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A facile solid-state synthesis and *in vitro* antimicrobial activities of some 2,6-diarylpiperidin/tetrahydrothiopyran and tetrahydropyran-4-one oximes

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Abstract

Some 2,6-diarylpiperidin/tetrahydrothiopyran/tetrahydropyran-4-one oximes were synthesized in dry media under microwave irradiation and were evaluated for their *in vitro* antibacterial activity against clinically isolated bacterial strains i.e. *S.aureus, β-H.Streptococcus, E.coli, P.aeruginosa, S.typhii* and *in vitro* antifungal activities against fungal strains i.e. *C.albicans, Rhizopus, A.niger* and *A.flavus.* Structure-activity relationships for the synthesized compounds showed that compounds **12** and **15** exerted excellent antibacterial activity against all the tested bacterial strains except **15** against *S.aureus* and *β-H.streptococcus.* Against *C.albicans* and *A.flavus*, compound **15** exerted potent antifungal activities while against *Rhizopus*, compound **16** showed promising activity.

Keywords: *2,6-diarylpiperidin-4-one oximes, 2,6-diaryltetrahydrothiopyran-4-one oximes, 2,6-diaryltetrahydropyran-4-one oximes, antibacterial activity, antifungal activity*

Introduction

Organic reactions under solvent-free conditions involving easily separable solid catalysts are receiving considerable attention in recent times, particularly from the point of view of green chemistry. Solvent-free solid state synthetic methods have been shown to be very efficient and advantageously coupled with microwave (MW) activation [1] and many organic reactions have been carried out using "microwave induced organic reaction enhancement" (MORE) technique delivering high yields in a short reaction time compared with the conventional heating mode performed in preheated thermostat oil bath [2]. The use of supported reagents has attracted much attention because of the selectivity, reactivity and associated ease of manipulation [3]. Microwave induced chemical reactions [4] especially on solid supports and those conducted in solvent less systems, [5] have gained popularity. Now-a-days, bioactive heterocyclic ring systems having 2,6-diarylpiperidin-4-one and their analogous thiopyran and pyran nuclei have aroused great interest due to their wide variety of biological properties such as antiviral, antitumour [6,7], central nervous system [8], local anesthetic [9], anticancer [10], and antimicrobial activity [11] and their derivative piperidine are also biologically important and act as neurokinin receptor antagonists [12], analgesic and anti-hypertensive agents [13]. Oximes of various substituted piperidones were also reported to exhibit antimicrobial, analgesic, local anesthetic and antifungal activities [14].

In the course of broad programme in developing biologically active molecules, we have recently reported the synthesis of 2,6-diarylpiperidin-4-one derivatives and evaluated their biological importance [15–17]. Consequently it was planned to synthesize 2,6-diarylpiperidin-4-one oximes, their analogous

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2,6-diaryltetrahydrothiopyran-4-one oximes and 2,6-diaryltetrahydropyran-4-one oximes. In turn to extend our knowledge in structure-activity relationship, all the synthesized compounds are tested for their *in vitro* antibacterial and antifungal activities and the influence of some structural variations by varying the substituents at the phenyl ring in the synthesized compounds towards their biological activities is evaluated.

Experimental

Chemistry

Performing TLC assessed the reactions and the purity of the products. All the reported melting points were taken in open capillaries and were uncorrected. A conventional (*unmodified*) domestic microwave oven equipped with a turntable (LG, MG-395 WA, 230V ~ 50 Hz, 760 W) was used for the irradiation. IR spectra were recorded in KBr (pellet forms) on a Nicolet-Avatar−330 FT-IR spectrophotometer and note worthy absorption values (cm^{-1}) alone are listed. ^1H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz respectively on Bruker AMX 400 NMR spectrometer using $CDCl_3$ as solvent. The ESI + ve MS spectra were recorded on a Bruker Daltonics LC-MS spectrometer and satisfactory microanalysis was obtained on a Carlo Erba 1106 CHN analyzer (Table I).

