Research Article

Antimicrobial, molecular docking and *in vitro* SAR studies of pyrazole clubbed imino phenyl derivatives

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Abstract

Objective: Pyrazoles are well known five membered heterocyclic compounds. Pyrazoles and its derivatives have excellent biological activities which cause intensive interest in scientists, especially in the synthesis and investigation of its biological activities such as antibacterial, antifungal, antiviral and anti-inflammatory. The objective of present study was to synthesis the compounds containing both imino group and pyrazole ring and investigation of their biological activity. **Materials and methods**: The five membered cyclic nitrogen containing compounds exhibiting a broad spectrum of biological activities such as antioxidant, analgesic, antibacterial, antifungal activities. The in cooperation of imino or azo group into this compound might have been enhanced its biological activities. Therefor here we focused to synthesis the compounds containing both imino group and pyrazole ring as nitrogen containing heterocyclic compounds. The structure of all the synthesized pyrazole clubbed imino compounds confirmed by different spectroscopic techniques and their biological activities were screened. Molecular docking studies were examined by the software Arguslab 4.0.1. R**esults:** The synthesized compounds showed good to moderate biological activities both experimentally and theoretically. **Conclusion:** Most of the synthesized compounds bearing electron withdrawing group at para position of phenyl group were found to be exhibiting more biological activities. Molecular docking studies also supported the findings.

Keywords: 1,3-Diphenyl pyrazol-4-carboxaldehyde, antibacterial activity, antifungal, Vilsmeir -Haack reaction, molecular docking, alamar blue assay

Introduction

One of the most important five membered heterocyclic compound is pyrazole (Arora et al., 2012). Many pyrazole-based Schiff's bases are known to be medically important and used to design medicinal compounds because of its outstanding pharmacological (Milad et al., 2014), agrochemical (Fathy et al., 2017), photographic, catalytic, liquid crystal, antitumor (Kendre et al., 2013), anticancer (Rokade & Sayyed, 2009) and other applications (Dadiboyena et al., 2009; Carrión et al., 2008; Azam et al., 2007; Abid et al., 2009). In medicine pyrazole derivatives-based drugs have been patented due to their anti-microbial activities (Azam et al., 2007; Farag et al., 2008b). Similarly, anti-inflammatory, analgesic, NOS inhibitor, antiviral (Rokade & Sayyed, 2009) activities are also widely investigated (Farag et al., 2008a).

From the literature, imino compounds are exhibiting biological activities such as inhibition of DNA and RNA, protein synthesis, carcinogenesis (Balbi et al., 2006), and nitrogen fixation. Imino compounds also have application in the field of hypnotic drugs for nervous system as well as having biological activities against bacteria and fungus (Saad et al., 2011).

Recognizing the importance of the above two class of the compounds, pyrazoles, and imino compounds, in biological activity, we interested in preparing the compounds containing both pyrazole and imino group. In this work we synthesized some pyrazole clubbed imino compounds. We investigated the biological activities of all the synthesized title compounds, varying from moderate to good which supported our observations.

Materials and methods

All chemicals and reagents used in the synthesis were of

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analytical grade and obtained from Sigma-Aldrich and Merck. Melting points were taken on a Yanaco MP-S3 microscopic melting point apparatus. The FT-IR spectra were recorded in KBr pellets on a Brucker Equinox-55 FT-IR apparatus. The ^{1}H-NMR spectra were recorded on an INOVA- 400 (using TMS as internal standard, DMSO-*d*6 as solvent).

General procedure for the synthesis of the title compounds

The general procedure for the synthesis of the intermediates and target compounds were illustrated in figure 1 and 2. Intermediate 1,3-diphenyl pyrazol-4-carboxaldehyde (3) was prepared from acetophenone (1) and phenyl hydrazine (2) and followed by Vilsmeir-Haack reaction as shown in scheme 1. The formed pyrazole-4-carboxaldehyde on condensation reaction with p-substituted aniline to afford compound title compounds (4a-4f)) illustrated in figure 2.

