RESEARCH REVIEW JOURNALS
Volume-1
Issue-2
February-2016

ISSN: 2455-3085 (Online)
RESEARCH REVIEW International Journal of Multidisciplinary
www.rrjournals.com

Review of Related Literatures of Synthesis, Characterization and Therapeutic Evaluation of Sulphur, Nitrogen and Oxygen Containing Novel heterocyclic Compounds and their Antimicrobial Activities

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1. INTRODUCTION

All the synthesized compounds were identified using their IR, H NMR and mass spectral data. In many cases NMR and elemental analysis data are employed to support the characterization. Review of related literature provides useful and necessary direction in the field of research.

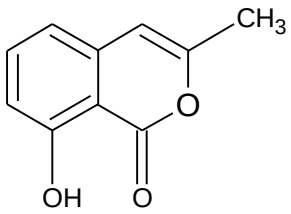
2. REVIEW OF RELATED LITERATURE SYNTHESIS, CHARACTERIZATION AND THERAPEUTIC EVALUATION

Review of Related Literature Synthesis, characterization and therapeutic evaluation of sulphur, nitrogen and oxygen are given as follows:

2.1 R. D. Barry Appeared There Were Only A Few Valid Reports Of The Biological Activities Of Isocoumarins.

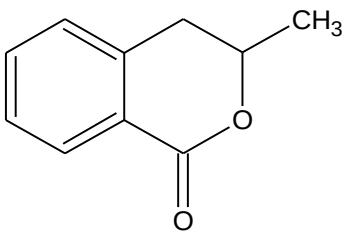
R. D. Barry[1] appeared there were only a few valid reports of the biological activities of isocoumarins. A literature survey of the later period shows that isocoumarins display a wide range of biological activities. A large number of 3-phenylisocoumarin[2] has been tested for various pharmacological activities. Some of these are useful sweeteners, anti-corrosives, fluorescent agents and laxatives, whereas others possess anti-inflammatory, anti-allergic, anti-malarial activities and have proved to be useful in the treatment of asthma[3-4].

Mellein (**1**) has been found in several insects. The defensive secretion of termites[5], Australian onerine ants[6], the mandibular gland secretion of *Camponotusherculeanus, C. lighiperda*and *C. pensylvanicus*[7] (carpenter ants) and the male hair pencil of the oriental fruit moth[8], all contain mellein. Mellein and its dihydroderivatives[9] are found in the defensive secretions of tenebrionid beetle, *Apsenapubescencs*.

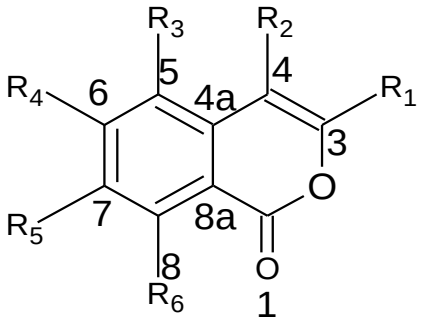


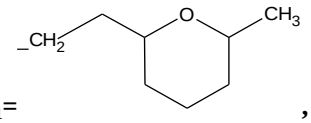
(**1**)

Many fungal isocoumarins exhibit antifungal activities[10] particularly oospolactone[11] (2)**,** chladosporin[12](3a), 6-methoxymellein[13](3b)**,** 3-phenyl-3,4- dihydroisocoumarins carboxylic acid[14]



(2)



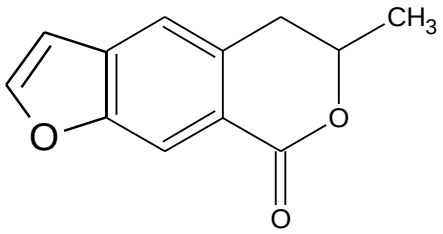


(3a R_1= , R_2=R_3=R_4=R_5=H, R_6=-OH)

(3b R_1= -CH_3, R_2=R_3=R_5=H, R_4=-OCH_3, R_6=-OH)