2,6-diarylpiperidin-4-ones **1-3**, 2,6-diaryltetrahydrothiopyran-4-ones **4-6** and 2,6-diaryltetrahydropyran-4-ones **7-9** were respectively prepared according to literature procedures previously described [18–20].

Synthesis of 2,6-diphenylpiperidin-4-one oxime 10. 2,6-diphenylpiperidin-4-one **1** (0.001 mol) and hydroxylamine hydrochloride (0.001 mol) were mixed thoroughly with CaO (50 mg) in an alumina bath. The mixture was placed inside a microwave oven and irradiated for 5-10 min. (monitored by TLC) and the alumina bath containing the reaction mixture was taken out from the oven, cooled and $CHCl_3$ (15 mL) was added to the crude mixture in order to obtain a suspension with the catalyst. The catalyst was removed by simple filtration. The $CHCl_3$ layer was dried over anhydrous sodium sulphate and distilled off under reduced pressure yielded 2,6-diphenylpiperidin-4-one oxime **10**. IR (KBr) (cm^{-1}): 3250, 3031, 2917, 2801, 1674, 1600, 754, 700; ^1H NMR (δ ppm): 2.00 (s, 1H, H_1), 3.94 (dd, 1H, H_{2a}, $J_{2a,3a} = 11.4$ Hz), 3.88 (dd, 1H, H_{6a}, $J_{6a,5a} = 11.6$ Hz), 3.54 (t, 1H, H_{5e}, $J_{6a,5e} = 2.98$ Hz), 2.56 (t, 1H, H_{3e}, $J_{2a,3e} = 2.92$ Hz), 2.36-2.40 (m, 1H, H_{3a}), 2.01-2.03 (m, 1H, H_{5a}), 7.48-7.18 (m, 10H, H_{arom}), 8.00 (s, 1H, N-OH).

The compounds **11-18** were synthesized similarly.

2,6-bis(4-methylphenyl)piperidine-4-one oxime. **11** IR (KBr) (cm^{-1}): 3248, 3028, 2914, 2841, 2804, 1671, 1604, 748, 696; ^1H NMR (δ ppm): 1.98 (s, 1H, H_1), 3.92 (dd, 1H, H_{2a}, $J_{2a,3a} = 11.30$ Hz), 3.86 (dd, 1H, H_{6a}, $J_{6a,5a} = 11.41$ Hz), 3.51 (t, 1H, H_{5e}, $J_{6a,5e} = 2.95$ Hz), 2.54 (t, 1H, H_{3e}, $J_{2a,3e} = 2.90$ Hz), 2.32 (s, 6H, CH_3 at phenyl ring); 2.35-2.37 (m, 1H, H_{3a}), 2.03-2.05 (m, 1H, H_{5a}), 7.52-7.09 (m, 8H, H_{arom}), 8.03 (s, 1H, N-OH).

2,61-bis(4-chlorophenyl)piperidine-4-one oxime. **12** IR (KBr) (cm^{-1}): 3253, 3035, 2921, 1677, 1598, 762, 705; ^1H NMR (δ ppm): 2.02 (s, 1H, H_1), 3.96 (dd, 1H, H_{2a}, $J_{2a,3a} = 11.7$ Hz), 3.89 (dd, 1H, H_{6a}, $J_{6a,5a} = 11.8$ Hz), 3.56 (t, 1H, H_{5e}, $J_{6a,5e} = 2.94$ Hz), 2.58 (t, 1H, H_{3e}, $J_{2a,3e} = 2.92$ Hz), 2.39-2.42 (m, 1H, H_{3a}), 2.07-2.09 (m, 1H, H_{5a}), 7.52-7.24 (m, 8H, H_{arom}), 8.06 (s, 1H, N-OH).

