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Synthesis of 4-(Biphenyl-4-yl)-2-(Substituted Phenyl)-1-Phenyl-1H-Imidazoles

Bipin Kumar Verma* and Girendra Kumar Gautamb

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***Corresponding Author Email:** bipinpharma@yahoo.co.in

Abstract

Current interest in the new molecules containing the imidazole nucleus remains high in both laboratory and in clinical areas because of the increasing spectrum of biological activity found among these derivatives. In this project we have synthesized and evaluated a number of derivatives containing an imidazole moiety. The used imidazole rings an essential component in antimicrobial activity and plays an important role in biological function. The derivatives were prepared according to previous literature. The widespread application of these procedures is to synthesize these small molecules with proves its utility in treatment of microbial infection disease. In continuation of our efforts in search of potent antimicrobial agents which can be developed as safer and effective, we have been decided to study new derivatives which contain imidazole moiety in it and to further evaluate their pharmacological activity in order to improved & better therapeutic action. Imidazole played an important role for this purpose and this nucleus may serve as new template for the synthesis of safer & potential antimicrobial agents. In view of the wide spectrum of important biological activities including antibacterial, antifungal, antiprozoal, anti-inflammatory, anticancer, anti-anthelmintic and analgesics etc of imidazole derivatives, it was considered worthwhile to work on this system i.e. imidazole skeleton. The aim of the present studies has been to synthesize a new series of imidazole which, may be used as antimicrobial drugs based on their efficacy, lesser or no side effects and low cost involved in their preparation. The title compounds (**3i-xii**) were synthesized as per synthetic protocol (scheme-2). In this scheme biphenyl ethanone (**1**; starting material) was treated with selenium dioxide to get 2-(biphenyl-4-yl)-2-oxoacetaldehyde (**2**). Compound 2 was refluxed with different aromatic aldehydes in presence of ammonium acetate and glacial acetic acid, followed by treatment with chlorobenzene in THF to get twelve new imidazole derivatives (**3i-xii**). The title compounds (**4i-xii**) were synthesized as per synthetic protocol (scheme-3). In this scheme biphenyl ethanone (**1**; starting material) was prepared by heating biphenyl with anhy. $AlCl_3$ in presence of CS_2 and acetic anhydride. The biphenyl ethanone (**1**; starting material) was treated with selenium dioxide to get 2-(biphenyl-4-yl)-2-oxoacetaldehyde(**2**).Biphenyl-2-oxoacetaldehyde **(2)** was refluxed with different aromatic aldehydes in presence of ammonium acetate and glacial acetic acid to get new imidazole derivatives (**3i-xii**). 4-(Biphenyl-4-yl)-2-(substituted phenyl)-1-phenyl-1H-imidazoles (**3i-xii**) were refluxed with chlorobenzene in THF to get desired compounds (**4i-xii**). These final compounds showed different TLC spot, R_f value and melting point while comparing with starting compound (**3i-xii**).

