# SYNTHESIS AND ANTI DIABETIC ACTIVITY OF SOME NEW 2-(SUBSTITUTED PHENYL)-4H-CHROMEN-4-ONE DERIVATIVES

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**Summary**

A new series of 2-(substituted phenyl) chromen-4-one derivatives were synthesized. All the synthesized compounds were purified and Rf values were checked. The structures of these compounds were confirmed by IR, NMR, and CHN analysis. These compounds were subjected to anti diabetic activity. All the compounds have shown promising anti diabetic activity.

**Key words:** Chromone derivatives, Anti diabetic activity, CHN analysis

## Introduction

A number of natural and synthetic Benzopyrone derivatives have been reported to exert notably antimicrobial, antitubercular and antifungal activity. [1-3] Benzopyrone having Chromone (γ -Benzopyrone) moiety are associated with interesting physiological activities such as anti microbial anti tubercular anti inflammatory anti diabetic antiviral anticancer.[4-12]

In view of these observations and our interest in the synthesis of biologically active bi heterocycle possessing Chromone nucleus, we have modified 5-amino-6-hydroxy-2-phenyl-4H-Chromen-4-one V by reacting it with thiourea to yield 2-amino-7-phenyl chromen (5,6-d) imidazol-9 (3H)-one $A_1$ for its versatile biological activity. Compound V was treated with urea to yield 7-phenyl-1H-Chromeno (5,6-d) oxazole-2, 9-dione $A_2$. Compound v was treated with chloroacetyl chloride to get 8-phenyl chromeno (6,5-b) (1,4) oxazine-2, 10 (1H, 3H)-dione $A_3$. Compound v was treated with substituted aldehydes to yield 2-(4-substituted phenyl)-7-phenyl-9H-chromeno (5,6) oxazol-9-one $A_4$ and $A_5$ to explore activities associated with this nucleus and screened them for anti-inflammatory activity. The unique structure of compound V has facilitated for getting compound $A_1$ to $A_5$, which would possess the promising anti-inflammatory activity.

## Material and Methods

**Antidiabetic Activity** [13]

The compounds synthesized during the present work were subjected to anti diabetic activity. Using wistar albino rats.

**Method:** Alloxan induced tail-tipping method. The animals were selected of either sex weighing between 150-200 gms of body weight. The experimental animals kept on fasting for 24 hrs, and then known quantity of Alloxan was induced to increase the body glucose level. The experimental compounds were thus induced and the glucose level was measured by tail tipping method-using glucometer. The results were recorded and calibrated

**Experimental**

Melting points were determined in open capillary method and are uncorrected. Purity of the compound was checked on Silica gel TLC plates. IR spectra were recorded on Thermo Nicolate IR 200 spectrophotometer using KBr disc method. $^{1}$HNMR spectra were recorded on Bruker AMX-400, DMSO d6 as internal standard. Combustion analyses were found to be within the limits of permissible errors.

**Synthesis of 1-(2,5dihydroxy phenyl)-3-phenyl-1, 3-propanedione II** [14]

54 gm (0.15 mole) of 2,5-dibenzoyloxy acetophenone I was dissolved in 325 ml of dry pyridine and was heated to 50 o in a flask. Further 7.3 g (0.13 moles) of finely powdered potassium hydroxide were added with stirring. Stirring was continued till the solid separated out. The reaction mixture cooled to room temp. Acidified with 187 ml of 10% acetic acid solution and the solid separated out was filtered, dried and recystallized from rectified spirit to get the product (24.4 g), yield 64%.

**Synthesis of 6-hydroxy-2-phenyl-4H-chromen-4-one III**. [14]

25.6 g (0.1 mole) of 1-(2,5-dihydroxyphenyl)-3-phenyl-1, 3-propanedione II was dissolved in 75 ml of glacial acetic acid in a 500 ml of round bottom flask and 4 ml of conc. Sulphuric acid was added with constant stirring. The reaction mixture was refluxed for 2h and cooled. The contents of the flask were poured in to beaker containing crushed ice. The solid separated out was filtered and it was recystallized from n-hexane to get the (17.2 g), yield 68%, m.p 240-42$^{0.}$

**Synthesis of 6-hydroxy-5-nitro-2-phenyl-4h-chromen-4-one IV**. [15]

A mixture of 6-hydroxy-2-phenyl-4h-chromen-4-one III (5.1 g, 0.02 moles) and concentrated sulphuric acid (30 ml) was stirred at $0^0$ for 30 min. Then a mixture of conc. Nitric acid (1.5 ml) and sulphuric acid (5 ml 98%) were added. The temperature was kept at 0-5 $^0$ during the period of addition, and the mixture was then continuously stirred for 2 h at $5^0$The reaction mixture was poured into ice cold water the precipitate formed was filtered dried and recystallized from acetone to get the product (4.02 g), yield 78%, m.p. 210-12$^0$.