2,6-diphenyltetrahydrothiopyran-4-one oxime. **13** IR (KBr) (cm^{-1}): 3172, 3060, 2900, 1649, 748, 696; ^1H NMR (δ ppm): 4.20 (dd, 1H, H_{2a}, $J_{2a,3a} = 12.16$ Hz), 4.14 (dd, 1H, H_{6a}, $J_{6a,5a} = 12.4$ Hz), 3.96 (dd, 1H, H_{5e}, $J_{6a,5e} = 2.44$ Hz), 2.93 (dd, 1H, H_{3e}, $J_{2a,3e} = 2.72$ Hz), 2.77 (dd, 1H, H_{3a}, $J_{3a,3e} = 13.52$ Hz), 2.37 (dd, 1H,

Table I. Physical and analytical data of 2,6-diarylpiperidin/tetrahydrothiopyran and tetrahydropyran-4-one oximes **10-18**.

Compound	X	Y	Yield (%)	m.p° C	Elemental analysis (%) C Found (calculated)	H Found (calculated)	N Found (calculated)	m/z (M^+) Molecular formula
10	NH	H	90	169-171	76.62 (76.66)	6.79 (6.81)	10.47 (10.52)	267 $C_{17}H_{18}N_2O$
11	NH	CH_3	85	148-150	77.49 (77.52)	7.49 (7.53)	9.47 (9.52)	295 $C_{19}H_{22}N_2O$
12	NH	Cl	88	161-163	60.88 (60.91)	4.78 (4.81)	8.32 (8.36)	336 $C_{17}H_{16}Cl_2N_2O$
13	S	H	92	186-188	72.01 (72.05)	6.01 (6.05)	4.92 (4.94)	284 $C_{17}H_{17}NOS$
14	S	CH_3	90	194-196	73.25 (73.27)	6.75 (6.80)	4.47 (4.50)	312 $C_{19}H_{21}NOS$
15	S	Cl	85	182-184	57.91 (57.96)	4.25 (4.29)	3.93 (3.98)	353, $C_{17}H_{15}Cl_2NOS$
16	O	H	90	149-150	76.33 (76.38)	6.37 (6.41)	5.21 (5.24)	268 $C_{17}H_{17}NO_2$
17	O	CH_3	83	161-163	77.23 (77.26)	7.15 (7.17)	4.70 (4.74)	296 $C_{19}H_{21}NO_2$
18	O	Cl	80	144-146	60.70 (60.73)	4.47 (4.50)	4.13 (4.17)	337 $C_{17}H_{15}Cl_2NO_2$

H_{5a}, $J_{5a,5e} = 13.62$ Hz), 7.40-7.29 (m, 10H, H_{arom}), 7.55 (s, 1H, N-OH).

2,6-bis(4-methylphenyl)tetrahydrothiopyran-4-one oxime. **14** IR (KBr) (cm^{-1}): 3170, 3057, 2896, 1647, 744, 693; ^{1}H NMR (δ ppm): 4.17 (dd, 1H, H_{2a}, $J_{2a,3a} =$ 12.16 Hz), 4.12 (dd, 1H, H_{6a}, $J_{6a,5a} = 12.30$ Hz), 3.94 (dd, 1H, H_{5e}, $J_{6a,5e} = 2.43$ Hz), 2.91 (dd, 1H, H_{3e}, $J_{2a,3e} = 2.70$ Hz), 2.75 (dd, 1H, H_{3a}, $J_{3a,3e} = 13.54$ Hz), 2.30 (s, 6H, CH_3 at phenyl ring); 2.35 (dd, 1H, H_{5a}, $J_{5a,5e} = 13.60$ Hz), 7.37-7.26 (m, 8H, H_{arom}), 7.51 (s, 1H, N-OH).

2,6-bis(4-chlorophenyl)tetrahydrothiopyran-4-one oxime. **15** IR (KBr) (cm^{-1}): 3175, 3066, 2905, 1652, 756, 690; ^{1}H NMR (δ ppm): 4.22 (dd, 1H, H_{2a}, $J_{2a,3a} =$ 12.18 Hz), 4.16 (dd, 1H, H_{6a}, $J_{6a,5a} = 12.41$ Hz), 3.97 (dd, 1H, H_{5e}, $J_{6a,5e} = 2.40$ Hz), 2.95 (dd, 1H, H_{3e}, $J_{2a,3e} = 2.71$ Hz), 2.78 (dd, 1H, H_{3a}, $J_{3a,3e} = 13.55$ Hz), 2.39 (dd, 1H, H_{5a}, $J_{5a,5e} = 13.64$ Hz), 7.45-7.31 (m, 8H, H_{arom}), 7.58 (s, 1H, N-OH).

