Research Article

Catalytic Synthesis of Novel N-(2H-chromen-3-yl)-phenylacetamide Derivatives and their Antibacterial Activity

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ABSTRACT

In this study is reported about a series of substituted phenylacetamide derivatives with coumarin moiety. Novel N-(2H-chromen-3-yl)-phenylacetamide derivatives 4(a-f) were synthesized by one pot catalytic reaction of 4-hydroxycoumarin 1, benzaldehyde analogues 2(a-f) and acetamide. Reactions are performed under reflux conditions using nano-Feo and nano-ZnO as surface catalysts. The structures of the synthesised compounds were established by FT-IR and NMR spectrometric data and their elemental analysis. Compounds of series 4(a-f) were screened for their antibacterial activity against S. aureus, E. coli and Klebsiella by Diffusion Disc Method. Antibacterial activity of the synthesized compounds was examined by measuring the zones of inhibition around the disks impregnated with the corresponding solutions in N, N-DMF concentration 2 mg/mL , 4 mg/mL and 6 mg/mL. The synthesized compounds exhibited considerable antibacterial activity. Also the impact of substitutions in antimicrobial activity is explored.

Keywords: Chromen-4-one, phenylacetamide, condensiation, zones of inhibition.

INTRODUCTION

Coumarins also known as benzopyran-2-ones are important class of heterocyclic compounds that have been found as ingredient of the plant world. Many such derivatives are well known for their biological activities[1,2] such as antimicrobial[3-5], antifungal[6] and antimalarial[7]. It was reported that a significant number of substituted benzopyran-2-ones showed anticoagulant, anti-HIV[8,9], sedative, analgesic and hepatoprotective activity[10-12]. It is indicative that many of naturally and synthetic coumarins have found widespread usage in pharmacies[13]. Novobiocin, chartesium and coumaromycin are potent antibiotics with benzopyrone moiety. Many of coumarins exhibited antioxidant[14-16] and antitumor activity[17]. On the other hand, acetamide derivatives also have great importance and demonstrate a wide range of antioxidant and anti-inflamatory activity[18]. Also some heterocyclic acetamide derivatives reported to have antimicrobial, analgesic and anti-inflamatory activity[19]. The biological activity is conditioned by their structure and the presence of different substituents on the benzopyrone ring indicates their impact on the type and potency of biological activity. Despite continuous efforts, the relationship between structure and biological activity of these derivatives, so far has not yet been sufficiently clarified. Extraordinary biologically importance of compounds with benzopyran-2-one moiety has generated a constant interest for their synthesis and research. In view of the considerable importance of these derivatives and in continuation of our previous studies[20-22], the present work is aimed at the design and synthesis of new phenylacetamide derivatives with benzopyran-2-one moiety which could serve as pharmaceutical products. Moreover the study includes testing of target compounds for their antibacterial activity against *S. Aureus*, *E. Coli* and *Klebsiella*.

MATERIALS AND METHODS

Synthesis reactions were conducted by refluxing under catalytic conditions. All the chemicals used in the synthesis were of analytical grade as commercial reagents of Aldrich Company. Reactions were monitored by TLC using Merck Kieselgel-60 (F-254) as the stationary phase and a mixture of benzene, toluene, glacial acetic acid (v/v/v, 85:10:5) as the mobile phase. The synthesized compounds were purified by crystallization from ethanol. Melting points were determined in a paraffin oil bath with open capillary tube. FT-IR spectra were recorded in KBr discs on Shimadzu 8400xFTIR spectrometer with 4 cm^{-1} resolution. ^{1}H-NMR and ^{13}C-NMR spectra were recorded in DMSO on UNITYplus-300"NMR 1" spectrometer and chemical shifts were reported in ppm downfield from TMS as an internal standard (δ0.00).

Screening of the antibacterial activity of the synthesized compounds was done on the basis of Standard Disc Method[24] using standard discs (d=5.0 mm, maximum capacity 10 pg). The experiments were carried out at three different concentrations and standard discs were previously impregnated with 2 mg/mL, 4 mg/mL and 6 mg/mL solutions of the compounds in N,N-DMF. The zones of inhibition are measured after incubation of target bacterial cultures for 48 hours.

Preparing of surface catalysts

Preparing of nano-ZnO (catalyst A)

Equimolar amount of Zinc acetate (9.1 g, 0.05 mol) and oxalic acid (5.4 g, 0.06 mol) are crushed in a porculan dish for 60 min. at room temperature. Obtained zinc acetate as micro-particles is stored in an electric oven and heated at 450 ^{o}C for 30 min. After cooling, nano-ZnO product (3.17 g, particle 20-36 nm) is obtained with 78.5% yield.

Preparing of ano-FeO (catalyst B)

A 500 mL round bottom flask containing 300 mL of N,N-DMF is heated at 140 ^{o}C, then 30 mL 0.1 M of $FeCl_3$ solution is added. The mixture is refluxed with stirring for 8 hours and after cooling the solid residue is separated on a centrifuge (4000 rpm for 30 min.). Remaining solvent is evaporated in vacuum (under 10 mmHg) at 80 ^{o}C, then the solid product is stored in an electric oven and heated at 450 ^{o}C for 30 min. and finally obtained nano-FeO (0.44g, yield= 61.7%) is stored in a glass flash.

