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Full Length Research Article

Synthesis, Characterization, Biological Activity of 1-Aryl-4-Phenylamino-1-Butanone Hydrochloride

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Abstract

The present study aimed to synthesize 1-Aryl-4-Phenylamino-1-butanone Hydrochloride from propiophenone, formaldehyde and aniline by using Mannich reaction. The optimum reaction conditions for the synthesis of 1-Aryl-4-Phenylamino-1-butanone Hydrochloride mono Mannich bases reported in this study were investigated by changing the mol ratios of reactants, solvents and acidity level. It was observed that the most suitable mol ratio of propiophenone, formaldehyde and aniline hydrochloride reactants was 1:1.2:1 and most suitable reaction medium was ethanol containing concentrated hydrochloric acid. The synthesized compound was confirmed by UV-Vis, FTIR and NMR studies to check the purity of the synthesized compound. The synthesized 1-Aryl-4-Phenylamino-1-Butanone Hydrochloride was effective against *Micrococcus leuteus* (Microorganism) bacteria. From the Molecular docking studies, it was found to have almost higher binding interaction (-11.36 kcal/mol) than that of other compounds towards the active site of the enzyme.

***Key words*:** Mannich base, Biological activity, Molecular Docking studies, *Micrococcus leuteus*

β-Phenylaminoketones are valuable compounds for the synthesis of quinoline derivatives [1-6]. The biological activities of β -Phenylaminobutanones with Aryl hydrazines and formaldehydes has reported recently [7]. A small number of compounds exhibited a higher binding affinity to androgen receptor that its endogen ligand. From the Mannich base and their derivatives we can prepare the some other biologically active compounds and this reaction was helpful in pharmaceutical fields [8-12]. Taking into considerartion the potential of β-Phenylaminobutanones in organic synthesis and medicinal chemistry, the current study investigates the synthesis and biological activities of novel 1-Aryl-4-Phenylamino-1-Butanone Hydrochloride.

MATERIALS AND METHODS

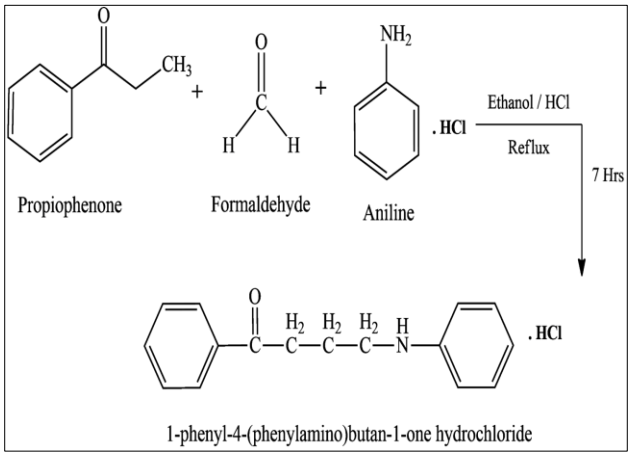
Melting point of the synthesized compound is 196°C and it was determined by using melting point apparatus equipped with thermometer. Unless stated otherwise, solvents and chemicals were obtained from commercial sources and used without further purification. The ^{1}H and ^{13}C NMR spectra of the new compounds were measured at 400 and 115 MHz respectively using Bruker Avance Neo NMR instrument in DMSO. Chemical shifts are reported as δ values (ppm) relative to tetramethylsilane (δ 0.0) as internal standard. Splitting patterns were designated as follows: s, singlet; bs, broad singlet; d, doublet; dd, doublet of doublet; t, triplet; m, multiplet. The empirical formula and the molecular weight of the compound was $C_{16}H_{18}ClNO$ and 276 respectively. Silica gel-G plates (Merck) were used for TLC analysis with a mixture of n-hexane and ethyl acetate as eluent.

