group (OH) is an e -I group have ability to withdraw the electron from the ring, which makes the phenyl ring less electrophilic, reducing its reactivity. This could explain why p-OH-phenyl (100 µg/mL) and p-CH3-phenyl (100 µg/mL) show weaker antifungal activity compared to the chlorine- and bromine-substituted compounds. The methyl group (CH3) is a relatively neutral group, and it does not significantly enhance or reduce the reactivity of the phenyl ring in the same way electron-withdrawing groups do. This might explain why p-CH3-phenyl also shows weaker antifungal activity than the halogen-substituted compounds.

The electronic effect of the substituent groups play a vital role in modulating the interaction of compound with the fungal membrane and other cellular components. Electron-withdrawing groups like Cl (in p-Cl-phenyl) tend to increase the compound ability to disrupt the fungal membrane or interact with enzymes. p-OH-phenyl (12.5 µg/mL) is the most effective compound against Proteus mirabilis. The hydroxyl group (OH) enhances the compound reactivity, making it more potent against bacterial growth. Other notable compounds include p-Br-phenyl with MIC values of 25 µg/mL from 5b and 6d, p-OH-phenyl at 25 µg/mL from 5c, p-Cl-phenyl and p-CH3-phenyl show higher MIC values (50 µg/mL or 100 µg/mL), suggesting they are less potent against Proteus mirabilis. The hydroxyl group (OH) can also form hydrogen bonds, which might improve the compound's ability to interact with bacterial proteins, enzymes, or structural components. This could help the compound better penetrate the bacterial cell or disrupt cellular functions, increasing its effectiveness. Electron-Donating Groups (like OH in p-OH-phenyl) tend to increase the compounds ability to interact with bacterial enzymes, disrupt the cell membrane, and affect cell wall synthesis. The hydroxyl group increases the reactivity of the molecule, allowing it to bind more effectively to bacterial proteins or disrupt cellular functions. This is likely why p-OH-phenyl is the most effective compound, with the lowest MIC of 12.5 µg/mL. -I Groups (like Cl and Br) make the compound more electrophilic but less likely to donate electrons to interact with bacterial targets. This may explain why p-Cl-phenyl and p-Br-phenyl have slightly higher MIC values.

The compound p-Cl-phenyl at 12.5 µg/mL for Corynebacterium striatum shows the lowest MIC value overall, making it the most potent compound for this bacterium in the dataset. This suggests that p-Cl-phenyl is the most effective against C. striatum compared to the other compounds, as it can inhibit bacterial growth at a lower concentration. For Streptococcus pyogenes, no single compound stands out with consistently lower MIC values across the different substitutions, but p-Br-phenyl with an MIC of 25 seems to be one of the better

options compared to others like p-OH-phenyl and p-CH3-phenyl. The distinct electronic and

steric effects of the substituents on the phenyl ring are the cause of the reduced MIC values in some situations (such as for p-Cl-phenyl). Chlorine (p-Cl) may provide a combination of electron-withdrawing properties and molecular shape that optimizes the interaction with bacterial cell targets, increasing its effectiveness. In contrast, other substituents like methyl (p-CH3) or hydroxyl (p-OH) may not interact as strongly or may have less optimal effects on bacterial cells.



Acknowledgement:

The authors express their sincere thanks to the Faculty of Chemical Sciences, Shri Ramswroop Memorial University, Barabanki, for providing laboratory facilities. They are also thankful to the BBAU Lucknow Central University for the spectral data.

DECLARATIONS

FINDING

We did not receive any specific grant for this research from any funding agencies in the public, commercial, or not-for-profit sectors

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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