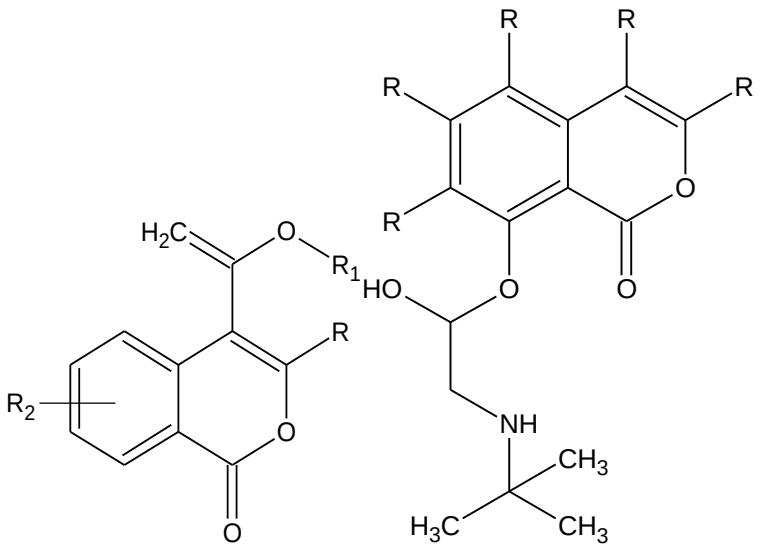
and 3-phenyl-4-(hydroxyacetyl)-3,4-dihydroisocoumarin.

Coriandrin (4), one of the two naturally occurring furoisocoumarinsknown to date, was isolated in 1988 from dry coriander leaves[15]. In addition tothe expected psoralen activity, it shows *in vitro* anti-HIV activity[16].



(4)

6-[2-Chloro-4-(trifluoromethyl) phenoxy] -3, 4- dihydroisocoumarin has shown herbicidal activity and its application of 1kg/ha almost totally controlled *Schinochloa crus-galli, Sinapis alba* and other weeds. Twenty isocoumarins derivatives were tested for biological activities towards rice, radish, barnyard grass and *A. niger*. At 100 ppm, 4-carboxy-6-chloro- **(5**, R=R1=H, R2=6-Cl**)**, 4-carboxy-7-chloro- **(**R=R1=H, R2=7-Cl**)**, and 6-chloro-4 ethoxycarbonyl-3-methylisocoumarin **(**R=Me, R1=Et, R2=6-Cl**)**, were phytotoxic to radish and rice plants while 4-ethoxycarbonyl-6,7-dimethoxy-3-methylisocoumarin **(**R=Me, R1=Et, R2=6,7-$(OMe)_2$**)**, was phytotoxic toradish. 3-Methyl-, 3,7-dimethyl- and 6-methoxy-3-methylisocoumarins inhibitedthe growth of *A. niger*.



(5) **(6)**

Several isocoumarins[17]**(6)** (R=H, alkyl, alkenyl, alkoxy, nitro) are useful as antihypertensives, antiarrhythmics and β-sympatholytics. These wereprepared starting from 3-hydroxyhomophthalic acid. Antiarrhythmic activity of**(6)** (R=H) was comparable to that of pindolol (standard). Isocoumarins with different substituents, isolated from the fungus *Ceratocysistisfimbriatacoffea,* were found to have toxic activity on coffee tree leaves and horse radish peroxidase. Compound also exhibits antiviral activity as well as a distinct inhibiting activity on 3α-hydroxysteroid dehydrogenase (3α -HSD).

A new isocoumarin 2-(8-hydroxy-6-methoxy-1-oxo-1*H*-2-benzopyran -3-yl)propionic acid (NM-3)[41-40]**,** which is an analogue of the natural product cytogenin, induces the lethality of human carcinoma cells by generation of reactive oxygen speciesand inhibits angiogenesis. It increases the antitumour effects of radiotherapy with toxicity and Potentiates Dexamethasone-Induced Apoptosis of Human Multiple Myeloma Cells. It also increases the antitumor effects of various existing chemotherapeutic drugs in breast and prostate tumor model systems, as measured by TGI. Dihydroisocoumarin PF1223from the culture of *Neosartoryaquadricincta* inhibit the specific binding of the non competitive antagonist [^{3}H] EBOB to housefly head membranes. This compound at 2.2 µM inhibited [^{3}H] EBOB binding by 65%.

