
Research Article



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**SYNTHESIS AND BIOLOGICAL EVALUATION OF NOVEL SERIES OF
MODIFIED QUERCETEIN DERIVATIVES**

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Abstract

Some novel compounds are synthesized with the reaction between o-hydroxy acetophenone and 1H-indole 3-carbaldehyde. Completion of reaction was monitored on TLC using silica gel-G coated plates by using Hexane: ethyl acetate (3:2) as the eluent and observed in the UV light. In this manner 10 novel compounds are prepared and subjected to biological screening. The newly synthesized compounds were characterized using IR, ¹H-NMR. Anti oxidant activity is determined by nitric oxide radical scavenging activity and hydrogen peroxide scavenging activity. Anti oxidant activity revealed that all the synthesized compounds have shown significant anti-oxidant activity when compared with that of standard drug. The compounds **3b**, **3c**, **3f** and **3j** showed more activity as compared to the other derivatives. IC₅₀ values were calculated by statistical regression analysis to find out the concentration to show 50% scavenging activity.

Key words: Quercetin, Anti-oxidant activity, Nitric oxide radical scavenging activity.

Introduction

Quercetein derivatives have important applications in the field of medicinal chemistry. Quercetin chemically, 2-(3, 4-dihydroxy phenyl)-3, 5, 7-trihydroxychromen-4-one belongs to the flavonoid group of polyphenols. Quercetin which is reported in onion, apple, citrus fruits, red grapes etc. exhibits wide range of biological activities such as antibacterial, antioxidant, antidiabetic, anticancer, anti-inflammatory etc. Quercetin is frequently present in nature as glycosides (sugar derivatives) such as rut (also known as quercetin rutinoside) in which the sugar moiety

is disaccharide. Quercetin is also referred to as quercetin aglycon or sugarless form of rutin (the main constituent in tea). Quercetin is a potent antioxidant, providing cardiovascular protection by reducing oxidative damage to LDL-cholesterol, the underlying cause of heart disease. Quercetin also blocks an enzyme that leads to accumulation of sorbitol, which has been linked to nerve, eye, and kidney damage in diabetes. Indoles particularly have been the subject of great research interest owing to their appearances in the structures of complex biologically active compounds. Indole moiety

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which is of great biological interest reported with antimicrobial, anti-inflammatory, anti cancer activity.

Materials and Methods

Melting points were determined by open glass capillary method and are un corrected. The structures have been confirmed by spectral analysis like IR and ^1H NMR

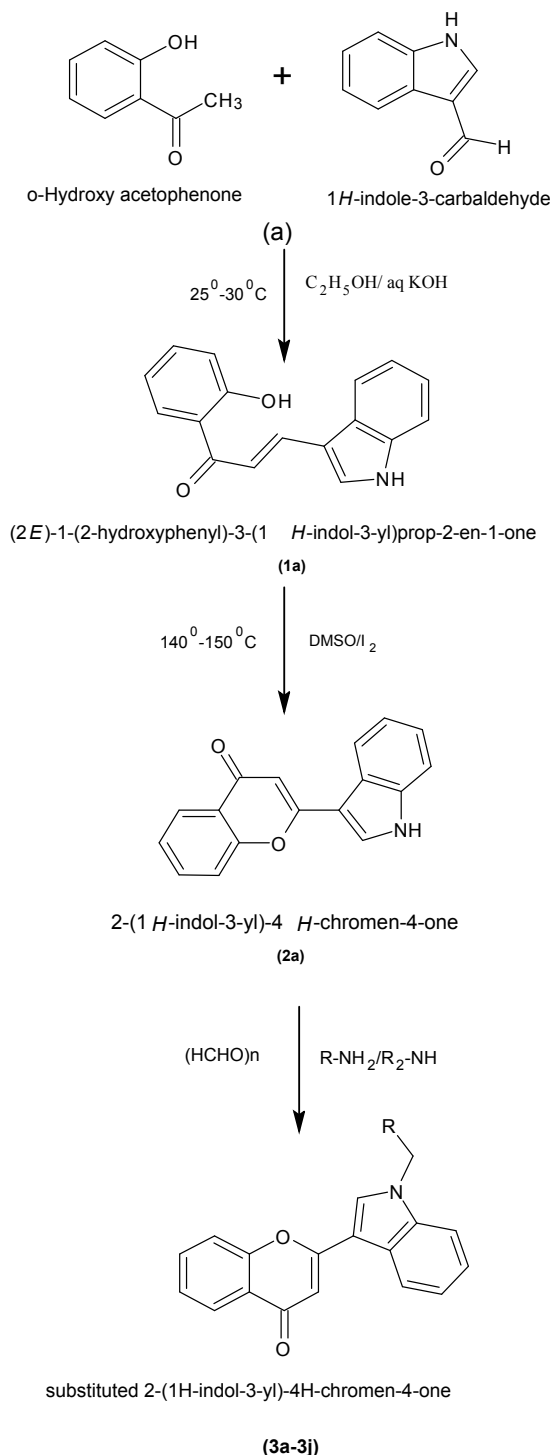
Step 1:- Synthesis of 1-(2-hydroxyphenyl)-3-(1H-indol-3-yl) prop-2-en-1-one: (1a)

