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Research Article

MICROWAVE-ASSISTED SYNTHESIS AND CHARACTERIZATION OF TRIPHENYLIMIDAZOLYL DERIVATIVES AND THEIR ANTI-FUNGAL AND ANTI-INFLAMMATORY ACTIVITY

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ABSTRACT

An novel and highly efficient rapid microwave induced synthesis of newer desired aminobenzylated triphenyl imidazole hybrids is described. The Synthesized of Synthesis of 4,5-diphenyl-2-(2,3,4-trimethoxyphenyl)-4H-imidazole (DPI-1a-DPI-1d) Cyclization of benzil with appropriate aromatic aldehydes in the presence of ammonium acetate and glacial acetic. The mixture is subjected to microwave heating for 3-5 min in a oven. which further undergoes mannich condensation reaction with bezaldehyde and various aromatic secondary amines in presence of methanol under same irradiation technique for 2-3 min yielded the N-((4,5-diphenyl-2-(2,3,trimethoxyphenyl)-lH-imidazol-l-yl)phenyl)methyl)-substituted amine (TPI-1a-TPI-1d).The constituents of the newly synthesized compounds have been established on the basis of their Physicochemical Parameters,Spectral analysis and Anti-bacterial activity of Parent nucleus of triphenylimidazolyl amine derivatives.

Keywords: Triphenylimidazolyl derivatives, Mannich Condensation, Anti-fungal, Anti-inflammatory activity.

INTRODUCTION

Triphenyl-imidazole amine is a privileged structural motif, which has played, a pivotal role in the drug discovery process. Nitrogen containing heterocycles paved way for the active research in Pharmaceutical Chemistry. The study of triphenyl-imidazolyl amine derivatives has been a developing field within the realm if heterocydic chemistry for the past several decades because of their ready accessibility through synthesis, wide range of chemical reactivity and manifold biological activities. This structural template shows remarkable pharmacological activities such as antibacterial[1-2], anti-inflammatory[3-4], anticonvulslve[5], anthelmintic[6], antiulcer[7], antiviral[8], antitumour[9], antispasmodic[10], antioxIdant[11] anti-tubercular[12]. Intrigued by these investigations and as a part of our initial efforts to discover potentially active new agents; we; decided to synthesize with this functionality coupled with mannich base could furnish better therapeutic results, To our knowledge mannich reaction using benzaldehyde have not been reported as yet This initiated us to explore the amlnobenzylated reaction as well as Anti-inflammatory and Antimicrobial properties of target compounds[13-15]

MATERIALS AND METHODS

All the reagents used were of analytical grade. Melting points of the title compounds were determined using a open capillary tube type equation here and are unconnected. Infra red spectra (cm^1) were recorded on Perkin-Elmer spectrophotometer as pellets on KBr discs. The ^{1}HNMR (400MHz) spectra were recorded on Bruker-Avance 11 spectrometer In DMSO-d_6 using TMS as an internal standard (chemical shifts in δ ppm). The splitting patterns are designated as follows: s, (singlet), d, (doublet), t, (triplet), m, (multiplet). Mass spectra were recorded on Shimadzu LCMS-

SL2010A (70ev) mass spectrometer. The reactions were monitored by thin layer chromatography (TLC) using precoated silica gel G plates of E-Merck. The spots were developed In Iodine chamber.

Microwave-assisted Technique

Synthesis of 4,5-diphenyl-2-(2,3,4-trimethoxyphenyl)-4H-imidazole (DPI-1a-DPI-1d)

A mixture of Benzil (25mmol,5.25g), 2,3,4-trimethoxy benzaldehyde (25mmol) and ammonium acetate (10g) in 5 ml glacial acetic acid, the contents were thoroughly mixed. .the reaction mixture was subjected to microwave irradiation in a Laboratory or domestically available panasonic microwave oven having a maximum power 80-100 W and operated at 120 **±** 5 °c for 3-5 min in domestic microwave oven and then it is allowed to reach to room temperature , After the reaction mixture was left overnight and filtered. The filtrate was neutralized with ammonium hydroxide and the second crop of the precipitate were combined and recrystallised from ethanol. Yield 89 %, m.p 136°c, Rf value 0.69.

