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1,5 Bis(2-hydroxyphenyl)pent-1,4-diene-3-one: a miraculous compound with versatile applications

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Abstract. Use of synthetic chemicals to protect human from various life threatening diseases , and crops particularly food and cash crops from different yield-limiting factors (pests and weeds) has become the inevitable necessity of today, though their detrimental impact on ecosystem is alarming. To achieve the goal of conservation of nature and protection of environment (1), therefore the search for safer molecules with versatile applications in pharmaceutical and agriculture industries has gained momentum. It has led to explore products of natural origin as key intermediates. Such products are relatively broad spectrum, bioefficacious, biodegradable and environmentally safe. Among various plant derived bioactive moieties chalcones and related compounds (chalconoids) (Figure 1A&B) are gaining increasing attention of scientists worldwide.These have been documented to possess quite a number of activities of pharmacological and agricultural interests (2,3).Their structure activity relationship is exhaustively studied by different groups of scientists. Now, it is well established that α,β-unsaturated carbonyl group in particular arrangement as in chalcone nucleus and hydroxylation on benzene ring at particular positions are key factors responsible for bioactivity of the molecule.

Based on such prior knowledge a systematic and comparative study has been carried out by Rani et al (4), starting with the basic nucleus of chalcone, to optimize structural model in terms of number and position of double bonds and hydroxyl groups on aromatic rings. It revealed 1,5-bis(o-hydroxyphenyl)-1,4-pentadien-3-one, I (Figure 2) as a lead compound possessing broad spectrum biological activity against a panel of gram positive and negative human pathogenic bacteria as well as soil borne plant pathogenic fungi.

These valued observations prompted us to summarize an updated spectrum of applications of the compound **I**. Current report offers a new subject to the researchers to unveil the mechanism of interaction of living system with **I** that would help the chemists to design safer broad spectrum bioactive molecules.

Keywords*:* Chalcones, Anticancer, Phase 2 enzymes, Michael acceptor.

1. Introduction

I is a member of a class of compounds known as bis benzylidene alkanones first synthesized by Borshce and Geyer (5). They synthesized it by condensing salicylaldehyde (2mole) with acetone (1mole) in solution of NaOH followed by reaction with CO2 .Bergmann et al., used 50% HCl in place of CO2 treatment to give the compound (6). Friedrich reported synthesis of red colored potassium salt of I by using KOH in nitrogen atmosphere in the dark or in artificial illumination (7). Mentzer and his coworkers have reported the formation of I while developing paper chromatographic method for detecting acetone and methyl ethyl ketone by converting them into salicylaldehyde derivatives ,acetone produced two spots ,one corresponding to 1,5-bis(o-hydroxyphenyl)-1,4-pentadien-3-one (I) and the other to 4-(o-hydroxyphenyl)-3-buten-2-one (8). I can also be synthesized by more facile synthesis involving aldol condensation of salicylaldehyde with acetone in a solution of alcoholic NaOH followed by precipitation of compound with dil. HCl. After recrystallization of crude mass with ethanol I is obtained as yellow colored needle- like crystals with melting

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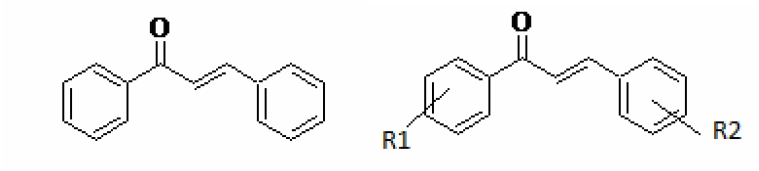
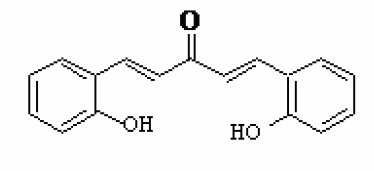
point around 1600C. It readily dissolves in organic solvents, but insoluble in water. When heated with 10% aqueous alkali the substance decomposes, regenerating salicylaldehyde and acetone (9).

Compound I is well characterized with different analytical techniques. Khalaf et al. reported detailed IR analysis of the compound (10). Mahapatra and Nayak analysed the effects of R and 2nd ethylenic bond on C=O stretching frequencies (11). Khalaf et al. also assigned charge transfer and $\pi \quad \pi^*$ bands in the UV spectra of the compound and determined acid dissociation constant form spectral measurements in buffer solutions (10). 1HNMR and 13CNMR spectra of compounds are well in agreement with the structure assigned. The molecular ion peak in the mass spectra appears at m/z 248.0845.



