SYNTHESIS OF CHROMANONES AND FLAVONES LEADING TO THE SYNTHESIS OF NEW INDAZOLE DERIVATIVES AND EVALUATING ITS BIOLOGICAL ACTIVITY

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Abstract

The chromanone formation starting from 2-phenyl-4-formyl-2H-1,2,3-triazole **(1)** with 2-hydroxy acetophenone under basic condition was done to achieve the α, β-unsaturated ketone i.e., the chalcone viz., 1-phenyl-3-(2-phenyl-2H-1,2,3-triazol-4-yl)-2-propene-1-one **(2)**. This compound on cyclization under acidic condition yielded a flavone **(8)** containing 2-phenyl-2H-1,2,3-triazole as substituent. Further, this compound **(2)** on reacting with ethyl aceto acetate gave 3-(2'-Hydroxyphenyl)-5-(2-phenyl-2H-1,2,3-triazol-4-yl)6-carbethoxy cyclohex-2-en-1-one **(3)** which on treatment with hydrazine yielded the corresponding oxoindazole **(4)** the target compound i.e., 4-(2-Phenyl-2H-1,2,3-triazol-4yl)-6-(2-hydroxyphenyl)-3,3a,4,5-tetrahydro-3(*2H*)-oxoindazole **(4)** in good yield.

Key words*:* Chromanones, flavones, 2-phenyl-2H-1,2,3-triazole, pyrazole, oxoindazole, antibacterial activity.

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Introduction

1,2,3-Triazoles have been found to have numerous applications in organic synthesis[01-08], as well as in medicine[09-14] and industry as biologically active systems, as dyestuffs[15] and fluorescent compound, as corrosion inhibitors[16], as photo stabilisers and as agrochemicals[17-19]. Though as on date many reviews have been written on 1,2,3-triazoles, 2-phenyl-4-formyl-2H-1,2,3-triazole **(1)** seems to be neglected for its synthetic applications. This rare compound containing versatile formyl group offers a great scope to study its reactivity and show its utility in the formation of a range of heterocyclic compounds. The synthesis of chalcones from **(2)** and further developing into oxoindazoles was of special interest and to further screen for its biological activity.

J. L. Ribsomer and G. Sumrell[20] have reported the disubstituted condensation product of the aldehyde and acetone. On similar lines we have synthesised some compound in our laboratory. The one discussed here is condensation of aldehyde **(1)**[21] with 2-hydroxy acetophenone under basic condition to obtain the α, β -unsaturated ketone, the corresponding chalcone viz., 1-phenyl-3-(2-hydroxy-2H-1,2,3-triazol-4-yl)-2-propen-1-one **(2)**. This was then cyclised to get 4-chromanone **(7)** viz., 2,3-dihydro-2-(2-phenyl-2H-1,2,3-triazol-4-yl)-*4H*-1-benzopyran-4-one.