General procedure for preparation of 1-aryl-4-phenylamino-1-butanone hydrochloride

1 equivalent of propiophenone (5ml) and 1.2 equivalent of formaldehyde (1.9ml) and 1 equivalent aniline hydrochloride (covert aniline into aniline hydrochloride by adding con. HCl drop by drop adjust the pH range within 2 and dry at room temperature ethanol will evaporate and get the aniline hydrochloride). It was observed that the suitable reaction medium was ethanol. These 1.1:2.1 reactant mixture is dissolved in 50ml ethanol containing concentrated hydrochloric acid (compared with the reaction without solvent and using only ethanol) and then reflux (65°C), the reaction was carried in 7 hours, after that we used as TLC (Thin Layer Chromatography) for monitoring the reaction the difference between reactant and product will be obtained. After the completion of the reaction the reaction mixtures were heated in acidic, Isopropanol. The compounds were purified by crystallization and obtained pure brown colored solid with the yield of 85%.

RESULTS AND DISCUSSION

After the purification using column chromatography and recrystallization the pure compound of 1-Aryl-4-Phenylamino-1-butanone will obtained. The compound was soluble in DMSO and water and sparingly soluble in ethanol.



Scheme 1: Synthetic pathway for the synthesis of the compound

TIR studies

Infrared spectroscopy is the measurement of the interaction of infrared radiation with matter by absorption, emission, or reflection. It is used to study and identify chemical substances or functional groups in solid, liquid, or gaseous forms. It can be used to characterize new materials or identify and verify known and unknown samples. The method or technique of infrared spectroscopy is conducted with an instrument called an infrared spectrometer which produces an infrared spectrum.

Table 1 FTIR Spectral data

Wave numbers	Assigned group
3382.10 cm^{-1}	NH_{str} (In amine)
2568.91 to 2697.33 cm^{-1}	$C\text{-}H_{Str}$ (In methyl group)
3030 cm^{-1}	$C\text{-}H_{str}$ (In aromatic)
1677.40 to 1738.44cm^{-1}	$C{=}O_{str}$
Below 1500 cm^{-1}	Finger print region (Bending vibrations)

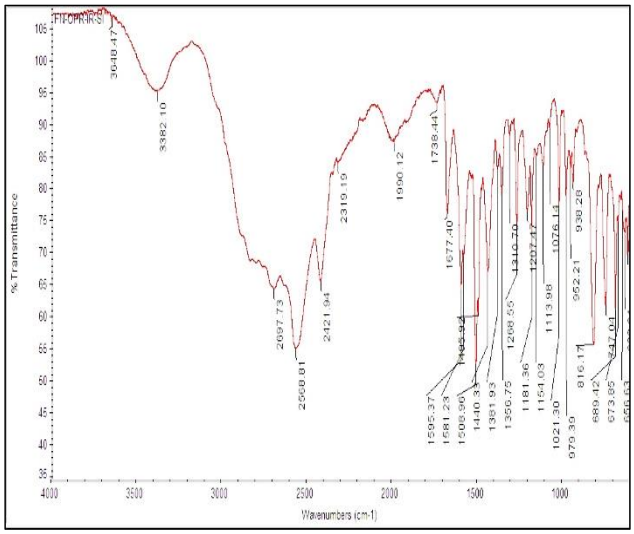


Fig 1 FTIR Spectrum of 1-Aryl-4-Phenylamino-1-Butanone Hydrochloride

UV-Vis Spectroscopy

The UV spectrum of the compound taken in ethanol gave a λ_{max} peak at 430 nm also in agreement with the structure.

