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SYNTHESIS, CHARACTERIZATION AND THEIR ANTI-OXIDANT ACTIVITY OF XANTHONE CONJUGATED AMINO ACIDS

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ABSTRACT

A novel series of some Xanthone conjugated amino acids derivatives as depicted as in the scheme and all are synthesized by conventional method. The synthesized compounds were characterized by physical methods like melting point, R_f value, % yield and solubility. Synthesized structures are conformed by UV, FT-IR, 1HNMR and MASS spectral analysis. The synthesized analogs were evaluated for their antioxidant activity by DPPH and H_2O_2 methods. From the results compound 3b, 3e and 3i exhibited significant antioxidant activity due to presence of higher hydrophobic planar substitutions.

KEYWORDS

Phenylalanine, Different Aminoacids, Antioxidant activity, Ascorbic acid, DPPH and Diclofenac sodium.

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INTRODUCTION

Heterocyclic compounds containing a ring made up, in addition to carbon atoms, other elements (heteroatoms), most often nitrogen, oxygen, and sulfur and less frequently phosphorus, boron, and silicon. Xanthine derivatives are fused heterocyclic structures with hetero atoms. Xanthine is very useful units in the fields of medicinal and pharmaceutical chemistry and has been reported to exhibit a variety of biological activities. Following attachment and adsorption of viral particles to specific receptors on host cells, enveloped viruses must enter the host cell by making a fusion pore, fusing their own lipid bilayer envelope coat with that of the plasma cell membrane. Fusion occurs via at least two classes of viral proteins in the

envelope[1]. The class I model pertains to influenza haemagglutinin, HIV-1 gp120 and the F-proteins from paramyxoviridae[2] and class II involves E proteins of the flaviviridae and the E1 protein of Semliki Forest virus[3]. The compound is classified as aromatic due to the presence of a sextet of π-electrons, consisting of a pair of electrons from the protonated nitrogen atom and one from each of the remaining four atoms of the ring. Xanthine and its derivatives have been used as ant proliferative, anticonvulsant[4], antitubercular[5], antimicrobial[6], antiviral[7], S and transformations as reaction intermediates.

These findings have motivated us to synthesize biologically active heterocycles, particularly for antioxidant activity. In our search for new therapeutic agents, we have synthesized novel Xanthine derivatives and performed a first evaluation of their antioxidant activity. The constitution of derivatives has been supported by IR, H-NMR and Mass spectral data.

MATERIAL AND METHODS

The synthesized compounds were screened for antioxidant activity. Fourier Transform IR spectrometer (model Shimadzu 8700) in the range of 400-4000cm^{-1} Using KBr pellets and values are reported in cm^{-1} and the spectra were interpreted. ^{1}H-NMR was scanned on Avance-400 MHz instrument. Chemical shifts are expressed in δ (ppm) relative to TMS as an internal standard using DMSO-d_6 as solvent. Mass spectra were recorded on Mass spectrophotometer (model Shimadzu) by LC- MS and the spectra were interpreted. Precoated Silica gel G plates were used to monitor the progress of reaction as well as to check the purity of the compounds**.** Chloroform: methanol (7:3) used as a mobile phase.

General procedures

Benzophenone compound is cycled with 2M Solution of sodium hydroxide is added to solution of benzophenone in 1, 4-Dioxane then heated 60^{o}C, yields' hydroxyl xanthone xanthone. Xanthone is alkylated with ethyl chloroacetate with potassium carbonate base. Ester xanthone is hydrolysis with 2M Solution of sodium hydroxide to yield acid Xanthone derivatives. Different amino acids are protected using HBTU or DCC coupling reagents to form amino acids conjugated xanthone[8,9].