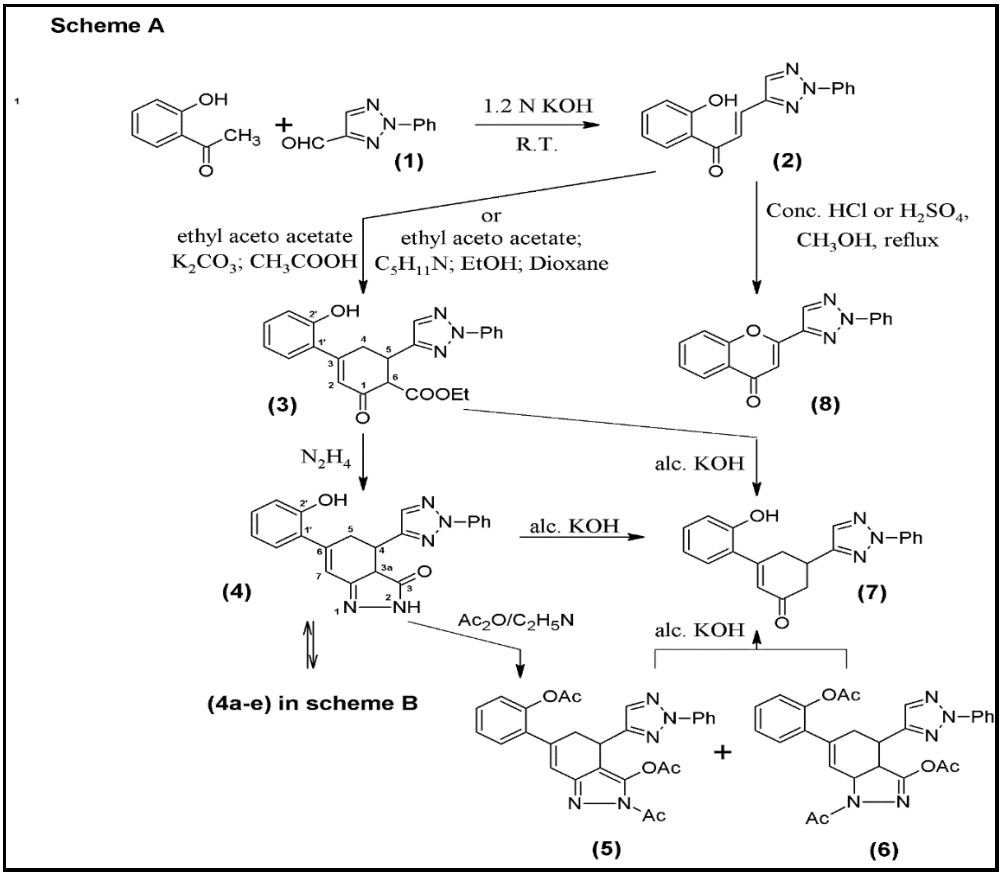
Chromanones are dihydrobenzopyranones[27]. The above compound **(2)** was then converted to flavones and also used to prepare oxoindazoles.

Results and discussion

Pyrazole derivatives are known to have remarkable biological activity.

Here pyrazolobezocycloalkanes and 4,6-diaryl-2,3-disubstituted-benzo[c]pyrazoles have been studied and found to possess varying degree of antifertility and hormonal activities[22-24].

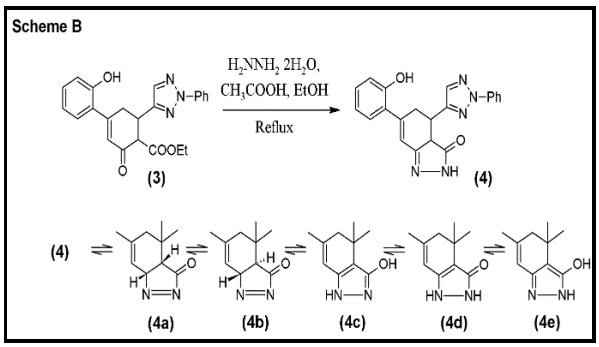
In this **(Scheme-A)** we have reported the synthesis of 4-(2-phenyl-2H-1, 2, 3-triazol-4-yl)-6-(2'-hydroxyphenyl)-3, 3a, 4, 4-tetrahydro-3(*2H*)-oxoindazole **(4)** and derivatives and screened for their biological activities.



3-(2-hydroxyphenyl)-5-(2-phenyl-2H-1,2,3-triazol-4-yl)6-carbethoxcyclohex-2-en-1-one **(3)** required for the synthesis of *2H*-indazole derivative was obtained by the Michael condensation of 2'-hydroxy chalcone **(2)** with ethyl aceto acetate in two routes. In one case ethanolic piperidine was employed for condensation[25, 26]. However, in the second method

where the reactants were taken in dry acetone and anhydrous K_2CO_3 under reflux temperature yielded purer product and in better yields. The structure was characterised by IR and PMR spectra.