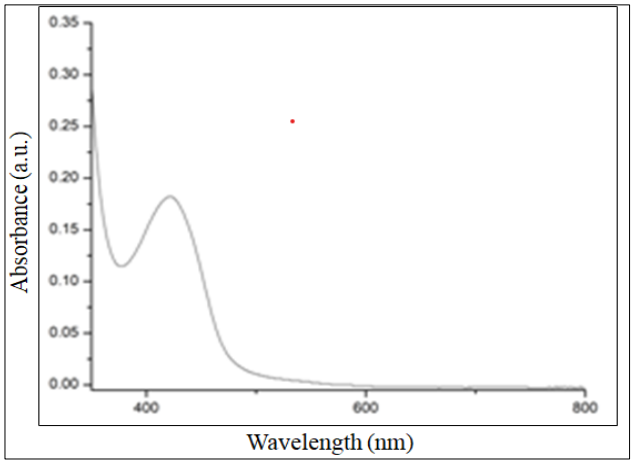


Fig 2 UV-Vis spectrum of 1-Aryl-4-Phenylamino-1-Butanone Hydrochloride

^{1}H-NMR Spectroscopy

In the ^{1} H-NMR spectrum of compound, the protons of the two methylene groups located on next to the carbonyl group were observed as multiplets (2 x 2 H) at δ 2.96-3.17 and 3.18-3.21 ppm, while the two protons of the methylene located next to the nitrogen atom were observed as a triplet at δ 3.28 ppm (J = 6.7 Hz) and the two protons of the methylene located next to the carbonyl group were observed as a triplet at δ 3.55 ppm (J = 6.9 Hz). The phenyl ring aromatic protons were observed as multiplets at δ 7.22-7.34 ppm (5 H), δ 7.53-7.69 ppm (3 H) and δ 7.96-7.98 ppm (2 H). A broad singlet at δ 9.23 ppm (1 H) suggested an NH proton, in accordance with the proposed chemical structure.

^{1}H-NMR (400 MHz, DMSO –D_6) δ 2.96-3.17 (2H, m), 3.18-3.21 (2H, m), 3.28 (2H, t, J = 6.7 Hz), 3.55 (2H, t, J = 6.9 Hz), 7.22-7.34 (5H, m), 7.53-7.69 (3H, m), 7.96-7.98 (2H, m), 9.23 (1H, br s).

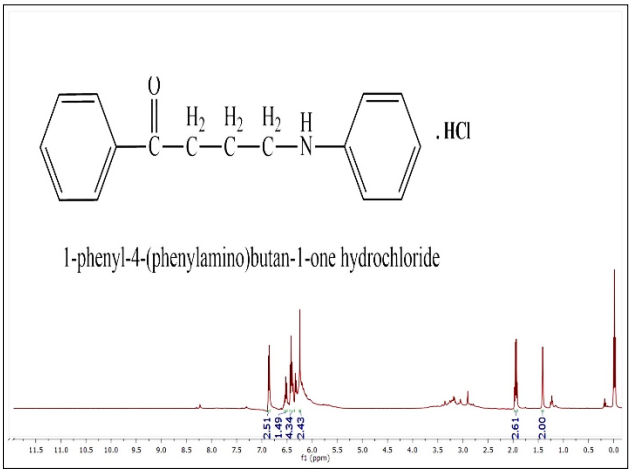


Fig 3 ^{1}H NMR of 1-aryl-4-phenylamino-1-butanone hydrochloride

^{13}C-NMR Spectroscopy

^{13}C NMR chemical shifts follow the same principles as those of ^{1}H, although the typical range of chemical shifts is much larger than for ^{1}H (by a factor of about 20). The chemical shift reference standard for ^{13}C is the carbons in tetramethylsilane (TMS), whose chemical shift is considered to be 0.0 ppm.

In the ^{13}C-NMR spectrum of compound, methylene carbons at δ 32.2, 35.1, 42.4 and 48.4 ppm, aromatic carbons at δ 127.4, 128.6, 129.31, 129.34, 129.5, 134.4, 136.5 and 144.6 ppm and a carbonyl carbon at δ 200 ppm were observed, all in agreement with the proposed structure.

^{13}C-NMR-DMSO-d_6 δ 32.2, 35.1, 42.4, 48.4, 127.4, 128.6, 129.31, 129.34, 129.5, 134.4, 136.5, 137.9, 197.6.