Spectral Data

Compound No.3a: (2-((9-oxo-4a, 9a-dihydro-9H-xanthen-3-yl) oxy) acetyl) glycine: IR, Cm^{-1} (KBr)

3501(-OH *Str*, Ar-OH), 3205(-NH Str, Amide), 3100(-CH *Str*, benzene), 2944, 2834(-CH *Str,* Alkyl), 1705 (C=O *Str*), 1544(C=N *Str*), 1347(C-N *Str*), 1180(C-N *Str*), 1078(N-N *Str*). ^{1}HNMR (DMSO, δppm): 11.9740(s, 1H, -COOH), 9.7901(s, 1H, -NH), 7.6895-7.3852(s, d, t, 7H, Ar-H), 4.1735(s, 2H, -CH_2CO), 3.1095(s, 1H, -CH-). Mass (EI-MS): 327.07(M), 328.21(M + 1).

Compound No.3b: (2-((9-oxo-4a, 9a-dihydro-9H-xanthen-3-yl) oxy) acetyl) alanine: IR, Cm^{-1} (KBr)

3577(-OH *Str*, Ar-OH), 3237(-NH Str, Amide), 3077(-CH *Str*, benzene), 2935, 2835(-CH *Str,* Alkyl), 1705(C=O *Str*), 1581(C=N *Str*), 1387(C-N *Str*), 1166(C-N *Str*), 1032(N-N *Str*). ^{1}HNMR (DMSO, δppm): 12.0276(s, 1H, -COOH), 9.5269(s, 1H, -NH), 7.9492-7.7624(s, d, t, 7H, Ar-H), 4.5276(s, 2H, -CH_2CO), 3.3080(s, 1H, -CH-), 2.0736(s, 3H, -CH_3). Mass (EI-MS): 341.09(M), 342(M+1, 100%), 340(M-1).

Compound No.3c: (2-((9-oxo-4a, 9a-dihydro-9H-xanthen-3-l) oxy) acetyl) valine: IR, Cm^{-1} (KBr)

3519(-OH *Str*, Ar-OH), 3418(-NH Str, Amide), 3078(-CH *Str*, benzene), 2989, 2867(-CH *Str,* Alkyl), 1714(C=O *Str*), 1491(C=N *Str*), 1314(C-N *Str*), 1172(C-N *Str*), 1080(N-N *Str*). ^{1}HNMR (DMSO, δppm): 12.0992(s, 1H, -COOH), 9.6362(s, 1H, -NH), 7.9453-7.7518(s, d, t, 7H, Ar-H), 4.4594(s, 2H, -CH_2CO), 3.1869(d, 2H, -CH-), 2.1487-2.1289(s, 6H, -CH_3). Mass (EI-MS): 369.12(M), 370.32(M + 1), 368.03(M -1).

Compound No.3d: (2-((9-oxo-4a, 9a-dihydro-9H-xanthen-3-yl) oxy) acetyl) leucine: IR, Cm^{-1} (KBr)

3588(-OH *Str*, Ar-OH), 3234(-NH Str, Amide), 3080(-CH *Str*, benzene), 2943, 2892(-CH *Str,* Alkyl), 1717(C=O *Str*), 1511(C=N *Str*), 1258(C-N *Str*), 1177(C-N *Str*), 1007(N-N *Str*). ^{1}HNMR (DMSO, δppm): 12.0453(s, 1H, -COOH), 9.6286(s,

1H, -NH), 7.9457-7.7528(s, d, t, 7H, Ar-H), 4.4582(s, 2H, -CH_2CO), 3.1887(t, 1H, -CH-), 2.1894-2.1277(d, 6H, -CH_3). Mass (EI-MS): 383.14(M), 383.02(M + 1), 381.04(M -1).

Compound No.3e: 2-(2-((9-oxo-4a, 9a-dihydro-9H-xanthen-3-yl) oxy) acetamido) heptanoic acid. IR, Cm^{-1} (KBr)

3593(-OH *Str*, Ar-OH), 3295(-NH Str, Amide), 3095(-CH *Str*, benzene), 2944, 2884,2838(-CH *Str,* Alkyl), 1711(C=O *Str*), 1543(C=N *Str*), 1276(C-N *Str*), 1157(C-N *Str*), 1055(N-N *Str*). ^{1}HNMR (DMSO, δppm): δppm): 12.0544(s, 1H, -COOH), 9.5643(s, 1H, -NH), 7.9864-7.5427(s, d, t, 7H, Ar-H), 4.7653(s, 2H, -CH_2CO), 3.1235(t, 1H, -CH-), 2.4763-2.0953(d,q,s, 9H, -C_4H_9). Mass (EI-MS): 383.14(M), 384.76(M + 1), 382, 04(M -1).