Synthesis of N-substituted phenylacetamide (general procedure)

4-Hydroxycoumarin (3.24 g, 0.02 mol), equimolar amount of corresponding benzaldehyde (0.02 mol) and acetamide (1.2 g, 0.02 mol) are dissolved in 10 mL of ethanol, then nano FeO (0.22 g, 15 mol%, 0.003 mol) or nano ZnO (0.25 g, 15 mol%, 0.003 mol) is added as surface catalyst. The reaction mixture is stirred for 15 minutes at room temperature, and then refluxed at 110 ^{o}C for about 3 hours. Flowing of reaction is monitored with TLC. After cooling, the mixture is dissolved in ethanol and the catalyst is removed on a centrifuge. Crystallization from ethanol gave corresponding product of N-substituted phenylacetamide.

N-[(4-Hydroxy-2-oxo-2H-chromen-3-yl)-phenyl-methyl]-acetamide 4a; white crystalline product, mp=233-235 ^{o}C, yield (A;18.82 %, B; 8.5%), FT-IR (KBr disc, cm^{-1}): 3520, 3300-3000, 3075, 2960, 1690, 1600, 1270, 757. ^{1}H-NMR; (δ, ppm) 8.1 (s, 1H, N-H), 7.6-7.4 (m, 3H, Ar), 7.2-7.0 (m, 6H, Ar), 5.8 (1H, OH), 5.5 (s, 1H, C-H), 2.1 (s, 3H, CH_3). ^{13}C-NMR; (δ, ppm) 175.2 (C=O), 164.2 (C=O), 163.4, 153,3, 151.0, 144.2, 130.9, 130.5, 129.4, 128.6, 128.1, 126,9, 126.2, 94.0, 42.2 (C-H), 19.6 (CH_3).

N-[(4-Hydroxy-2-oxo-2H-chromen-3-yl)-(2-hydroxy-phenyl)-methyl]-acetamide 4b; white crystalline product, mp=143-146 ^{o}C, yield (A;59.85 %, B; 46.31%), FT-IR (KBr disc, cm^{-1}): 3420, 3350-3000, 3080, 2990, 1720, 1595, 1230, 785. ^{1}H-NMR; (δ, ppm) 8.0 (s, 1H, N-H), 7.6-7.2 (m, 4H, Ar), 6.8-6.6 (m, 4H, Ar), 5.7 (1H, OH), 5.6 (s, 1H, C-H), 4.9 (1H, OH, 2.0 (s, 3H, CH_3). ^{13}C-NMR; (δ, ppm) 176.7 (C=O), 163.9 (C=O), 158.5, 152.4, 156.4, 150.9, 142.6, 129.2, 128.8, 128.6, 128.5, 128.1, 126.9, 125.4, 116.6, 93.6, 34.3 (C-H), 20.4 (CH_3).

N-[(4-Hydroxy-2-oxo-2H-chromen-3-yl)-(3-nitrophenyl)-methyl]-acetamide 4c; yellow crystalline product, mp=215-217 ^{o}C, yield (A;21.18 %, B; 29.47%), FT-IR (KBr disc, cm^{-1}): 3520, 3360-3010, 3050, 2930, 1680, 1605, 1525, 1340, 1250, 755. ^{1}H-NMR; (δ, ppm) 8.1 (s, 1H, N-H), 7.9-7.8 (m, 2H, Ar), 7.4-7.0 (m, 6H, Ar), 5.9 (1H, OH), 5.7 (s, 1H, C-H), 2.2 (s, 3H, CH_3). ^{13}C-NMR; (δ, ppm) 174.3 (C=O), 165.6 (C=O), 156.8, 153.2, 151.7, 150.4, 149.7, 144.2, 128.2, 127.9, 127.5, 126.6, 124.6, 120.2, 115.8, 92.0, 30.9 (C-H), 22.5 (CH_3).

