Synthesis, Characterization and Screening of Substituted4-Biphenyl Acétamides Against *Fusarium-udum*

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Abstract

Biphenyl derivatives constitute the class of polycyclic aromatic hydrocarbon containing more than one aromatic ring and have been found to be most effective against the many therapeutic diseases. Therefore, a new series of Substituted-4-Biphenyl-Amides have been synthesized by condensation of 4-Biphenyl Acetic Acid with different primary aromatic as well as aliphatic amines.4-Biphenyl Acetic Acid was first treated with Thionyl Chloride in dry benzene to prepare substituted-4-biphenyl acetyl chloride, which is then treated with different aliphatic or aromatic amines to synthesize various substituted-4-biphenyl Acid-amide derivatives. All these compounds are characterized by the analytical spectroscopic techniques to evaluate the structure elucidation. The synthesized biphenyl compounds were screened for antimicrobial and antifungal activity via disc diffusion method against Fusarium udum fungus. Inspite of antimicrobial and antifungal activity these derivatives are also rich in other curative activities such as analgesics, antipyretics, anti-inflammatory, anticancer, antibacterial, anti-psychotic and anxiolytic activities etc. However, in this article we have screened anti-fungal properties for our synthesized compounds and exhibits good activity when they tested against Fusarium-udum.

Keywords**: **Synthesis, 4-Biphenyl Acetic Acid (4-BPAA), Substituted-4-Biphenyl Acid-Amides, Spectral studies, Anti-Fungal Properties.

Introduction

The biphenyls with independent benzene rings have been categorized in the Class of Polyphenyl Compounds or isolated Polynuclear hydrocarbons. These are the polynuclear aromatic hydrocarbons (PAHs) having more than one aromatic nucleus. Biphenyl acetic acid itself and its derivatives have been found to be effective against many therapeutic diseases. One of the therapeutic disease has been screened against *Fusarium udum.* This is the causal agent of wilt disease of pigeon pea which survives in off season on plant trashes in the soil. This has the ability to produce a number of biologically active substances that cause diseases to the plants. The most common among the biologically active substances are enzymes involved in breakdown of cell wall of plants so that they can enter plant tissue. The pathogen produce fusaric acid toxin having phototoxic properties. Its polysaccharides cause blockage in xylem tissue results in shortage of water and mineral solvents in translocation process of plants.

Therefore, there's need to discover novel antifungal agents targeting *Fusarium udum* infection. Biphenyl derivatives have considerable attention due to their wide range of antifungal activities. Biphenyl acetamide analogs have been reported as important pharmacological molecules having significant antifungal properties against *Fusarium udum.*

The present research deals with the investigation of six synthesized biphenyl compounds on fungal species *Fusarium udum*. All the six compounds of 4-Biphenyl acetamide derivatives namely N-phenyl-4-Biphenyl acetamide, N-p Toluene-4-Biphenyl acetamide, N-2-pyridine-4-Biphenyl acetamide, N-p-benzoic acid-4-Biphenyl acetamide, N-2-chloro-4-Biphenyl