N-((1,3-Diphenyl-1H-pyrazol-4-yl) methylene amine (4a)

The compound was obtained by the reaction between 1,3-diphenyl pyrazol-4-carboxaldehyde with aniline. Yield: 76%, pale yellow powder, mp. 121^{0}C; IR (cm^{-1}): 3047 (ArCH str), 1459 (ArC=C str), 1628 (C=N str), 1231 (C-N str); ^{1}HNMR (ppm): 9.13 (s, 1H, HC=N),8.47(s, CH of pyrazole ring) 6.98-8.31 (m, 15H, aromatic H), ^{13}CNMR: 109 -142 ppm (all aromatic carbons); Ms: m/z: 324 (M^{+}).

4-{((1,3-Diphenyl-1H-pyrazol-4-yl) methylene) amino} phenol (4b)

When 1,3-diphenyl pyrazol-4-carboxaldehyde undergo condensation reaction with 4-aminophenol yielded 4 (b). Yield: 36%, yellow powder, mp. 126^{0}C; IR (cm^{-1}): 3418 (OH str), 3037 (ArCH str), 1451 (ArC=C str), 1622 (C=N str), 1227 (C-N str); ^{1}HNMR (ppm): 4.98 (s, 1H, OH), 8.97 (s, 1H, HC=N), 8.43(s, 1H, CH of pyrazole ring), 6.98-8.31 (m, 15H, aromatic H), ^{13}CNMR: 109 -142 ppm (all aromatic carbons); Ms: m/z: 339 (M^{+}).

4-Bromo-N-((1,3-diphenyl-1H-pyrazol-4-yl) methylene) aniline (4c)

The compound was synthesized by the condensation reaction between 1,3-diphenyl pyrazol-4-carboxaldehyde and 4-amino-1-bromobenzene. Yield: 34%, dark yellow powder, mp. 142^{0}C; IR (cm^{-1}): 3035 (ArCH str), 1459 (ArC=C str), 1622 (C=N str), 1231 (C-N str), 746 (C-Br str); ^{1}HNMR (ppm): 8.93 (s, 1H, HC=N), 7.00-8.46 (m, 15H, aromatic H); ^{13}CNMR: 109-142 ppm (all aromatic carbons); Ms: m/z: 401 (M^{+}).

N-((1,3-Diphenyl-1H-pyrazol-4-yl)-4-methoxy aniline (4d)

The condensation reaction was carried out between 1,3-diphenyl pyrazol-4-carboxaldehyde and 4-amino-1-methoxybenzene to obtain 4(d).Yield 34%, dark yellow solid, mp 129^{0}C; IR (cm^{-1}): 3032 (ArCH str), 1457 (ArC=C str), 1616 (C=N str), 1225 (C-N str); ^{1}HNMR (ppm): 3.04 (s, 3H, OCH_3), 9,17 (s, 1H, HC=N), 7.02-8.24 (m, 15H, aromatic H), ^{13}CNMR: 109-142 ppm (all aromatic carbons),54 ppm (methoxy carbon); Ms: m/z: 353 (M^{+}).