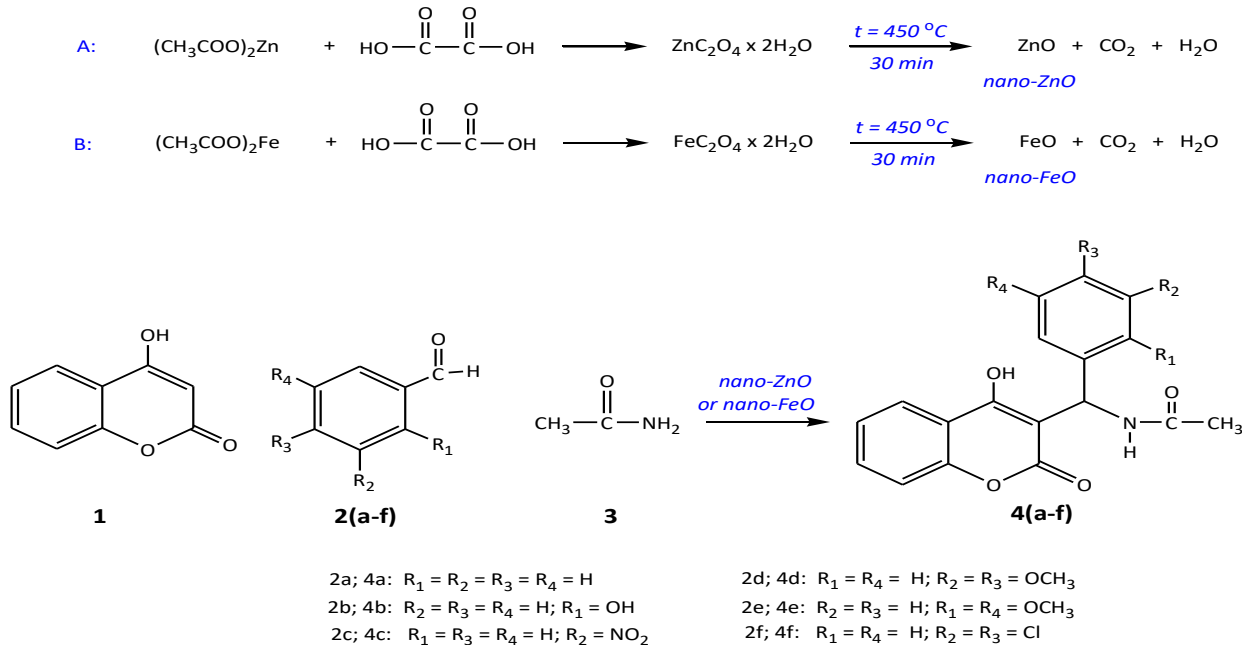
N-[(4-Hydroxy-2-oxo-2H-chromen-3-yl)-(3,4-dimethoxy-phenyl)-methyl]-acetamide 4d; pale yellow crystalline product, mp=174-176 ^{o}C, yield (A;36.78 %, B; 25.63%), FT-IR (KBr disc, cm^{-1}): 3525, 3380-3020, 3064, 2935, 1697, 1600, 1224, 771. ^{1}H-NMR; (δ, ppm) 8.0 (s, 1H, N-H), 7.6-7.3 (m, 4H, Ar), 6.7-6.4 (m, 3H, Ar), 5.8 (1H, OH), 5.6 (s, 1H, C-H), 3.8 (s, 6H, OCH_3), 2.1 (s, 3H, CH_3). ^{13}C-NMR; (δ, ppm) 170.8 (C=O), 163.5 (C=O), 162.4, 162.3, 151.7, 150.4, 149.7, 144.2, 128.2, 127.9, 127.5, 126.6, 124.6, 120.2, 115.8, 92.0, 58.5 (OCH_3), 40.8 (C-H), 20.8 (CH_3).

N-[(4-Hydroxy-2-oxo-2H-chromen-3-yl)-(2,5-dimethoxy-phenyl)-methyl]-acetamide 4e; yellow crystalline product, mp=186-189 ^{o}C, yield (A;51.24 %, B; 38.13%), FT-IR (KBr disc, cm^{-1}): 3576, 3390-3025, 3072, 2944, 1695, 1609, 1224, 766. ^{1}H-NMR; (δ, ppm) 8.2 (s, 1H, N-H), 7.6-7.4 (m, 4H, Ar), 6.6-6.4 (m, 3H, Ar), 5.9 (1H, OH), 5.5 (s, 1H, C-H), 3.7 (s, 6H, OCH_3), 2.0 (s, 3H, CH_3). ^{13}C-NMR; (δ, ppm) 172.6 (C=O), 164.7 (C=O), 163.0, 162.9, 153.4, 151.0, 149.2, 145.3, 129.7, 128.2, 127.7, 126.4, 123.6, 120.2, 115.8, 93.7, 56.5 (OCH_3), 32.4 (C-H), 22.2 (CH_3).

N-[(4-Hydroxy-2-oxo-2H-chromen-3-yl)-(3,4-dichloro-phenyl)-methyl]-acetamide 4f; yellow crystalline product, mp=206-208 ^{o}C, yield (A;42.65 %, B; 27.95%), FT-IR (KBr disc, cm^{-1}): 3615, 3420-3030, 3082, 2944, 1714, 1611, 1228, 759. 720. ^{1}H-NMR; (δ, ppm) 8.1 (s, 1H, N-H), 7.9-7.6 (m, 5H, Ar), 7.0-6.8 (m, 2H, Ar), 5.6 (1H, OH), 5.4 (s, 1H, C-H), 2.0 (s, 3H, CH_3). ^{13}C-NMR; (δ, ppm) 176.8 (C=O), 169.2 (C=O), 164.7, 163.6, 154.5, 152.8, 148.2, 143.3, 130.5, 129.2, 127.5, 126.8, 124.3, 121.8, 116.2, 94.4, 41.2 (C-H), 20.6 (CH_3).

