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Synthesis, structural characterization and antimicrobial evaluation of some novel piperidin-4-one oxime esters

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Abstract: Fifteen novel biologically active piperidin-4-one oxime esters **8**–**22** were synthesized in good yields. These compounds were prepared in reactions of carboxylic acids, *in situ* activated using $POCl_3$ and pyridine, with piperidin-4-one oximes. The structures of the title compounds were elucidated based on FTIR, NMR (1D and 2D) and mass spectral analyses. Single crystal XRD studies of compounds **12** and **20** provided further unambiguous evidence for the proposed structure. All the synthesized compounds were tested for their *in vitro* antibacterial and antifungal activities. Many of these derivatives exhibited good activity against *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Trichoderma viride* and *Aspergillus flavus*.

Keywords: piperidin-4-one oxime; aromatic acid; mixed anhydride; *gauche* interaction; conformation; single crystal XRD.

INTRODUCTION

Substituted piperidines and their analogues are basic structural units in numerous naturally occurring alkaloids and drug candidates. A search of piperidines and their derivatives revealed thousands of references to this simple ring system in medicinal and clinical research.[1] In particular, chiral centers at C2 and/or C6 of the piperidine ring were found to be essential for a defined activity, such as CNS,[2] anti-HIV,[3] anti-proliferative,[4] anti-cancer,[5] anti-inflammatory[6] and anti-oxidant[7] activities. Furthermore, the piperidine ring serves as a building block in synthetic and medicinal chemistry as more complex alkaloids include acridone and morphine, which themselves exhibit biological activities.[8]

Oximes[9] and their derivatives represent an important class of organic molecules that attract the interest of both synthetic and medicinal chemists. Oxime esters have showed great potential in biologically active molecules, such as RBPP9 inhibitors,[10] anti-proliferative[11] and anti-convulsant[12] agents, and in

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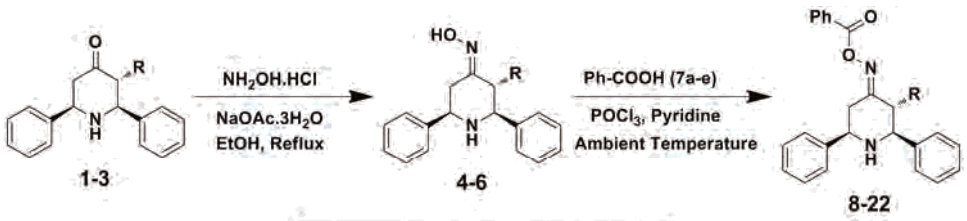
agrochemical[13] industries. In addition, oxime esters, such as OXE-1 and OXE-2, were employed as photoinitiators,[14] as they meet the specific requirements desired for color filter displays in LCDs. Recently, oxime esters were reported to exhibit DNA-cleaving[15] ability in a process triggered by UV light.

The formation of the ester is a simple dehydration process, which can be easily catalyzed by strong acids. Previously, numerous methods were documented for the synthesis of esters *via* direct coupling of a carboxylic acid with an alcohol, often involving the use of stoichiometric activators and coupling reagents.[16] In addition, several reports describe the synthesis of esters in good yields using coupling reagents such as dicyclohexylcarbodiimide/4-(*N*,*N*-dimethylamino)pyridine (DCC/DMAP),[17] diethyl azodicarboxylate/triphenylphosphine (DEAD/Ph_3P),[18] *N*,*N*-dimethyl phosphoramidic dichloride[19] and diethyl chlorophosphate.[20] However, some drawbacks still remain due to the formation of byproducts, difficulties in handling and long reaction times. Consequently, a practical and efficient synthesis of oxime esters in good yields under mild conditions is still needed. In this context, an attempt was made with phosphorus oxychloride ($POCl_3$),[21] which is a commercially available and relatively inexpensive superior reagent, and affects carboxylic group activation under mild conditions with excellent yields of the products.

Herein, the synthesis and structural characterization are reported of some novel 3-alkyl-2,6-diphenylpiperidin-4-one oxime esters **8**–**22** through carboxylic acids **7a**–**e**, *in situ*-activated using $POCl_3$ and pyridine as base as well as solvent, with 3-alkyl-2,6-diphenylpiperidin-4-one oximes **4**–**6** in good yields (Scheme 1). The key compounds, 3-alkyl-2,6-diphenylpiperidin-4-ones[22] **1–3** and their oximes[9,23] **4–6** were prepared using literature methods.



Compound	R	Ph
8, 13, 18	Me, Et, *i*-Pr	C_6H_5
9, 14, 19	Me, Et, *i*-Pr	3-C_5H_4N
10, 15, 20	Me, Et, *i*-Pr	*p*-Cl-C_6H_4
11, 16, 21	Me, Et, *i*-Pr	*p*-NO_2-C_6H_4
12, 17, 22	Me, Et, *i*-Pr	*m*-Me-C_6H_4

Scheme 1. General synthetic route for the synthesis of piperidin-4-one oxime esters **8**–**22**.