Compound No.3f: (2-((9-oxo-4a, 9a-dihydro-9H-xanthen-3-yl) oxy) acetyl) glutamine IR, Cm^{-1} (KBr)

3517(-OH *Str*, Ar-OH), 3403, 3240(-NH Str, Amide), 3098(-CH *Str*, benzene), 2943, 2884, 2835(-CH *Str,* Alkyl), 1705(C=O *Str*), 1572(C=N *Str*), 1267(C-N *Str*), 1104(C-N *Str*), 1032(N-N *Str*). ^{1}HNMR (DMSO, δppm): 12.2463(s, 1H, -COOH), 9.6743, 9.0432(s, 3H, -NH, -NH_2), 8.0763-7.3645(s, d, t, 7H, Ar-H), 4.8432(s, 2H, -CH_2CO), 3.3423(t, 1H, -CH-), 2.8743-2.5432(t,d, 4H, -C_2H_4). Mass (EI-MS): 398.11(M), 399.43(M + 1), 397.43(M -1).

Compound No.3g: 3-hydroxy-2-(2-((9-oxo-4a, 9a-dihydro-9H-xanthen-3-yl) oxy) acetamido) butanoic acid: IR, Cm^{-1} (KBr)

3574(-OH *Str*, Ar-OH), 3372(-NH Str, Amide), 3090(-CH *Str*, benzene), 2925, 2893(-CH *Str,* Alkyl), 1708(C=O *Str*), 1545(C=N *Str*), 1274(C-N *Str*), 1121(C-N *Str*), 1013(N-N *Str*). ^{1}HNMR (DMSO, δppm): 11.6790(s, 2H, -COOH, -OH), 9.4995(s, 1H, -NH), 8.4983-7.1838(s, d, t, 7H, Ar-H), 4.6290(s, 2H, -CH_2CO), 3.2967(d, 2H, -CH-), 2.2104(d, 3H, -CH_3). Mass (EI-MS): 371.10(M), 372.54(M + 1), 370.65(M -1).

Compound No.3h: (2-((9-oxo-4a, 9a-dihydro-9H-xanthen-3-yl) oxy) acetyl) phenylalanine: IR, Cm^{-1} (KBr)

3574(-OH *Str*, Ar-OH), 3372(-NH Str, Amide), 3132, 3090(-CH *Str*, benzene), 2925, 2893(-CH *Str,* Alkyl), 1708(C=O *Str*), 1596(C=N *Str*), 1304(C-N *Str*), 1121(C-N *Str*), 1013(N-N *Str*). ^{1}HNMR (DMSO, δppm): 12.360(s, 2H, -COOH), 9.2701(s, 1H, -NH), 7.9062-7.5387(s, d, t, 12H, Ar-H), 4.6319(s, 2H, -CH_2CO), 3.3660(t, 1H, -CH-), 2.653-2.3452(t, 2H, -CH_2). Mass (EI-MS): 417.12(M), 418.43(M + 1), 416.04(M -1).

Compound No.3i: (2-((9-oxo-4a, 9a-dihydro-9H-xanthen-3-yl) oxy) acetyl) tyrosine: IR, Cm^{-1} (KBr)

3532(-OH *Str*, Ar-OH), 32485(-NH Str, Amide), 3098, 3021(-CH *Str*, benzene), 2989, 2843(-CH *Str,* Alkyl), 1712(C=O *Str*), 1556(C=N *Str*), 1322(C-N *Str*), 1134(C-N *Str*), 1044(N-N *Str*). ^{1}HNMR (DMSO, δppm): 12.3919(s, 2H, -COOH, -OH), 9.7966(s, 1H, -NH), 8.5792-7.7612(s, d, t, 12H, Ar-H), 4.6904(s, 2H, -CH_2CO), 3.2541(t, 1H, -CH-), 2.3042(d, 2H, -CH_2). Mass (EI-MS): 433.12(M), 434.65(M + 1), 432.32(M -1)