RESULTS AND DISCISSION

By condensation reaction of 4-hydroxycoumarin 1 with benzaldehyde analogues 2(a-f), in presence of acetaldehyde, corresponding N-[(4-Hydroxy-2-oxo-2H-chromen-3-yl)-phenyl-methyl]-acetamides 4(a-f) are synthesized in moderate and good yield. Corresponding heteroaryl-acetamides are synthesized by one pot condensation reaction under catalytic conditions using nano-ZnO and nano-FeO surface catalysts. Synthesis of substituted N-[(chromen-3-yl)-phenyl-methyl]-acetamides are summarized in scheme 1.



Scheme 1

Structural characterization of the synthesized products is based on spectrometric IR and NMR data. The IR spectrum of compound 4a showed an absorption signal at 3520 cm^{-1} confirming the presence of NH group. The absorption signal at 3300-3000 cm^{-1} appears due to ν(OH) stretching vibrations while the absorption at 3075 cm^{-1} due to aromatic ν(CH) stretching vibrations. The absorption signal at 2960 cm^{-1} correspond to ν(CH) stretching vibrations of methyl group. The sharp peak at 1690 cm^{-1} is responsible for ν(C=O) stretching vibrations, whereas the absorption peak at 1600 cm^{-1} results from aromatic ν(C=C) stretching vibrations. On the other hand, the peak at 1270 cm^{-1} results due to lactonic ν(C-O-C) stretching mode, while the sharp peak at 757 cm^{-1} results from characteristic aromatic δ(C-H) oop bending vibrations. In the ^{1}H-NMR spectrum of 4a, two multiplets of aromatic protons appeared at 7.6-7.4 and 7.2-7.0 ppm, while a proton singlet resulting from N-H is appeared at 8.1 ppm. Proton singlets at 5.5 ppm correspond to C-H proton, whereas a three-proton singlet due to CH_3 group appears at 2.1 pp. In the ^{13}C-NMR spectrum two signals at 175.2 and 164.2 ppm result from C=O carbons, while at 42.2 and 19.6 ppm appears corresponding signals for CH and CH_3.

The IR spectrum of compound 4b, show a signal at 3420 cm^{-1} and a broad absorption at 3350-3000 cm^{-1} responsible for ν(NH) and ν(OH) stretching vibrations, a peak at 3080 cm^{-1} for aromatic ν(CH) stretching, while the absorption peak at 2990 cm^{-1} due to methyl ν(CH) stretching vibrations also is appeared. The sharp peak at 1720 cm^{-1} results from ν(C=O) stretching vibrations, whereas the peak at 1595 cm^{-1} correspond to aromatic ν(C=C) stretching vibrations. A signal at 1230 cm^{-1} is characteristic for stretching vibrations of lactonic (C-O-C) system and the sharp peak at 785 cm^{-1} result from aromatic δ(C-H) bending oop vibrations. In the ^{1}H-NMR spectrum of 4b, beside multiplets of aromatic protons, a proton singlet resulting from N-H appears at 8.0 ppm. A proton singlet at 5.6 ppm corresponds to C-H proton, while a three-proton singlet due to CH_3 group appears at 2.0 ppm. In the ^{13}C-NMR spectrum, characteristic signals of C=O carbons showed at 176.7 and 163.9 ppm, whereas corresponding signals for CH and CH_3 appeared at 34.3 and 20.4 ppm. Two signals at 176.7 and 163.9 ppm displayed due to C=O carbons, whereas two another singlets at 34.3 and 20.4 ppm correspond to CH and CH_3 group.

The IR spectra of compound 4c show a broad absorption peak at 3360-3010 cm^{-1} which is responsible for ν(OH) stretching vibrations and a peak at 3520 cm^{-1} due to ν(NH) stretching vibrations, while the signals at 3050 and 2930 cm^{-1} appear due to aromatic and methyl ν(CH) stretching vibrations. The peak at 1680 cm^{-1} is responsible for absorbing the ν(C=O) stretching vibrations while a signal at 1605 cm^{-1} results from aromatic ν(C=C) stretching vibrations. The sharp peak at 1525 cm^{-1} results from ν(NO_2) asymmetric stretching vibrations, while absorption signal at 1340 cm^{-1} reflects ν(NO_2) symmetric stretching vibrations. The mode at 1250 cm^{-1} is characteristic for lactonic (C-O-C) stretching vibrations, while the sharp peak at 755 cm^{-1} appears from aromatic δ(C-H) bending oop vibrations. On the other hand, in the ^{1}H-NMR spectrum of 4c displayed the multiplet signals of aromatic protons at 7.9-7.8 and 7.4-7.0 ppm. A proton singlet resulting from N-H at 8.4 ppm and two singlets at 5.7 and 2.2 ppm due to CH and CH_3 displayed as well. In the ^{13}C-NMR spectra, two signals at 174.3 and 165.6 ppm, that correspond to C=O and another signals at 30.9 and 22.5 ppm resulting from CH and CH_3 are appeared.