EXPERIMENTAL

All the purchased reagents and solvents were of reagent grade and used without further purification. Completion of reactions was monitored by TLC on silica gel-coated aluminum sheets (Type 60 GF254). The melting points were measured in open capillaries and are uncorrected. The FTIR spectra were recorded on Avatar-300 FTIR spectrometer in KBr disks. The NMR (1D and 2D) spectra were recorded on a Bruker 400 MHz spectrometer. The chemical shift values are reported in ppm from TMS.

The analytical and spectral data of the synthesized compounds are given in the Supplementary material to this paper.

*General procedure for the synthesis of piperidin-4-one oxime esters (**8**–**22**)*

A mixture of 3-methyl-2,6-diphenylpiperidin-4-one oxime (0.700 g, 2.5 mmol) and benzoic acid (0.335 g, 2.75 mmol) in dry pyridine (5 mL) was stirred at room temperature (29 °C), $POCl_3$ (0.25 mL, 2.75 mmol) was added dropwise to the mixture and stirring was continued for 15 min. The progress of the reaction was monitored by TLC. After completion of the reaction, the crude product was neutralized with dilute nitric acid and the desired product was regenerated with sodium bicarbonate solution. The crude product was then recrystallized from ethanol to obtain the pure piperidin-4-one oxime ester **8** in good yield (0.6 g, 86 %). The above general method was adopted for the synthesis of compounds **9**–**22** of this series.

RESULTS AND DISCUSSION

Chemistry

In the present investigation, first the reaction of 3-methyl-2,6-diphenyl piperidin-4-one oxime (**4**, 1 equiv.) and benzoic acid (**7a**, 1.1 equiv.) in pyridine as base as well as solvent was studied using various reagents (1.1 equiv.) to examine the feasibility of the reaction. As shown in Table I, a trace amount of product was formed with PCl_5, while moderate yields were obtained with $SOCl_2$ and DCC. Finally, $POCl_3$ gave the corresponding 3-methyl-2,6-diphenyl piperidin-4--one oxime ester **8** in good yield.

TABLE I. Formation of oxime ester from oxime with benzoic acid utilizing various reagents

Entry	Substrate (equiv.)	Reagent (equiv.)	Time, min	Yield[a], %
1	PhCOOH (1.1)	PCl_5 (1.1)	120	Trace
2	PhCOOH (1.1)	$SOCl_2$ (1.1)	80	60
3	PhCOOH (1.1)	DCC (1.1)	90	45
4	PhCOOH (1.1)	$POCl_3$ (1.1)	15	86

[a] Isolated yield

Next, $POCl_3$ was utilized as the reagent in varying amounts, from 0.5 to 2.0 equiv, for the synthesis of 3-methyl-2,6-diphenylpiperidin-4-one oxime ester **8**. Using equimolar quantities of benzoic acid **7a** and $POCl_3$, the desired product was obtained in 86 % yield (Entry 2, Table II). However, 0.5 equiv. of $POCl_3$ resulted in a poor yield of the product (Entry 1, Table II) compared to when 1.1 equiv. of $POCl_3$ was taken, while using 1.5 and 2.0 equiv. of $POCl_3$ resulted in moderate yields (Entries 3 and 4, Table II).

TABLE II. Optimization of reaction conditions with varying amounts of $POCl_3$

Entry	Substrate (equiv.)	$POCl_3$ (equiv.)	Time, min	Yield[a], %
1	PhCOOH (1.1)	0.5	30	trace
2	PhCOOH (1.1)	1.1	15	86
3	PhCOOH (1.1)	1.5	25	80
4	PhCOOH (1.1)	2.0	20	69

[a]Isolated yield

To study the scope and limitation of this protocol, $POCl_3$ and pyridine were used with wide ranges of aromatic/heteroaromatic acids and piperidin-4-one oximes. These methodologies resulted in good yield of products with short reaction times for all the substrates (Table III). The purity of products was high after a single recrystallization; extraction steps and chromatographic separation are thus avoided. The final products were well characterized using FTIR, NMR (1D and 2D) and mass spectrometry. The structures of compounds **12** and **20** were fully established by single crystal XRD analysis.