Keywords

Imidazoles, TLC Spot, R_f Value

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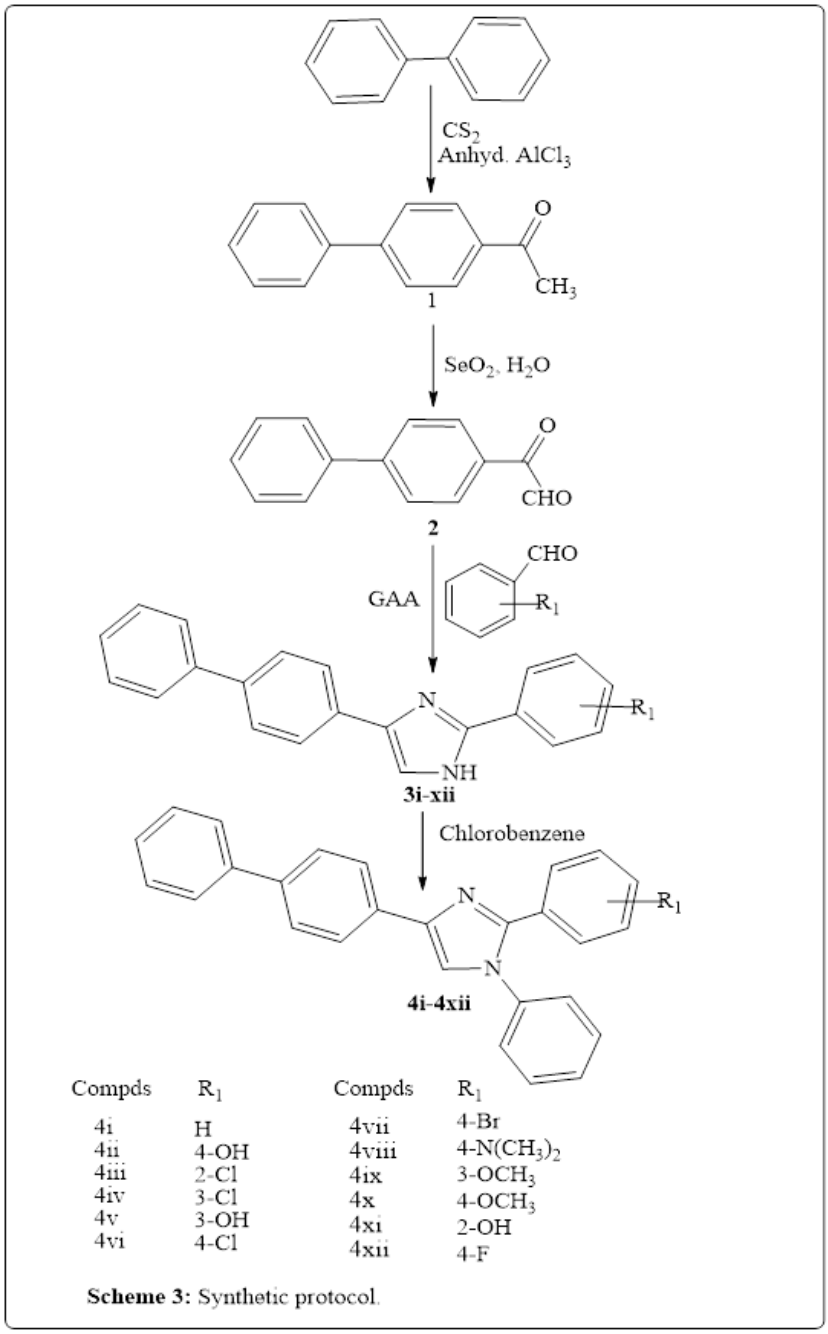
INTRODUCTION

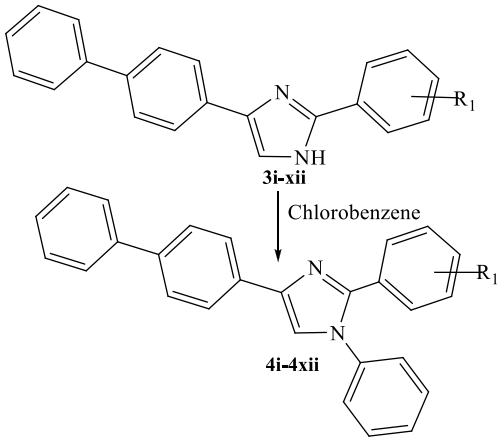
The structures of newly prepared compounds were established on the basis of modern analytical techniques (FT-IR, ^{1}H-NMR and mass spectral data) and elemental analysis. The final compounds were purified by recrystallization with suitable solvent and found pure on TLC examination. The substituent (R), irradiation time, yield, melting point, molecular formula and molecular weight of the newly synthesized compounds are provided in experimental part. **Synthetic Series-3 (Scheme 3).**



Compds	R_1	Compds	R_1
4i	H	4vii	4-Br
4ii	4-OH	4viii	4-N(CH_3)$_2$
4iii	2-Cl	4ix	3-OCH_3
4iv	3-Cl	4x	4-OCH_3
4v	3-OH	4xi	2-OH
4vi	4-Cl	4xii	4-F

Scheme 3: Synthetic protocol.