Compound No.4j: Compound.3j: (2-((9-oxo-4a, 9a-dihydro-9H-xanthen-3-yl) oxy) acetyl) methionine: IR, Cm^{-1} (KBr)

3504(-OH *Str*, Ar-OH), 3287(-NH Str, Amide), 3088, 3021(-CH *Str*, benzene), 2987, 2867(-CH *Str,* Alkyl), 1706(C=O *Str*), 1556(C=N *Str*), 1323(C-N *Str*), 1143(C-N *Str*), 1029(N-N *Str*). ^{1}HNMR (DMSO, δppm): 12.0240(s, 2H, -COOH), 9.3949(s, 1H, -NH), 8.8995-7.1838(s, d, t, 12H, Ar-H), 4.3941(s, 2H, -CH_2CO), 2.9979(t, 1H, -CH-), 2.2183(t, 4H, -C_2H_4). Mass (EI-MS): 401.09(M), 402.43(M + 1), 400.90(M -1).

Antioxidant activity

An antioxidant is a molecule capable of slowing or preventing the oxidation of other molecules. Oxidation is a chemical reaction that transfers electrons from a substance to an oxidizing agent. Oxidation reaction can produce free radicals which start chain reaction that damage cells. Antioxidant terminates these chain reactions by being oxidized themselves. Although oxidation reactions are crucial for life, they can also be damaging, hence plants and animals maintain a complex system of multiple steps of antioxidants such as glutathione, vitamin C, E as well as enzymes such as catalyse, superoxide dismutase and various peroxidases. Low levels of antioxidant or inhibition

of the antioxidant enzymes causes oxidative stress and may damage or kill cells[10-12].

DPPH Method

To evaluate the antioxidant potential of all the synthesized compounds *in-vitro* free radical scavenging activity using DPPH (2, 2-diphenyl-1-picryl hydrazyl) reduction method[13]. The test solutions were prepared in similar manner as that of standard Ascorbic acid and the absorbance was recorded at 516nm after duration of 30 mints. The percentage inhibition was calculated by the formula:

$$\% \text{ Inhibition} = \frac{\text{Abs of Control} - \text{Abs of test}}{\text{Abs of Control}} \times 100$$

The IC_{50} value represented the concentration of the compounds that caused 50% inhibition.

Hydrogen peroxide scavenging activity

Hydrogen peroxide scavenging assay: A solution of hydrogen peroxide (40mM) was prepared in phosphate buffer (50mM, pH 7.4). 1 ml of test compound (10, 50, 100, 200, 500µg/ml) in ethanol was added to 0.6 ml hydrogen peroxide solution. Absorbance of test solution was measured at 230nm after 10 min against a blank solution containing phosphate buffer without hydrogen peroxide. Hydrogen peroxide solution served as control[14]. Ascorbic acid was used as reference standard. The percentage of hydrogen peroxide scavenged is calculated as follows:

Percentage scavenged = $((A_s - A_c)/A_c) \times 100$

Where A_c is the absorbance of control, A_s is the absorbance of test. The IC_{50} value represented the concentration of the compounds that caused 50 % inhibition.

RESULTS AND DISCUSSION

Synthesis

The characterization data of all compounds 3a-3l are given the experimental section. All the synthesized compounds gave satisfactory analysis for the proposed structures, which were confirmed on the basis of their elemental analysis by FT-IR, LC-MASS, 1H NMR data. The present work which involve reaction between substituted Xanthine derivatives with different amino acids in the presence of Dioxane to form title compounds (3a-3l).