Table 1: Physical properties of compounds 4(a-f) and their elemental analysis

Nr	Molecular formulas	Molecular Mass	Elemental analysis (%), calc / found	mp/ °C	Yield (%) (A)	Yield (%) (B)
4a	$C_{18}H_{15}NO_4$	309.12	(C-69.87; H-4.89; N-4.53; O-20.70) (C-69.83; H-4.91; N-4.49)	233-235	18.82	8.50
4b	$C_{18}H_{15}NO_5$	325.12	(C-66.44; H-4.65; N-4.31; O-24.61) (C-66.41; H-4.66; N-4.28)	143-146	59.85	46.81
4c	$C_{18}H_{14}N_2O_6$	354.11	(C-60.99; H-3.98; N-7.91; O-27.11) (C-60.96; H-4.00; N-7.88)	215-217	21.18	29.47
4d	$C_{20}H_{19}NO_6$	369.15	(C-65.01; H-5.19; N-3.79; O-26.01) (C-64.98; H-5.16; N-3.81)	174-176	36.78	25.63
4e	$C_{20}H_{19}NO_6$	369.15	(C-65.01; H-5.19; N-3.79; O-26.01) (C-64.97; H-5.18; N-3.76)	186-189	51.24	38.13
4f	$C_{18}H_{13}NO_4Cl_2$	378.10	(C-57.13; H-3.46; N-3.70; O-16.93; Cl-18.78) (C-57.09; H-3.44; N-3.67; Cl-18.76)	206-208	42.65	27.95

In the IR spectra of the compound 4d, an absorption peak displayed at 3525 cm^{-1} due to ν(NH) and a broad absorption signal appears at 3380-3020 cm^{-1} responsible for ν(OH) stretching vibrations whereas two absorption peaks at 3064 and 2935 cm^{-1} correspond to aromatic and methyl ν(CH) vibrations. A sharp peak at 1697 cm^{-1} corresponds to ν(C=O) stretching vibrations, while the absorption signal at 1600 cm^{-1} results from aromatic ν(C=C) stretching vibrations. The absorption peak at 1224 cm^{-1} corresponds to lactonic ν(C-O-C) stretching vibrations, whereas at 771 cm^{-1} due to aromatic δ (CH) oop vibrations. The ^{1}H-NMR spectra of 4d, a proton singlet at 8.0 ppm results from N-H, while two multiplets at 7.6-7.3 and 6.7-6.4 ppm appear due to aromatic protons. A six-proton singlet at 3.8 ppm displayed from OCH_3 protons, while singlets for CH and CH_3 protons appeared at 5.6 and 2.1 ppm. The ^{13}C-NMR spectra exhibited two signals at 170.8 and 163.5 ppm due to C=O carbons, while signals at 58.5, 40.8 and 20.8 ppm appear due to OCH_3, CH and CH_3 carbons.

In the IR spectra of compound 4e, the peak at 3576 cm^{-1} resulted from ν(NH) stretching vibrations and a broad absorption signal at 3390-3025 cm^{-1} which is responsible for ν(OH) stretching vibrations also appeared. The absorption signal at 3072 cm^{-1} correspond to aromatic ν(CH) stretching vibrations and the peak at 2944 cm^{-1} results from methyl ν(CH) stretching vibrations. The intensive sharp peak at 1695 cm^{-1} correspond to ν(C=O) stretching vibrations, while the characteristic peak at 1609 cm^{-1} resulted from ν(C=C) stretching vibrations of aromatic moiety. A signal at 1224 cm^{-1} results from lactonic ν(C-O-C) vibrations, while the sharp peak at 766 cm^{-1} is characteristic for δ(CH) oop bending vibrations. In the ^{1}H-NMR spectra of 4e are shown a singlet at 8.2 ppm due to N-H proton and multiplets of aromatic protons at 7.6-7.4 and 6.6-6.4 ppm. Three singlets at 5.5, 3.7 and 2.0 ppm displayed from CH, OCH_3 and CH_3 protons.

IR spectrum of compound 4f exhibit the absorption signal at 3615 cm^{-1} responsible for ν(NH), a broad absorption at 3420-3030 cm^{-1} due to ν(OH) stretching vibrations and a signal at 3082 cm^{-1} resulted from aromatic ν(CH) stretching vibrations. The peak at 2944 cm^{-1} results from the absorptions of methyl stretching vibrations, while the signal at 1714 cm^{-1} reflects the ν(C=O) stretching vibrations. The peak at 1611 cm^{-1} displayed due to ν(C=O) stretching mode, signals at 1228 and 720 cm^{-1} are characteristic for lactonic ν(C-O-C) and ν(C-Cl) stretching vibrations, while the sharp peak at 759 cm^{-1} is characteristic for aromatic δ(C-H) oop bending vibrations. In the ^{1}H-NMR spectra of 4f, a proton singlet at 8.1 ppm results from N-H, whereas two multiplets at 7.9-7.6 and 7.0-6.8 ppm displayed due to aromatic protons. A singlet at 5.4 ppm displayed from CH protons, while the singlet CH_3 protons appeared at 2.0 ppm. The ^{13}C-NMR spectra exhibited two signals at 176.8 and 169.2 ppm due to C=O carbons, while signals at 40.8 and 20.8 ppm appear due to CH and CH_3 carbons. In the ^{13}C-NMR spectrum, characteristic signals of C=O carbons showed at 176.8 and 169.2 ppm, whereas signals resulting from CH and CH_3 appeared at 41.2 and 20.6 ppm.