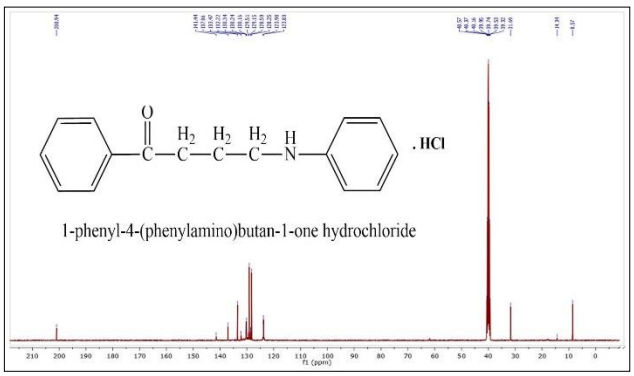


Fig 4 ^{13}C NMR of 1-Phenyl-4-(phenylamino)butanone hydrochloride

Molecular modeling study

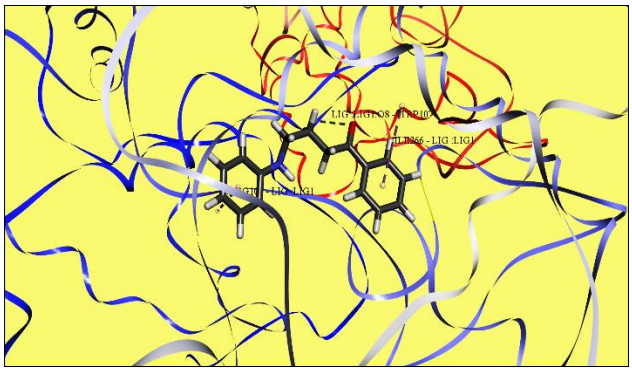


Fig 5 Molecular modeling of 1-aryl-4-phenylamino-1-butanone hydrochloride with *1SJ2*

Molecular docking methodology

In order to probe the structural interactions of the oxadiazolo furans with the enzyme, InhA, molecular docking was done by utilizing autodock4. The crystal structure of *Mycobacterium tuberculosis* (PDB ID: *1sj2*) was retrieved from the Protein Data Bank (http://www.rcsb.org). The active sites of the enzyme were identified by using Q-Site Finder: an energy-based method for the prediction of protein-lig and binding sites. The final docked conformations were ranked according to their binding free energy.

Molecular docking result

To validate the accuracy of the docking software, Autodock4., the co-crystallized ligand 1-Aryl-4-phenylamino-1-butanone Hydrochloride was redocked within cavity of 1sj2. The compound -Aryl-4-phenylamino-1-butanone Hydrochloride was found to have almost higher binding interaction (-11.36 kcal/mol) than that of other compounds towards the active site of the enzyme. Para substituted phenyl system of the present scaffold was found to make good binding interaction towards the active site of the enzyme with a close proximity to the co-factor.

Antibacterial activity

Antimicrobial activity of samples was carried out using disk diffusion method. Petriplates were prepared with 20 mL of sterile muller hinton agar (MHA, Himedia) for bacteria. The selected human pathogens were swabbed on the solidify media. The compounds were dissolved in 20% dimethyl sulfoxide (DMSO) and were tested at 2mg/disk concentration. Control was maintained separately: Streptomycin for bacteria was used as positive control. The loaded disks were placed on the surface of the medium and left for 30 mins at room temperature for diffusion [13-15]. The plates were incubated overnight at 37^{o} C and zones of inhibition were recorded (bacteria)

Table 2 Antibacterial activity of synthesized compounds

Microorganism	MTCC No.	Zone of inhibition (in mm)			
		CI	IN1	IM1	Streptomycin (10 µm/mL)
Salmonella typhimurium	3224	-	-	-	-
Shigella flexneri	1457	13	-	15	-
Micrococcus leuteus	106	14	-	19	17

