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Synthesis, Biological Evaluation of Novel Coumarin-Piprazine Derivatives

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Abstract: We report on the synthesis of new coumarin coupled with piprazine derivatives at position 4. The proposed structures were confirmed by spectral studies (IR, MS, ^{1}H NMR and ^{13}C NMR). All the synthesized compounds was screened for antimicrobial and antioxidant activities. The results indicated that 2-(4-(2-(2-oxo-2H- chromen-4-yloxy)acetyl)piperazin-1-yl)acetamide (**5h**) has the potential antimicrobial as well as antioxidant activity.
Keywords: coumarin, piprazine, antimicrobial, and antioxidant.

Introduction

Coumarin and its derivatives represent one of the most active classes of compound possessing a wide spectrum of biological activity[1-4]. Many of these compounds have proven to be active as antibacterial[5-7].antifungal[8], anti-inflammatery[9], anticoagulant [10]. Anti-HIV[11] and antitumor agents[12]. Coumarins are widely used as additives in food , perfumes, cosmetics[13], pharmaceuticals and optical brightners[14] and would dispersed fluorescent and laser dyes[15]. Coumarins also have the super thermal stability and outstanding optical properties including extended spectral response, high quantum yields and superior photo stability.Optical applications of these compounds such as laser dyes, nonlinear optical chromophors, fluorescent whiteners, flurescent probes, polymer science, optical recording and solar energy collectors have been widely investigated[16-26]. Among the coumarins 4-hydroxy coumarin and its derivatives have been effectively used as anticoagulants for the treatment of disorders in which there is excessive or undesirable cloterting, such as thrombophlebities[27], pulmonary embolism[28] and certain cardiac conditions[29].Several comparative pharmacological investigations of the 4-hydroxy coumarin derivatives have shown it to have good anticoagulant activity combined with low side effects and little toxicity[30]. Antioxidant possess the ablity to protect the cellular organcells from damage caused by free radicals induced oxidative stress . Free radicals used include hydroxyl radical, superoxide anion radical and hydrogen peroxide. Highly reactive free radicals which are formed by exogenous chemicals, stress or in the food system are capable of oxidizing biomolecules, resulting in cancer, coronary heart disease and hypertension[31]. Generally, most of the free radicals generated from metabolism are scavenged by endogenous defense system such as catalase, superoxide dismutase and peroxide-glutathione system[32].

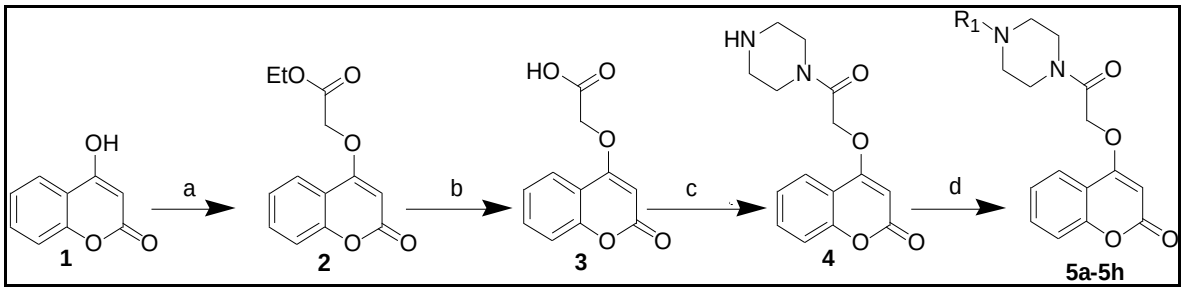
Experimental section

All chemicals and reagents are used in the current study were commercial grade. The IR spectra were obtained on a Nicolet 6700 FT-IR spectrometer. IR spectra obtained in transition mode from samples in KBr