Reticulol produced from a strain of *Streptoverticillium*, was found to be active against Topo I mediated DNA relaxation *in vitro*. The treatment with 45 µM reticulol afforded inhibitory activity, but with 0.45 and 4.5 µM reticulol, relaxation of DNA was not significantly reduced. The potency of 45 µM reticulol in inhibiting relaxation was almost the same as that of 0.1 mMcamptothecin (molecular weight 348.34). Consequently, reticulol exhibited Topo I-inhibitory efficacy similar to a positive control, camptothecin. This result demonstrated that reticulol blocked the relaxation of DNA with the formation of supercoiled DNA by inducing the inactivation of Topo I.

Seven new naturally occurring 3-butylisocoumarins were isolated and identified from the lipophilic extracts of aerial as well as underground parts of *Asteraceae-Anthemideae*. The antifungal activities of all naturally occurring derivatives were determined in a germ-tube inhibition test against a susceptible strain of rice blast fungus *Pyriculariagrisea*. The 3-butyl side chain is prerequisite for high activity. Eleven new guanidino-, amino alkoxy- and isothiureidoalkoxy substituted isocoumarins are potent mechanism based inhibitors for blood coagulation serine proteases and other trypsin-like enzymes. In many cases, the inhibited enzymes are very stable. These isocoumarins are effective anticoagulants in human plasma.

2.2 Ghulam Qadeer. Nasim Hasan Rama and Syed Jabbar Hussain Shah, "A new total synthesis of natural isocoumarin, Thunberginol B". *ARKIVOC,* 2007, (xiv), 12-19. [2]

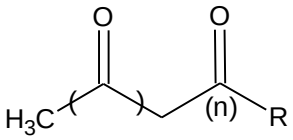
Reduction of cinnamic acid with sodium amaglum yielded 3(3',5'-dimethoxyphenyl) propionic acid which exhibited a broad singlet at δ 11.66 ppm for COOH in ^{1}H NMR which is exchangeable with D2O. The carboxylic carbonyl absorption in IR spectrum was observed at 1722 cm^{-1}. The mass spectrum of the propionic acid showed a molecular ion peak at m/z 210 and a characteristic peak at m/z 165 [M^{+} -COOH]. 3-(3′,5′-Dimethoxyphenyl)propionic acid on cyclization with poly-phosphoric acid furnished the 5,7-dimethoxy-1-indanone and its structure was confirmed by the disappearance of broad singlet due to OH proton (Exchangeable) and removal of one aromatic proton in ^{1}H NMR while carbonyl absorption in IR spectrum appeared at 1685 cm^{-1}. Mass spectrum of the indanoneshowed molecular ion peak at m/z 192.

2.3 M. Arfan*et al*. 3, 5Dimethoxyhomophthalicacid is a key intermediate for the synthesis

M. Arfan*et al*. 3,5Dimethoxyhomophthalic acid is a key intermediate for the synthesis of highly biological active naturally and unnaturally occurring isocoumarins and 3,4dihydroisocoumarins. It was synthesized efficiently in five steps from 3,5dimethoxybenzaldehyde[2] via a series of reactions including synthesis of 3,5-dimethoxycinnamic acidand 3-(3′,5′-dimethoxyphenyl)- propionic acid. Cyclization of 3-(3′,5′-dimethoxyphenyl)propionic acid to 5,7-dimethoxy-1-indanoneand oxidative decomposition of methyl 2-hydroxy-2-(5,7-dimethyoxy-1-oxo-1*H*-inden-2(3H)ylidene)acetateto 3,5 -dimethoxyhomo-phthalic acid. 3, 4Dimethoxybenzoylchloridewas prepared from 3, 4-dimethoxybenzoic acid on reaction with thionyl chloride. Direct condensation of 3, 4Dimethoxybenzoylchloride with 3, 5-dimethoxy-homophthalicacid **at** 200^{o}C afforded 3-(3',4'-dimethoxyphenyl) -6,8-dimethoxyisocoumarin**.** This isocoumarin was purified by HPLC. Complete demethylation of isocoumarin with hydrobromic acid (48%) in acetic acid gave 3-(3', 4'-dihydroxyphenyl)-6, 8-dihydroxyisocoumarin**.**