Compounds **(4i-xii)** synthesis of 4-(Biphenyl-4-yl)-2-(substituted phenyl)-1-phenyl-1H-imidazoles were prepared from Scheme 3. Compounds (**4i-4xii**) were prepared from scheme 3; **4-(Biphenyl-4-yl)-2-(substituted phenyl)-1-phenyl-1*H*-imidazoles (4i-xii).**



Compds	R_1	Compds	R_1
4i	H	4vii	4-Br
4ii	4-OH	4viii	4-$N(CH_3)_2$
4iii	2-Cl	4ix	3-OCH_3
4iv	3-Cl	4x	4-OCH_3
4v	3-OH	4xi	2-OH
4vi	4-Cl	4xii	4-F

CHEMISTRY

The title compounds (**4i-xii**) were synthesized as per synthetic scheme outline. In this scheme biphenyl ethanone (**1**; starting material) was prepared by heating biphenyl with anhy. $AlCl_3$ in presence of CS_2 and acetic anhydride. The biphenyl ethanone (**1**; starting material) was treated with selenium dioxide to get 2-(biphenyl-4-yl)-2-oxoacetaldehyde (**2**). Biphenyl-2-oxoacetaldehyde **(2)** was refluxed with different aromatic aldehydes in presence of ammonium acetate and glacial acetic acid to get new imidazole derivatives (**3i-xii**). 4-(Biphenyl-4-yl)-2-(substituted phenyl)-1-phenyl-1H-imidazoles (**3i-xii**) were refluxed with chlorobenzene in THF to get desired compounds (**4i-xii**). The usual work up of the reaction mixture followed by recrystallized from ethanol gave pure compounds (**4i-xii**). The compound was found pure on TLC examination (B: A, 9:1) and T: E: F (5:4:1), and its spectral data was found satisfactory for the proposed structures. The structures of newly prepared compounds were established on the basis of modern analytical techniques (FT-IR, ^{1}H-NMR and mass spectral data) and elemental analysis. The final compounds were purified by recrystallization with suitable solvent and found pure on TLC examination.

Structural Investigations

The starting material 1-(biphenyl-4-yl) ethanone (biphenyl ethanone, **1**) was prepared by heating biphenyl with anhydrous $AlCl_3$ in the presence of CS_2 and acetic anhydride. The usual work up of the reaction mixture followed by recrystallized from ethanol gave pure compound. The purity of the compound was verified with the help of TLC (B: A, 9:1). % age yield- 80%, m.p.- 152-165 $^{\circ}$C. IR spectra are very informative and provided evidence for the formation of the expected structures. In general, IR spectra of acetophenone showed a strong band of C=O at 1683 cm^{-1}. Whereas ^{1}H-NMR further confirmed the structure due to the presence of a singlet of CH_3 at 2.61 ppm. Compound **2** [2-(biphenyl-4-yl)-2-oxoacetaldehyde] was synthesized from 1-(biphenyl-4-yl) ethanone(**1**) in the presence of selenium dioxide and after work out of reaction gave a yellow liquid which was found pure on TLC examination (TEF 5: 4: 1). The structure of compound 2 was confirmed on the basis of spectral studies. In IR spectra a band at 2851 cm^{-1} for aldehydic C-H stretching was very clear. The ^{1}H-NMR spectra left no doubt with singlet of aldehydic proton at 9.81 ppm.

Compound **2** [2-(biphenyl-4-yl)-2-oxoacetaldehyde] was refluxed with different aromatic aldehyde in the presence of ammonium acetate and glacial acetic acid. The usual work up of the reaction mixture followed by recrystallized from acetone to get the desired products (**3i-xii**). The compound was found pure on TLC examination (TEF 5:4:1). The structures of compounds were confirmed on the basis of their IR and ^{1}H-NMR spectral studies. In IR spectral studies, the compounds showed intense bands in the region 1535-1633 cm^{-1} of (C=N) stretching due to the ring closure. In addition, the absorption bands at 1351-1367 cm^{-1}are attributed to the (C-N) stretching vibrations, which also confirm the formation of desired imidazole ring in the compounds. Whereas ^{1}H-NMR spectra further confirm the structure due to disappearance of the peak of aldehydic proton and appearance of a single peak of NH (imidazole ring) at 11.23 ppm due to ring closure. 4-(Biphenyl-4-yl)-2-(substituted phenyl)-1-phenyl-1H-imidazoles(**3i-xii**) were refluxed with chlorobenzene in THF to get desired compounds(**4i-xii**). The usual work up of the reaction mixture followed by recrystallized from ethanol gave pure compounds(**4i-xii**). The compound was found pure on TLC examination (B: A, 9:1) and T: E:F(5:4:1), and its spectral data was found satisfactory for the proposed structures.