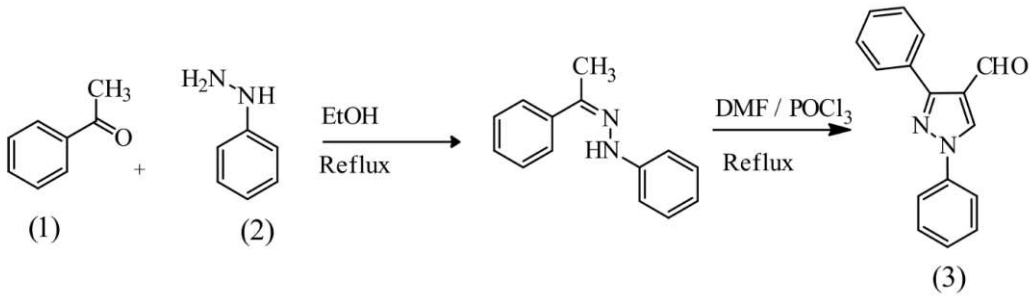

Figure 1. Schematic representation of synthesis of pyrazole carboxaldehyde

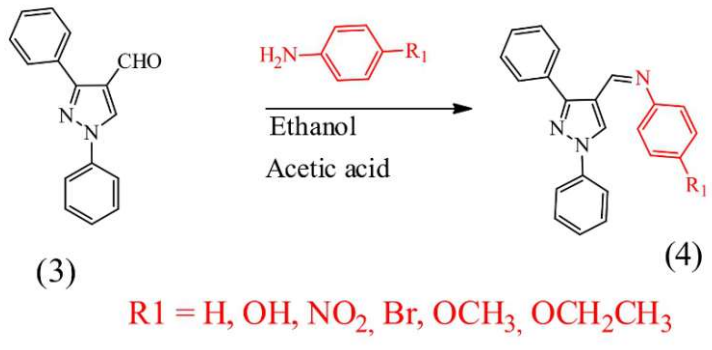

Figure 2. Schematic representation of synthesis of N-phenyl pyrazole derivatives

N-((1,3-Diphenyl-1H-pyrazol-4-yl) methylene-4-ethoxyaniline (4e)

The compound was synthesized by the reaction between 1,3-diphenyl pyrazol-4-carboxaldehyde with 4-amino-1-ethoxybenzene. Yield: 31%, dark yellow solid, mp. 133^{0}C, IR (cm^{-1}): 3030 (ArCH str), 1441 (ArC=C str), 1601 (C=N str), 1208 (C-N str); ^{1}HNMR (ppm): 1.16 (t, 3H, CH_3), 4.54 (q,CH_2), 9.71 (s, 1H, HC=N), 7.00-8.32 (m, 15H, aromatic H), ^{13}CNMR: 109-142 ppm (all aromatic carbons), 59 and 76 ppm (ethoxy carbons); Ms: m/z: 367(M^+).

N-(1,3-Diphenyl-1H-pyrazol) methylene)-4-nitroaniline (4f)

The compound was obtained by the reaction between 1,3-diphenyl pyrazol-4-carboxaldehyde with 4-nitroaniline. Yield: 42%, reddish brown solid, mp. 146^{0}C, IR (cm^{-1}): 3041 (ArCH str), 1449 (ArC=C str), 1611 (C=N str), 1214(C-N str), 1398 and 1547 cm^{-1} (NO_2 stretchings) ; ^{1}HNMR (ppm): 9.64 (s, 1H, HC=N),8.35(s, CH of pyrazole ring), 7.00-8.12 (m, 14H, aromatic H), ^{13}CNMR: 109-142 ppm (all aromatic carbons), Ms: m/z: 368(M^+).

Antibacterial activity

The antibacterial activity (Desai et al., 2013) of the all the synthesized compounds have been studied by adopting standard protocols available in the literature. Antibacterial activity (in vitro) of the synthesized compounds were screened against the representative panel of bacteria such as Escherichia coli MTCC443, Pseudomonas aeruginosa MTCC-1688, Staphylococcus aureus MTCC-96 and Streptococcus pyogenes MTCC-442. Ciprofloxacin was selected as the standard antibacterial drug.

Antifungal activity

Antifungal activity was studied against two fungal species, Candida Albicans MTCC-227 and Aspergillus Niger MTCC-282. Fluconazole was used as the standard antifungal. Using broth micro dilution method, the minimal inhibitory concentration (MIC) of all the synthesized compounds was determined according to National Committee for Clinical Laboratory Standards (NCCLS) (Khalil and Collins, 2010). All the synthesized compounds were screened for antibacterial and antifungal activities against bacteria and fungi used in the present protocol and the result were tabulated in table 1.