**Synthesis of 5-amino-6-hydroxy-2-phenyl-4H chromen 4- one** [14]

Iron powder (8g) was added portion wise to a hot mixture of 6-hydroxy-5-nitro-2-phenyl-4h-chromen-4-one IV (5.66 g, 0.02 moles) in ethyl alcohol (20 ml) and conc. Hydrochloric acid (30 ml) at reflux temperature. After completion of the addition, the refluxing was continued for 6h. Upon cooling a white precipitate formed was filtered off washed with water, dried and recystallized from methanol to get product (3.1g) yield 56%, m.p. 180-82$^0$.

**Synthesis of 2-amino-7-phenyl chromen (5, 6-d) imidazol-9- (3H)-one $A_1$.**

A mixture of V (0.5 g 0.002 mole) and thiourea (2.28 g, 0.03 mole) was heated at 130-140 $^0$ for 15 min the reaction mixture melted and re-solidified, treated with hot water, filtered off and recystallized from ethanol to get the product (0.3 g), yield 62%, m.p. 194-95$^0$.

**Synthesis of 7-phenyl-1H-chromeno (5, 6-d) oxazole-2, 9-dione $A_2$**

A mixture of V (0.5 g, 0.002 mole) and urea (1.8 g, 0.03 mole) was heated at 100$^0$ for 15 min, the reaction mixture melted and re-solidified, treated with hot water, filtered off and recystallized from ethanol to get the product (0.24 g), yield 48%, m.p. 208-09$^0$.

**Synthesis of 8-phenyl chromeno (6, 5-b) (1, 4) oxazine-2, 10 (1H, 3H)-Dione $A_3$**

A mixture of V (0.5 g, 0.002 moles), chloroacetyl chloride (0.17 ml, 0.002 moles) and anhydrous potassium carbonate (0.5g) in dry acetone (20 ml) was refluxed for 3h, cooled then poured into ice-cold water. The precipitate formed was filtered off and recystallized from ethanol, yield 57% (0.28 g), m.p. 231-32$^0$.

**Synthesis of 2-(4-substituted phenyl)-7-phenyl-9H-chromeno (5, 6) oxazol-9-one $A_4$, $A_5$**

To a solution of V (0.5g, 0.002 mole) in glacial acetic acid and the appropriate aldehydes namely nitro benzaldehyde and p-chloro benzaldehyde (0.002 mole) was refluxed for 15 hrs, cooled and poured into ice-cold water. The precipitate formed was filtered off and recystallized from pet. Ether, $A_4$: yield 39% (0.19 g), m.p. 178-79$^0$, $A_5$: yield 41% (0.21g), m.p.136-37$^0$.

## Results and Conclusions

A new series of 2-(substituted phenyl) chromen-4-one derivatives were synthesized and the structures of these compounds were confirmed by IR, NMR, and CHN analysis. These compounds were subjected to anti diabetic activity.

Compound $A_3$, $A_4$, $A_5$ have given excellent anti diabetic against Glibenclamide as a standard drugs. With the suitable molecular modification of these synthesized compounds, they may prove as a potent anti diabetic agent.

**SPECTRAL DATA**

**$A_1$ : IR (KBr) $cm^{-1}$ :** 3232(-NH str.), 3055 (Ar-CH str.), 1652 (C=O pyrone), 1500 (Ar-C-C str.), 1331 (C-O str.). **$^1$ H NMR (d ppm):** 11.89 (s, 1H, NH), 7.0-7.63 (m, 8H, Ar-H), 6.56 (d, 2H, $NH_2$)

**$A_2$ : IR (KBr) $cm^{-1}$:** 3238(-NH str.), 3046 (Ar-CH str.), 1689 (C=O pyrone), 1501 (Ar-C-C str.), 1331 (C-O str.). **$^1$ H NMR (d ppm):** 11.59 (s, 1H, NH), 7.52-7.62 (m, 8H, Ar-H).

**$A_3$: IR (KBr) $cm^{-1}$:** 3238(-NH str.), 3085(Ar-CH str.), 1651 (C=O pyrone), 1501 (Ar-C-C str.), 1301 (C-O str.). **$^1$ H NMR (d ppm):** 10.73 (s, 1H, NH), 7.0 -7.63 (m, 8H, Ar-H), 6.96 (d, 2H, $CH_2$).