Synthetic Series-3 (Scheme 3)

Compounds **(4i-xii)** synthesis of 4-(Biphenyl-4-yl)-2-(substituted phenyl)-1-phenyl-1H-imidazoles were prepared from Scheme 3.

Chemistry

The title compounds (**4i-xii**) were synthesized as per synthetic scheme outline. In this scheme biphenyl ethanone (**1**; starting material) was prepared by heating biphenyl with anhy. $AlCl_3$ in presence of CS_2 and acetic anhydride. The biphenyl ethanone (**1**; starting material) was treated with selenium dioxide to get 2-(biphenyl-4-yl)-2-oxoacetaldehyde (**2**). Biphenyl-2-oxoacetaldehyde **(2)** was refluxed with different aromatic aldehydes in presence of ammonium acetate and glacial acetic acid to get new imidazole derivatives (**3i-xii**). 4-(Biphenyl-4-yl)-2-(substituted phenyl)-1-phenyl-1H-imidazoles (**3i-xii**) were refluxed with chlorobenzene in THF to get desired compounds (**4i-xii**). The usual work up of the reaction mixture followed by recrystallized from ethanol gave pure compounds (**4i-xii**). The compound was found pure on TLC examination (B: A, 9:1) and T: E: F (5:4:1), and its spectral data was found satisfactory for the proposed structures. The structures of newly prepared compounds were established on the basis of modern analytical techniques (FT-IR, ^{1}H-NMR and mass spectral data) and elemental analysis. The final compounds were purified by recrystalization with suitable solvent and found pure on TLC examination.

STRUCTURAL INVESTIGATIONS

The starting material 1-(biphenyl-4-yl) ethanone (biphenyl ethanone, **1**) was prepared by heating biphenyl with anhydrous $AlCl_3$ in the presence of CS_2 and acetic anhydride. The usual work up of the reaction mixture followed by recrystallized from ethanol gave pure compound. The purity of the compound was verified with the help of TLC (B: A, 9:1). % age yield- 80%, m.p.- 152-165 $^{\circ}$C. IR spectra are very informative and provided evidence for the formation of the expected structures. In general, IR spectra of acetophenone showed a strong band of C=O at 1683 cm^{-1}. Whereas ^{1}H-NMR further confirmed the structure due to the presence of a singlet of CH_3 at 2.61 ppm. Compound **2** [2-(biphenyl-4-yl)-2-oxoacetaldehyde] was synthesized from 1-(biphenyl-4-yl) ethanone (**1**) in the presence of selenium dioxide and after work out of reaction gave a yellow liquid which was found pure on TLC examination (TEF 5: 4: 1). The structure of compound 2 was confirmed on the basis of spectral studies. In IR spectra a band at 2851 cm^{-1} for aldehydic C-H stretching was very clear. The ^{1}H-NMR spectra left no doubt with singlet of aldehydic proton at 9.81 ppm.

Compound **2** [2-(biphenyl-4-yl)-2-oxoacetaldehyde] was refluxed with different aromatic aldehyde in the presence of ammonium acetate and glacial acetic acid. The usual work up of the reaction mixture followed by recrystallized from acetone to get the desired products (**3i-xii**). The compound was found pure on TLC examination (TEF 5:4:1). The structures of compounds were confirmed on the basis of their IR and ^{1}H-NMR spectral studies. In IR spectral studies, the compounds showed intense bands in the region 1535-1633 cm^{-1} of (C=N) stretching due to the ring closure. In addition, the absorption bands at 1351-1367 cm^{-1}are attributed to the (C-N) stretching vibrations, which also confirm the formation of desired imidazole ring in the compounds. Whereas ^{1}H-NMR spectra further confirm the structure due to disappearance of the peak of aldehydic proton and appearance of a single peak of NH (imidazole ring) at 11.23 ppm due to ring closure. 4-(Biphenyl-4-yl)-2-(substituted phenyl)-1-phenyl-1H-imidazoles (**3i-xii**) were refluxed with chlorobenzene in THF to get desired compounds (**4i-xii**). The usual work up of the reaction mixture followed by recrystallized from ethanol gave pure compounds (**4i-xii**). The compound was found pure on TLC examination (B: A, 9:1) and T: E:F (5:4:1), and its spectral data was found satisfactory for the proposed structures.