Chemistry and characterization of compounds: In Compound.3a: (2-((9-oxo-4a, 9a-dihydro-9H-xanthen-3-yl) oxy) acetyl) glycine. IR bands at IR, Cm-1 (KBr): IR, Cm^{-1} (KBr): 3501(-OH *Str*, Ar-OH), 3205(-NH Str, Amide), 3100(-CH *Str*, benzene), 2944,2834(-CH *Str,* Alkyl), 1705 (C=O *Str*), 1544(C=N *Str*), 1347(C-N *Str*), 1180(C-N *Str*), 1078(N-N *Str*). ^{1}HNMR (DMSO, δppm): 11.9740(s, 1H, -COOH), 9.7901(s, 1H, -NH), 7.6895-7.3852(s, d, t, 7H, Ar-H), 4.1735(s, 2H, $-CH_2CO$), 3.1095(s, 1H, -CH-). Mass (EI-MS): 327.07(M), 328.21(M + 1). In Compound.3b: (2-((9-oxo-4a, 9a-dihydro-9H-xanthen-3-yl) oxy) acetyl) alanine IR bands at IR, Cm^{-1} (KBr): IR, Cm^{-1} (KBr): 3577(-OH *Str*, Ar-OH), 3237(-NH Str, Amide), 3077(-CH *Str*, benzene), 2935, 2835(-CH *Str,* Alkyl), 1705(C=O *Str*), 1581(C=N *Str*), 1387(C-N *Str*), 1166(C-N *Str*), 1032(N-N *Str*). ^{1}HNMR (DMSO, δppm): 12.0276(s, 1H, -COOH), 9.5269(s, 1H, -NH), 7.9492-7.7624(s, d, t, 7H, Ar-H), 4.5276(s, 2H, $-CH_2CO$), 3.3080(s, 1H, -CH-), 2.0736(s, 3H, $-CH_3$). Mass (EI-MS): 341.09(M), 342(M+1, 100%), 340(M-1). In Compound.3c: (2-((9-oxo-4a,9a-dihydro-9H-xanthen-3-yl)oxy) acetyl) valine IR bands at IR, Cm^{-1} (KBr): IR, Cm^{-1} (KBr): 3519(-OH *Str*, Ar-OH), 3418(-NH Str, Amide), 3078(-CH *Str*, benzene), 2989, 2867(-CH *Str,* Alkyl), 1714(C=O *Str*), 1491(C=N *Str*), 1314(C-N *Str*), 1172(C-N *Str*), 1080(N-N *Str*). ^{1}HNMR (DMSO, δppm): 12.0992(s, 1H, -COOH), 9.6362(s, 1H, -NH), 7.9453-7.7518(s, d, t, 7H, Ar-H), 4.4594(s, 2H, $-CH_2CO$), 3.1869(d, 2H, -CH-), 2.1487-2.1289(s, 6H, $-CH_3$). Mass (EI-MS): 369.12(M), 370.32(M + 1), 368.03(M -1). In Compound.3d: Compound.3d: (2-((9-oxo-4a, 9a-dihydro-9H-xanthen-3-yl) oxy) acetyl) leucine. IR bands at IR, Cm^{-1} (KBr): 3588(-OH *Str*, Ar-OH), 3234(-NH Str, Amide), 3080(-CH *Str*, benzene), 2943, 2892(-CH *Str,* Alkyl), 1717(C=O *Str*), 1511(C=N *Str*), 1258(C-N *Str*), 1177(C-N *Str*), 1007(N-N *Str*). ^{1}HNMR (DMSO, δppm): 12.0453(s, 1H, -COOH), 9.6286(s, 1H, -NH), 7.9457-7.7528(s, d, t, 7H, Ar-H), 4.4582(s, 2H, $-CH_2CO$), 3.1887(t, 1H, -CH-), 2.1894-2.1277(d, 6H, $-CH_3$). Mass (EI-MS): 383.14(M), 383.02(M + 1), 381.04(M -1).

In Compound.3e: (2-((9-oxo-4a, 9a-dihydro-9H-xanthen-3-yl) oxy) acetyl) alanine. IR bands at IR, Cm^{-1} (KBr): IR, Cm^{-1} (KBr): 3593(-OH *Str*, Ar-OH), 3295(-NH Str, Amide), 3095(-CH *Str*, benzene), 2944, 2884,2838(-CH *Str,* Alkyl), 1711(C=O *Str*), 1543(C=N *Str*), 1276(C-N *Str*), 1157(C-N *Str*), 1055(N-N *Str*). ^{1}HNMR (DMSO, δppm): δppm): 12.0544(s, 1H, -COOH), 9.5643(s, 1H, -NH), 7.9864-7.5427(s, d, t, 7H, Ar-H), 4.7653(s, 2H, $-CH_2CO$), 3.1235(t, 1H, -CH-), 2.4763-2.0953(d,q,s, 9H, $-C_4H_9$). Mass (EI-MS): 383.14(M), 384.76(M + 1), 382, 04(M -1).