Antibacterial activity of the compounds 4(a-f)

Following this study, compounds 4 (a-f) are screened for their antibacterial activity. Our research is oriented to test the activity against bacteria *S. aureus*, *E. coli* and *Klebsiella*, on the basis of Standard Disc Method[23], by measuring the zones of inhibition. The discs have previously been impregnated with solutions of the compounds in N, N-DMF with respective concentrations of 2 mg mL^{-1}, 4 mg mL^{-1} and 6 mg mL^{-1}. Incubation of target bacterial cultures has done for 48 hours. Results expressed in mm are summarized in fig. 1, 2 and 3.

Compounds of series 4 show significant antimicrobial activity against these microorganisms. Compounds 4f and 4b were most active against *S. aureus*, compounds 4f and 4c show the most activity against *E. Coli* whereas 4d and 4e were more active against *Klebsiella*.

Antibacterial activity against *E. Coli* and *Klebsiella* shown as bactericide activity is displayed in a moderate range. Furthermore, these compounds express both bacteriostatic and bactericide activity against *S. Aureus*. Bacteriostatic activity is exhibited in large range (+2.5 mm), whereas bactericide activity showed smaller zones of inhibition. Benzopyran-2-one moiety showed considerable impact on antimicrobial activity. Likewise, the impact of polar hydroxy, chloro, methoxy and nitro groups is distinctive. It is particularly noted the impact of the chloro group affected the increasing of antibacterial activity against *S. aureus* and *Klebsiella*. The impact of the hydroxy group of 4b, which has affected the increase of antibacterial activity against S. aureus has been particularly noted. Moreover, nitro group of 4b has shown significant impact on the range of inhibition of *E. coli*. The impact of ethoxy group of 4d and 4e also has been noted.

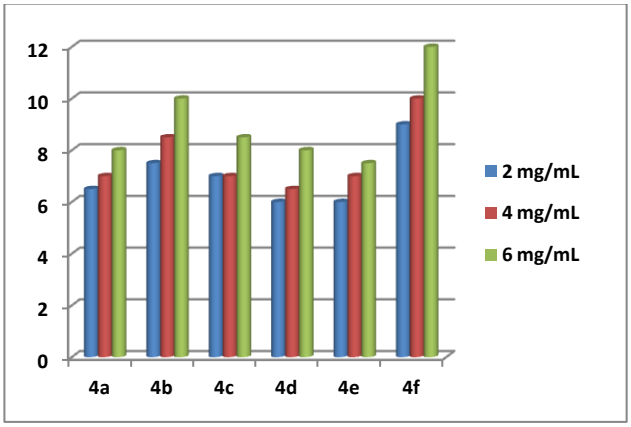


Figure 1: Graphical presentation of zones of inhibition (mm) against *S. aureus*

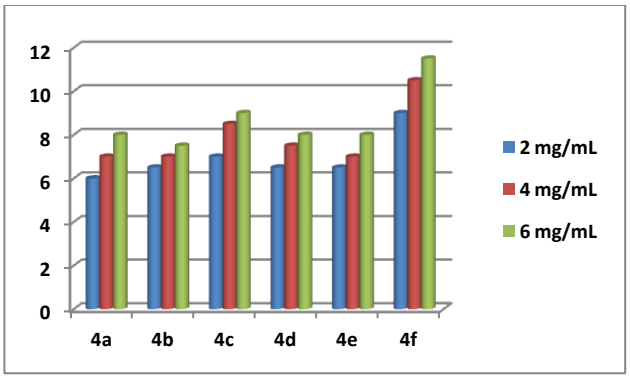


Figure 2: Graphical presentation of zones of inhibition (mm) against *E. coli*

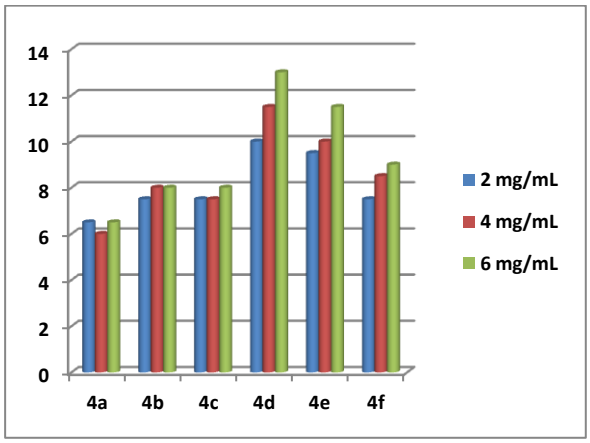


Figure 3: Graphical presentation of zones of inhibition (mm)) against *Klebsiella*

It has been assumed that antibacterial activity may result as a consequence of the involvement of these compounds in enzymatic reactions. The synthesized compounds may cause enzymatic inhibition cell wall construction of the microorganisms. However, the mechanism of enzymatic inhibition has not been fully studied yet. In general, by increasing the concentration of solvents, their antimicrobial activity is ncreased.