Compound **(3)** was subjected to hydrolysis and in situ decarboxylation by heating with ethanolic KOH followed by acidification gave 3-(2-hydroxyphenyl)-5-(2-phenyl-2H-1,2,3-triazol-4-yl)cyclohex-2-en-1-one **(7)**. The reaction of **(3)** with hydrazine hydrate in the presence of ethanol, acetic acid (3:1) under reflux afforded the corresponding 4-(2-phenyl-2H-1,2,3-triazol-4-yl) -6-(2-hydroxyphenyl)-3, 3a, 4, 5-tetrahydro-3(*2H*)-oxoindazole **(4)** in good yields[27, 28]. In this compound, the heterocyclic ring could exist theoretically in as many as six tautomeric forms **(4, 4a-e) (Scheme B)**. Since the PMR spectrum of each product exhibited all the signals of the tautomer **(4)**, it is definitely contributing to the dynamic equilibrium.



Further acetylation of the above indazolones **(4)** with acetic anhydride in the presence of pyridine gave the corresponding acetate whose PMR spectra displayed 4-6 singlets for both N-acetyl groups but no signal for 3a-proton. Obviously, each of these acetates is a mixture of two compounds **(5 and 6)** which however is not amenable to separation by chromatography. The entire work has been outlines in the **scheme A and B** respectively.

Experimental (Scheme A and B)

Melting points were determined in open capillaries and are uncorrected. IR spectra was recorded on Shimadzu 5300, Jasco FTIR-300 in KBr and PMR on VXRO-300 using TMS as an internal standard (chemical shift in δ ppm). The reactions were monitored on TLC and purification were carried out using solvents ethanol, methanol, ethyl acetate-pet ether (60-80). All the chemicals used were from Qualigens, S. D. Fine Chemicals, and Merck brand.

Satisfactory elemental (C, H, N) analysis was obtained for compounds 2-8 respectively.

1-(2'-Hydroxyphenyl)-3-(2-phenyl-2H-1,2,3-triazol-4-yl)-2-propen-1-one (2):

To a solution of 2-phenyl-4-formyl-2H-1,2,3-triazole (1, 0.057mol) in 1.2 N alc. KOH (8.4 g in 100cm^3 ethanol) under cold condition was added 2-hydroxyacetophenone (0.0577 mol, approximately 7cm^3) gradually and was allowed to stand at room temperature for three days when yellow crystalline solid separated out which was filtered washed with cold ethanol and was purified with ethanol. Yield = 80%; m.pt. → 133ºC

Elemental analysis

Mol Formula: $C_{17}H_{13}O_2N_3$	%C	%H	%N
Calculated	70.09	4.50	14.42
Found	70.04	4.43	14.37

IR(KBr) cm^{-1} (2): 3108, 3060 (OH stretch); 1691 (C=O); 1648 (C=C stretch of α, β unsaturated ketone); 1584 (C=N).

PMR ($CDCl_3$) in δ ppm): 6.96 (d, 1H, C_β-H), 7.08 (d, 1H, C_α-H), 7.40-8.15 (m, 10H, Ar-H), 12.70 (s, 1H, OH exchangeable), 7.40-7.54 (m, 5H, Ar-H of triazole), 7.90 (s, 1H, H-5, of triazole), 7.96 (d, 1H, C_3-H), 8.06 (d, 1H, C_4-H), 8.15 (d, 1H, C_5-H) 7.93, (d, 1H, C_6-H).

3-(2'-Hydroxyphenyl)-5-(2-phenyl-2H-1,2,3-triazol-4-yl)6-carbethoxy cyclohex-2-en-1-one (3):

Method (A): To a solution of 2'-hydroxychalcone (VIII-1; 0.01mol) in dry acetone (25 cm^3) was added ethyl aceto acetate (2.6 g; 0.020 mol) and anhydrous K_2CO_3 (5.52 g; 40 mmol). The reaction mixture was refluxed for 3 hours and then left overnight at room temperature. The mixture was filtered and the mother liquor was evaporated to dryness. The residue was crystalized from ethanol. Yield = 67%; m.pt → 203-5ºC.