A solution of NaOH (0.05mol) in water (25ml) and ethanol (15ml) was stirred and cooled. To this solution indole-3-carbaldehyde (0.05mol), o-hydroxy acetophenone (0.05mol) was added. The temperature of the mixture was kept at 25-30°C and stirring was continued for 3hrs. After keeping the reaction mixture in the refrigerator overnight, the chalcones that are separated out are collected and the reaction mixture was diluted with water. The separated solid was filtered and recrystallised from ethanol. Completion of reaction was monitored on TLC using silica gel-G coated plates by using Hexane: ethyl acetate (3:2) as the eluent and observed in the UV light.

Step 2:- Synthesis of 2-(1H-indol-3-yl)-4 H-chromen-4-one (2a):

1-(2-hydroxyphenyl)-3-(1H-indol-3-yl)prop-2-en-1-one (0.01mol) dissolved in 10ml DMSO, iodine (500mg) was added and mixture was refluxed for 2 hrs. On cooling up to 20°C; solid separated on pouring into 20ml cold water which was kept overnight in hypo solution. Separated solid obtained was filtered, washed with coldwater and recrystallized from ethanol. Completion of reaction was monitored on TLC using silica gel-G coated plates by

using Hexane: ethyl acetate (3:2) as the eluent and observed in the UV light.



Step 3:- Synthesis of substituted 2-(1H-indol-3-yl)-4 H-chromen-4-one: (P₁-P₁₂)

To the suspension of 2-(1H-indol-3-yl)-4H-chromen-4-one (0.05mol) in ethanol was added appropriate primary or secondary amines (0.05mol) and paraformaldehyde

(0.05mol) and stirred for 6hrs, and left overnight the solution was poured into crushed ice and resulting solid was collected, washed dried. Recrystallization from the DMF. Completion of reaction was

monitored on TLC using silica gel-G coated plates by using Hexane: ethyl acetate (3:2) as the eluent and observed in the uv light.

Table No. 01

Compound	R	M.p°C	Yield %	Molecular formula
3a	C ₆ H ₅ N	145-147	78	C ₂₃ H ₁₇ N ₃ O ₂
3b	C ₆ H ₅ NO ₂	159-160	87	C ₂₃ H ₁₇ N ₃ O ₄
3c	C ₆ H ₅ NO ₂	150-152	67	C ₂₃ H ₁₇ N ₃ O ₄
3d	C ₆ H ₅ NO ₂	195-196	57	C ₂₃ H ₁₇ N ₃ O ₄
3e	C ₇ H ₅ Br	98-100	90	C ₂₄ H ₁₇ BrN ₂ O ₂
3f	C ₁₁ H ₁₃ N ₂	118-120	75	C ₂₈ H ₂₅ N ₃ O ₂
3g	C ₅ H ₈ NO	155-157	89	C ₂₂ H ₂₀ N ₂ O ₃
3h	C ₃ H ₈ N	205-207	91	C ₂₂ H ₁₈ N ₂ O ₂
3i	C ₅ H ₁₀ N	134-137	95	C ₂₂ H ₂₂ N ₂ O ₂
3j	C ₇ H ₂ N ₃	135-136	76	C ₂₃ H ₁₄ N ₄ O ₂