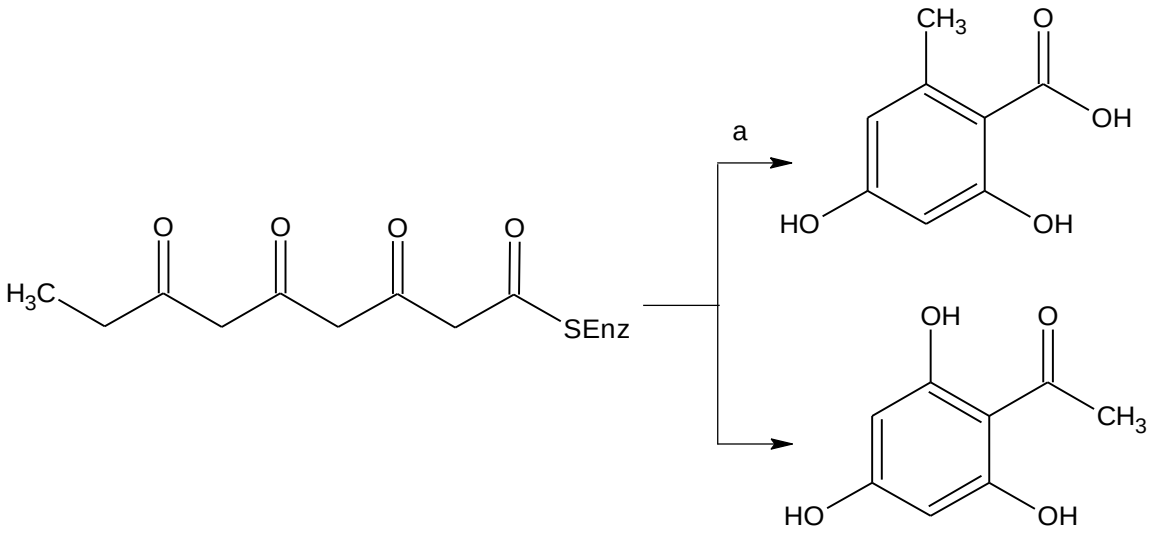
2.4 J. N. Collie (1907) made the first suggestion

J. N. Collie (1907) made the first suggestion of the biosynthesis of certain classes of aromatic compounds, by the head to tail condensation of acetate units. These considerations were based upon the reactivity of synthetic linear β-polyketones (**6**, synthetic linear β-polyketones in which; n ≥2) which underwent aldol type condensations to form aromatic phenolic compounds.



(6)

