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Synthesis, characterization, computational calculation and biological studies of some 2,6-diaryl-1-(prop-2-yn-1-yl)piperidin-4-one oxime derivatives

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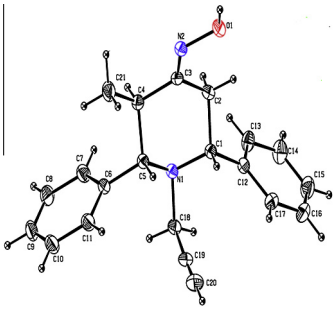
HIGHLIGHTS

- Series of 2,6-diaryl-1-(prop-2-yn-1-yl)piperidin-4-one oxime derivatives were synthesized and characterized.
- 2,6-Diaryl-1-(prop-2-yn-1-yl)piperidin-4-one oxime compounds were confirmed by IR, NMR and Mass spectroscopy.
- Compound **17** structure is elucidated by single crystal XRD analysis.
- Better antimicrobial activities are observed.

GRAPHICAL ABSTRACT



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ABSTRACT

A new series of 2,6-diaryl-1-(prop-2-yn-1-yl)piperidin-4-one oximes (**17**–**24**) were designed and synthesized from 2,6-diarylpiperidin-4-one oximes (**9**–**16**) with propargyl bromide. Unambiguous structural elucidation has been carried out by investigating IR, NMR (^{1}H, ^{13}C, ^{1}H–^{1}H COSY and HSQC), mass spectral techniques and theoretical (DFT) calculations. Further, crystal structure of compound **17** was evaluated by single crystal X-ray diffraction analysis. Single crystal X-ray structural analysis of compound **17** evidenced that the configuration about C=N double bond is *syn* to C-5 carbon (*E*-form). The existence of chair conformation was further confirmed by theoretical DFT calculation. All the synthesized compounds were screened for *in vitro* antimicrobial activity against a panel of selected bacterial and fungal strains using Ciprofloxacin and Ketoconazole as standards. The minimum inhibition concentration (MIC) results revealed that most of the 2,6-diaryl-1-(prop-2-yn-1-yl)piperidin-4-one oximes (**17**, **19**, **20** and **23**) exhibited better activity against the selected bacterial and fungal strains.

Introduction

Heterocyclic acetylenic amines are very important class of compounds due to their pharmacological properties such as activity, low toxicity and more easily absorbed into the body than their olefinic and saturated analogues [1–4]. Moreover various prop-2-nylamines are used as drugs, pesticides [5], anticancer [6] and antibacterial agents [7]. Activation of a terminal alkyne C—H bond by transition metal catalysts is a reaction of fundamental interest in organic synthesis [8,9]. It has also been claimed that the acetylenic bond is not considered essential for activity but favours entry in the central nervous system (CNS) by reducing the base strength [10]. Some of the N-substituted piperidone derivatives have demonstrated fascinating potential applications including anti-HIV, cytotoxins, 5α-reductase inhibitors, CARM1

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inhibitors, anti-proliferative, antioxidant and antimicrobial activities [11–16]. In addition piperidone oximes were also reported to exhibit nerve-agent anti-dote [17] analgesic, local anaesthetic and antifungal activities [18]. Recently the synthesis of 2,6-diarylpiperidin-4-one oxime derivatives and their biological importance are discussed elaborately [19–26]. Aiming at extending our knowledge in structure–activity relationship, we considered that it is valuable to synthesis a system that unites biolabile functional groups like prop-2-yn-1-yl with piperidin-4-one oximes. In this work the biologically active 3-alkyl-2,6-diaryl-1-(prop-2-yn-1-yl)piperidin-4-one oximes (**17**–**24**) were synthesized and characterized by IR, NMR (^{1}H, ^{13}C, ^{1}H–^{1}H COSY and HSQC) Mass spectra and DFT analysis. Further crystal structure of compound **17** was evaluated by single crystal X-ray diffraction technique. The X-ray diffraction analysis is used to predict the location of N-Alkylated propargyl group. The reaction sequence involves successive N-alkylation of the corresponding hydantoin, followed by secondary amine. The synthetic procedure was optimized for all steps and could easily be carried out on a multigram scale. All the synthesized compounds were screened for *in vitro* antimicrobial activities.

Experimental

General characterization techniques

TLC was carried out to monitor the course of the reaction and the purity of the product. Melting points were recorded in open capillaries and were uncorrected. IR spectra were recorded on AVATAR 330 FT-IR spectrometer KBr pellets. ^{1}H NMR spectra were recorded at 400 MHz on BRUKER AMX spectrophotometer using $CDCl_3$ and TMS as internal standard. ^{13}C NMR spectra were recorded at 100 MHz on BRUKER AMX 400 MHz spectrometer using $CDCl_3$ and the ^{1}H–^{1}H COSY, ^{1}H–^{13}C COSY correlation spectra were recorded on BRUKER AMX 400 MHz NMR spectrometer using standard parameters. Mass spectra were recorded with JEOL GCMATE II instrument. All the chromatographic purifications were performed with silica gel (100–200 mesh) whereas all TLC (silica gel) was performed on silica gel coated (Merk Kiesel 60 GF-254, 0.2 mm thickness) sheets. All reagents and solvents are commercially obtained (Alfa AeSar, Himedia) and used directly without any further purification.