Synthesis of 4-(biphenyl-4-yl)-1,2-diphenyl-1H-imidazole (4i): Synthetic Series-3 (Scheme_3)

The inhibition of microbial growth under standardized condition may be utilized for demonstrating the therapeutic efficacy of any subtle change in the antibiotic molecule. Which may not be detected by chemical method will be revealed by a reduction in the anti-microbial activity and hence microbiological assays are very useful for resolving doubts regarding possible loss of potency of antibiotics and their preparations of the antibiotic having a known activity. The in-vitro antibacterial and antifungal activities of the synthesized compounds were carried out by microdilution susceptibility test using cup-plate technique. Antibacterial activity of newly synthesized compounds (**4i-xii**) was screened against bacterial strains viz. *Escherichia coli (E. coli,* MTCC 2961*), Staphylococcus aureus (S. aureus,* MTCC 3160*), Bacillus subtilis (B. subtilis,* MTCC 121*), Klebsiella pneumoniae (K. pneumoniae,* MTCC 3040*) and Micrococcus luteus (M. luteus,* MTCC 7527*)*. The anti-fungal activity was screened against fungal strains viz. *Candida albicans (C. albicans,* MTCC 227*), Aspergillus niger (A. niger,* MTCC 277*) and Aspergillus flavus (A. flavus,* MTCC 418*)*.

Evaluation of Anti-microbial Screening

The synthetic compounds were prepared retaining the functional groups responsible for anti-microbial activity and tested in-vitro against representatives of Gram positive and Gram-negative bacteria as well as fungi. It was found that the synthesized compounds were more effective against the Gram-positive bacteria when compared to Gram-negative bacteria. It is believed that the strong lipophilic character of the molecule plays an essential role in producing antimicrobial effect. The lipophilicity (hydrophobicity) of a compound is an important physical property that influences membrane permeation, dissolution rate and bioavailability of compounds which is a primary factor in controlling the interaction of drugs with biological systems. The lipophilicity of a compound may be expressed in terms of log P, which is considered to be very important factor for prediction of antimicrobial activity [1-2]. The octanol/water partition coefficient C logP is a measure of hydrophobicity/ liphophilicity [3]. Furthermore, it is a crucial factor governing passive membrane partitioning, influencing permeability (i.e. increasing logP enhances permeability). Drugs with high partition coefficients (hydrophobic) are preferentially distributed to lipophilic compartments such as lipid bilayers of cells while hydrophilic drugs (low partition coefficients) preferentially are found in hydrophilic compartments such as blood serum. The values of C log P were calculated using Chem Draw Ultra 8.0 software integrated with Cambridge Software (Cambridgesoft Corporation) obtained results shown in Table **11**. Molar refractivity (MR), the measure of steric factor, bulkiness of the molecule and its polarizability [4] was also calculated using Chem Draw Ultra 8.0 software integrated with Cambridge Software (Cambridgesoft Corporation) to explain the activity behavior of the synthesized compounds and obtained results showed in Table **11**. Molar refractivity is the molar volume corrected by the refractive index. It has been inferred after the correlation of the antimicrobial data with the values of C logP and molar refractivity; the compounds having greater values of C logP and molar refractivity showed better antimicrobial activity. The permeability of the membrane of the bacteria plays an important role for the determination of antibacterial activity. The antibacterial activity of the compounds may be related to cell wall structure of the bacteria. This is possible because the cell wall is essential for the survival of many bacteria and some antibiotics are able to kill bacteria by inhibiting a step in the peptidoglycan synthesis. Gram negative bacteria have a relatively thin cell wall consisting of a few layers of peptidoglycan surrounded by a second lipid membrane containing lipopoly sachharides and lipoproteins. In contrast Gram positive bacteria possess a thick cell wall containing many layers of peptidoglycan and teichoic acids. These differences in cell wall structure can produce differences in the antibacterial susceptibility and some antibiotics which are effective against Gram-positive bacteria are found to be ineffective against Gram negative bacteria [5].