**$A_4$: IR (KBr) $cm^{-1}$ :**3073 (Ar-CH str.), 1661 (C=O pyrone), 1516 (Ar-C-C str.), 1280 ($NO_2$.) ,679 (-Cl str.). **$^1$ H NMR (d ppm):** 6.94-7.64 (m, 8H, Ar-H).

**$A_5$: IR (KBr) $cm^{-1}$:**3062 (Ar-CH str.), 1682 (C=O pyrone), 1588(Ar-C-C str.), 1452 (C-N str.), 1360 (C-O str.), 1263 (-CN str.). **$^1$ H NMR (d ppm):** 6.94-7.64 (m, 8H, Ar-H).

**SCHEME**

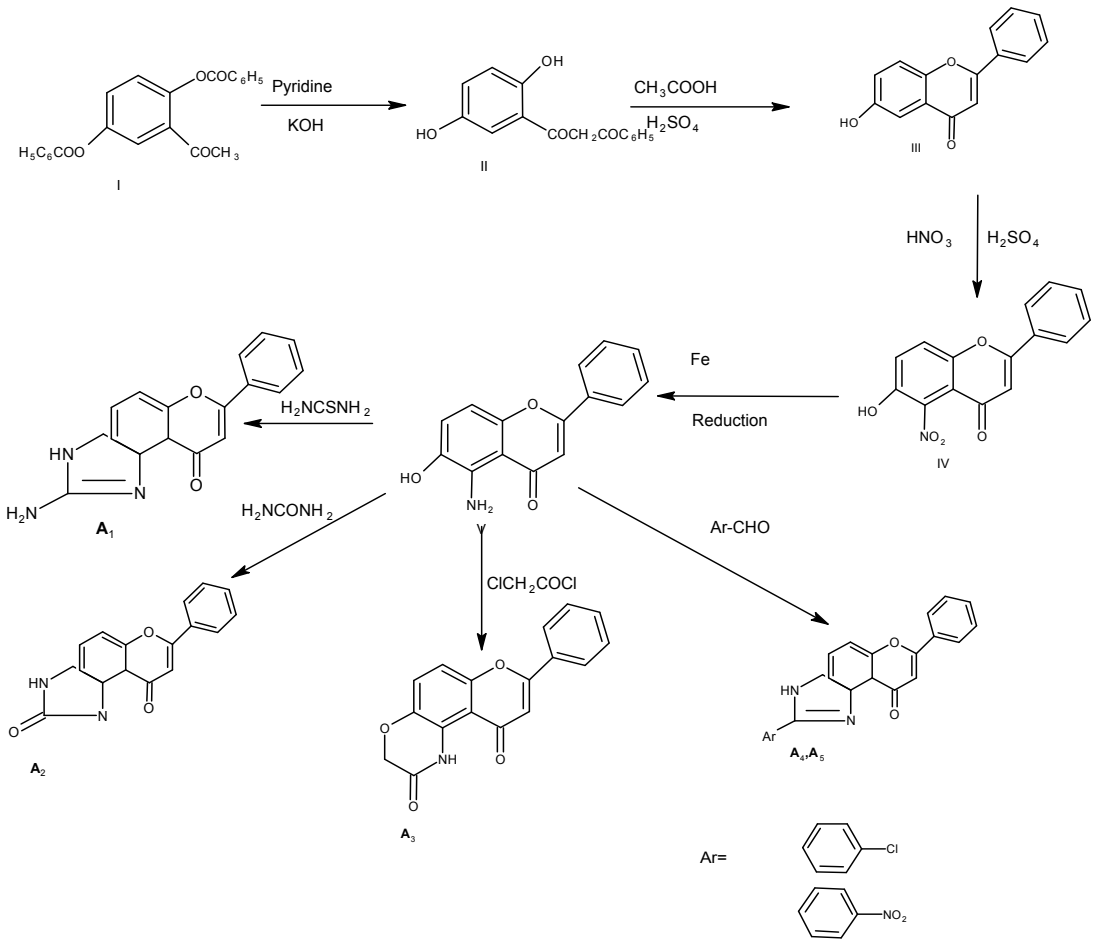

**Table no 1: Analytical data of synthesized compounds ($A_1$-$A_5$)**

| Compd. | Mol. Formula | Mol. Wt. | Yield % | m.p. ° C | Elemental analyses Calcd.(Found) | | |
|---|---|---|---|---|---|---|---|
| | | | | | C | H | N |
| $A_1$ | $C_{16}H_{11}N_3O_2$ | 277 | 62 | 194-195 | 69.3 (69.52) | 4.0 (3.92) | 15.15 (15.21) |
| $A_2$ | $C_{16}H_9N_3O_4$ | 279 | 48 | 208-209 | 68.82 | 3.25 | 5.02 |
| $A_3$ | $C_{17}H_{11}NO_4$ | 293 | 57 | 231-232 | 69.62 | 3.48 | 4.78 |
| $A_4$ | $C_{22}H_{12}NO_3Cl$ | 373 | 39 | 178-179 | 70.69 (70.42) | 3.24 (3.58) | 3.75 (4.00) |
| $A_5$ | $C_{16}H_{12}N_2O_5$ | 384 | 41 | 136-137 | 68.75 | 3.15(3.50) | 7.29 |

The combustion analysis of compounds synthesized is within the limits of permissible errors.

