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DESIGNED BIOACTIVE SYNTHESIS OF 4-(4, 5-DIPHENYL-1H-IMIDAZOL-2-YL)-N-PHENYLBENZAMIDE ANALOGOUS PROMOTED BY MG $(NO_3)_2$ $6H_2O$

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ABSTRACT

A simple, highly versatile and an efficient pathway of synthesis of a novel series of 4-(4, 5-diphenyl-1H-imidazol-2-yl)-N-phenylbenzamide analogous. These derivatives can be obtained from4-(4, 5-diphenyl-1H-imidazol-2-yl) benzoic acid with substituted aromatic amine in the presence of Mg $(NO_3)_2$ $6H_2O$ as a low-cost and readily available catalyst in ethanol as solvent. 4-(4, 5-diphenyl-1H-imidazol-2-yl) benzoic acid can be synthesized from the mixture of benzil, carboxy benzaldehyde and ammonium acetate in acetic acid in the presence of molecular iodine at 70°C. The main advantages of this process are cost effectiveness of catalyst, easy work-up and purification of products by non-chromatographic methods, excellent yields and very low reaction time. The newly obtained derivatives were confirmed by advanced spectroscopic data such as FTIR, 1HNMR, 13CNMR and LCMS and the structural determination of the desired compounds were determined by elemental analysis.

KEYWORDS

4-(4, 5-diphenyl-1H-imidazol-2-yl) benzoic acid, of 4-(4, 5-diphenyl-1H-imidazol-2-yl)-N-phenylbenzamide, Benzil, Mg $(NO_3)_2$ $6H_2O$ and Antimicrobial activity.

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INTRODUCTION

The importance of the amide functional group emerges from their presence in many crucial moieties such as proteins, fabrics, fertilizers, insecticides, plastics, drugs, and in a vast number of synthetic structures. For this reason, it is very relevant to improvement new methods of process for an efficient synthesis of amides. The traditional methods require the transformation of the acid into

the corresponding acid chloride, to use the Schotten-Baumann reaction, or coupling reagents commonly used in peptide synthesis[1-4]. Although these methods produce amides under mild reaction conditions and good yields, stoichiometric amounts of activating reagent are required, and an equivalent of waste is generated, making these low-atom economy processes. Besides, the removal of the corresponding by-product cansbe tedious increasing the cost of the transformation. New methodologies described for the synthesis of amides[5,6] involve the use of catalysts, and employ starting materials such as esters[7-17], aldehydes[18-27], alcohols[28-33] nitriles[34-45] and oximes[46-56]. The catalysts are mainly based on expensive metals such as rhodium, ruthenium, iridium and palladium. Although the use of cheaper metals such as copper, iron, titanium, hafnium and zirconium have been recently reported[5,6,44]. Transamination reactions to convert primary amides into more complex amides, and the acylation of amines to produce secondary amides are also important transformations reported in this field. The direct synthesis of secondary amides from nonactivatedcarboxylic acids is an important transformation that has been less exploited and studied Secondary and tertiary amides can be obtained by condensation of the acid and the amine, but the competing acid–base reaction makes this coupling challenging, overcome by forcing conditions. 4 Thermal amidation the absence of a catalyst have been previously reported and are favoured by the use of a polar solvents such as toluene. The direct synthesis of primary amides by this methodology is more challenging due to the low nucleophilic nature of the nitrogen source, and the use of coupling reagents is unrequited. The use of catalysts is an attractive approach for the direct formation of primary amides. The most relevant methodologies reported in this regard involve the use of enzymes such as lipase boric acids, Group IV metals such as zirconium, titanium, and heterogeneous catalyst as $ZrOCl_2 8H_2O$ and CAN combined with microwave radiation. Although, the latter methodologies have been reported to be difficult to reproduce. 90 The number of catalytic protocols reported for the synthesis of primary amides is still limited[43,51]. In this work, we present a new protocol for the synthesis of amides from non activated carboxylic acids by direct coupling using a low-cost, readily available, and easy to manipulate catalyst and nitrogen source. The present investigation, the synthesis of designed bioactive synthesis of 4-(4, 5-diphenyl-1H-imidazol-2-yl)-N-phenylbenzamide analogous promoted by Mg $(NO_3)_2$ $6H_2O$ as shown Scheme No.1.