Method (B): To a solution of 2'-hydroxychalcone (VIII-1); 10 mmol) in ethanol (30 cm^3) and dioxane (0.5 cm^3) was added ethyl aceto acetate (2.6 g; 20 mmol) in presence of piperidine (0.1 cm^3). The mixture was refluxed for 3 hours and then left overnight at room temperature. The mixture was poured in ice-water and the solid obtained was filtered washed with water and cold ethanol and was crystallised from ethanol. Yield was 52%. The tlc and the m.pt was identical with the compound by method **(A)**.

Mol Formula: $C_{23}H_{21}O_4N_3$	%C	%H	%N

Calculated	68.47	5.25	10.42
Found	68.43	5.19	10.36

IR(KBr) cm^{-1} (3): 3000 (OH stretch); 1725 (C=O of ester); 1620 (C=O); 1595 (C=N).
PMR (DMSO-d_6) in δ ppm): 1.23 (t, 3H, -OCH_2-CH_3), 2.96 (d, 2H, C_4-H), 3.51 (m, 1H, C_5-H), 3.92 (q, 2H, -CH_2- ester), 4.34 (d, 1H, C_6-H), 6.51 (s, 1H, C_2-H), 7.2-8.01 (m, 10H, Ar-H and H_5 of triazole), 12.1 (s, 1H, OH).

3-(2'-Hydroxyphenyl)-5-(2-phenyl-2H-1,2,3-triazol-4-yl) cyclohex-2-en-1-one (7):
Method A: A solution of **(3)** (10 mmol) in ethanol (20 cm^3) and aq. KOH (1.68 g/10cm^3, 30 mmol) were refluxed for 3 hours, cooled, diluted with water and acidified with dil. HCl. The product was crystallized from ethanol. Yield = 55%; m.pt→ 108°C.

Mol Formula: $C_{20}H_{17}O_2N_3$	%C	%H	%N
Calculated	72.49	5.17	12.68
Found	72.45	5.13	12.63

IR(KBr) cm^{-1} (7): 2960 (OH); 1735 (C=O); 1630 (C=C); 1600 (C=N).
PMR (DMSO-d_6) in δ ppm): 2.56 (d, 2H, C_4-H), 3.22-3.25 (d, 2H, C_6-H), 3.50-3.53 (m, 1H, C_5-H), 6.46 (s, 1H, C_2-H), 12.3 (s, 1H, OH), 7.0-8.01 (m, 10H, Ar-H and H-5 of triazole), 7.3-7.49 (m, 5H, Ar-H attached to triazole), 7.66 (s, 1H, H-5 of triazole), 6.9 (m, 1H, C_3-H), 7.3 (d, 1H, C_4-H), 8.01 (d, 1H, C_5-H), 7.0 (d, 1H, C_6-H).

Method B: A solution of **(5/6)** (0.0025 mol) in ethanol (20 cm^3) and aq. KOH (1.0 g/10cm^3) were refluxed for 3 hours, cooled, diluted with water and acidified with dil. HCl when the solid separated out. The product obtained was filtered, washed with water and was crystallized from ethanol. The compound obtained was identical with compound **(7)** obtained by method from **(3 and 4)**. The yield was 35%.