Antimycobacterial activity

The in vitro antitubercular activity of all the synthesized compounds was screened against M. tuberculosis H37Rv by microplate alamar blue assay (Huang Young, Tao Zhuo, Junhong Liu, 2014). The result was tabulated in the table 1. It was observed that the all compounds showed very weak antitubercular activity at MIC 12.8µg/ml vis-à-vis 0.4µg/ml for standard drug INH. The poor antitubercular activity by title compounds might probably be due to their lower lipophilicity, indicated by their C log P values, and thereby reduced cell wall permeation.

Molecular Docking

In the present study we used the Arguslab 4.0.1 version software for docking to prepare input files. Using this, binding conformations of the prepared compound and its free energy of binding in the active site of the MurD ligase were tabulated. The protein structure of MurD ligase was obtained from protein data bank. Before docking all the miscellaneous residues, water molecules, and heterocyclic compounds were removed from the protein crystallographic structure to activate the binding site for the synthesized compounds only. H - bond lengths were also tabulated (table 2, figure 4).

Results and Discussion

The chemistry behind the synthesis of the title compounds is that condensation of acetophenone with phenyl hydrazine followed by Vilsmeir-Haack reaction to yield pyrazole-4-carboxaldehyde which on again undergo condensation reaction with substituted aromatic amines to form imino compounds and characterized by different spectroscopic techniques.

IR Spectral data

IR spectrum the synthesized compounds were taken in KBr pellets at a range of 4000-400 cm^{-1}. All the compounds showed a peak in the region 3049-3020 cm^{-1} indicated the aromatic ArC-H stretching. The peak appeared in IR spectrum in the range 1462-1435, 1623-1601 and 1239-1211 cm^{-1} indicated Ar C=C, ArC=N and ArC-N stretching respectively. There was a sharp peak at 746 cm^{-1} indicated the C-Br stretching. All the nitro compounds showed two sharp peaks at the range of 1398 and 1547 cm^{-1} indicated the symmetric and unsymmetrical stretching of nitro group.

NMR spectral data

The structure of the synthesized compounds was confirmed ^{1}HNMR spectral data at room temperature. All the compounds showed a singlet peak in the region of 8.93–9.40 ppm indicated HC=N proton, and the peak (singlet) at 8.43- 8.38 ppm indicated the pyrazole CH proton. All aromatic protons were fall in between 6.98 - 8.12 ppm as multiplets. The compound with OH group sowed a singlet peak near 5ppm. A singlet peak near 3.4 indicated the OCH_3 protons. For compounds with ethoxy group a triplet was found near 1ppm and a quartet at 4.5 ppm. Therefore, the NMR data agreed with the proposed structures of the pyrazole clubbed imino phenyl derivatives.^{13}CNMR studies all the aromatic carbons were fall between 109–147 ppm and aliphatic protons at 54–79 ppm.

Biological studies on pyrazole clubbed imino derivatives (4a-4f)

Antibacterial activity (in vitro), antifungal activity and antitubercular activity of the synthesized pyrazole derivatives of imino phenyls were studied and tabulated in table 1.

Antimicrobial activity

Among the pyrazole clubbed imino phenyl derivatives, S. aureus is found to be more active against 4c and 4f, and inactive against 4a and 4e. The compounds 4b,4c, are 4f are active against E. Coli and inactive against 4a and 4e. P. aerugivosa is more active against 4c and 4f and less active against 4e. S. pyrogenes is active against 4b,4c and 4f and inactive against 4a and 4e. The phenyl derivatives of pyrazoles are also displayed an outstanding antifungal activity with MIC 0.2 µg/ml against A. niger than fluconazole. Here also the activity is found to be independent of substituents all exhibiting good antifungal activity against *C. albicans* (MIC 50 µg/ml. Here also these compounds are less active than standard antifungal fluconazole (MIC 30µg/ml).