Synthesis of N-((4,5-dlphenyl-2-(2,3,4-trimethoxyphenyl)-lH-imidazol-l-yl)phenyl) methyl) -substituted amine (TPI-1a-TPI-1d)

4,5-diphenyl-2-(2,3,4-trimethoxyphenyl)-4H-Imldazole derivatives were dissolved in methanol and undergoes mannich condensation reaction with benzaldehyde and appropriate aromatic secondary amines the contents were thoroughly mixed. .the reaction mixture was subjected to microwave irradiation in a Laboratory or domestically available panasonic microwave oven having a maximum power 80-100 W and operated at 120 **±** 5 °c for 2-3 min in domestic microwave oven and then it is allowed to reach to room temperature, yielded the corresponding N,N-disubstituted-2,4,5-triphenyl-IH-imldazol-l-yl methanamine analogues. and the resulting dense oily product was recrystallised from ethanol to afford a white solid substance. The physicochemical parameters of the target compounds were tabulated in Table 1.

N-((4,5-dlphenyl-2-(2,3,4-trtmethoxvphenyt)-lH-imidazol-l-yl) phenyl) methyl)-N- phenyl benzenamine (1a). IR (KBr) cm^{-1}: 3088.60 (Aromatic -CH stretching), 2935.56 (Aliphatic -CH stretching), 1519.74 (aromatic C=C stretching), 1432.44 (C=N stretching), 1041.94 (C-N stretching), 1244.44 (C-O-C stretching). ^{1}HNMR(400 MHz,DMSO-d_6) δ ppm: 6.14 (s.lH.CH), 3.84 (s,9H,(OCH_3)3), 6.54-8.26 (m,27H,Ar-H). Mass: m/z 643.78

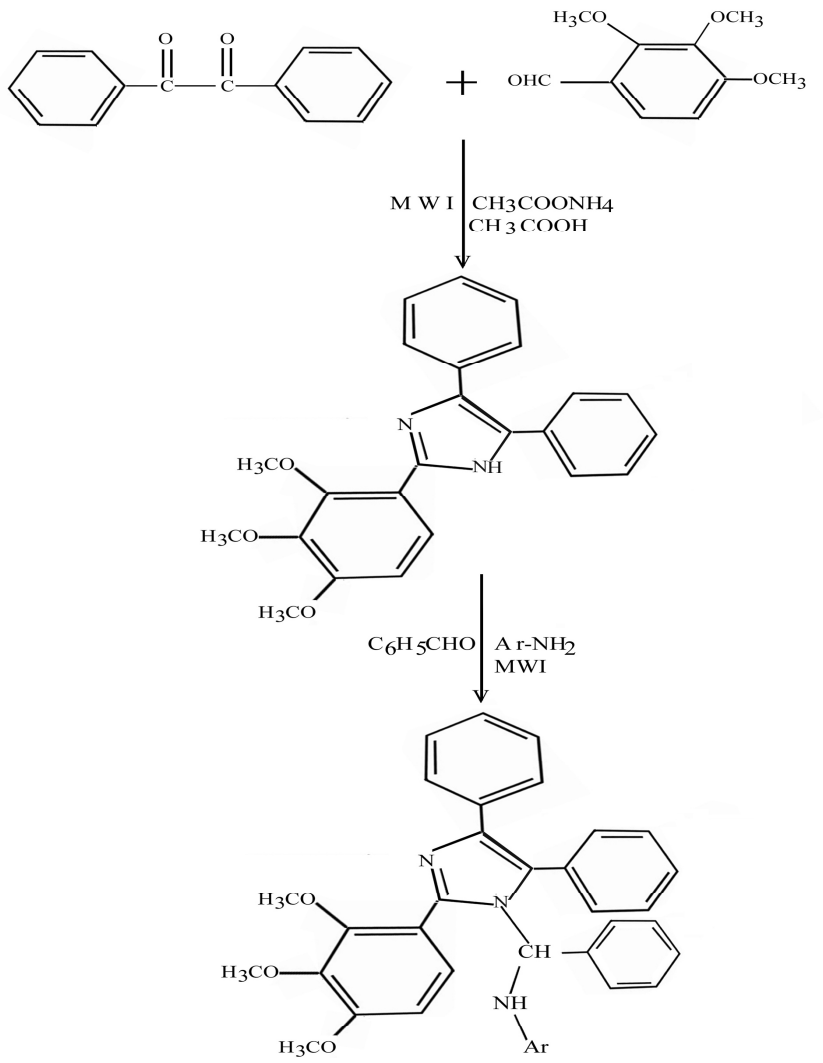
N-({4-5-dlphenyl-2-(2,3,4-trimethoxyphenyl)-1H-lmidazol-l-)yl)phenyl)methyl)plperazine (1b) IR (KBr) cm^{-1} 3035.48 (Aromatic -CH stretching), 2971.39 (Aliphatic -CH stretching), 1597.06 (aromatic C=C stretching), 1490.06 (C=N stretching). 1071.10 (C-N stretching), 1238.18 (C-O-C stretchmg). ^{1}H-NMR(4,00 MHz,DMSO-d_6) δ ppm: 6.12 (s.lH,CH), 3.86 (s,9H,($OCH_,)_3$), 2.16(s,lH,NH), 6.34-8.26 (m,25H,Ar-H). Mass: m/z 561.69