Antioxidant activity

All the synthesized compounds 3a-3j were screened for their *in vitro* antioxidant activity by DPPH* method and Hydrogen peroxide method using ascorbic acid as the standard.

The observations revealed that 3b,3e and 3i exhibited significant antioxidant activity by DPPH method with IC_{50} value at 36.04, 39.09 and 43.04µg/ML, By hydrogen peroxide method with IC_{50} value at 39.98 (3d), 340.98(3e) and 38.02(3i)µg/ML. The most of compounds exhibited moderate activity. The compounds 3a and 3f exhibited least activity with IC_{50} value respectively.

Table No.1: Physical properties of (3a-3j)

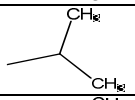
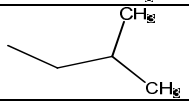
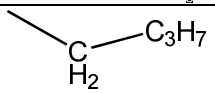
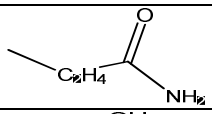
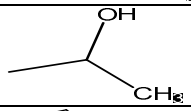
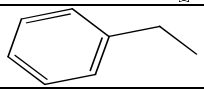
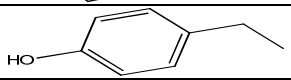
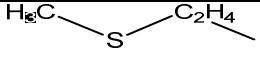
Code	R	Mol. Formula	Mol. wt ($g.mol^{-1}$)	M.P (^oC)
3a	-H	$C_{17}H_{13}NO_6$	327.07	219-221
3b	- CH_3	$C_{18}H_{15}NO_6$	341.09	178-181
3c		$C_{20}H_{19}NO_6$	369.12	192-194
3d		$C_{21}H_{21}NO_6$	355.87	204-206
3e		$C_{21}H_{21}NO_6$	383.14	167-169
3f		$C_{20}H_{18}N_2O_7$	398.11	183-185
3g		$C_{19}H_{17}NO_7$	371.10	212-214
3h		$C_{24}H_{19}NO_6$	417.12	181-183
3i		$C_{24}H_{19}NO_7$	433.12	226-228
3j		$C_{20}H_{19}NO_6S$	401.09	251-253

Table No.2: Antioxidant activity [IC_{50} (Mean ± S.E.M)] of novel xanthone conjugated amino acids (3a-3j)

S.No	Compounds	IC_{50} (Mean ± S.E.M) µg/ mL
1	3a	67.73
2	3b	36.04
3	3c	40.94
4	3d	68.09
5	3e	39.09
6	3f	82.93
7	3g	46.02
8	3h	59.03
9	3i	43.04
10	3j	69.28
11	Ascorbic acid	32.45

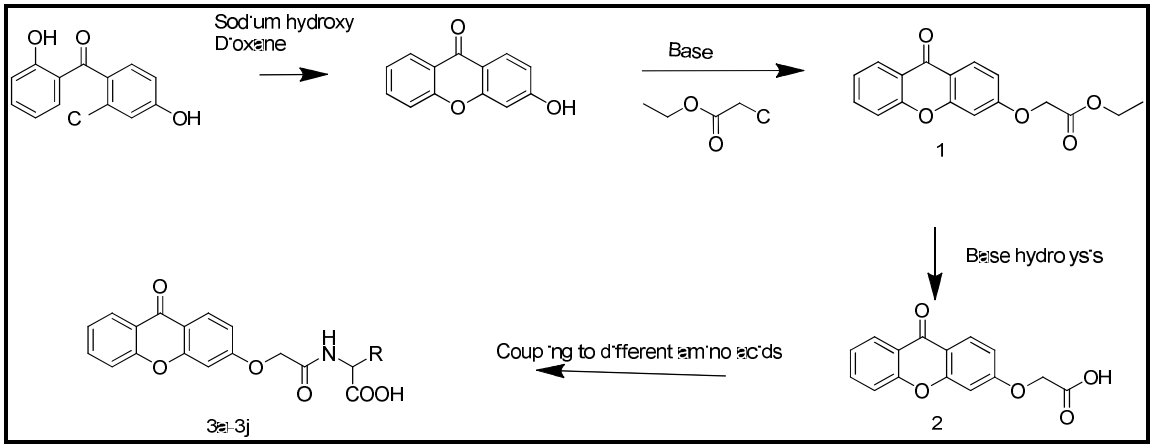
Table No.3: The percentage inhibition of hydrogen peroxide is calculated and the results are presented in the table novel xanthone conjugated amino acids (3a-3j)