4-(2-Phenyl-2H-1,2,3-triazol-4yl)-6-(2-hydroxyphenyl)-3,3a,4,5-tetrahydro-3(*2H*)-oxoindazole (4):
A mixture of **(3)** (0.005mol), hydrazine hydrate (0.3 cm^3) and acetic acid in ethanol was refluxed on a water bath for 4 hours, evaporated in vacuo and the residue crystallized from ethyl acetate-pet ether (60-80°C). Yield = 61%; m. pt. → 216°C

Mol Formula: $C_{21}H_{17}O_2N_5$	%C	%H	%N
Calculated	67.91	4.61	18.86
Found	67.88	4.56	18.81

IR(KBr) cm^{-1} (4): 2900-3200 (NH/OH); 1700 (C=O); 1640 (C=O of amide); 1601 (C=N).
PMR (DMSO-d_6) in δ ppm): 3.22 (d, 2H, C_5-H), 4.31 (d, 1H, C_{3a}-H), 4.60-4.88 (m, 1H, C_4-H), 6.78 (s, 1H, C_7-H), 7.40-8.20 (m, 10H, Ar-H and H-5 of triazole), 12.73 (s. 1H, -OH).

Acetylation of 4-(2-Phenyl-2H-1,2,3-triazol-4yl)-6-(2-hydroxyphenyl)-3,3a,4,5-tetrahydro-3(*2H*)-oxoindazole (VIII-3) to give tri-acetyl derivative (5 and 6):
The indazole derivative **(4)** 0.0025 mol) was acetylated by refluxing with acetic anhydride (0.75 cm^3) and excess of pyridine (approximately 10 cm^3) for 3 hours. The mixture was poured in acidified ice-water with stirring when solid separated out, was filtered, washed with little dilute acetic acid followed by water and crystallized from methanol to give an inseparable mixture of **(5)** and **(6)**. Yield = 72%; m. pt. → 167-169°C.

IR(KBr) cm^{-1} (5 and 6): 2924 and 2854 (C-H stretch); 1734 (C=O of acetyl group); 1666 >N-CO-CH_3).

PMR (DMSO-d_6) in delta ppm): 1.65, 1.81, 2.16, 2.28, 2.55, 2.58 (6s, 9H N-CO-CH_3 and -O-CO-CH_3), 1.25-1.57 (d, 2H, C_5-H), 4.6 (t, 1H, C_4-H), 7.26 (s, 1H, C_7-H), 7.42-8.48 (m, 10H, Ar-H and H-5 of triazole), 7.42-7.59 (m, Ar-H, attached to triazole), 8.48 (s, H-5 of triazole), 8.00 (d, 1H, C_3-H), 8.2 (d, 1H, C_4-H), 8.3 (d, 1H, C_5-H), 7.79 (d, 1H, C_6-H).

2,3-Dihydro-2-(2-phenyl-2H-1,2,3-triazol-4-yl)-*4H*-1-benzopyran-4-one (8):
(0.001 mol) of compound **(2)** was refluxed in methanol containing few drops of HCl or H_2SO_4 for 6 hours. The reaction mixture was then poured into an ice-water with constant stirring. Brownish-yellow compound separated and was filtered and recrystallized from ethanol to furnish colourless needles. Yield = 69%; m.pt. → 135°C.

Mol Formula: $C_{17}H_{11}O_2N_3$	%C	%H	%N
Calculated	70.58	3.83	14.53
Found	70.54	3.77	14.49

IR(KBr) cm^{-1} (8): 1691 (C=O of chromanone)); 1603 (C=N).

PMR ($CDCl_3$) in delta ppm): 3.35 (d, 2H, -CH_2-, C3 position of chromanone), 5.71 (t, 1H, -CH-, C_2 position of chromanone), 7.26-8.15 (m, 10H, Ar-H), 7.35-7.54 (m, 5H, Ar-H of phenyl group

attached to triazole, 7.26 (s, 1H, H-5 0f triazole), 7.13 (d, 1H, C_5-H), 8.15 (d, C_6-H), 8.06 (d, 1H, C_7-H), 7.98 (d, 1H, C_8-H).

Table- 1 Antibacterial activity of compounds at 2mg/ml concentration by ditch plate method[29].