CONCLUSIONS

Novel derivatives of N-(2H-chromen-3-yl)-phenylacetamide 4(a-f) are synthesized in the moderate and high yield under catalytic conditions using nano-ZnO and nano-FeO as surface catalyst. It was assumpted that nano-ZnO was more active surface catalyst. It has been concluded that compounds 4f and 4b show significant activity against *S. aureus,* compounds 4f and 4c display more activity against *E. Coli*, whereas 4d and 4e were more active against *Klebsiella* bacteria. The impact of polar groups in antibacterial activity was significant. Antibacterial activity is shown to be proportional to the concentration of these compounds.

REFERENCES

1. Mohamed HM, Abd El-Wahab AHF, Ahmed K A, El-Agrody AM, Bedair AH, Eid FA, Khafagy MM, (2012), Synthesis, Reactions and Antimicrobial Activities of 8-Ethoxycoumarin Derivatives, Molecules, 17, 971-988.

2. http://www.mdpi.com/1420-3049/17/1/971

3. Rajasekaran S, Rao GK, Pai S, Rajan A, (2011), Design, synthesis, antibacterial and in vitro antioxidant activity of substituted 2H-benzopyran-2-one derivatives, International Journal of ChemTech Research, 3, 2, 555-559. http://sphinxsai.com/vol3.no2/chem/chempdf/CT=06%28555-559%29AJ11.pdf

4. Desai NC, Satodiya HM, Rajpara KM, Joshi VV, Vaghani HV, (2013), Microwave assisted synthesis of new coumarin based 3-cyanopyridine scaffolds bearing sulfonamide group having antimicrobial activity, Indian Journal of Chemistry, B 52B. http://nopr.niscair.res.in/bitstream/123456789/19640/1/IJCB%2052B%287%29%20904-914.pdf

5. Rehman S, Ikram M, Baker RJ, Zubair M, Azad E, Min S, Riaz K, Mok KH, Rehman S, (2013), Synthesis, characterization, in vitro antimicrobial, and U2OS tumoricidal activities of different

coumarin derivatives, Chemistry Central Journal, 7, 68. http://ccj.springeropen.com/articles/10.1186/1752-153X-7-68

6. Mayekar SA, Mulwad VV, (2008), Synthesis and antibacterial activity of 6-(5phenyl- {1,3,4}thiadiazol-2-ylimino)-benzopyran-2-ones. Indian J. Chem. 47 (B) (2008) 1438–1442. http://nopr.niscair.res.in/bitstream/123456789/2006/1/IJCB%2047%289%29%201438-1442.pdf

7. Araújo RS, Guerra FQ, O Lima E, Simone CA, Tavares JF, Scotti L, Scotti MT, Aquino TM, Moura RO, Mendonça FJ, Barbosa-Filho JM (2013). Synthesis, Structure-Activity Relationships (SAR) and in Silico Studies of Coumarin Derivatives with Antifungal Activity, Int J Mol Sci. 10, 14(1), 1293-309. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3565321/

8. Sashidhara KV, Kumar A, Dodda RP, Krishna NN, Agarwal P, Srivastava K, Puri SK, (2012), Coumarin-trioxane hybrids: synthesis and evaluation as a new class of antimalarial scaffolds, Bioorg Med Chem Lett. 15, 22(12), 3926-30. http://www.ncbi.nlm.nih.gov/pubmed/22607674

9. Carbone RA, Chimirri A, De Clercq E, Monforte AM, Monforte P, Pannecouque C, Zappala M, (2002), Synthesis and anti-HIV activity of 2,3-diaryl-1,3-thiazolidin-4-(thi)one derivatives, Farmaco. 2002 Sep, 57(9):747-51. http://www.ncbi.nlm.nih.gov/pubmed/12385525

10. Yu D, Suzuki M, Xie L, Natschke SL, Lee KH, (2003), Recent progress in the development of coumarin derivatives as potent anti-HIV agents. Med. Res. Reiv. 23, 322–345. http://www.ncbi.nlm.nih.gov/pubmed/12647313

11. Ahmed B, Khan SA, Alam T. (2003), Synthesis and antihepatotoxic activity of some heterocyclic compounds containing the 1, 4-dioxane ring system. Pharmazie. Mar, 58(3), 173-6.