acetamide and N-p-bromo-phenyl-4-Biphenyl acetamide have shown antifungal activities against *Fusarium udum.* Literature findings have also been shown its various therapeutic uses, such as: anti-inflammatory agent[1], as analgesic[2], antipyretic[3], antiarthritis[4], antirheumatoid[5], antihypertensive[2] and a binder to human blood plasma-prealbuen etc.4-Biphenyl acetic acid itself has been reported to possess many effective pharmacological activities, such as anti-inflammatory, analgesic, antibacterial[6]and topical steroidal anti-inflammatory activity[7].The Ointment containing-4-biphenyl acetic acid work very effectively as anti-inflammatory as well as analgesic agents[8]. Even the cyclodextrin inclusion complexes of 4-Biphenyl acetic acid are reported to show effective mono-nuclearrogenic anti-inflammatory properties and its phenyl alkanamide derivatives have shown agro horticultural bactericidal activity[9]. Substituted biphenyls can also be used as anti-allergic drugs[10] and anti-inflammatory drugs[7]. Substituted biphenyl-4-acetamides have therapeutic use in the treatment of cancer[11].The title compound of biphenyl is also used as an antitumor agent[12]Biphenyl-3-acetamide,2-amino-thiazole shows anti-tumor activity also used in the treatment of cancer, Alzheimer disease, viral infection, auto-immune disease or neurodegenerative disorder[13]. 2-Biphenyl-acetic acid and 2-biphenyl acetamide used as agrochemical antifungal agent[1].Biphenyl containing compounds possesses anti-psychotic and anxiolytic activity[19].Some of the Biphenyl hydrazide- hydrazone are known to exhibit very good anti-microbial activity[20,21]. Some of the compounds having biphenyl moiety possess valuable medicinal properties like anti-hypertensive and calcium channel blockers [22, 23].Tetrazole are very well known to possess antimicrobial properties[24]. PCBs are proved to cause reproductive, endocrine and neurological disorders, thyroid dysfunction, cognitive and motor deficits. Prenatal exposures are known to cause increased susceptibility to infectious diseases in earlychildhood[25].PCB, s influenced plants diffuse oxygen in soil promoting the growth of aerobic microbes. Soil aeration is also improved by formation of air channels when roots die, decay and by direct root oxygen release[26].Molecules containing biaryl moieties are relatively common within natural products. For their preparation, nature has developed an ample array of biosynthetic strategies[27]. A number of these biaryl natural products belong to the biogenetic class of lignans[28].During the last few years, we have been investigating a range of analogs of natural products[29].These products and many derivatives thereof, both of natural and synthetic origin, have been reported to display antioxidative, anti-inflammatory, anti-tumor, anti-diabetic, anti-microbial, anti-neurodegenerative, anti-depressant, pain Control, astrointestinal, cardiovascular and liver protective properties, among others [30,31].Until 1971, 61% of PCBs were used in closed electrical systems, 13% were used in nominally closed systems, and 26% were used in open-end applications. After 1971, almost 100% of all PCBs produced were used in closed electrical systems [32]. In the present work we describe the synthesis of the first representatives of previously unknown imidazoles, benzimidazoles containing a 4-biphenyl group at position 2, and different substituents at the nitrogen atom N. The presence of not one but two "privileged" fragments in the molecules of these compounds, namely, imidazoles, benzimidazoles and biphenyl, should promote multitarget action. We also collected and analyzed the data on the activity of the synthesized biphenyl compounds with respect to a number of biological targets important for the therapy of diabetes mellitus and its vascular complications[33-36].In view of these observations and in continuation of our research work on biologically active biphenyl derivatives, it is proposed to synthesize Substituted biphenyl acid-amide derivatives derived by the condensation of 4-biphenyl acetic acid precursor first with thionyl-chloride and then with different primary amines.

Materials and methods

Preparation of media

Czepeck's media was prepared for the growth of fungus *Fusarium udum*, dissolved the contents of Czepeck's media as described are agar-agar (7.5 gm), KH_2PO_4 (500 mg), $MgSO_4.2H_2O$ (250 mg), KCl (500 mg), $FeSO_4$ (trace amount), Yeast powder (500 mg),

$NaNO_3$ (1gm), dextrose (5 gm) and distilled water. The media was subjected to sterilization by autoclaving at 15 psi for 15 minutes. Cool down to room temperature before inoculation.

Fungal culture preparation

Small volume of fungal culture was inoculated in autoclaved media and subjected to incubation at 37˚C for 4-5 days. Spreading of fungal culture to solidified Czepeck's agar (15ml.) plates was done with the help of spreader. The culture was allowed to grow at 30^{o}C for 4-5 days of incubation. After sufficient growth, 3 mm pieces of fungal cultures were cut with the help of cork borer and placed on another Czepeck's agar plate already having 1ml. solution of the compound to be tested.

Preparation of Biphenyl compounds

All six biphenyl derivatives were dissolved in absolute ethyl alcohol to make 1000 ppm solution which were further diluted to make 500 ppm and 250 ppm solution in 3 replicates. One control was taken having absolute ethanol only. All these preparations were inoculated in 12 plates, 3 plates for each concentration including control in one experiment.

Identification of antifungal properties of six biphenyl derivatives on *Fusarium udum*