pellets in the range of 400-4000 and the values expressed in cm^{-1}. NMR spectra were recorded on bruker both ^{1}H NMR and ^{13}C NMR werr determined in $CDCL_3$ or DMSO-d_6 solution by using 400 and 100 MHz spectrometers. Respective proton chemical shifts (δ) are relative to tetramethylsilane (TMS, δ= 0.00) as internal standard and expressed in ppm. Spin multiplicities are given as s (singlet), d (doublet). T (triplet),m (multiplet). Melting ponts were determined using melting point apparatus and are uncorrected. Mass spectra were recorded on EIMS (shimadzu) and ESI-esquire 300 Bruker Daltonics instrument. The purity of the compounds was checked by HPLC. The progress of all reactions was monitored by TLC on 2 × 5 cm pre-coated silica gel 60F 254 plates of thickness of 0.25 mm (Merck).

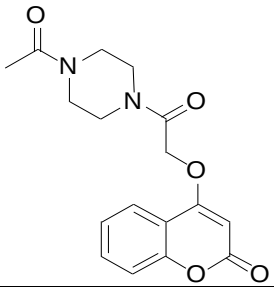
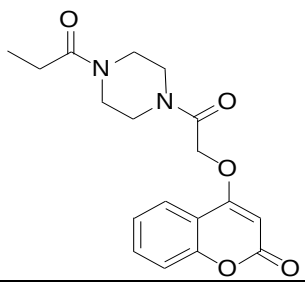
Chemistry

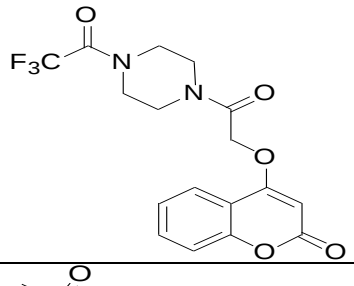
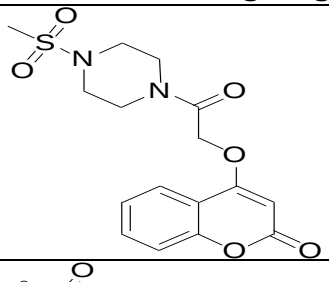
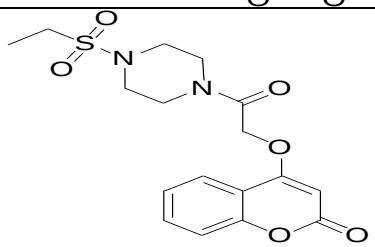
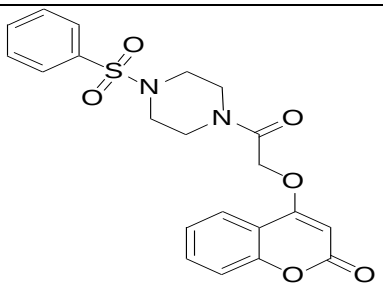
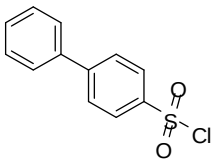
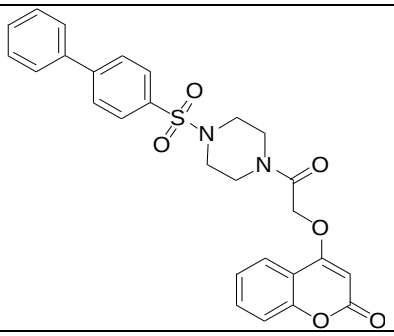
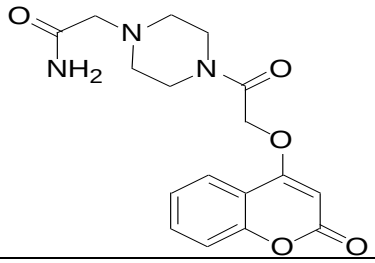
Coumarins are a class of compounds found widely in nature, they show a broad spectrum of activities and are frequently associated with low toxicity[33] and they can be considered as a privileged scaffold and an ideal framework for the design of compounds that can interact with different targets as their inherent affinity for several biological targets[34] Like ensaculine, one kind of AChE inhibitors, a coumarin derivative containing piprazine ring can affect some cellular functions potently and selectively[35-44]. Since piprazines and its derivatives are important pharmacophores, they are effective ingredients in many marketed drugs like olaparib[45,46.] These results prompted us to synthesize new derivatives of coumarins with a piprazine skeleton for the sake of finding new potential antimicrobial agents as well as total antioxidant activity. Based on these things mentioned above, we synthesized a series of novel coumarins-piprazine derivatives (**5a-h**)and its described in scheme **1**. Structures of the synthesized compounds 5a-5h are presented in table **1.**