Results and discussion

Anti oxidant activity: Anti oxidant activity done by two methods nitric oxide radical scavenging method and hydrogen peroxide scavenging method. All the compounds and the standard were dissolved and made up with DMSO (solvent)- stock solution (100µg/100ml) and from stock solution various concentrations (two fold dilutions) of 50, 100, 200, 400 and 800µg/ml were prepared in different volumetric flasks. To each solution 1ml sodium nitroprusside solution was added. Standard (Ascorbic acid) of again same five concentrations were

prepared by adding 1 ml sodium nitroprusside solution in phosphate buffer saline. All the above preparations were incubated at 37°C for 2.5hrs. After incubation 1ml of GRIESS reagent (Phosphoric acid + sulfanilamide+α-naphthylethylene dihydrochloride) was added and made up with phosphate buffer to the mark immediately before recordings of readings. All the solution mixtures acquired pink colour appearance whose absorbance was measured at 546nm using blank as phosphate buffer saline.

Table No. 02: Nitric Oxide Radical Scavenging Activity

Compound	% Scavenging Activity					IC ₅₀ values (µg/ml)
	50 µg/ml	100 µg/ml	200 µg/ml	400 µg/ml	800 µg/ml	
3a	26.26	42.92	46.29	59.38	76.09	194.98
3b	46.21	53.15	63.6	72.5	83.6	72.44
3c	40.6	50.08	59.38	69.36	80.47	97.72
3d	16.8	34.0	54.29	62.75	75.42	208.29
3e	15.2	25.7	44.14	58.03	67.7	251.18
3f	59.38	71.46	74.9	86.6	88.38	16.89
3g	50.37	57.40	63.46	67.21	77.06	46.77
3h	21.0	30.89	56.8	63.9	69.0	213.79
3i	33.42	46.80	70.03	71.08	76.68	109.64
3j	52.73	63.9	72.9	82.28	82.40	31.33
Ascorbic acid	55.5	72.3	79.04	88.72	94.19	25.11

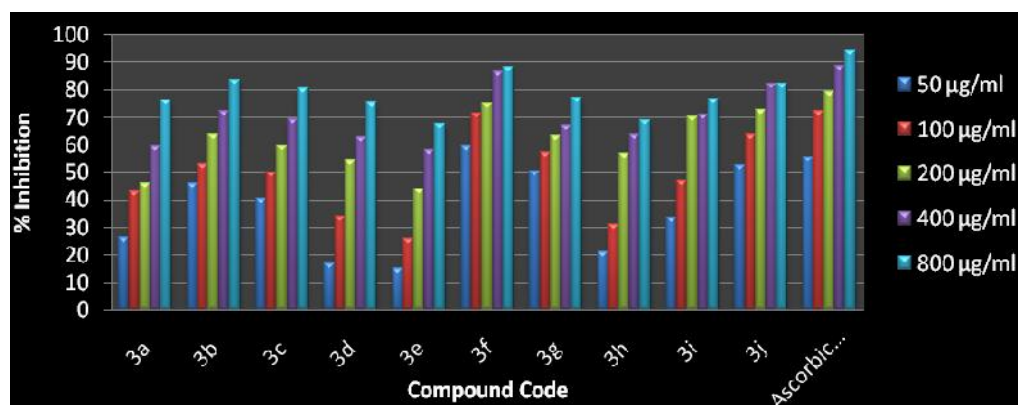


Figure No. 01: Nitric oxide Scavenging Activity

Spectroscopic data of synthesized compounds

3a. IR (KBr cm^{-1}): Ar NH str 3239, C=O str 1717, C-O-C str 1296, Ar C-N str 1335, Aliphatic C-H str 2886, Ar =C-H str 3017, C-H bend (OOP) 884, =C-H bend 1006, Ar C=C str 1612, Mono substituted 760,641. **^1H NMR Spectral data (δ in ppm):** (t,NH,1H), (d, CH₂, 2H), (m, ArH, 14H).

3b. IR (KBr cm^{-1}): Ar NH str 3447, C=O str 1685, C-O-C str 1293, Ar C-N str 1319, Aliphatic C-H str 1242, Aliphatic C-H str 2836, Ar =C-H str 3017, C-H bend (OOP) 883, =C-H bend 1040, Ar C=C str 1577, N-O str 1541, di substituted p-position 787. **^1H NMR Spectral data (δ in ppm):** (t,NH,1H), (d, CH₂, 2H), (m, ArH, 14H).