A B

Fig 1: A) Chalcone nucleus B) Chalconoid



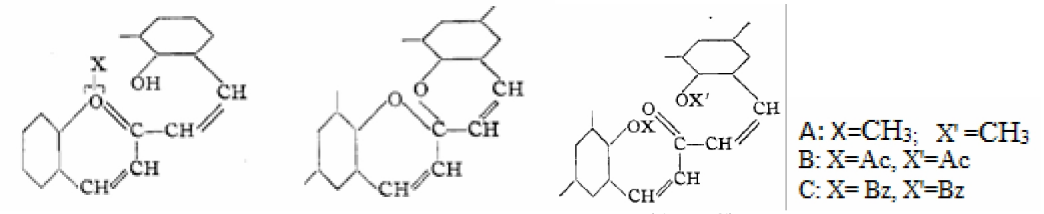
I

Fig 2: 1,5-bis(o-hydroxyphenyl)-1,4-pentadien-3-one (I)

2. Application Spectrum of I

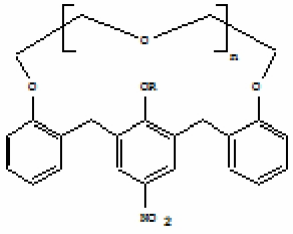
2.1. As reaction intermediate

According to Mora and Szeki disodium salt of I and its dehydrated product can serve as reaction intermediate to synthesize a number of compounds viz., benzopyrilium salts (II), di phenospiropyran, 2-chromenol (III), dimelyther (IV A), diacetate (IVB), dibenzoate (IVC) (12).



II III IV(A,B,C)

Kraft et al. (13) reported synthesis of crown ether like macrocyclic compounds (V) (R = H, n = 1-5) by cyclocondensation of disalicyclideneacetone with oligoethylene glycol ditosylates, followed by hydrogenation and double aldol condensation with sodium 2-nitromalondialdehyde.



V

2.2. As polymer stabilizer and cross linking agent

During their investigation on stabilization of low-density polythene by polyfunctional compounds, Suleimanova and coworkers (14) found effectiveness of bis(2-hydroxybenzal)acetone (I) comparable to that of common antioxidant Bisalkofen BP and light stabilizer Benzon OA. I also prevented polyethene from sticking to rolls during processing. Akhmedzade et al. (15) investigated the effect of I and other related compounds on the formation of supramolecular structures of polypropylene (II) during thermal and light-induced aging. I was found to be the most effective among all the tested compounds. It had both thermal and light-stabilizing effects. The change in mechanical and rheological properties of polypropylene proved that I also acted as crosslinking agent causing structural changes in polypropylene, which was also confirmed by a microscopic study of polypropylene films.

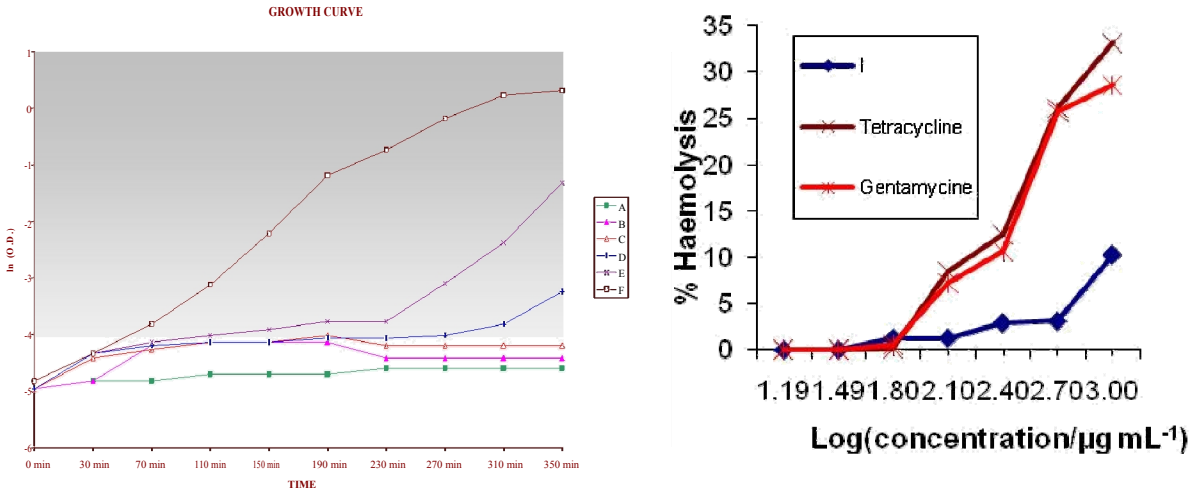
2.3. As corrosion inhibitor

Quireshi and Jamal (16) studied inhibiting behavior of **I** and other related compounds on corrosion of mild steel in sulfamic acid solutions using weight loss and potentiodynamic polarization techniques. All investigated compounds showed good inhibition efficiencies (IE) which varied with the nature and concentration of the inhibitors. Also, the presence of iodide ions further increased IE of all the tested compounds as a result of the synergistic effect. In a similar kind of study IE of **I** to inhibit corrosion of N-80 alloy in boiling hydrochloric acid (HCl) by the weight loss method was found to be 98.7% (17).

2.4. Biological activity

2.4.1. As antimicrobial agent

In 1949, Schraufstatter and Bernt reported antibacterial action of I against *Staphylococcus aureus*, *S. partyphi*, *Trichophyton gypseum* and *Mycobacterium tuberculosis* at different concentrations (18). A series of compounds structurally related to I were screened for antibacterial activity against *Enterococcus faecium* (19). The Minimum Inhibitory Concentration of I, evaluated graphically, was found to be 65µgml . The effect of compound I on the growth of *E.faecium* was also studied by turbidimetric method with increasing concentration of I in nutritive broth (Figure 3A). The study correlates the activity of I with presence of α,β unsaturated carbonyl group and hydroxyl group at 2 and 2' positions of the benzene ring.