N-(4,5-diphenyl-2-(2,3,4-trimethoxyphenyl)-1H-imidazol-1-yl) phenyl) methyl) -N-napthalen-1-amine (1c). IR (KBr) cm^{-1} 3446.65 (Aromatic -CH stretching), 2928.82 (Aliphatic -CH stretching), 1596.32 (aromatic C=C stretching), 1443.65 (C=N stretching), 1242.24 (C-N stretching), 1248.64 (C-O-C stretching). ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 6.42 (s.lH.CH), 3.82 (s,9H,(OCH3)3, 7.13-8.26 (m,29H,Ar-H). Mass: m/z 693.83

N-(4,5-dlphenyl-2-(2,3,4-trtmethoxyphenyl)-1H-imidazol-1-yl)phenyl)methyl)piperidine(1d). IR (KBr) cm^{-1}: 3012.71 (Aromatic -CH stretching), 2993.28 (Aliphatic -CH stretching), 1657.32 (aromatic C=C stretching), 1478.24 (C=N stretching), 1238.14 (C-N stretching),1177.96 (C-O-C stretching).^{1}NMR(400 MHz,DMSO-d_6) δ ppm: 6.16 (s.lH,CH), 3.82 (s,9H,(OCH_3) $_3$), 6.82-8.26 (m,29H,Ar-H). Mass: m/z 559.71.

Chemistry

2-substituated-4,5-diphenyl imidazole root nucleus were syntheslsed by refluxing benzil with 2,3,4-trimethoxy benzaldehyde ie in presence of cyclising agents ammonium acetate and glacial acetic acid. In the next step, the prepared dipheny! imldazole analogus undergoes mannich condensation reaction with benzaldehyde and various substituted aromatic secondary amines resulted in the formation of target compounds (Scheme 1)



Scheme 1: Synthetic scheme of Triphenylimidazolyl amine derivatives

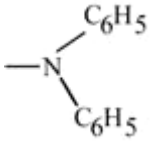
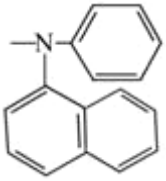
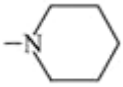
RESULTS AND DISCUSSION