Compound	Micro-Organism		
	S. aureus	**B. subtilis**	**E. coli**
3	+	+	+
4	++	++	++
5	+	+	+
6	+	+	+
7	-	-	-
8	+	+	+
(-) inactive; (+) mildly active; (++) moderately active; (+++) very active			

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References

1. H. Koopman; Rec. Trans., **1961**, 80,1075.
2. L. Claisen And J. Shadwell; Ber., **1879**, 12, 353.
3. E. Bamberger And Ed. Demuth; Ber., **1901**, 34, 1330.
4. Satish M. Bhalekar, Z. A. Filmwala, Brijesh Singh And P. S. Fernandes; Indian Journal Of Heterocyclic Chemistry; Vol 10, **2001**, Pp. 229-230.
5. Brijesh Kumar N. Singh And P. S. Fernandes; Indian Journal Of Heterocyclic Chemistry; Vol 12, **2003**, Pp. 371-374.
6. Brijesh Kumar N. Singh And P. S. Fernandes; Indian Journal Of Heterocyclic Chemistry; Vol 13, **2003**, Pp. 25-28.
7. Brijesh Kumar N. Singh And P. S. Fernandes; Indian Journal Of Heterocyclic Chemistry; Vol 13, **2003**, Pp. 19-24.
8. Brijesh Kumar N. Singh And P. S. Fernandes; Indian Journal Of Heterocyclic Chemistry; Vol 16, **2006**, Pp. 33-38.
9. L. I. Smith And J.W. Opie; Org. Syn. Coll. Vol., **1955**, 3, 56.
10. Vogel "Text Book Of Practical Organic Chemistry", 5th Ed., **1994**.
11. O. Kamm; Org. Syn., Coll. Vol., **1941**, 1, 445.
12. W. E. Kuhn; Org. Syn., Coll. Vol., **1943**, 2, 447.
13. O. Diels; Ber., **1901**, 34, 1758.
14. E. L. Martin; Org. Syn., **1943**, 2, 501.
15. V. L. Komarewsky, C. H. Riesz And F. L. Morritz In A. Weissberger, Ed.; Technique Of Organic Chemistry, Vol. 2, 2nd Ed., (Wiley-Intersciences, New York), **1956**, 94.
16. F. J. Mcquillin In A. Weissberger, Ed.; Technique Of Organic Chemistry, Vol. 2, 3rd Ed., (Wiley-Intersciences, New York), **1963**, 580.
17. R. L. Augustine; Catalytic Hydrogenation, (Marcel Dekker, New York), **1965**.
18. R. Adams, V. Voorhees And R. L. Shriner; Org. Syn., Coll. Vol. 1, **1944**, 463.
19. H. C. Brown; Tetrahedron, **1966**, 8(1), 149.
20. J. L. Riebsomer And G. Sumrell; J. Org. Chem; **1948**, 3, 807.
21. C. Hudson And R. Hann; J. Am. Chem. Soc., **1944**, 66, 735.
22. R.V. Coombs And W. J. Houlihan; Us Pat., 1974. 3843, 666; Chem. Abstr., **1975**, 82, 57684y.
23. N. K. Sanjwan And S. N. Rastogi; Indian J. Chem., **1981**, 2013, 135.
24. M. Prasad And S. N. Rastogi; Indian J. Chem., **1982**, 21b, 747.

A. C. Jain, P. Arya And A. Sharma; Heterocycles, **1983**, 20, 2369.

25. E. Emilwiez And S. Von Kostanecki; Ber. Dt. Chem. Ges., **1899**, 32, 311.
26. J. Bergellini And M. Filkestein; Gazzetta, **1912**, 42(Ii), 417.
27. V. R. Shah, C. G. Joshi And A. B. Kulkarni; Chemy Ind., **1955**, 1062.
28. L. J. Bradshaw; Laboratory Microbiology (W. B. Saunders Company, Philadelphia, London, Toronto) **1979**.