2,6-diphenyltetrahydropyran-4-one oxime. **16** IR (KBr) (cm^{-1}): 3226, 3030, 2896, 1661, 736, 690; ^{1}H NMR (δ ppm): 4.78 (dd, 1H, H_{2a}, $J_{2a,3a} = 10.30$ Hz), 5.13 (dd, 1H, H_{6a}, $J_{6a,5a} = 12.53$ Hz), 3.33-3.35 (m, 1H, H_{5e}), 2.68-2.72 (m, 2H, H_3), 2.83-2.85 (m, 1H, H_{5a}), 7.62-7.14 (m, 10H, H_{arom}), 7.90 (s, 1H, N-OH).

2,6-bis(4-methylphenyl)tetrahydropyran-4-one oxime. **17** IR (KBr) (cm^{-1}): 3223, 3027, 2891, 1658, 733, 688; ^{1}H NMR (δ ppm): 4.77 (dd, 1H, H_{2a}, $J_{2a,3a} =$ 10.29 Hz), 5.10 (dd, 1H, H_{6a}, $J_{6a,5a} = 12.54$ Hz), 3.31-3.33 (m, 1H, H_{5e}), 2.28 (s, 6H, CH_3 at phenyl ring); 2.65-2.69 (m, 2H, H_3), 2.80-2.82 (m, 1H, H_{5a}), 7.58-7.11 (m, 8H, H_{arom}), 7.87 (s, 1H, N-OH).

2,6-bis(4-chlorophenyl)tetrahydropyran-4-one oxime. **18** IR (KBr) (cm^{-1}): 3229, 3035, 2899, 1665, 739, 696; ^{1}H NMR (δ ppm): 4.79 (dd, 1H, H_{2a}, $J_{2a,3a} =$ 10.29 Hz), 5.15 (dd, 1H, H_{6a}, $J_{6a,5a} = 12.55$ Hz), 3.36-3.38 (m, 1H, H_{5e}), 2.71-2.75 (m, 2H, H_3), 2.87-2.89 (m, 1H, H_{5a}), 7.68-7.19 (m, 8H, H_{arom}), 7.92 (s, 1H, N-OH).

Microbiology

Materials. All the clinically isolated bacterial strains namely Staphylococcus aureus, β-Heamolytic streptococcus, Escherichia coli, Pseudomonas aeruginosa, Salmonella typhii and clinically isolated fungal strains namely Candida albicans, Rhizopus, Aspergillus niger and Aspergillus flavus are obtained from Faculty of Medicine, Annamalai University, Annamalainagar-608 002, Tamil Nadu, India.

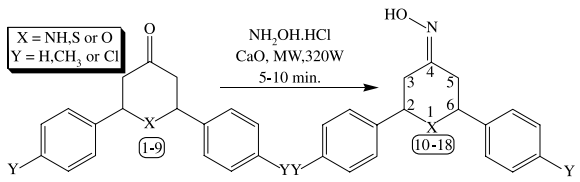
In vitro *antibacterial and antifungal activity*. The *in vitro* activities of the compounds were tested in Sabouraud dextrose broth (SDB) (Hi-media, Mumbai) for fungi and nutrient broth (NB) (Hi-media, Mumbai) for bacteria by two-fold serial dilution method [21]. The respective test compounds **10-18** were dissolved in dimethylsulfoxide to obtain 1 mg mL^{-1} stock solution. Seeded broth (broth containing microbial spores) was prepared in NB from 24 h old bacterial cultures on nutrient agar (Hi-media, Mumbai) at 37 ± 1°C while fungal spores from 1 to 7 days old Sabouraud agar (Hi-media, Mumbai) slant cultures were suspended in SDB. The colony forming units (cfu) of the seeded broth were determined by plating technique and adjusted in the range of 10^4-10^5 cfu/mL. The final inoculums size was 10^5cfu/mL for antibacterial assay and 1.1-1.5 × 10^2 cfu/mL for antifungal assay. Testing was performed at pH 7.4 ± 0.2 for bacteria (NB) and at a pH 5.6 for fungi (SDB). Exactly 0.4 mL of the solution of test compound was added to 1.6 mL of seeded broth to form the first dilution. One milliliter of this was diluted with a further 1 mL of seeded broth to give the second dilution and so on till six such dilutions were obtained. A set of assay tubes containing only seeded broth was kept as control. The tubes were incubated in BOD incubators at 37 ± 1°C for bacteria and 28 ± 1°C for fungi. The minimum inhibitory concentrations (MICs) were recorded by visual observations after 24 h (for bacteria) and 72-96 h (for fungi) of incubation. Ciprofloxacin was used as standard for bacteria studies and Amphotericin-B was used as standard for fungal studies.