X-ray crystallography

Crystal was grown by slow evaporation technique using chloroform as solvent. X-ray diffraction intensity data was collected on Bruker AXS SMART APEXII single crystal X-ray diffractometer equipped with graphite monochromated Mo$K\alpha$ (λ = 0.7103 Å) radiation and CCD detector. Crystals were cut to suitable size and mounted on a glass fibre using cyanoacrylate adhesive. The unit cell parameters were determined from 36 frames measured (0.5° phi-scan) from three different crystallographic zones and using the method of difference vectors. The intensity data were collected with an average fourfold redundancy per reflection and optimum resolution (0.75 Å). The intensity data collection, frames integration, Lorentz and polarization correction and decay correction were done using *SAINT-NT* (version 7.06a) software. Empirical absorption correction (multi-scan) was performed using *SADABS* [27] programme. Crystal structure was solved by direct methods using *SHELXS-97* [28]. The structure was then refined by the full-matrix least-squares method using *SHELXL-97*. The refinement converged to a final *R*-factor of 0.047. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 985707 for **17**. Copies of the data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223 336 033: or e-mail: deposit@ccdc.cam.ac.uk.

General procedure for synthesis of compounds

*Synthesis of 3-alkyl-2,6-diarylpiperidin-4-ones (**1**–**8**)*

The all parent 2,6-diarylpiperidin-4-ones were synthesized by adopting the literature procedure of Noller and Baliah [29] with the condensation of respective ketones, aldehydes and ammonium acetate in warm ethanol in 1:2:1 ratio.

*Synthesis of 3-alkyl-2,6-diarylpiperidin-4-one oximes (**9**–**16**)*

To the stirred solution of 3-methyl-2,6-diphenylpiperidin-4-one (1 mmol) in ethanol, sodium acetate (1.5 mmol) and hydroxylamine hydrochloride (1.5 mmol) were added. The reaction mixture was refluxed for 2 h and monitored by thin layer chromatography. After completion of reaction, the reaction mixture was slowly poured into ice-cold water and after cooling to room temperature, the crude product was obtained. Then it was subjected to recrystallization from ethanol to get pure oxime **9** with excellent yield. The same procedure was followed for the other piperidones to get their corresponding oximes (**10**–**16**).

*Synthesis of 3-alkyl-2,6-diaryl-1-(prop-2-yn-1-yl piperidin-4-one oximes (**17**–**24**)*

To a stirred solution of 3-alkyl-2,6-diphenylpiperidin-4-one oxime (1 mmol) in dry DMF (10 mL) and potassium carbonate (1.4 mmol) was added. After stirring for 10 min, propargyl bromide (1.4 mmol) was added drop wise to the reaction mixture in a period of 15 min. It was stirred at (40 °C) for 2 h and the progress of the reaction was monitored by thin layer chromatography. After completion of the reaction, the mixture was diluted with water (20 mL) and extracted with ethyl acetate (2 × 20 mL). The combined organic layer was washed with water (2 × 20 mL), dried over anhydrous sodium sulphate (5 g), filtered and concentrated under reduced pressure to get the crude product. It was further recrystallized with chloroform. The physical data of compounds (**17–24**) is shown in Table 1.

*(E)-3-methyl-2,6-diphenyl-1-(prop-2-yn-1-yl)piperidin-4-one oxime (**17**).* Yield: 88%, White Solid: IR (KBr, cm^{-1}); ν_{mas} 3286 (OH), 3147 (C≡CH), 1601 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$); δ (ppm) 0.82 (d, J = 6.0 Hz, 3H, CH_3); 2.70 (m, 1H, H-3a); 3.59 (d, J = 13.6 Hz, 1H, H-5e); 3.46 (d, J = 10.4 Hz, 1H, H-2a); 3.79 (d, J = 11.6 Hz, 1H, H-6a); 2.94, 2.83 (AB quartet, J = 17.6, 18.0 Hz, 2H, H-7a, H7b); 2.22 (d, 2H, H-5a); 2.16 (s, 1H, H-9, acetylene proton); 7.29–7.48, (m, 10H, aromatic protons); 9.04 (s, 1H, oxime OH); ^{13}C NMR (100 MHz, $CDCl_3$); δ (ppm) 12.7 (CH_3); 71.8 (C-2); 43.0 (C-3); 159.5 (C-4); 33.8 (C-5); 63.8 (C-6); 40.0 (C-7); 77.6 (C-8); 73.9 (C-9); 141.8, 142.8 (Aromatic ipso carbon).

*(E)-2,6-bis(4-methoxyphenyl)-3-methyl-1-(prop-2-yn-1-yl)piperidin-4-one oxime (**18**).* Yield: 85%, White Solid: IR (KBr, cm^{-1}); ν_{mas} 3279

Table 1
Physical data of compounds **17**–**24**.

Compound	R_1	R_2	X	Melting point (°C)	Mass (*m*/*z*)
1, 9, **17**	CH_3	H	H	158–160	317.62
2, 10, **18**	CH_3	H	OMe	157–159	–
3, 11, **19**	CH_3	H	Cl	189–191	–
4, 12, **20**	CH_3	H	Br	190–192	–
5, 13, **21**	CH_3	H	Me	190–192	–
6, 14, **22**	CH_2CH_3	H	H	150–152	–
7, 15, **23**	CH_3	H	F	158–160	–
8, 16, **24**	CH_3	CH'_3	H	180–182	–