Scheme 1: (a) BrCH2COOEt, K2CO3, DMF, 50-60°C (b) LiOH, THF, H2O, 0°C-RT(c) piperazine, EDCI, HOBt, DIPEA, DMF, 25-30°C (d) R_1Cl, TEA, DCM, 0°-5°C.

Table :1

S. NO	ENTRY	R_1Cl	Product	MELTING POINT
1	5a	CH3COCl		196-198°C
2	5b	CH_3CH_2 COCl		202-204°C

3	5c	CF_3COCl		190-193°C
4	5d	CH_3SO_2Cl		242-245°C
5	5e	$CH_3CH_2SO_2Cl$		236-238°C
6	5f			186-188°C
7	5g			210-213°C
8	5h	ICH_2CONH_2		246-248°C

Procedure for synthesis of Ethyl 2-(2-oxo-2H-chromen-4-yloxy)acetate (2)

Ethyl bromoacetate (1.2 mol eq) was added to a solution of 4-hydroxycoumarin 1 (1.0 mol eq.), potassium carbonate (1.5 mol eq) in DMF (10 mL) and heated to 50-60 ^{o}C for 4 hrs. The progress of the

reaction was monitored by TLC (Mobile phase Ethyl acetate/hexane). After completion of reaction, the mixture was poured into the ice-cold water, filtered and dried under vacuum to obtain 2 as a white solid.

White solid; Yield 84%; mp 100-103^{o}C; Purity by HPLC 98%; IR (KBr, cm^{-1}): 3079 (C-H, aromatic), 2988 (C-H, aliphatic), 1716 (C=O, lactone), 1704 (C=O, ester), 1622 (C=C, alkene); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.82-7.84 (d, 1H), 7.58-7.55 (t, 1H), 7.34-7.29 (m, 2H), 5.68 (s, 1H), 4.57-4.54 (t, 2H), 4.34-4.31 (t, 2H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 168.57, 164.35, 161.5, 152.8, 132.9, 124.37, 122.9, 116.5, 115.0, 91.3, 65.52, 54.7 ; EI-MS: m/z 249.0 (M+1, 100%).

Procedure for the synthesis of 2-(2-Oxo-2H-chromen-4-yloxy)acetic acid (3)

Solution of lithium hydroxide (1.2 mol eq.) in water (2 mL) was added to ethyl 2-(2-oxo-2H-chromen-4-yloxy)acetate **2** (1.0 mol eq.) in THF (5mL) at 0°C and stirred at 0 °C for 1 hours. Completion of the reaction was confirmed by TLC (Mobile phase Ethyl acetate /hexane) and THF was distilled off in Rota vapor. The obtained solution was washed with ethyl acetate (20 mL). The aqueous layer was acidified with 2N HCl (pH 1.0-2.0) and the obtained solid was filtered, washed with hexane and dried under vacuum to give **3** as a white solid.

White solid; Yield 78%; mp 227-230 ^{o}C; Purity by HPLC 99%, IR (KBr, cm^{1}); 3080 (C-H, aromatic), 2926 (C-H,aliphatic),1770 (C=O, lactone), 1720 (C=O, acid), 1629 (C=C, alkene); ^{1}H NMR (400 MHz, DMSO): δ_H 7.81-7.79 (d, 1H), 7.63-7.61 (d, 1H), 7.37-7.35 (d, 2H), 5.86 (s, 1H), 4.92 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 168.57, 164.3, 161.5, 152.8.0, 132.97, 122.9, 116.5, 115.0,91.37, 65.52 ; EI-MS: m/z 221.0 (M+1, 100%).