Results and discussion

Chemistry

The oximes [22] of aldehyde and ketone served as protecting, selective activating groups [23] and intermediates for many reactions such as the preparation of amides by Beckmann rearrangement. Further, oximes are used for the purification of carbonyl compounds. The oximes can be prepared by the addition of hydroxylamine to aldehydes and ketones. The formation of oximes is usually catalyzed by acids [24]. The preparations of oximes from aldehydes or ketones using hydroxylamine as reactant and sulphuric acid as catalyst [24] have many disadvantages. This procedure is not applicable for acid-sensitive compounds, the yields of the oximes are pH dependent [25] and it requires costly solvent like pure ethanol. Cyclohexanone oxime is synthesized by liquid-phase ammoximation of cyclohexanone using ammonia, hydrogen peroxide as the oxidizing agent and titanium silicate as the catalyst. The ammoximation reaction is suitable for the synthesis of several oximes [26] but use of H_2O_2 and titanium silicate increased the cost of production. To avoid liquid phase oximation reactions, we use CaO as a solid catalyst for the above reactions. In continuation of our interest in synthesizing pharmacologically important compounds

in '*dry media*' [15,16,27], we wish to report CaO as an efficient catalyst for oximation by microwave irradiation under solvent free conditions. Target molecules, 2,6-diarylpiperidin/tetrahydrothiopyran/tetrahydropyran-4-one oximes **10–18** are synthesized as a result of single-step solid-state synthetic strategy. In a typical experiment, appropriate 2,6-diarylpiperidin/tetrahydrothiopyran/tetrahydropyran-4-ones **1–9** was mixed with CaO and hydroxylamine hydrochloride in an alumina bath and the mixture was irradiated in a microwave oven with a power level of 320W for 5 to 10 min. yield the title compounds in high yields with shorter time period in dry media under MW irradiation than the classical method [22], which require a longer reaction time using ethanol as solvent medium and the use of column chromatographic technique to purify the products. CaO catalyst was shown to be one of the most efficient MW absorber with a very high specificity to MW heating. It was able to reach a temperature of 90°C after 3 minutes of irradiation in a domestic oven (320 W). 50 mg of CaO to 0.001 moles of substrates is the most acceptable ratio in terms of efficiency and safety; a power level of 320 watts is the most suitable one. The importance of the title compounds is due to their diverse potential, broad-spectrum biological activity. The schematic representation and the analytical data of compounds **10–18** are given in Scheme 1 and Table I, respectively. The structure of the newly synthesized compounds **10–18** is confirmed by melting point, elemental analysis, MS, FT-IR, one-dimensional ^{1}H NMR spectroscopic data.



Scheme 1. Solid-state synthesis of biolabile oximes under microwave irradiation.