Table 1. Compounds code Substituted (-R_1), log P and molar refractivity of title compounds (**4i-xii**).

Compd.	Subs. (-R)	C log P	Molar Refractivity
4i	H	3.87	88.91
4ii	4-OH	5.67	112.01
4iii	2-Cl	4.41	113.73
4iv	3-Cl	5.98	114.01
4v	3-OH	6.13	106.89
4vi	4-Cl	5.93	113.27
4vii	4-Br	5.71	110.31
4viii	4-$N(CH_3)_2$	5.21	112.25
4ix	3-OCH_3	5.71	113.11
4x	4-OCH_3	6.72	113.81
4xi	2-OH	5.32	112.37
4xii	4-F	5.62	111.29

Anti-bacterial activity

Experimental Procedure

In-vitro antibacterial activity of the synthesized compounds was tested by disc diffusion method under standard condition using Muller Hinton Agar medium [1]. The test organisms were first cultured in Nutrient broth and incubated for 24 hrs at 37ºC and then freshly prepared bacterial cells were spread onto the Muller Hinton agar plates in a laminar flow cabinet. The test compounds which were previously dissolved in DMSO were then soaked onto sterile discs of Whatman filter paper no. 1 (6 mm diameter).

The discs were then placed onto the surface of the previously prepared inoculated plates and incubated. After 24 hrs of incubation at 37ºC, the diameter of zone of inhibition was measured for each compound in mm. The activity was compared with standard antibiotic ciprofloxacin (positive control) and a disc impregnated with dimethylsulfoxide (DMSO) was used as a negative control [6-7]. All the tests were performed in triplicate and the average was taken as final reading.

The results of anti-bacterial screening of all the newly synthesized compounds are showed in Table **12** and **13**. Compound **4iv** [4-(biphenyl-4-yl)-2-(4-chlorophenyl)-1H-imidazole] and compound **4x** [4-(biphenyl-4-yl)-2-(4-methoxyphenyl)-1H-imidazole] showed notable activity against E. coli, B. subtilis and K. pneumoniae. Some of them showed moderate activity and others rest good activity. Compounds (**4ii, 4v & 4xii**) were shown moderate activity against E. coli, S. aureus, M. luteus and K. pneumonia, whereas remain compounds showed mild activity against few bacterial strains. Results of the antibacterial activity shown in Table **12** as zone of inhibition and Table **13** as percentage inhibition against various bacterial strains, while maximum activity was observed at 100 µg/mL. **Table 12.** Antibacterial activity measure by zone of inhibition of title compounds (**4i-xii**).