12. http://www.ncbi.nlm.nih.gov/pubmed/12685811

13. Okamoto T, Kobayashi T, Yoshida S, (2007), Synthetic Derivatives of Osthole for the Prevention of Hepatitis, Medicinal Chemistry, 3, 35-44. https://www.researchgate.net/publication/6537198_Synthetic_Derivatives_of_Osthole_for_the_Prevention_of_Hepatitis

14. Atmaca M, Bilgin HM, Obay BD, Diken H, Kelle M, Kale E, (2011). The hepatoprotective effect of coumarin and coumarin derivates on carbon tetrachloride-induced hepatic injury by antioxidative activities in rats. J. Physiol. Biochem., 67, 569-576. http://www.ncbi.nlm.nih.gov/pubmed/21656273

15. Rajasekaran S, Rao GK, Pai S, Rajan A, (2011), Design, synthesis, antibacterial and in vitro antioxidant activity of substituted 2H-benzopyran-2-one derivatives, International Journal of ChemTech Research, 3, 2, 555-559. http://sphinxsai.com/vol3.no2/chem/chempdf/CT=06%28555-559%29AJ11.pdf

16. Tyagi YK, Kumar A, Raj HG, Vohra P, Gupta G, Gupta RK, (2005), Synthesis of novel amino and acetyl amino-4-methylcoumarins and evaluation of their antioxidant activity. Eur. J. Med. Chem. 40, 413–420. http://www.freepaperdownload.us/1748/Article6425150.htm

17. Osman H, Arshad A, Lam CK, Bagley MC, (2012), Microwave-assisted synthesis and antioxidant properties of hydrazinyl thiazolyl coumarin derivatives, Chemistry Central Journal, 6:32. http://ccj.springeropen.com/articles/10.1186/1752-153X-6-32

18. Rodriguez SV, Guinez RF, Matos MJ, Santana L, Uriarte E, Lapier M, Maya JD, Azar CO, (2013), Synthesis of coumarin–chalcone hybrids and evaluation of their antioxidant and trypanocidal properties, Med. Chem. Commun., 4, 993-1000. http://pubs.rsc.org/en/Content/ArticleLanding/2013/MD/c3md00025g#!divAbstract

19. Nawrot-Modranka J, Nawrot E, Graczik J, (2006), In vivo antitumor, in vitro anti- bacterial activity and alkylating properties of phosphorohydrazine derivatives of coumarin and chromone. Eur. J. Med. Chem. 41 1301–1309. https://www.researchgate.net/publication/6882253_In_vivo_Antitumor_in_vitro_Antibacterial_Activity_and_Alkylating_Properties_of_Phosphorohydrazine_Derivatives_of_Coumarin_and_Chromone

20. Autore G, Caruso A, Marzocco S, Nicolaus B, Palladino C, Pinto A, Popolo A, Sinicropi MS, Tommonaro G, Saturnino C, Acetamide Derivatives with Antioxidant Activity and Potential Anti-Inflammatory Activity, Molecules 2010, 15, 2028-2038; https://www.google.com/search?source=hp&q=acetamide+derivatives+activity&oq=acetamide+derivatives+activity&gs_l=psy-ab.3...1051.18192.0.19281.40.38.2.0.0.0.134.3540.32j6.38.0....0...1.1.64.psy-ab..0.39.3462...0j0i131k1j0i131i46k1j46i131k1j0i22i30k1j33i160k1j33i21k1.0.G9aU5zgNCbI doi:10.3390/molecules15032028

21. Nayak PS, Narayana B, Sarojini BK, Hegde K, Shashidhara KS, Design and synthesis of novel heterocyclic acetamide derivatives for potential analgesic, anti-inflammatory, and antimicrobial activities, Medicinal Chemistry Research, September 2014, Volume 23, Issue 9, pp 4280–4294, https://link.springer.com/article/10.1007/s00044-014-1003-3

22. Hoti R, Nura-Lama A, Mulliqi-Osmani G, Troni N, Gashi F, Ismaili H,Thaci V, (2014), Synthesis of 4-Triazolylamino- and 4-Benzothiazolylamino-3- nitro-2H-[1]-Benzopyran-2-ones and their Antimicrobial Activity, Orbital:The Electronic Journal of Chemistry, 6(3), 184-190. http://www.orbital.ufms.br/index.php/Chemistry/article/view/564/pdf

23. Hoti R, Tron, N, Nura-Lama A, Mulliqi-Osmani G, Ismaili H, Thaci V, (2017), Novel [(3-nitro-2-oxo-2h-chromen-4-ylamino)-phenyl]phenyl-azetidin-2-ones and their antimicrobial activity, Eur. Chem. Bull., 6(2), 83-88. http://eurchembull.com/index.php/ECB/article/view/1961/pdf_75

24. Hoti R, Troni N, Ismaili H, Mullqi-Osmani G, Thaci V, (2017), Novel Heteroarylamino-chromen-2-ones and Their Antibacterial Activity, Chemistry, Bulgarian Journal of Science Education, 26 (4), 605-614. http://khimiya.org/show_issue.php?y=2017&vol=26&issue=4&i_id=68

25. Bauer AW, Kirby AW, Sherris, J.C. &Turck, M. (1966). Antibiotic susceptibility testing by standardized single disc method. Amer. J. Clin. Path., 44, 493-496.

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