Structure Activity Relationship (SAR)

The biological studies indicated that the presence of electron releasing or withdrawing group on phenyl ring extensively increases the conjugation and this will affect the bioactivity and exhibit broad-spectrum of antimicrobial activity. It is expected that bioactivity for these compounds appeared to be a combination of the factors such as inclusion and substitutions on the pyrazole ring, the presence of the imino bond, steric hindrance, and the presence of phenyl ring on pyrazole. Usually heterocyclic compounds enhance the pharmacological behavior and it was true in our case. SAR study would help to understand the effect of different substation on pyrazol ring and electronic effect on microbial strain (Huang Young, Tao Zhuo, Junhong Liu, 2014). The substituents on both pyrazole moiety and phenyl ring were chosen carefully for establishing different electronic environment on the new molecules. Methoxy and ethoxy groups were chosen as electron donating groups on aromatic ring and hydroxy, nitro and bromo groups are electron withdrawing groups from the aromatic system (Pai et al., 2016). From the experiment it was found that the compounds with electron withdrawing groups on phenyl ring show enhanced biological activities. From the result of antimicrobial activity, the presence of hydrophobic substituents in the 4^{th} positions of phenyl ring provide a positive impact on antimicrobial activity and its physiochemical properties. The activity order for substitution at 4^{th} position of the phenyl ring of the synthesized compounds follows the order NO_2>Br>OH>H>OCH_3>OCH_2CH_3 (Ravi et al., 2020). It was noted that as the chain length increases the inhibitory activity generally decrease, compounds with methoxy group was more active than corresponding ethoxy compounds (De Oliveira

Table 1. Antibacterial, antifungal, and ant-tuberculosis activities of pyrazole clubbed phenyl derivatives (inhibition zone measured in mm)

Compounds	*S. aureus*	*E. Coli*	*P. aerugi*	*S. pyrogenes*	*A. niger*	*C. albicans*	*M. tubercuosiss*
4a	4	6	7	8	0.2	100	100
4b	9	11	13	14	0.2	50	100
4c	16	17	20	19	0.2	100	30.2
4d	8	9	9	11	0.2	100	30.2
4e	7	3	6	8	0.2	100	100
4f	12	17	13	16	0.2	70	30.2
Ciprofloxacin	24	22	23	23	-	-	-
Fluconazole	-	-	-	-	30	30	-
INH	-	-	-	-	-	-	0.4

Table 2. Binding energy of the compound and H-bond length calculated using Argus lab 4.0.1

Compounds	Best ligand pose energy (Kcal/mol)	H-bond length (A^0)
4a	-10.2604	2.9974
4b	-11.0262	2.24715, 2.6391, 2.9920
4c	-10.9661	2.8308, 2.6609
4d	-10.9429	2.3930, 2.5381
4e	-8.97291	2.5203
4f	-10.9379	2.5805, 2.5739

Cabral et al., 2007). It was noted and true in our case also, that compounds having N in the heterocyclic system are better pharmacological agents than the compounds of simple benzene analogue. The antibacterial activity against E. coli improved when substitutions pattern was changed by the introduction of electron withdrawing groups such as bromo, nitro and hydroxy groups. In case of *S. aureus*, electron withdrawing groups at 4th position of phenyl ring showed good activity and inhibition (MIC= 12.5 µg/ml). From table 1, nitro, bromo and hydroxy substituents at 4th position of phenyl groups are active against S. pyogenes at 50µg/ml MIC.