Procedure for the synthesis of 4-(2-(piprazine-1-yl)ethoxy)-2H-chromen-2-one (4)

A mixture of 2-(2-Oxo-2H-chromen-4-yloxy)acetic acid **3**(1.0 Eq), EDCI(1.2 Eq) and HOBt(1.0 Eq) were taken in DMF(5mL) strirred at RT. To this piprazine (1.0 Eq) was charged to the reaction mass at0-5 ^{OC} then followed by addition of DIPEA (3.2 Eq). The reaction mixture was stirred at 25-30^{o}C for 8 hours. Completion of the reaction was monitored by TLC then the reaction mixture was poured into the ice. Solid formed and it was filtered, washed with hexane, dried under vacuum gave **4** as brown solid.

Brown solid, mp 192-195 °C, yield 84%, purity by HPLC 99.4%. IR (KBr, cm^{-1}): 3070 (C-H, aromatic), 2962 (C-H, aliphatic), 1716 (C=O, lactone), 1669 (C=O, amide), 1624 (C=C, alkene); ^{1}H NMR (400 MHz, $CDCl_3$):δ_H 7.87-5.68 (m, 5H), 4.89 (s, 2H), 3.65-3.49 (t, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 164.8,163.9, 162.5, 153.5, 132.9, 124.3, 123.1, 117.0, 115.3, 91.7, ,80.8, 67.0, 45.0, 42.12); EI-MS: m/z 289.1 $[M+H]^{+}$, 100%).

General procedure for the synthesis of 5a-5h

To a solution of 4-(2-(piperazine-1-yl)ethoxy)-2H-chromen-2-one **(4**) (1.0Eq) in DCM were added triethylamine (2.0 Eq) at 0-5°C.Then the acid chlorides or trifluoroacetic anhydride or corresponding sulphonyl chloride or iodoacetamide (1.5 Eq) was added at 0-5°C. The reaction was stirred at same temperature for 1 hr. Reactin completion was monitored by TLC then the reaction mixture was diluted with DCM and water (10 mL) separated organic layer and its washed with brine solution. Organic layer was dried over anhydrous sodium sulphate and filtered and it was evaporated under reduced pressure obtained Solid. Washed with hexane, dried under vaccum to obtain **5a-5h.**

4-(2-(4-acetylpiperazin-1-yl)-2-oxoethoxy)-2H-chromen-2-one (**5a**)

Brown solid; mp 196-198°C; Yield 91%, Purity by HPLC 99.1%; IR (KBr, cm^{-1}): 3070 (C-H, aromatic), 2962 (C-H, aliphatic), 1716 (C=O, lactone), 1669 (C=O, amide), 1624 (C=C, alkene); ^{1}H NMR (400 MHz, $CDCl_3$):δ_H 7.87-7.85 (d, 1H), 7.58 (m, 1H), 7.35-7.30 (m, 2H), 5.6 (s, 1H), 4.8 (s, 2H), 3.6 (s, 2H), 3.4 (s, 6H),2.3(s,3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 164.9, 163.7, 162.5, 153.4, 132.8, 124.3, 123.1, 117.2, 115.1, 91.8, 80.6, 67.2, 45.4, 42.2, 20.8; EI-MS: m/z 331 (M+1), 100%).

4-(2-oxo-2-(4-propionylpiprazin-1-yl)ethoxy)-2H-chromen-2-one (5b)

Pale brown solid; mp 202-204°C; Yield 88%, Purity by HPLC 99.6%; IR (KBr, cm^{-1}): 3078 (C-H, aromatic), 2960 (C-H, aliphatic), 1714 (C=O, lactone), 1668 (C=O, amide), 1620 (C=C, alkene); ^{1}H NMR (400 MHz, $CDCl_3$):δ_H 7.86-7.84 (d, 1H), 7.56 (m, 1H), 7.34-7.31(m, 2H), 5.6 (s, 1H), 4.7 (s, 2H), 3.6 (s, 2H), 3.4 (s,