Compd.	*E. coli* (MTCC-1687)		*S. aureus* (MTCC-2940)		*B. subtilis* (MTCC- 441)		*M. luteus* (MTCC 7527)		*K. pneumonia* (MTCC 3040)	
	50 µg/mL ± SD[b]	100 µg/mL ± SD	50 µg/mL ± SD	100 µg/mL ± SD	50 µg/mL ± SD	100 µg/mL ± SD	50 µg/mL ± SD	100 µg/mL±SD	50 µg/mL ± SD	100 µg/mL±SD
4i	9.15 ± 1.11	11.17 ± 1.15	nt	nt	10.31 ± 1.13	11.12 ± 1.41	8.11 ± 1.51	9.41 ± 1.05	nt	nt
4ii	19.15 ± 1.32	21.11 ± 1.03	15.21 ± 1.41	17.31 ± 1.11	18.21 ± 1.41	21.51 ± 1.05	nt	nt	21.11 ± 1.01	23.11 ± 1.15
4iii	12.11 ± 1.17	13.01 ± 1.21	nt	nt	11.11 ± 1.31	13.01 ± 1.43	nt	nt	13.11 ± 1.71	15.03 ± 1.11
4iv	23.18 ± 1.11	25.15 ± 1.21	15.61 ± 1.41	16.13 ± 1.32	24.1 ± 1.61	25.11 ± 1.23	17.61 ± 1.42	18.11 ± 1.17	21.15 ± 1.19	23.37 ± 1.11
4v	18.12 ± 1.31	19.13 ± 1.11	14.11 ± 1.15	16.13 ± 1.51	17.32 ± 1.41	19.12 ± 1.11	18.31 ± 1.12	19.41 ± 1.03	17.21 ± 1.17	18.31 ± 1.15
4vi	14.31 ± 1.21	16.13 ± 1.11	nt	nt	18.13 ± 1.12	19.21 ± 2.13	14.11 ± 1.25	15.17 ± 1.12	18.31 ± 1.11	19.05 ± 1.15
4vii	15.21 ± 1.31	16.01 ± 1.12	nt	nt	12.41 ± 1.21	14.01 ± 1.01	nt	nt	15.13 ± 1.11	16.03 ± 2.13
4viii	nt	nt	13.11 ± 1.31	15.21 ± 1.21	14.71 ± 1.35	15.41 ± 2.01	nt	nt	14.31 ± 1.14	15.43 ± 1.03
4ix	14.11 ± 1.12	15.31 ± 1.05	11.12 ± 1.61	13.21 ± 1.17	nt	nt	15.01 ± 1.11	17.51 ± 1.43	13.11 ± 1.15	14.11 ± 1.31
4x	21.17 ± 1.32	23.41 ± 1.12	18.11 ± 1.03	19.11± 1.31	22.05 ± 1.27	24.21 ± 1.61	nt	nt	25.01 ± 1.31	26.72 ± 1.15
4xi	nt	nt	13.71 ± 1.82	14.51 ± 1.29	11.03 ± 1.11	12.57 ± 1.41	10.21 ± 1.12	11.51 ± 1.31	nt	nt
4xii	17.13 ± 1.11	19.41 ± 1.41	15.21 ± 1.21	18.31 ± 1.13	16.31 ± 1.05	17.11 ± 1.31	nt	nt	18.16 ± 1.57	20.13 ± 1.43
Cipro.	27.17 ± 1.05	28.13 ± 1.19	29.17 ± 1.51	30.71 ± 1.11	27.41 ± 1.31	29.01 ± 1.51	28.31 ± 1.33	29.11 ± 1.11	29.51 ± 1.21	30.11 ± 1.03

Measure zone of inhibition in millimeter, SD; Standard Deviation, Compd.; Compunds, Cipro; Ciprofloxacin, nt; means not tested compounds.

Antifungal activity

Experimental Procedure

In-vitro antifungal activity of the synthesized compounds was tested by disc diffusion method under standard conditions using Potato dextrose agar medium [2]. Sterile discs of Whatman filter paper no.1 (6 mm diameter) containing specific amounts of an antifungal agent fluconazole (300 mg for the synthesized compounds) were placed on the surface of an agar plate inoculated with a standardized suspension of the microorganisms tested. The plates were incubated at 28±2ºC for 72 hrs for evaluating antifungal activity. A paper disc impregnated with dimethylsulfoxide (DMSO) was utilized as negative control [7-8].

The nutrient agar medium was prepared and autoclaved at 15 lbs pressure for 20 minutes and this media was poured into petri plates and was allowed to solidify. On the surface of media microbial suspension was spread with the help of sterilized cotton swab. Cups were made by boring into agar surface with a previously sterilized cork borer and scooping out the punched part of agar. Four cavities or cups were made in the medium and different concentrations of the test compounds and standard drug Fluconazole were poured in these cavities. The

plates were kept at room temperature for 1 hr and then incubated at 37±0.5 °C for 24 hrs. The diameter of the zone of inhibition formed around the cavities (cups) after 24 hrs incubation was measured and percentage inhibition of the compound were evaluated. A solvent control was also run to know the activity of the blank.

The results of anti-fungal screening of all the newly synthesized compounds are presented in Table **14** and **15**. Compound **4iv** [4-(biphenyl-4-yl)-2-(4-chlorophenyl)-1H-imidazole] and compound **4x** [4-(biphenyl-4-yl)-2-(4-methoxyphenyl)-1H-imidazole] showed notable activity. Some of them compounds (**4ii, 4v & 4xii**) were shown moderate activity and others rest good activity. Some of the synthesized compounds tested were endowed with a medium activity against A. flavus. Results of the antifungal activity are reported in Table **14** as zone of inhibition and Table **15** as percentage inhibition against various fungal strains, while maximum activity was observed at 100 µg/Ml. **Table 15.** Antifungal activity as percentage inhibition of the synthetic compounds (**4i-xii**).