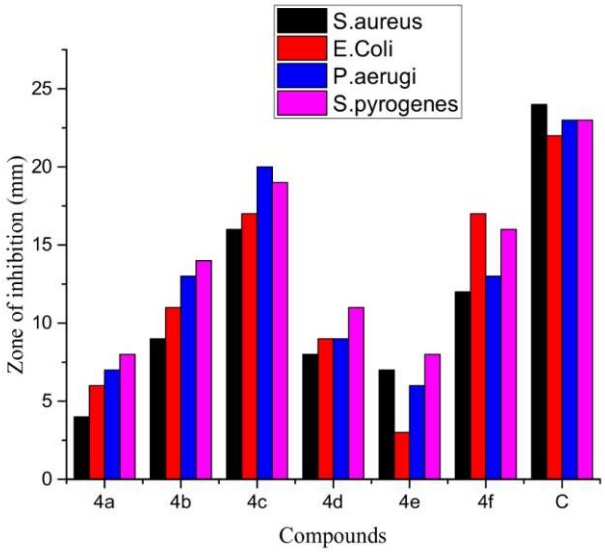

Figure 3. Bar chart showing antibacterial activity of the compounds

Antituberculosis activity

The antitubercular efficacy of the prepared pyrazole clubbed imino derivatives was explored against M. tuberculosis by microplate blue Almar assay as reported in the literature (Mustapha et al., 2018) and the result were tabulated in table 1. It was observed that the compounds showed very weak tubercular activity. The poor activity may due to their lower lipophilicity and there by reduced the cell wall penetration.

Molecular docking studies

The synthesized compounds 4a-4f docked in the active site of MurD ligase using Arguslab 4.0.1 software and the results of docking were tabulated in table 2. The H bond length of the synthesized compounds with active site of the proteins were also measured. The docking confirmations were represented in the figure 4.

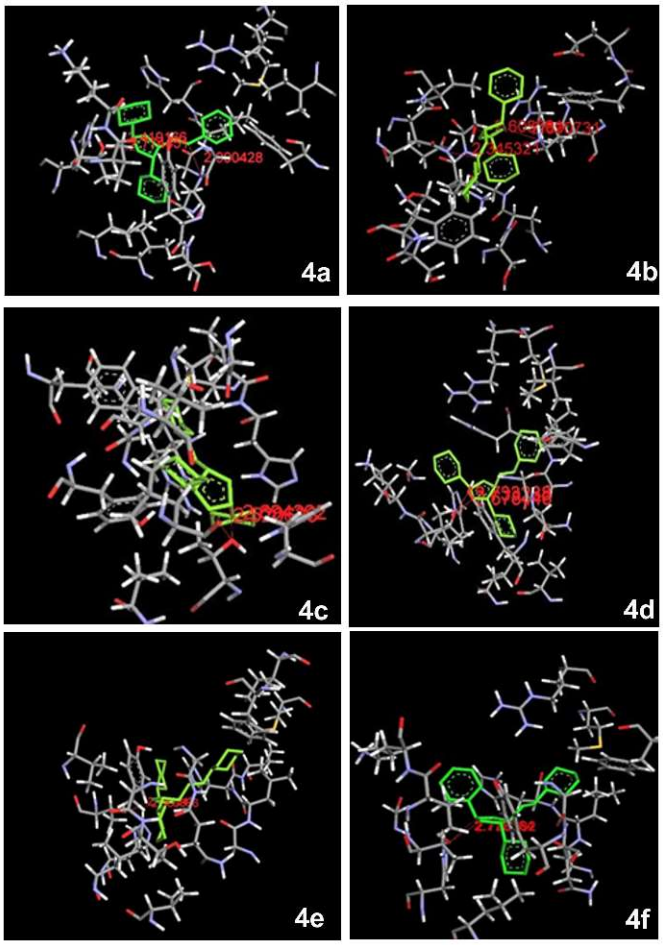

Figure 4. Binding pose of the synthesized compounds (green colour) in the active site of the target protein (H bonding also included showed in red colour)

Conclusion

We synthesized 6 different pyrazole clubbed imino phenyl derivatives, and all were well characterized by different spectroscopic techniques. In this study antimicrobial properties of the synthesized compounds were evaluated. Most of the derivatives are found active and this may due to the greater lipophilicity of the phenyl group. We observed that the in cooperation of electron withdrawing group like bromo, nitro and hydroxy groups on the title compounds showed excellent activity against all type of bacterial strains, which was better than the biological activity of the compounds with electron donating groups as methoxy and ethoxy. The present article reports the antibacterial and antifungal activities of different pyrazole terminated imino compounds. Molecular study was carried out using the software 4.0.1 and minimum ligand pose binding energy of all the synthesized compounds in MurD Ligase protein also tabulated.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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