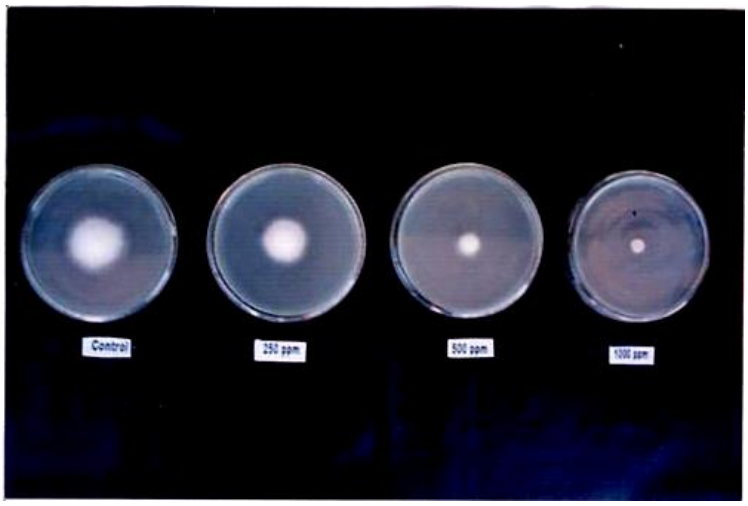
Efficacy of all six compounds was tested by measuring zone of inhibition using disc diffusion method. One compound of volume 1ml one at a time at the concentration of 250 ppm, 500 ppm, 1000 ppm and one as control was added to 12 plates containing 15 ml of Czepeck's media respectively. The set of 4 Petri plates and 3 replicates were used having 12 plates in one experiment. Small pieces of size 3mm was cut from already grown fungal culture and placed on these 12 plates to check axenic nature of the compound.

Results and Discussions

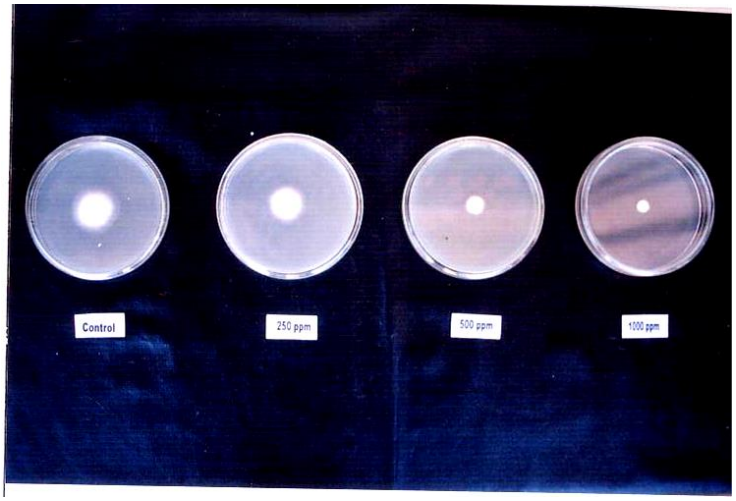
All the six compounds showed positive results and resist the growth of fungus *Fusarium udum*. The disc diffusion method was used for the identification of antifungal properties of all six biphenyl acetamide derivatives such as: a) N-Phenyl -4-Biphenyl acetamide - 2A, b) N-p-Toluene -4-Biphenyl acetamide - 4A, c) N-2-Pyridine -4-Biphenyl acetamide - 9A, d) N-p-benzoic acid -4-Biphenyl acetamide - 10A, e) N-2-Chlorophenyl -4-Biphenyl acetamide - 12A, f) N-p-bromo-phenyl -4-Biphenyl acetamide - 15A.

Table for the identification of anti-fungal Property of 4-Biphenyl acetamide derivatives on Fusarium Udum

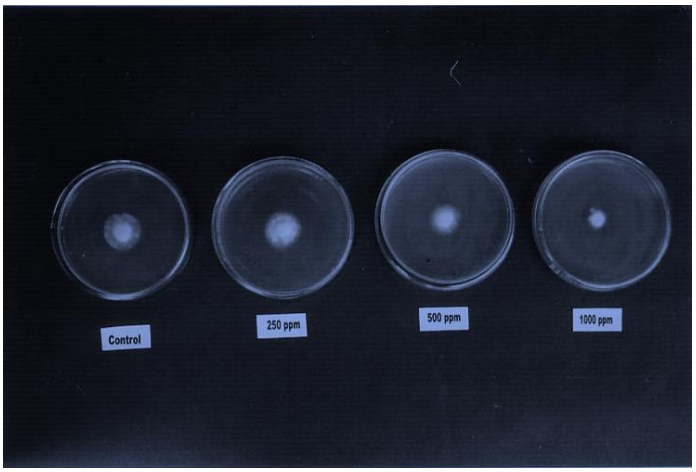
Sr. No.	Code	Time	Temperature	Control(Ethyl alcohol)	250 ppm	500 ppm	1000 ppm
1.	2A	178 hrs.	10±2^{o}C	12mm	9mm	7mm	5mm
2.	4A	175 hrs.	10±2^{o}C	8mm	7mm	5mm	4mm
3.	9A	200 hrs.	10±2^{o}C	10mm	8mm	7mm	5mm
4.	10A	120 hrs.	12±3^{o}C	15mm	11mm	6mm	2mm
5.	12A	144 hrs.	13±2^{o}C	27mm	18mm	12mm	3mm
6.	15A	120 hrs.	13±2^{o}C	9mm	6mm	4mm	1mm