**Table no.2: Anti diabetic activity of synthesized compound**

| Drug | Blood glucose level mg/dl (Mean ± SE) | | | |
|---|---|---|---|---|
| | 0 h | 1 h | 3 h | 6 h |
| **Control** | 123.3± 6.00 | 120.7± 5.54 | 122.3± 5.81 | 123.0± 6.4 |
| **Glibenclamide** | 385.8±21.37 | 230.8±12.35** | 156.8±10.87** | 93.4±4.9** |
| **$A_1$** | 387.5±19.27 | 250.7±14.19 | 200.1±13.09 | 125.5±7.1 |
| **$A_2$** | 368.3±17.57 | 243.9±13.19 | 193.7±12.17 | 135.6±7.2 |
| **$A_3$** | 379.2±20.29 | 233.3±12.57** | 154.9±10.25** | 95.3±4.2** |
| **$A_4$** | 383.1±19.47 | 220.8±11.47** | 149.7±9.57** | 93.5±4.5** |
| **$A_5$** | 385.7±23.29 | 219.7±11.09** | 145.3±9.01** | 91.3±3.9** |

$p<0.05$ *, $p<0.01$**, Statistical ANOVA followed by Dunnet't' test when compared with 0 hour reading. The drugs have shown significant anti diabetic activity. The drugs have shown moderate anti diabetic activity on oral administration.

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**References**


1. Ramesh, Yuvarajan, new flavon methyl ether from Helictres iscora, J. Natural Products, 58, 1995, 1242-1243.
2. Chullia A.J, Bachir Bennini, Two flavonol conjugates from Erica cinerea, J. NaturalProducts, 58, 1995,560-563.
3. Gournelis, Dimitris C, The flavonoids Erica verticillata, J. Natural Products, 58, 1995, 1065-1069.
4. Andreas C, Rajendra M, Constance R, The flavonoids as DNA Topoisomerase antagonists and poisons: structure activity relationship, J. Natural Products, .58, 1995, 217-225.
5. Ye-Shi Li, Young Liu , The flavonoids glycosides from Epimedium pubecens, J. Natural Products, 53(5), 1990,1337-1339.
6. Satyanarayan M R, Dravid G I K, Srimannarayana G ,The photochemical oxidation of 7-methoxy-3-phenyl-2-(furyl vinyl) chromone, Indian J. Chem,30, 1991,613-615.
7. Jehan A M, Hammouda H , Synthesis and biological activities of 5 H-Fluro (3,2-g) (1) benzopyrone-5-one derivatives, Indian J. Chem., 37B, 1998,68-72.
8. Amzad H, Synthesis of 3-methoxy-5-hydroxy-3, 4-methylenedioxy-6, 6-dimethoxy-pyrano (2, 3:7, 8) flavone, Indian J. Chem., 40 B, 2001, 93-95.
9. Basu D K, Murthy R.S, The structure activity relationship of benzopyrones towards their anti-autocoid and anti-acetylcholine activity, Indian J.Pharmacology, 2002,185-194.
10. Liu D F, Cheng C, A facile and practical preparation of 5,7-dihydroxy-3-(4-nitro-phenyl)-4H-1-benzopyran-4-one, Indian J Heterocyclic Chem,28, 1991,641-1642.
11. Vinay P S, The synthesis of 3-(2-benzothiazolyl) chromones, Indian J Heterocyclic Chem., 13, 2003,95-96.
12. Khan M S, Poonam S., Synthesis of pyranochalcones and related cyclization products, Indian.J.Chem. 32B, 1993, 817-821.
13. Kulkarni S.K.,.Mehta A.K and Kunchandy, J.Arch. Int Pharmacodyn. Ther. 1986,279:324.
14. Notel Z M, El-Zahar M I, Abd El Karim, synthesis of Novel Coumarine Derivatives with Expected Biological activity, Molecules, 5, 2005,99-111.
15. Hodgetts, Asymmetric synthesis of (s)-2, 6-dimethylchroman-4-one, Tetrhedron Letters, 412, 2000, 8655-8658.