In the current study, totally a series of five different N,N -disubstituted 2,4,5-triphenyl-lH-lmidazole-l-yl-methanamine Hybrids were achieved with a versatile and efficient synthetic route (Mannich condensation reaction). The yields of all the synthesized heterocycles were found to be in the range.of 70-90%. The title compounds were characterized by physicochemical parameters like mp and R_f value. The spectral data also supported the assigned structures by showing the characteristics absorption peaks. The synthesized compounds were subjected to *Invitro* anti ,By visualizing the antimicrobial activity index. It was noticed that the synthesized scaffolds elicits mild to good activity agains gram positive, gram-negative bacterial strains and fungal strains at a concentration of 250 ug/ml.

Anti-Inflammatory activity revealed that all the synthesized the ides showed significant activity when compared with that of the standard drug Diclofenac Sodium.

It can be concluded that triphenyl- imldazole as a useful template for further development through modification or derivatisation to design more potent biologically active compounds.

Table 1: Physicochemical parameters of Triphenyl-imidazolyl derivaties

Compound Code	Ar	m.p(c)	Yield(%)	Mol.formula	Mol.Wt.	Rf values
1a		128-132	73.24	$C_{43}H_{37}N_3O_3$	643.77	0.82
1b		134-138	90.70	$C_{35}H_{36}N_4O_3$	560.69	0.73
1c		220-223	75.24	$C_{47}H_{39}N_3O_3$	693.83	0.88
1d		210-213	70.21	$C_{36}H_{35}N_3O_3$	559.71	0.79

Antifungal activity

Aspergillus niger and Candida albicans were employed for testing fungicidal activity using cup plate method[14]. The cultures were maintained on Sabouraud's agar slants. Sterilised sabouraud's agar medium was inoculated with 72 hr old suspension of fungal spores in a separate flask. About 25 ml of the inoculated medium was evenly spread in a sterilised petridish and allowed to settle down for 2 hr. The cups (10 mm in diameter) were punched in petridish and loaded with sample solution in DMSO. The plates were incubated at room temperature (30°c) for 48 hr. After the completion of the incubation period, the zone of inhibition of growth of the synthesized compounds (TPI-1a-1e) in the form of diameter in mm was measured. Along the test solution in each petridish, one cup was filled with solvent which acted as control. The antifungal activity of compounds was compared with a standard drug Griseofulvin. The results of antimicrobial profile were depicted In Table 2.

In vitro anti-Inflammatory activity

The *Invitro* anti-Inflammatory activity was evaluated by human red blood cell membrane (HRBC) stabilisation method[15]. This method involves the stabilisation of the human red blood cell membrane by hypotonicity induced membrane lysis. The lysosomal enzymes released during Inflammatory condition produces a variety of disorders. The extra cellular activity of these enzymes were said to be related to acute or chronic inflammation. The anti-inflammatory agents act by either inhibiting the lysosomal enzymes or by stabilising the lysosomal membrane, since the human red blood cell membranes are similar to lysosomal membrane components. The prevention of hypotonicity induced HRBC membrane lysis was taken as a measure of anti-inflammatory activity of the drug.

The synthesized target compounds were made into dose of 250ug/ml with 5% DMSO as solvent Diclofenac sodium was taken as a standard drug. The percentage membrane stabilization activity was calculated by the following formula and the results were tabulated in Table: 2

Percentage stabilisation = 100 - (OD of sample-OD of the product control) x 100/OD of test control

Table 2: In vitro Anti-fungal and Anti-Inflammatory activity of synthesized compounds

Compound Code	Antifungal activity Zone of Inhibition mm		Anti- Inflammatory activity Percentage *Stabillisation*
	A. Niger	C.Albicans	
1a	27	28	40.50
1b	27	28	59.33
1c	24	20	27.56
1d	26	29	61.24
1e	16	17	37.00
Ofloxacin	--	--	--
Griseofulvin	36	39	--
Diclofenac sodium	--	--	76.80

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