6H), 2.2 (s, 2H)1.1 (t, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 164.8, 163.9, 162.5, 153.5, 132.9, 124.3, 123.1, 117.0, 115.3, 91.7, 80.8, 67.0, 45.0, 42.12, 26.2, 10.1; EI-MS: m/z 345 (M+1, 100%)

4-(2-oxo-2- (4-(2, 2, 2-trifluoroacetyl)piperazine-1-yl)ethoxy)-2H-chromen-2-one (5c)

Yield:96%; white solid; mp 190-193°C; Purity by HPLC 94.8.%; IR(KBr,v, cm^{-1}):3083(C-H, aromatic),2976(C-H, aliphatic,1735(C= O, lactone), 1664 (C= O, amide), 1625(C= C, alkene); ^{1}H NMR (400 MHz, $CDCl_3$):δ_H 7.86(d, 1H).7.61-7.58(t, 1H),7.36-7.30(m, 2H), 5.73 (s, 1H),4.93 (s, 2H), 3.76 (s, 4H),3.69 (s, 2H),3.63 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 164.6, 164.3, 161.6, 152.7, 132.8, 124.3, 122.9, 116.4, 115.1, 91.4, 66.5, 45.0, 43.6, 43.0, 42.8, 42.7, 41.1 ; EI-MS: m/z 385.2 (M+1, 100%).

4-(2-(4-(methylsulfonyl)piperazin-1-yl)-2-oxoethoxy)-2H-chromen-2-one (5d)

Yield 96.6%; White solid ; mp 242-245°C; Purity by HPLC 95.6%; IR (KBr, cm^{-1}): 3078 (C-H, aromatic), 2936(C-H, aliphatic,1711 (C= O, lactone), 1682 (C= O, amide), 1618(C= C, alkene); ^{1}H NMR (400 MHz, $CDCl_3$):δ_H 7.86(d, 1H).7.61-7.58(t, 1H),7.36-7.30(m, 2H), 5.67 (s, 1H),4.90 (s, 2H), 3.80 (s, 4H),3.64(s, 2H), 3.30 (s, 2H), 2.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 164.7, 164.1, 162.3, 153.3, 132.8, 124.2, 122.8, 116.9, 115.1, 114.7, 91.7, 66.8, 45.5, 44.4, 43.1, , 41.9 ; EI-MS: m/z 367.1 (M+1, 100%).

4-(2-(4-(ethylsulfonyl)piperazin-1-yl)-2-oxoethoxy)-2H-chromen-2-one (5e)

Yield 93.2%; White solid ; mp 236-238°C; Purity by HPLC 97.6%; IR (KBr, cm^{-1}): 3081 (C-H, aromatic), 2934(C-H, aliphatic,1718 (C= O, lactone), 1688(C= O, amide), 1623(C= C, alkene); ^{1}H NMR (400 MHz, $CDCl_3$):δ_H 7.84(d, 1H).7.59-7.56(t, 1H),7.34-7.28(m, 2H), 5.68 (s, 1H),4.91 (s, 2H), 3.64(m, 4H), 3.40 (q, 2H), 2.62 (m, 4H).1.18 (t, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 164.8, 164.1, 162.6, 153.4, 132.9, 124.1, 123.0, 117.2, 115.6, 114.8, 91.9, 66.7, 49.8, 45.3, 44.2, 2.8; EI-MS: m/z 381.1 (M+1, 100%).

4-(2-oxo-2-(4-(phenylsulfonyl)piperazin-1-yl)ethoxy)-2H-chromen-2-one (5f)

Yield 90.8%; White solid ; mp 186-188°C; Purity by HPLC 98.6%; IR (KBr, cm^{-1}): 3071 (C-H, aromatic), 2924(C-H, aliphatic,1714 (C= O, lactone), 1678(C= O, amide), 1620(C= C, alkene); ^{1}H NMR (400 MHz, $CDCl_3$):δ_H 7.84(m, 3H),7.78-7.62(m, 3H)7.55-7.52(t, 1H),7.31-7.27(m, 2H), 5.68 (s, 1H), 4.89 (s, 2H), 3.62 (m, 4H), 3.42 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 164.6, 164.5, 162.4, 153.6, 133.6, 132.9, 130.8, 129.2(2C), 128.8(3C), 123.1, 116.8, 91.7, 66.8, 45.6,44.4; EI-MS: m/z 413 (M+1, 100%).