MATERIAL AND METHODS

All reagents, chemicals and solvents were purchased from Sigma Aldrich and Merck chemicals and they are used without further purification. The melting points of the newly synthesized compounds were measured by an instrument Agarwal thermo meter open capillary method using a Galen Kamp melting point apparatus and are uncorrected. The desired Products were characterized by spectroscopy data (FTIR, 1HNMR and 13CNMR spectra and LCMS). Bruker spectrometer was used to record IR spectra using KBr pellets. NMR spectra were recorded on a Bruker Avance (400-MHz) NMR and CDCl3 was used as a solvent. The purity of the substances and the progress of the reactions were checked on TLC**.**

General Methods for Synthesis of 4-(4, 5-diphenyl-1H-imidazol-2-yl) benzoic acid (3)

Taken clean and dry four neck rounded bottom flask fitted on the magnetic stirrer. The mixture of benzil (1mol), 4-carboxy benzaldehyde (1.150mol) and ammonium acetate (2mol) and acetic acid were introduced in a RBF and the appropriate amount catalyst such as molecular Iodine was added (3mmol). Then the reaction mixture was heated to reflux for the appropriated period of time. After completion of the reaction which was monitored by TLC as mobile phase (4:6-EtOAc: n-hexane), the mixture taken in an ethyl acetate and washed with water, the solid product can be separated and purified by recrystallization from ethanol. All of the desired product(s) were characterized by

comparison of their physical data with those of known compounds.

Characterisation of4-(4, 5-diphenyl-1H-imidazol-2-yl) benzoic acid

Pale yellow solid; Rf:0.45(EtOAc: n-hexane=4:6); Yield-92%: FTIR (KBr, cm-1): 3487 (NH), 2927, 2458, 1622 (C=C), 1512 (C=N); 1HNMR (400MHz, CDCl3) ppm: 11.854 (s, 1H, COOH), 11.241 (s, 1H, NH-imidazole), 8.119-8.0174 (m, 2H, Ar-H), 7.835-7.280 (m, 13H, Ar-H); 13CNMR (100MHz, $CDCl_3$) ppm: 175.45, 149.65, 139.54, 137.85, 131.89, 130.47, 129.84, 128.12, 128.98, 127.24, 127.65, 126.95; LCMS (m/z): 341.25 (M+H); Molecular formulae: $C_{22}H_{16}N_2O_2$; Elemental analysis: Calculated: C-77.63, H-4.74, N-9.40, Obtained: C- 77.69, H-4.72, N-9.48.

General producer of 4-(4, 5-diphenyl-1H-imidazol-2-yl)-N-phenylbenzamide

Taken clean and dry four neck rounded bottom flask fitted on the magnetic stirrer. The solvents ethanol introduced in RBF. The mixture of 4-(4, 5-diphenyl-1H-imidazol-2-yl) benzoic acid (1.150mol) and substituted aromatic amine (1mol) introduced in a RBF and the appropriate amount catalyst such as Mg $(NO_3)_2$ 6H2O was added (3mmol). Then the reaction mixture was heated to reflux for the appropriated period of time. After completion of the reaction which was monitored by TLC as mobile phase (5:5-EtOAc: n-hexane), the mixture taken in an ethyl acetate and washed with saturated solution of sodium bi carbonate, the solid product can be separated and purified by recrystallization from ethanol. All of the desired product(s) were characterized by comparison of their physical data with those of known compounds.