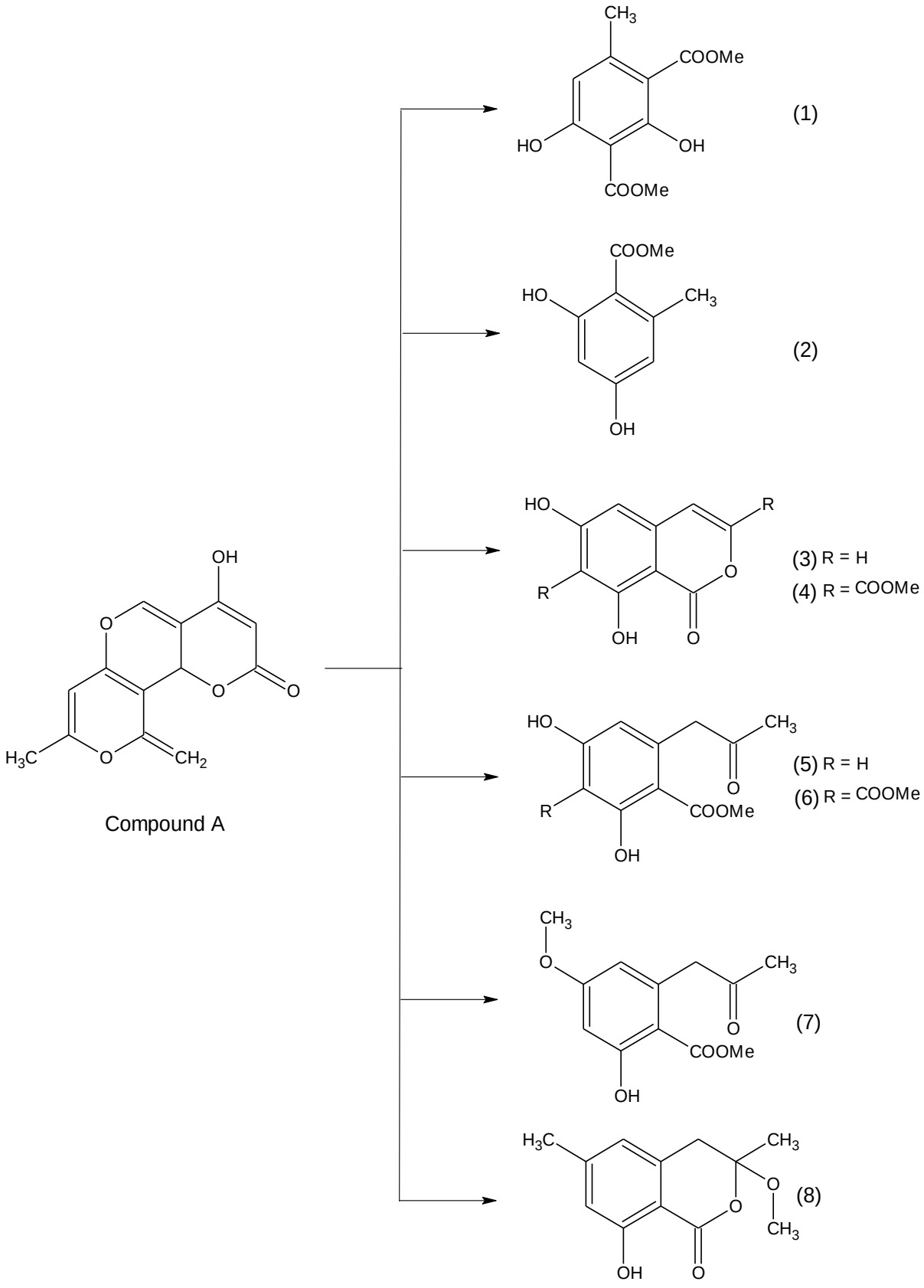
Biogenetic definitions of the aromatic polyketides are due to the work of Birch (1951), by whom a detailed theoretical analysis of carbon skeletons and oxygenation patterns of known compounds was first combined with an extensive series of tracer incorporation experiments. The elaboration of the β-ketide chain in metabolites derived from poly-β-ketideprecursors, normally proceeds by condensation of terminal unit of acetyl Co-enzyme A with chain building units of malonyl Co-enzyme A. llinic acid may be derived from a β-tetraketone, which might undergo the aldol or claisen type condensation. **(Scheme 1)**



Scheme 1.1

2.5 T. Money and F. W. Comer *et al.*

T. Money and F. W. Comer *et al.*[20]using pyrones as masked β- polycarbonyls provided the experimental verification of the acetate-malonate pathway for the synthesis of isocoumarins. Thus hydrolysis of trypyrone**(Compound A)** which is a protected β-pentaketideafforded eight crystalline compounds, six of which were obtained by internal aldol condensations of **(Compound A)** at positions 2 and7 **(Scheme 1.1)**. The products **(1)** and **(2)** appeared due to prior degradation of **(Compound A)**. The remaining products represented conversion of the intact C10 chain and are variants of the 2,7-aldol condensation of **(compound A)**. The most significant of these are 6,8-dihydroxy-3-methylisocoumarin (**3**, R = H) and 7-carbomethoxy-6,8-dihydroxy-3-methylisocoumarin (**5**, R = COOCH3). The structure of **(5)** was confirmed by spectroscopy and its conversion to dimethyl ester (**6**, R=COOCH3) which is another product of the reaction. The methyl ether (**7**) has been isolated from *Endothiaparasitica*, the lactol viz. 3,4-dihydro- 3,6-dimethoxy-8-hydroxy-3-methylisocoumarin **(8)** has also been isolated.This biogenetic type synthesis of isocoumarins and related compounds confirmed the acetate-malonate pathway for biosynthesis of such compounds. ^{14}C Labeledmalonate in these metabolites yields a product in which each of the chain building unit carries a label but the terminal unit of the chain is inactive. On the basis of structure analysis and tracer work many fungal metabolites appear to be derived biogenetically from the acetate and polymalonate pathway[21]. Early reduction of two carbonyl groups in the polyketide chain followed by the loss of oxygen function at C-6 and then aldol type condensation result in the aromatization, to give mellein. Loss of the oxygen function at C-6 of an isocoumarins is quite common but loss of the hydroxyl group at C-8 never occurs in those isocoumarins derived from acetate presumably a consequence of the cyclization mechanism[22].