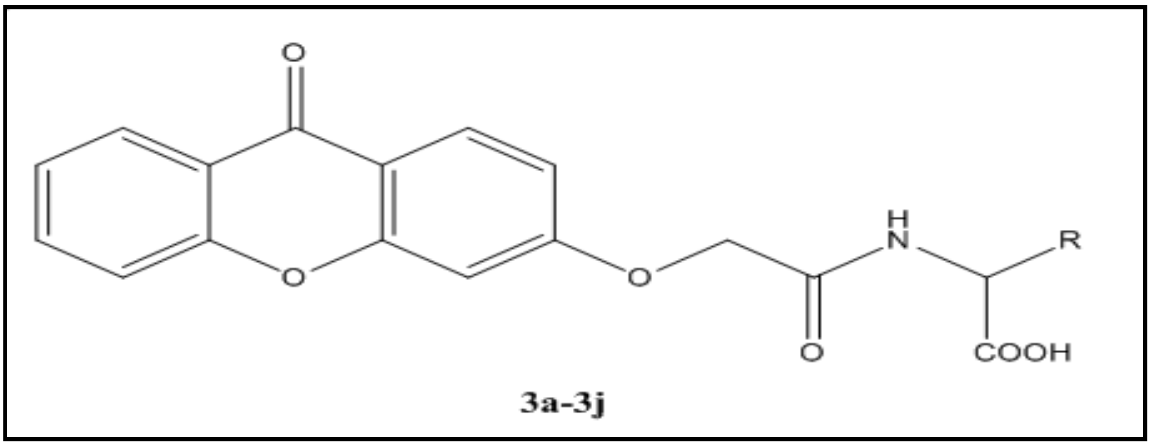
S.No	Compounds	IC_{50} (Mean ± S.E.M) µg/mL
1	3a	65.21
2	3b	42.76
3	3c	72.32
4	3d	39.26
5	3e	40.98
6	3f	52.65
7	3g	49.04
8	3h	57.34
9	3i	38.02
10	3j	66.32
11	Ascorbic acid	32.09

Values are expressed in mean ± SEM; (n = 3);

$^{\$}$ $p < 0.001$ = highly significant, $^{\#}p < 0.01$ = moderately Significant, $^{*}p < 0.05$ = Significant