Compd.	*C. albicans* (MTCC-3617)		*A. niger* (MTCC-281)		*A. flavus* (MTCC 418)	
	50 µg/mL ± SD	100 µg/mL ± SD	50 µg/mL ± SD	100 µg/mL ± SD	50 µg/mL ± SD	100 µg/mL ± SD
4i	41.12 ± 1.32	43.21 ± 1.11	50.41 ± 1.05	53.27 ± 1.87	43.21 ± 1.21	48.17 ± 2.11
4ii	55.67 ± 1.21	58.71 ± 1.92	62.11 ± 1.51	65.11 ± 1.32	60.43 ± 1.62	61.11 ± 1.32
4iii	37.11 ± 2.53	41.37 ± 1.21	51.42 ± 1.17	57.12 ± 1.51	nt	nt
4iv	70.12 ± 1.15	76.13 ± 3.41	69.21 ± 4.13	73.12 ± 3.41	72.41 ± 3.12	73.11 ± 1.42
4v	58.32 ± 1.12	64.21 ± 2.35	61.51 ± 1.62	63.25 ± 2.31	67.23 ± 2.11	68.21 ± 4.11
4vi	nt	nt	63.12 ± 2.53	66.31 ± 1.46	70.11 ± 1.32	71.31 ± 2.43
4vii	47.17 ± 2.31	61.61 ± 1.63	43.51 ± 2.17	58.31 ± 2.89	nt	nt
4viii	nt	nt	48.32 ± 3.12	63.27± 1.41	64.31 ± 4.11	69.27 ± 1.31
4ix	55.45 ± 1.11	48.31 ± 1.62	53.61 ± 2.17	54.01 ± 1.35	nt	nt
4x	72.41 ± 2.45	79.25 ± 1.53	65.23 ± 1.45	66.21 ± 2.43	68.98 ± 2.75	69.05 ± 1.25
4xi	nt	nt	48.17± 4.23	61.11 ± 1.62	nt	nt
4xii	64.12 ± 3.11	66.31 ± 1.25	59.21 ± 2.17	60.75 ± 1.35	57.21 ± 4.17	59.41 ± 2.31
Fluco.	100.00 ± 2.31	100.00 ± 2.17	100.00 ± 2.42	100.00 ± 2.49	100.00 ± 2.35	100.00 ± 3.52

Zone of inhibition represented in percentage inhibition, SD; Standard deviation, Fluco; Fluconazole, nt; means not tested compounds.

REFERENCES

[1] B.S. Holla, K.V. Malini, B.S. Rao, B.K. Sarojini, N.S. Kumari, Eur. *J. Med. Chem.,* 2003, *38,* 313.

[2] Z.H. Chohan, S.H. Sumrra, M.H. Youssoufi, T.B. Hadda, *Eur. J. Med. Chem.,* 2010, *45*, 2739.

[3] C. Hansch, A. Leo, S. Unger, K.H. Kim, D. Nikaitani, E. Lien, J. *Med. Chem.* 1973, *16* 1207.

[4] V. Austel, The medicinal chemist's approach, in Modern Drug Research, Paths to Better and Safer Drugs. Martin, Y.C. Kutter, E. Austel, V. Eds, Marcel Dekker, Inc. New York, 1989, 243.

[5] D.A. Smith, *Eur. J. Drug Metab. Pharm.* 1994, *3*, 193.

[6] L. Ustunes, V. Pabuccuoglu, T. Berkan, A. Ozer, J. Fac. Pharm. Ankara, 19*,* 124, 2005.

[7] M. Minoshima, J.C. Chou, S. Lefebvre, T. Bando, K. Shinohara, J.M. Gottesfeld, H. Sugiyama, Bioorg. Med. Chem., 18*,* 168, 2010.

[8] T. Maruyama, K. Onda, M. Hayakawa, N. Seki, T. Takahashi, H. Moritomo, T. Suzuki, T. Matsui, T. Takasu, I. Nagase, M. Ohta, Bioorg. Med. Chem., 17*,* 3283, 2009.