4-(2-(4-(biphenyl-4-ylsulfonyl)piperazin-1-yl)-2-oxoethoxy)-2H-chromen-2-one (5g)

Yield 89.2%; White solid ; mp 210-213°C; Purity by HPLC 96.8%; IR (KBr, cm^{-1}): 3077 (C-H, aromatic), 2927(C-H, aliphatic,1709 (C= O, lactone), 1680(C= O, amide), 1623(C= C, alkene); ^{1}H NMR (400 MHz, $CDCl_3$):δ_H 7.78(d, 3H),7.73-7.71(d, 1H),7.61-7.59 (d, 2H), 7.56-7.48 (m, 4H), 7.46-7.42 (m, 4H).5.6 (s, 1H), 4.8 (s, 2H), 3.78-3.6 (m, 4H) 3.1 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ164.7, 164.1, 162.3, 153.3, 146.5, 139.0, 133.6, 132.9, 129.2 (2C), 128.8 (2C), 128.3 (2C), 128.0 (2C), 127.5 (2C), 124.2, 123.1, 115, 91.7, 66.8, 45.5, 44.2. 43.15, 41.9; EI-MS: m/z 505.3 (M+1, 100%).

2-(4-(2-(2-oxo-2H- chromen-4-yloxy)acetyl)piperazin-1-yl)acetamide (5h)

Yield 92.2%; White solid ; mp 246-248°C; Purity by HPLC 98.9%; IR (KBr, cm^{-1}): 3083 (C-H, aromatic), 2926(C-H, aliphatic,1721 (C= O, lactone), 1680(C= O, amide), 1624(C= C, alkene); ^{1}H NMR (400 MHz, $CDCl_3$):δ_H 7.88-7.86 (d, 1H), 7.60-7.56 (t, 1H), 7.35-7.30 (m, 2H), 6.85 (s, 1H), 5.65 (s, 1H), 5.44 (s, 1H), 4.88 (s, 2H), 3.72(s, 2H), 3.55 (s, 2H), 3.09 (s, 2H), 2.63-2.61 (t, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): 173.0, 169.6, 167.1, 158.0, 137.4, 128.8, 128.1, 121.2, 120.1, 95.8, 70.1, 45.2, 45.0, 44.84, 44.63, 44.42, 44.21; EI-MS: m/z 346.2 (M+1, 100%).

2.2 Antimicrobial activity

The synthesized compounds **5a-5h** were examined for their anti-bacterial and anti-fungal activities by agar diffusion method. *Bacillus subtilis* ATCC 10876, *Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853 were used for testing the anti-bacterial activity. *Candida albicans* ATCC 66027 was used for testing anti-fungal activity. The strains were procured from Himedia, Mumbai. Amikacin and ketoconazole were used as standards for antibacterial and anti-fungal testing respectively. The solvent, Dimethylsulphoxide (DMSO) was the negative control.

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

The stock solution of test compounds (1000 µg/ml) was prepared in DMSO and a volume of 50 µl of each test compound was added into the wells (6 mm diameter) cut in the microbial culture inoculated agar medium, thus the concentration of each tested compound was 50 µg/well. The filter paper discs of amikacin and ketaconazole at a concentration of 10 and 30 µg respectively were tested. The agar plates were incubated at 37±0.5°C for 24 h (testing antibacterial activity) or 36 h (testing anti-fungal activity). The activity of compounds 4a-n and the standards were measured by zone of inhibition around the well or disc and its described in Table **2**.