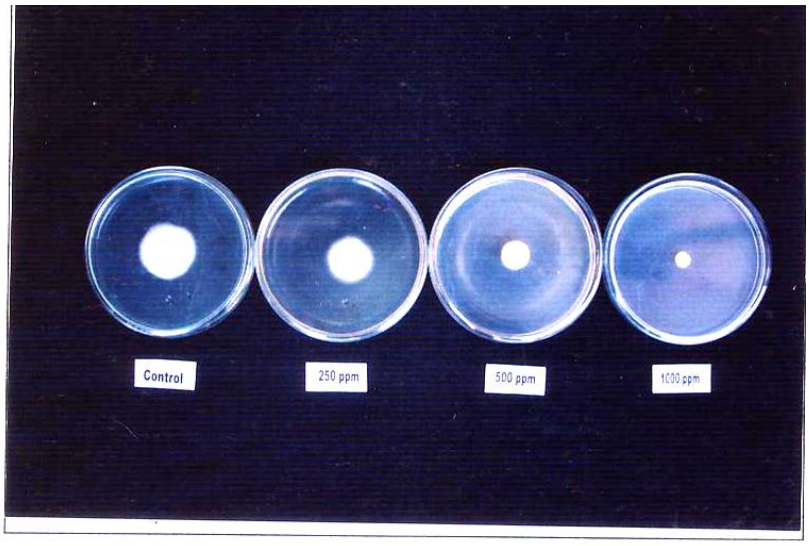
Antifungal property shown by N-p Toluene-4-Biphenyl acetamide (2A) on *Fusarium udum*



Antifungal property shown by N-p Toluene-4-Biphenyl acetamide (4A) on *Fusarium udum*

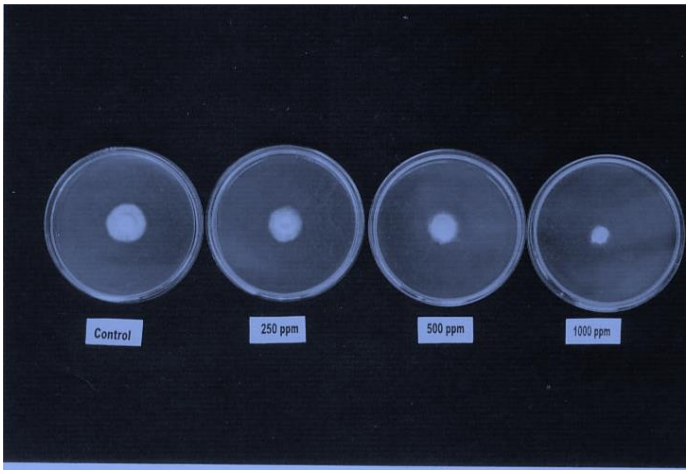


Antifungal property shown by N-2-Pyridine -4-Biphenyl acetamide (9A) on *Fusarium udum*



Antifungal property shown by N-p-benzoic acid -4-Biphenyl acetamide (10A) on *Fusarium udum*

Antifungal property shown by N-2-Chlorophenyl -4-Biphenyl acetamide (12A) on *Fusarium udum*



Antifungal property shown by N-p-bromo-phenyl-4-Biphenyl acetamide (15A) on *Fusarium udum*

Conclusion

Commercially available 4-biphenyl acetic acid (white crystalline solid) was used for the preparation of Substituted-4-biphenyl acetamide derivatives. 4-Biphenyl acetic acid was treated with thionyl chloride in dry benzene on water bath for 2-3 hrs at 70-80^{0}c and has been synthesized. These synthesized-4-biphenyl acetamide derivatives were crystallized and analyzed with the help of M.P., TLC, NMR, IR and Elemental analysis techniques. All the synthesized six organic compounds were tested against the fungus *Fusarium udum* for antimicrobial activity and were found to show good antifungal activity against the fungus. Thus, these compounds can be used as therapeutic agents for the treatment of plant infections by *Fusarium udum*. The culture of each species was incubated at 12 ± 3 ºC and the zone of the inhibition was measured after 120 hr. All compounds with concentration 250 ppm showed minimum growth while compounds with concentration 1000 ppm showed maximum growth when observed via disc diffusion method while the compounds with 500 ppm showed intermediate level of growth. These results justify further research to be done to clarify the mechanism of action of these compounds.

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