Characterisation of 4-(4, 5-diphenyl-1H-imidazol-2-yl)-N-phenylbenzamide

4-(4, 5-diphenyl-1H-imidazol-2-yl)-N-phenylbenzamide (5a)

Yellow solid; yield-85%, m.p-252-254^oC: ^{1}HNMR (400Mz, $CDCl_3$) ppm: 12.475 (s, 1H, N-H imidazole), 10.107 (s, 1H, -CONH-), 8.027-7.294 (m, 14H, Ar-H); ^{13}CNMR (100MHz, $CDCl_3$) ppm: 175.63, 163.74, 137.33, 135.62, 131.09, 130.66, 129.58, 129.11, 128.98, 128.55, 128.39, 128.04, 127.69, 120.74; LCMS (m/z): 416.25 (M+H); Molecular formule: $C_{28}H_{21}N_30$, Elemental Analysis: Calculated C-80.94, H-5.09, N-10.11. Obtained: C-80.85, H-5.07, N-10.20.

4-(4, 5-diphenyl-1H-imidazol-2-yl)-N-(4-hydroxyphenyl) benzamide (5b)

Yellow solid yield-89%, m.p 258-260^oC. ^{1}HNMR (400Mz, $CDCl^3$) ppm: 12.094 (s, 1H, N-H-imidazole), 9.046 (s, 1H, -CONH-), 8.945 (s, 1H, -OH), 7.942-7.306 (m, 9H, Ar-H), 7.186-7.047 (m, 4H, Ar-H); ^{13}CNMR (100MHz, $CDCl_3$) ppm: 174.69, 162.43, 150.09, 137.77, 135.07, 133.73, 129.44, 128.95,128.61, 128.04, 127.66, 127.03, 124.44, 117.62; LCMS(m/z): 432.09 (M+H). Molecular formule: $C_{28}H_{21}N_3O_2$. Elemental Analysis: Calculated: C-77.94, H-4.91, N-9.74. Obtained: C-77.87, H-4.90, N-9.85.

N-(3, 4-dimethoxyphenyl)-4-(4, 5-diphenyl-1H-imidazol-2-yl) benzamide (5c)

Pale Yellow solid yield-90%, m.p272-274^oC; ^{1}HNMR (400Mz, $CDCl_3$) ppm: 12.356 (s, 1H, NH imidazole), 10.056 (s, 1H, -CONH-), 7.892-7.356 (m, 9H, Ar-H), 7.213-7.045 (m, 3H, Ar-H-), 3.712 (s, 3H, -OCH_3), 3.623 (s, 3H, OCH_3). ^{13}CNMR (100MHz, $CDCl_3$) ppm: 174.69, 163.75, 148.22, 143.21, 137.04, 135.59, 133.35, 130.22, 29.65, 129.39, 128.74, 128.41, 128.12, 127.65, 114.74, 113.62, 106.74, 55.66. LCMS (m/z): 476.19 (M+H). Molecular formule: $C_{30}H_{25}N_3O_3$. Elemental Analysis: Calculated C-75.77, H-5.30, N-8.84. Obtained: C-75.70, H-5.28, N-8.92.

N-(4-chlorophenyl)-4-(4, 5-diphenyl-1H-imidazol-2-yl) benzamide (5d)

Yellow solid; yield-90%, m.p-269-271^oC. ^{1}HNMR (400Mz, $CDCl_3$) ppm: 12.764 (s, 1H, N-H imidazole), 10.049 (s, 1H, NHCO), 8.092-7.310 (m, 13H, Ar-H).^{13}CNMR (100MHz, $CDCl_3$) ppm: 175.49, 165.02, 138.64, 136.28, 132.94, 130.38, 129.76, 129.19, 128.83, 128.54, 128.27, 128.02, 127.84, 125.68, 120.33. LCMS (m/z): 451.35 (M+H). Molecular formule: $C_{28}H_{20}ClN_3O$, Elemental Analysis: Calculated C-74.75, H-4.48, N-9.34. Obtained: C-74.67, H-4.46, N-9.43.