3c. IR (KBr cm^{-1}): Ar NH str 3295, C=O str 1718, C-O-C str 1297, Ar C-N str 1336, Aliphatic C-H str 1243, Aliphatic C-H str 2375, Ar =C-H str 3015, C-H bend (OOP) 883, =C-H bend 1005, Ar C=C str 1699, N-O str 1558, di substituted p-position 599, 700, 805. **^1H NMR Spectral data (δ in ppm):** t,NH,1H), (d, CH₂, 2H), (m, ArH, 14H).

3d. IR (KBr cm^{-1}): Ar NH str 3393, C=O str 1734, C-O-C str 1297, Ar C-N str 1346, Aliphatic C-H str 1243, Aliphatic C-H str 2848, Ar =C-H str 3006, C-H bend (OOP) 852, =C-H bend 1008, Ar C=C str 1683, N-O str

1559, di substituted o-position 734. **^1H NMR Spectral data (δ in ppm):** (t,NH,1H), (d, CH₂, 2H), (m, ArH, 14H).

3e. IR (KBr cm^{-1}): Ar NH str 3361, C=O str 1719, C-O-C str 1243, Ar C-N str 1392, Aliphatic C-N str 1124, Aliphatic C-H str 3239, Ar =C-H str 2848, C-H bend (OOP) 871, =C-H bend 989. **^1H NMR Spectral data (δ in ppm):** (t,NH,1H), (d, CH₂, 2H), (m, ArH, 14H).

3f. IR (KBr cm^{-1}): C=O str 1749, C-O-C str 1229, Ar C-N str 1337, Aliphatic C-H str 1238, Aliphatic C-H str 2886, Ar =C-H str 3134, C-H bend (OOP) 828, =C-H bend 1009, Ar C=C str 1570. **^1H NMR Spectral data (δ in ppm):** (t, CH₂, 8H), (s, CH₂, 2H), (m, ArH, 15H).

3g. IR (KBr cm^{-1}): C=O str 1749, C-O-C str 1297, Ar C-N str 1335, Aliphatic C-H str 1138, Aliphatic C-H str 3012, Ar =C-H str 3134, C-H bend (OOP) 904, =C-H bend 1007, Ar C-H str 3239. **^1H NMR Spectral data (δ in ppm):** (s, CH₂, 2H), (t, CH₂, 4H), (t, CH₂, 4H), (m, ArH, 10H).

3h. IR (KBr cm^{-1}): C=O str 1772, C-O-C str 1296, Ar C-N str 1334, Aliphatic C-N str 1243, Aliphatic C-H str 2885, Ar =C-H str 2946, C-H bend (OOP) 885, =C-H bend 1006, Ar C=C str 1635. **^1H NMR Spectral data (δ in**

ppm): (s, CH₃, 6H), (s, CH₂, 2H), (m, ArH, 10H).

3i. IR (KBr cm⁻¹): C=O str 1751, C-O-C str 1297, Ar C-N str 1335, Aliphatic C-N str 1243, Aliphatic C-H str 2801, Ar =C-H str 3018, C-H bend (OOP) 885, =C-H bend 1006, Ar C=C str 1685. **¹HNMR Spectral data δ in ppm):** (t, CH₃, 6H), (q, CH₂, 4H), (s, CH₂, 2H), (m, ArH, 10H).

3j. IR (KBr cm⁻¹): C=O str 1749, C-O-C str 1296, Ar C-N str 1335, Aliphatic C-N str 1242, Aliphatic C-H str 2936, Ar =C-H str 3134, C-H bend (OOP) 884, =C-H bend 1005, Ar C=C str 1576. **¹HNMR Spectral data δ in ppm):** (m, ArH, 13H), (s, CH₂, 2H).

Conclusion

A 10 no of quercetine derivatives from 3a-3j have been synthesized and characterized by spectroscopic means. All the compounds were subjected to *in-vitro* anti-oxidant activity using ascorbic acid as a standard by two methods i.e. by Hydrogen peroxide scavenging method and nitric oxide radical scavenging method. Anti oxidant activity revealed that all the synthesized compounds have shown significant anti-oxidant activity when compared with that of standard drug. The compounds **3b**, **3c**, **3f** and **3j** showed more activity as compared to the other derivatives. IC₅₀ values were calculated by statistical regression analysis to find out the concentration to show 50% scavenging activity.

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