A B

Fig 3 : (A) Growth of *E.faecium* in media containing 1,5-Bis(2-hydroxyphenyl) pent-1,4-diene-3-one, at the indicated concentration (■)70 µg ml^{-1} , (▲) 60µg ml^{-1} ,(Δ) 50µg ml^{-1} , (+) 40 µg ml^{-1} (X) 30µg ml^{-1} , (□)0µg ml^{-1} . (B) Haemolytic activities of tested bioactive compounds [19, 4].

The same group of researchers established 1,5-bis(2-hydroxyphenyl)pent-1,4-diene-3-one as a lead compound with potential against a panel of human pathogenic bacterial strains, *Staphylococcus* (coagulase negative), *Escherichia coli, Pseudomonas aeruginosa, Acenetobacter* sp. and *Klebsiella pneumoniae.* Gentamycine and tetracycline were used as reference drugs. The mode of antibacterial action of **1** was studied by scanning electron microscopy, which showed membrane disruption and cell lysis of the organisms during the exposure of the tested compound (4).

In vitro toxicity tests demonstrated that **I** (Figure 3B) exhibits far less toxicity against human erythrocytes as compared to toxicity of gentamycin and tetracycline

In addition to showing effect on human pathogens the compound is reported to be a potent inhibitor of various plant pathogens as well. Mahapatra and Nayak have reported fungicidal activity of di- and tetrabromo derivatives of **I** against Pericularia oryzae, a fungus which infects the rice (11).

Rani et al. reported entirely new action of **I** while evaluating the antifungal activity of **I** in combination with different natural products viz nicotinic acid ,neem oil, asafoetida and usnic acid (a natural bioactive molecule

extracted from lichens)(20).The results confirmed good synergistic fungicidal action against the plant pathogenic fungi *Sclerotium rolfsii* ITCC 5226 and *Macrophomina phaseolina* ITCC 0482.

2.4.2. As anticancer agent

It is well established that the induction of phase 2 enzymes is the most effective strategy to minimize carcinogenicity due to reactive oxygen intermediates, electrophiles, harmful radiations and inflammation. There are a large number of inducers of synthetic and natural origin belonging to nine different classes. Among all these inducers a non- toxic phytochemical curcumin (21) is gaining world-wide attention because of its capability to induce quinone reduction ,quench superoxide radicals and stimulate phase 2 enzyme transcription (22). However due to low potency and poor absorption characteristics it's in vivo use is limited (23). In order to improve its application profile a large number of its derivatives and related compounds (curcuminoids) have been prepared and studied for their antioxidant activity .

After detailed analysis of the results, cited by different groups of scientists(22, 24-27), following structural parameters are identified, a curcumin derivative should possess to show better activity: i) Mono ketone structure in place of -di ketone as in curcumin , ii) analogues with 5 carbon spacer between the aromatic rings rather 7 carbon (as in curcumin) or 3carbon spacer (as in chalcone), iii) Substitution of hydroxyl group at benzene ring : hydroxyl group(s) at the ortho position(s) on the aromatic ring(s) enhanced dramatically their inducer potencies (22,28), iv)The symmetrical , -unsaturated ketone structure, and v) Michael acceptor functionalities (olefins or acetylenes conjugated to electron-withdrawing groups.

The compound **I** is found to be the most appropriate candidate as anticancer agent possessing all the structural requirements in one molecular union. It has two Michael reaction acceptor centers, hydroxyl groups at the ortho positions of both the aryl rings and double bonds symmetrically distributed around carbonyl group. Number of studies confirmed the antioxidant activity of **I** (27).

The exact mechanism of enhancement of inducer potency of ortho hydroxyl group is still unknown and it may be hypothesized that the inducers may activate the S anion or assist in proton transfer in the process of Michael addition [29] through inductive hydrogen bonding of phenolic hydroxyl groups (30).

2.4.3. As retinal pigment epithelial cells protectant

Bahner (7) obtained significant protection of retinal pigment epithelial cells (RPE cells) against photooxidative damage.The degree of protection was correlated with the efficacy in elevating cytoprotective glutathione levels and activities of NAD(P)H:quinone oxidoreductase. The results revealed that the magnitude of resistance to photooxidative damage paralleled the basal levels of glutathione and NAD(P)H:quinone oxidoreductase.

3. Conclusion

Any living system is highly stereospecific and stereoselective. Their response towards tailor-made molecules is sometimes unpredictable. However the ability of **I** to interact with diverse biological systems as per our expectations makes it a miraculous and ideal candidate to lead the researches focused mainly on designing of broad spectrum bioactive agents. On the basis of above discussion we can propose that **I** is architecturally perfect to fit into the receptor sites of the cells. However, the molecular events behind the demonstrated activities must still be determined.

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