N-(4-bromophenyl)-4-(4, 5-diphenyl-1H-imidazol-2-yl) benzamide (5e)

Palered, yield-90%. M.p-274-276^{o}C; ^{1}HNMR (400Mz, $CDCl_3$) ppm: 12.896 (s, NH, N-H imidazole), 10.145 (s, 1H, -CONH), 7.914-7.334 (m, 13H, Ar-H-). ^{13}CNMR (100MHz, $CDCl_3$) ppm: 176.28, 166.72, 137.02, 135.55, 133.09, 130.44, 129.87, 129.17, 128.87, 128.59, 128.21, 128.08, 127.69, 127.41, 124.06; LCMS (m/z): 596.22. Molecular formule: $C_{28}H_{20}BrN_3O$. Elemental Analysis: Calculated C-68.02, H-4.08, N-8.50. Obtained: C-67.94, H-4.06, N-8.59.

4-(4, 5-diphenyl-1H-imidazol-2-yl)-N-(3-nitrophenyl) benzamide (5f)

Palered, yield-85%; m.p-272-274^{o}C; ^{1}HNMR (400Mz, $CDCl_3$) ppm: 12.457 (s, 1HN-H, imida zole), 10.035 (s, 1H, -CONH), 8.542 (s, 1H, Ar-H), 7.947-7.326 (m, 13H, Ar-H-), ^{13}CNMR (100 MHz,$CDCl_3$) ppm: 175.28, 166.72, 137.02, 135.55, 133.09, 130.44, 129.87, 129.17, 128.87, 128.59, 128.21, 128.08, 127.69, 127.41, 124.06. LCMS (m/z): 460.02 (M^+). Molecular formule: $C_{28}H_{20}N_4O_3$. Elemental Analysis: Calculated C-73.03, H-4.38, N-12.17; Obtained: C-72.91, H-4.37, N-12.25.

Biological Evaluation

Antibacterial activity

100mL sterile conical flask of nutrient broth was inoculated with the test organisms and incubated at 370^{o}C overnight. By using a sterile pipette, 0.6mL of the broth culture of each test organism was added to 60mL of molten agar, mixed well and maintained at 450^{o}C. Sterile agar test plates of each test organism were prepared by pouring inoculated medium with uniform thickness. The agar was allowed to set and harden and wells of 4mm diameter were cut at equidistant using a sterile cork borer. Agar plugs were removed. 100lg/mL of test solutions were prepared in DMSO and were introduced into the wells using micropipette. The plates were kept at room temperature for 2 h for better diffusion of solution into the medium. The plates were incubated for 36h at370^{o}C. After incubation the diameter of inhibitory zones formed around each well was measured in millimeter (mm) using antibiotic zone scale. The assay was carried out in duplicate. DMSO was used as control and the antibacterial activity of the test compounds was compared with standard "Streptomycin".

Antifungal activity

Sterile molten potato dextrose agar (PDA) medium was inoculated with 50lL of fungal spore suspension aseptically and maintained at 450^{o}C temperature. The inoculated medium was mixed well and poured immediately in sterilized petriplates. Then five wells of 6mm diameter were punched using sterile borer and filled with 100lg/mL of test compounds (4a-4j) as well as sterile DMSO 100% as negative control. Plates were incubated for 24 h at 370C. Antifungal activity was determined by measuring the zone of inhibition. The zones produced by the test compounds were compared with the "ketoconazole.

RESULTS AND DISCUSSION

Chemistry

A simple, highly versatile and an efficient pathway of synthesis of a novel series of 4-(4, 5-diphenyl-1H-imidazol-2-yl)-N-phenylbenzamide analogous. These derivatives can be obtained from 4-(4, 5-diphenyl-1H-imidazol-2-yl) benzoic acid with substituted aromatic amine in the presence of Mg $(NO_3)_2$ 6H2O as a low-cost and readily available catalyst in ethanol as solvent. 4-(4, 5-diphenyl-1H-imidazol-2-yl) benzoic acid can be synthesized from the mixture of benzil, carboxy benzaldehyde and ammonium acetate in acetic acid in the presence of molecular iodine at 70^{o}C.