Scheme No.1





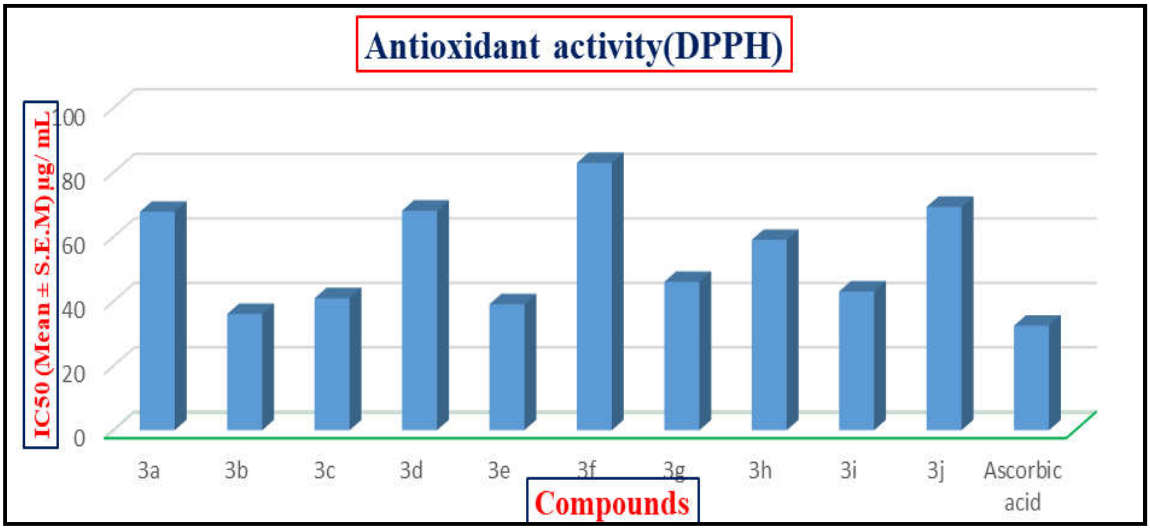


Figure No.1: Graphical representation of antioxidant activity novel xanthone conjugated amino acids (3a-3j) - IC_{50} (Mean ± S.E.M)

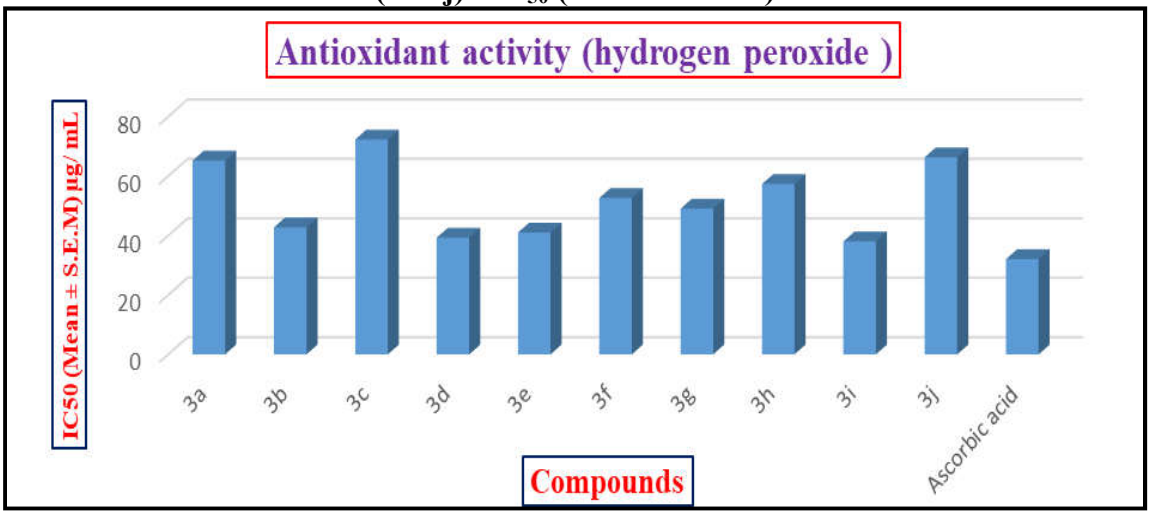


Figure No.2: Graphical representation of antioxidant activity novel xanthone conjugated amino acids (3a-3j). - IC_{50} (Mean ± S.E.M

CONCLUSION

In the present study, a series of novel xanthone conjugated amino acids (3a-3j) were synthesized according to the above mentioned procedures by conventional methods as mentioned in the scheme by the condensation of novel substituted novel xanthone conjugated amino acids derivatives and evaluated for their possible antioxidant activitiy. All these molecules were characterized by FTIR, ^{1}HNMR and Mass spectral analysis along with physical data. In conclusion, the present study reveals that the newly synthesized xanthone conjugated amino acids compounds (3a-3j) present in the synthesized compounds is responsible for the antioxidant activitiy and may serve as a lead molecule for further modifications to obtain clinically useful novel entities.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this paper.

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