Table : 2

Anti Microbial Activity: Zone of Inhibition (MMS)

COMPOUND	*E. coli ATCC 25922*	*P.aeruginosa ATCC 27853*	*B. subtilis ATCC 10876*	*S.aureus ATCC 25923*	*C. albicans ATCC 66027*
5a	28	-	-	-	-
5b	-	-	-	28	-
5c	-	-	-	-	22
5d	10	12	-	-	11
5e	-	-	24	-	18
5f	16	-	-	-	15
5g	13	-	34	-	9
5h	15	-	26	23	13
amikacin	17	17	20	18	-
ketokonazole	-	-	-	-	21

The synthesized compounds were tested for antibacterial activity and antifungal activity. For the antibacterial activity of the compound **5d** has shown good activity against both the Gram negative bacteria where as compound **5a**, **5f**, **5g**, and **5h** shows moderate activity against *E.coli* .Compound **5h** shows moderate activity against both the gram positive bacteria and **5e**, **5g** shows activity against *B.subtilis.* Antifungal activity of the all tested compounds shows good to moderate activity against *Candida albicans* except **5a** and **5b**.Compound **5d** and **5g** shows best antifungal activity which may be presence of piprazine ring having groups like metane sulfonyl and biphenyl sulfonyl at the postion of 4.

Total antioxidant activity

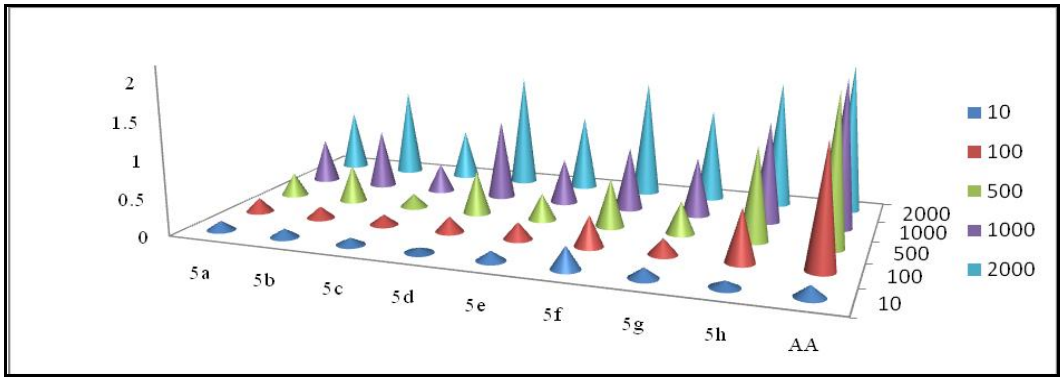


Figure:1 Antioxidant activity of compounds 5a-5h against standard Ascorbic acid (A_m – Activity relative to Ascorbic acid (AA)on molar basis)

The total antioxidant capacity of the compounds **5a**-5**h** was determined with phosphomolybdenum method using ascorbic acid as the standard. An aliquot of 0.1ml of compound (10, 100, 500, 1000, 2000μg) solution was combined with 2.0 ml of reagent (0.6 M sulfuric acid, 28 mM sodium phosphate and 4 mM ammonium molybdate). The tubes were capped and incubated in a boiling water bath at 95°C for 90 min. The samples are cooled to room temperature; the absorbance was measured at 695 nm against blank in UV spectrophotometer. The increased absorbance of the reaction mixture indicated increased antioxidant capacity.

According to the results presented in Figure 1, all the compounds exhibited moderate to good antioxidant activity when compared with standard ascorbic acid. Among all compounds, **5d**, **5f** and **5h** shows good antioxidant properties at at higher concentration.

Conclusion

In summary, a series of novel coumarin-piprazinederivatives **5a-h** was disclosed and well characterized by using spectral techniques such as IR, ^{1}H-NMR, ^{13}C-NMR and MS. All the synthesized compounds **5a**-5**h** were screened for their antimicrobial and antioxidant activities. Among the synthesized compounds **5d** and **5h** have shown good antimicrobial and antioxidant activity, it may be the presence of mesyl and acetamide functional group present in the 4th position of the piprazine contanining coumarin derivatives.

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