In continuation of our research work on the use of simple inorganic non-toxic catalysts, we report herein the efficacy of methane sulphonic acid as catalyst as well as solvent. In this study the multicomponent reaction strategy for the preparation of4-(4, 5-diphenyl-1H-imidazol-2-yl)-N-phenylbenzamide was obtained 4-(4, 5-diphenyl-1H-imidazol-2-yl) benzoic acid with substituted aromatic amine in presence Mg (NO3)26H2O or imidazole which can be synthesized by using benzil, 4-carboxy benzaldehyde and ammonium

acetate in presence of iodine as catalyst, in ethanol at reflux condition is introduced.

In a model reaction, the presence of the catalyst (5mol %), the mixture of 4-caboxy benzaldehyde (1mmol), benzil (1mmol) and NH_4OAc (2mmol) as ammonia source are stirred at 70^oC under solvent free conditions. The 4-(4, 5-diphenyl-1H-imidazol-2-yl) benzoic acid was obtained in 92% yield. Various kinds of functionalised titled were also subjected in the presence of methane sulphonic acid at reflux under solvent free conditions (Scheme No.1).

We observed that for aldehydes having either electron withdrawing or electron-releasing substituents in the Meta or para positions; the reaction proceeded very efficiently in all cases. This procedure provides trisubstituted imidazoles derivatives directly, in relatively short reaction times, high yields. Furthermore, we used benzoin instead of benzil and in this case corresponding products were achieved in good yields. In all cases, complete conversion was observed after appropriate time and the products were readily isolated in very high yields.

In summary, multistage procedures have been developed for the synthesis of titled derivatives catalyzed by $I_2$and Mg $(NO_3)_2$ 6H2O or imidazole in high yields. Moreover, easy work-up, clean reaction profiles, low cost, availability, low toxicity, stable under normal temperatures and pressures of the catalyst and short reaction time make this methodology a valid contribution to the existing processes in the field of 4-(4, 5-diphenyl-1H-imidazol-2-yl)benzoic acid derivatives synthesis.

NMR spectroscopy

The 1H NMR spectral analysis of the as synthesized compounds showed a characteristic peak at δ 11.356ppm clearly indicates the presence of N-Himidazole proton, the presence of aromatic protons in all the compounds is clearly identified by the chemical shift value at 8.119-6.862, in addition the presence of hydroxyl proton in the compounds showed 8.945 verified by the obtained chemical shift value at 3.741ppm methoxy proton respectively. The 13CNMR spectroscopies were examined in order to predict the structure of the as synthesized imidazoles. It was in good agreement with the literature. The δ value at 175ppm, 148ppm is obtained. The molecular weight of the titled compounds was obtained (M+2), (M+H) and M+ respectively.

Antibacterial activity

The *in vitro* antibacterial activity of the desired compounds (5a-5g) was compared with standard drug" Streptomycin'' as collected in (Table No.). As indicated in Table No.1, most of the newly obtained derivatives generally showed potent activity against all the tested bacterial strains. The derivatives "5c, 5d, 5f and 5g" showed excellent antibacterial potent activity against gram (+ve) bacterial strains viz; *E.coli, Aeruginosa* and *gram (-ve)* bacterial strains viz; *B.subtilis* and *Staphylococcus aureus* respectively due to such compounds possesses halogen atoms. The derivatives "5b" showed good active potential against bacterial strains. The compounds"5a and 5e" showed moderate activity against bacterial strains due to compounds having highly electron donating groups. These reveals that the results indicated that the compounds having electron withdrawing groups showed good activity than the compounds having electron donating groups. The derivatives containing halogen atoms showed excellent active potential against bacterial strains.

Streptomycin was used as standard. A 100 lg/mL of compound in each well.

Values are average of three readings.