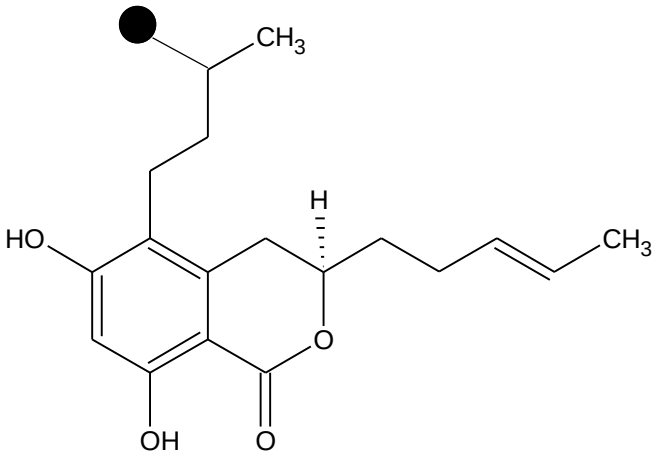


Scheme 1.2

2.6 Y. Suzuki(1907) isolated fusamarin from a strain of *fusarium sp.*

In 1970 Y. Suzuki[23] isolated fusamarin **(9)** from a strain of *fusarium sp.* first synthesis was completed in 1978 under the supervision of Prof. W. B.Whalley[24]. In the biosynthesis of fusamarin the main chain may be derived frompoly-β-ketide pathway and is biosynthesised from seven acetate units. The butyl chain at C-5 is supposed to be derived from isopentylpyrophosphate in which one carbon atom is missing presumably may involve anelectrophilic attack on the poly-β-ketide chain. This would be a

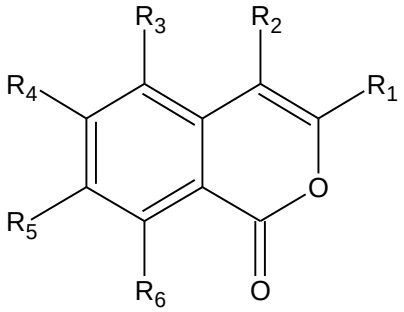
unique exampleof the deviation from the "biogenetic isoprene rule". 6,8-Dihydroxy-3-undecyl-3,4-dihydroisocoumarin[25]isolated from *Ononisnatrix*and peniolactol[26]isolated from *Peniophorasanguinea*Bres belong to poly-β-ketide pathway andcan be biosynthesized from ten and twelve acetate units and their synthesishave been completed under the supervision of Prof. N. H. Rama[27].

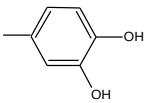
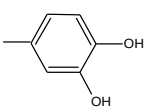
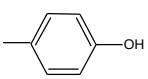


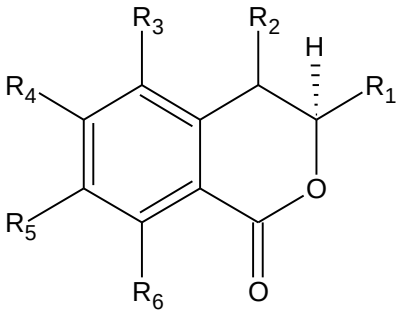
(9)

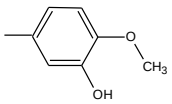
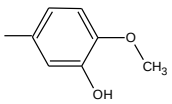
2.7 Wang et al examined the effects of the isolated compounds