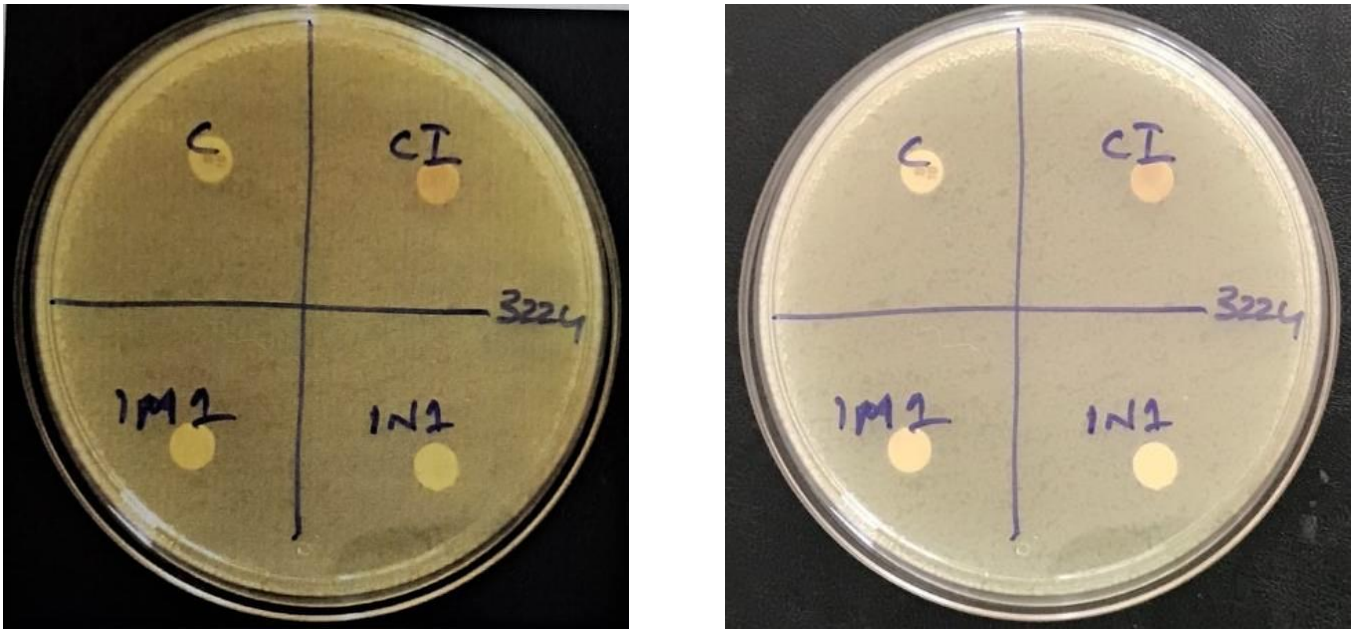


Fig 6 Antibacterial Assay plate for the Antibacterial activity of synthesized compounds [C1- 1-Aryl-3-phenylamino-1-propanone hydrochloride, IN1-3-(Phenylamino)1-(p-tolyl)propan-1-one hydrochloride, IM1- 1-Aryl-40phenylamino-1-butanone hydrochloride, C- control]

CONCLUSION

In conclusion, the syntheses in high reaction yield of 85% and the spectral data of the compound which are potential bioactive. The optimum reaction conditions for the synthesis of 1-aryl-4-phenylamino-1-butanone hydrochloride mono Mannich bases reported in this study were investigated by changing the mol ratios of reactants, solvent and acidity level, using as representative compounds. It was observed that the most suitable mol ratio of propiophenone, formaldehyde and aniline hydrochloride reactants was 1:1.2:1 (compared with 2:2.1) and the most suitable reaction medium was ethanol containing concentrated hydrochloric acid. Structural characterization by FTIR (Fourier transform infrared) and NMR supports their chemical identification of the synthesized compound. The Antibacterial activities revealed that the synthesized compound was effective against *Micrococcus leuteus* bacteria.

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