Antifungal activity

The *in vitro* antifungal activity of the desired compounds (5a-5g) was compared with standard drug" Ketonozole.'' as collected in (Table No.2). The *in vitro* antifungal activity of the tested derivatives (5a-5g) was investigated against *Aspergillus Niger, Aspergillusfavus and Candida albicans* using agar well diffusion assay and zones of inhibition of the test Compounds were expressed in mm as shown in Table No.2. Compounds 5e showed excellent active potential activity against the fungal strain. The compound having "5f and 5g" was observed to be good active potential against

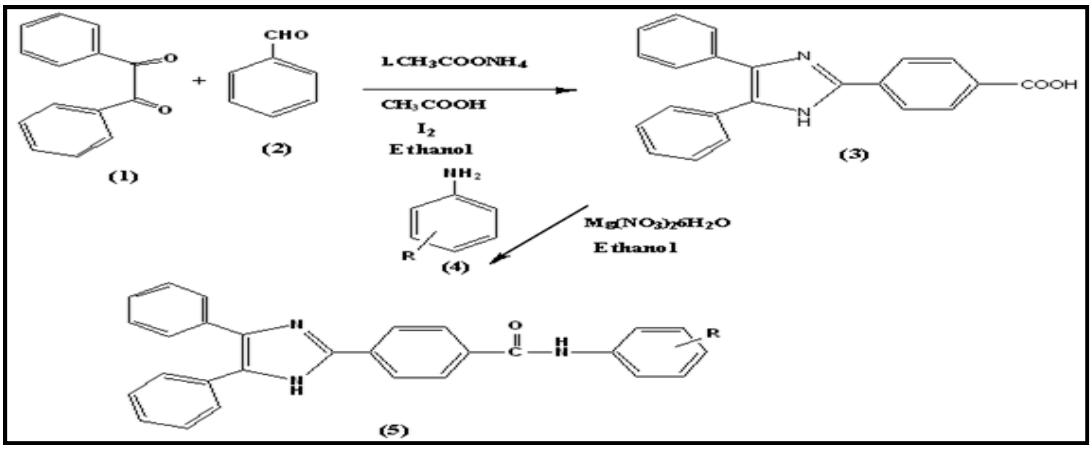
tested fungal strain. Compounds such as 5c and 5it is indicated that most of the compounds showed significant activity and few are moderately active as shown in Table No.2. The remaining derivatives showed moderate potent activities against *Aspergillusfavus*. These results reveals that the compounds possess electron attracting groups exhibited moderate activity while the compounds having electron attracting groups exhibited good against the fungal stains have demonstrated significant antifungal activity comparable to standard.

Table No.1: Antibacterial activity of the newly synthesized compounds (5a-5g) zones of inhibition (mm) of compounds (5a–5f) against tested bacterial strains

S.No	Compound	Anti-Bacterial Activity			
		Gram (+ ve) bacteria		Gram (- ve) bacteria	
		Escherichia coli	***Pseudomonas aureoginosa***	***Bacillus subtilis***	***Staphylococcus aureus***
1	5a	11	10	08	09
2	5b	14	15	14	13
3	5c	26	26	24	23
4	5d	25	24	21	22
5	5e	11	13	10	10
6	5f	24	25	19	21
7	Streptomycin	30	30	27	27
8	DMSO				

Table No.2: Antifungal activity of the synthesized compounds (5a-5f), zones of inhibition (mm) a of compounds (5a–5f) against tested fungal strains

S.No	Entry	Anti-Fungal Activity		
		Aspergillus Niger	**Aspergillusfavus**	**Candida albicans**
1	5a	07	07	06
2	5b	10	13	11
3	5c	17	15	16
4	5d	15	16	15
5	5e	19	18	18
6	5f	10	11	112
7	Ketonozole	22	22	22
8	DMSO			



Scheme No.1

CONCLUSION

To find out this experiment, we prepared the seven derivatives-(4, 5-diphenyl-1H-imidazol-2-yl)-N-phenylbenzamide analgueous. The derivatives having electron donating groups and electron attracting groups including halogen containing derivatives. The percentage of the derivatives acquired electron donating group (92%) compared with electron withdrawing group of the compounds. As shown Scheme No.1, these compounds obtained using Mg $(NO_3)_2$ $6H_2O$ an excellent coupling reagent. In addition to antimicrobial activity of these derivatives exhibited various active potential in various bacterial as well as antifungal activities.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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