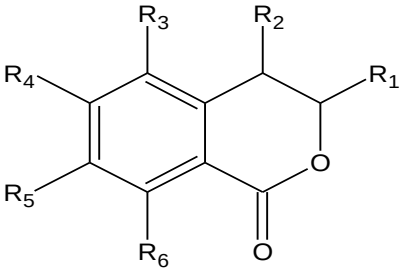
Wang et al[28] examined the effects of the isolated compounds [thunberginols A **(10)**, B **(11)**, C **(12)**, E **(13)**, and F **(17)**, phyllodulcin**(14)**, hydrangenol**(16)**] from HydrangeaeDulicis Folium, thunberginol G **(15)** and 3′-hydroxyhydrangeaic acid **(18)** derived from (**14)**on thedegranulations and/or releases of TNF-α and IL-4 *via* FcεRIsignaling in rat basophilic leukemia (RBL-2H3) cells. In addition, effects of the active constituents on increase in [Ca2+]i were examined to get some information for their mechanism of action. In conclusion, the 3-phenylisocoumarins thunberginols A **(10)** and B **(11)**] and a benzylidene-phthalidethunberginol F **(17)**] from the processed leaves of *Hydrangea macrophylla*var. *Thunbergii*(HydrangeaeDulcis Folium) substantially inhibited the degranulation byantigen and calcium ionophore A23187, and the releases of TNF-α and IL-4 by antigen in RBL-2H3 cells. With regard to structural requirements of the 3- phenylisocoumarins for the activity, the 3,4-double bond was essential for the strong activity and the 6-hydroxyl group and lactone ring enhanced the activity. The active compounds (**10)**, (**11)**and (**17)**inhibited increase in [Ca2]i in RBL-2H3 cells induced by antigen, but not by calcium ionophore A23187.

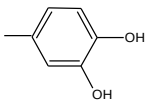
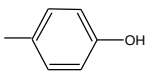


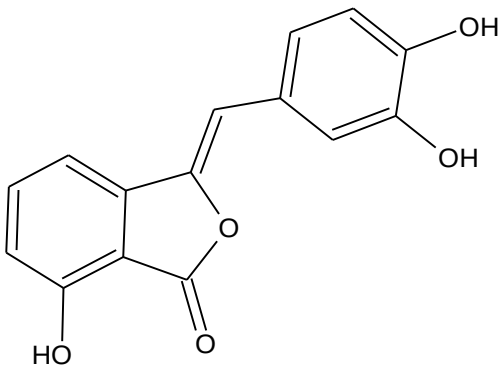
	R1	R2	R3	R4	R5	R6
Thunberginol A**(10)**		-H	-H	-H	-H	-OH
Thunberginol B**(11)**		-H	-H	-OH	-H	-OH
ThunberginolC**(12)**		-H	-H	-OH	-H	-OH



	R1	R2	R3	R4	R5	R6
Thunberginol E **(13)**		-H	-H	-OH	-H	-OH
Phyloducin **(14)**		-H	-H	-H	-H	-OH

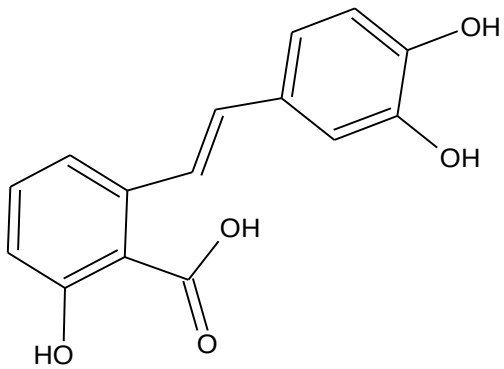


	R1	R2	R3	R4	R5	R6
Thunberginol G **(15)**		-H	-H	-H	-H	-OH
Hydrangenol **(16)**		-H	-H	-OH	-H	-OH



Thunberginol F

(17)



3-Hydroxyhydrangealic acid

(18)

3. CONCLUSION

From the above review of related literature it is concluded that different type of experiment were carried out. R. D. Barry appeared there were only a few valid reports of the biological activities of isocoumarins. Reduction of cinnamicacid with sodium amaglum yielded 3(3',5'-dimethoxyphenyl) propionic acid which exhibited a broad singlet carried out by G. Quadeer. M. Arfan*et al.* 3,5-Dimethoxyhomophthalic acid is a key intermediate for the synthesis of highly biological active naturally and unnaturally occurring isocoumarins and 3,4dihydroisocoumarins. J. N. Collie (1907) made the first suggestion of the biosynthesis of certain classes of aromatic compounds, by the head to tail condensation of acetate units. T. Money and F. W. Comer *et al.* using pyrones as masked β-polycarbonyls provided the experimental verification of the acetate-malonate pathway for the synthesis of isocoumarins. Y. Suzuki(1907) isolated fusamarin from a strain of *fusarium.* Wang et al examined the effects of the isolated compounds [thunberginols, phyllodulcin, hydrangenol fromHydrangeaeDulicis Folium, thunberginol Gand 3′-hydroxyhydrangeaic acid

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