Antibacterial activity

Biolabile 2,6-diarylpiperidin/tetrahydrothiopyran and tetrahydropyran-4-one oximes **10–18** were tested for their antibacterial activity *in vitro* against *S.aureus, β-H.Streptococcus, E.coli, P.aeruginosa and S.typhii.* Ciprofloxacin was used as standard drug. Minimum inhibitory concentration (MIC) in μg/mL values is reproduced in Table II. All the synthesized oxime derivatives **10–18** exhibit a wide range of antibacterial potency against the tested strains except compounds **10,11** and **16**, which did not show activity against *E.coli*, *S.typhii* and *β-H.Streptococcus.* Among the compounds having no substitution at the *para* position of phenyl rings (i.e., compounds **10, 13** and **16**) only exerted moderate activities against all the used bacterial strains. Structure-activity relationship results for the synthesized compounds have shown that piperidone oxime with electron with drawing chloro functional group at the *para* position **12** and tetrahydrothiopyran oxime with electron with drawing chloro functional group at the *para* position **15** exerted excellent antibacterial activity against all the tested bacterial strains except **15** against *S.aureus* and *β-H.Streptococcus.*

Antifungal activity

The *in vitro* antifungal activity of the synthesized novel heterocyclic oximes, **10–18** was studied against the fungal strains viz., *C.albicans, Rhizopus, A.niger* and *A.flavus.* Amphotericin-B was used as a standard drug. Minimum inhibitory concentration (MIC) in μg/mL values is reproduced in Table III. Compound **10** did not exerted antifungal activity against *C.albicans, A.niger* and *A.flavus.* Further introduction of electron donating methyl functional group at the *para* position of phenyl ring in **11** also did not promote activity against *C.albicans* even at 200 μg/mL while against *A.flavus*, it has registered maximum activity at 50 μg/mL. Also, this methyl group modification has marked antifungal activity against *A.niger* too. Against *C.albicans* and *A.flavus*, compound **15** exerted potent

Table II. *In vitro* antibacterial activity (MIC) values for compounds **10–18**.

Compounds	Minimum *S.aureus*	Inhibitory *β-H Streptococcus*	Concentration *E.coli*	(MIC) *P.aeruginosa*	in μg/mL *S.typhii*
10	200	200	–*	100	100
11	200	100	100	50	–*
12	6.25	200	12.5	12.5	25
13	100	100	100	50	200
14	50	100	100	25	50
15	50	100	25	6.25	6.25
16	50	–*	100	25	50
17	50	50	50	25	100
18	25	50	25	50	100
Ciprofloxacin	25	50	25	12.5	50

*No inhibition even at higher concentration i.e., at 200 μg/mL

Table III. *In vitro* antifungal activity (MIC) values for compounds **10-18**.

Compounds	Minimum Inhibitory Concentration (MIC) in μg/mL			
	C.albicans	*Rhizopus*	*A.niger*	*A.flavus*
10	–*	100	–*	–*
11	–*	100	50	50
12	100	–*	100	100
13	50	25	50	100
14	50	12.5	25	50
15	6.25	25	25	6.25
16	25	6.25	50	12.5
17	100	50	50	100
18	50	25	50	25
Amphotericin-B	25	25	50	50

*- No inhibition even at higher concentration i.e., at 200 μg/mL

antifungal activities while against *Rhizopus*, compound **16** showed promisable activities.

Conclusion

The present work describes the synthesis of 2,6-diarylpiperidin-4-one oximes **10-12**; 2,6-diphenyltetrahydrothiopyran-4-one oximes **13-15**; 2,6-diphenyltetrahydropyran-4-one oximes **16-18** and the results of their screening for antibacterial and antifungal activities. Several compounds display antimicrobial activity similar and us potent as that of Ciprofloxacin and Amphotericin-B. Results of the present investigation prompted us to broaden our investigation of structure-activity relationships in this piperidin-4-one/tetrahydrothiopyran and tetrahydropyran ring system so as to discover the factors underlying the biological activity and this aspect suggest molecules with optimum structural features for maximum activity, is currently under investigation by our research group.

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Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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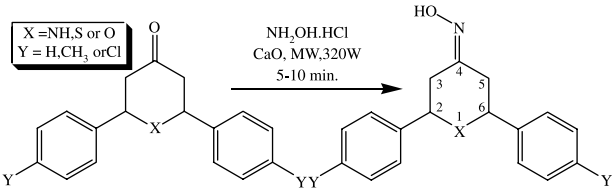

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