TABLE III. Substrate scope for piperidin-4-one oxime esters using $POCl_3$/pyridine

Cmpd.	R	Ar	Time, min	Yield[a] %	Cmpd.	R	Ar	Time, min	Yield[a], %
8	Me	C_6H_5	15	86	**16**	Et	*p*-NO_2-C_6H_4	20	95
9	Me	3-C_5H_4N	20	90	**17**	Et	*m*-Me-C_6H_4	25	75
10	Me	*p*-Cl-C_6H_4	20	79	**18**	*i*-Pr	C_6H_5	20	81
11	Me	*p*-NO_2-C_6H_4	15	92	**19**	*i*-Pr	3-C_5H_4N	25	89
12	Me	*m*-Me-C_6H_4	25	77	**20**	*i*-Pr	*p*-Cl-C_6H_4	25	73
13	Et	C_6H_5	20	85	**21**	*i*-Pr	*p*-NO_2-C_6H_4	20	86
14	Et	3-C_5H_4N	20	86	**22**	*i*-Pr	*m*-Me-C_6H_4	35	80
15	Et	*p*-Cl-C_6H_4	25	80					

[a]Isolated yield

FTIR spectral analysis

In general, compounds containing carbonyl group show absorption in the region of 1600–1750 cm^{-1}. In all the compounds **8**–**22**, a strong band appeared in the double bond region of the spectra at 1739–1752 cm^{-1}, which confirmed the formation of oxime ester (C=O). The imino group (C=N) in the piperidine ring gave a band at 1641–1607 cm^{-1}. A collection of bands observed in the region of 3272–3446 cm^{-1} and 2797–3087 cm^{-1} are due to the presence of a secondary amine (N–H) and aromatic and aliphatic C–H stretching.

NMR spectral analysis

For convenience, compound **8** was selected for the NMR spectral discussion. The two sets of signals appearing in the region 7.29–8.05 ppm for 15 protons revealed the presence of two Ph groups at the piperidine ring and one benzene

ring of the *O*-benzoyl group. Of these two sets of signals, one doublet that appeared in the downfield region at 8.03 ppm corresponded to the deshielded *ortho* H-atoms belonging to the *O*-benzoyl group. The remaining protons of Ph groups and the *O*-benzoyl group collectively gave a multiplet at 7.29–7.57 ppm. A doublet appeared in the upfield region of 1.07 ppm (J = 6.4 Hz) with a strong correlation in HSQC with the 11.84 ppm peak and a weak correlation with the 44.86 ppm; the signal at 1.07 ppm is due to Me(C3). A broad singlet appeared at 2.00 ppm, that showed no correlation in HSQC, was unambiguously assigned as the NH proton. In the downfield region, there are three doublets at 3.95, 3.66 and 3.56 ppm. Of these three signals, the two doublets at 3.95 (J = 11.6 Hz) and 3.66 ppm (J = 10 Hz) show strong correlation with 60.94 and 69.02 ppm signals and weak correlation with the 44.36 ppm signal. Obviously, these two signals are due to $H2_{ax}$ and $H6_{ax}$ (benzylic) protons. The latter doublet at 3.56 ppm (J = 13.6 Hz) shows strong correlation with 36.48 ppm signal, which is cross peak with the triplet center at 2.30 ppm, which confirmed that 3.56 and 2.30 ppm are due to $H5_{eq}$ and $H5_{ax}$ protons attached at the C5 carbon. A multiplet appearing at 2.67 ppm showed a strong correlation with the 44.36 ppm signal and a weak correlation with the 69.02 ppm signal, which confirmed the signal be assigned to the $H3_{ax}$ proton.

Akin to compound **8**, the chemical shift and coupling constant of C3 methyl, ethyl, isopropyl substituted analogous compounds **9**–**22** were assigned accordingly. Unlike compound **8**, in compounds **13**–**22**, the $H2_{ax}$ proton is deshielded by 0.14 ppm for the ethyl- and 0.38 ppm for the isopropyl-substituted compounds. Thee deviations indicate that the piperidine ring is flattened or distorted about the C2–C3 bond to decrease the *gauche* interaction. This interaction operates through space irrespective of the equatorial ethyl/isopropyl group at the C3 carbon and the phenyl group at the C2 carbon with an $H2_{ax}$ proton.

In the ^{13}C-NMR spectrum of compound **8**, the aromatic C-atoms appeared in the region of 126.9–129.6 ppm. The signals due to three *ipso* C-atoms were observed at 133.2, 142.0 and 143.0 ppm, respectively. Of these three signals, the one appearing at 133.25 ppm is due to an *ipso* carbon of the *O*-benzoyl group and the rest are due to *ipso* carbons attached to C2 and C6 carbons of piperidine ring. The imino carbon (C4) and *O*-benzoyl carbonyl carbon appear in the downfield region at 164.22 and 169.51 ppm, respectively. In the upfield region, the methyl group attached to the C3 carbon was observed at 11.84 ppm and piperidine ring carbons C2, C3, C5 and C6 appeared at 69.02, 44.36, 36.48, and 60.94 ppm, respectively.

Conformational analysis

The conformation of the piperidine ring and the orientation of the oxime ester group were studied from the values of the NMR coupling constant. Com-

pound **8** exhibited a large coupling constant $J_{6ax,5ax}$ (11.6 Hz) about the C5–C6 bond and about the C2–C3 bond (10 Hz) revealing the equatorial dispositions of the aryl rings at C2 and C6, and the alkyl group at C3. Thus, the synthesized compound **8** existed in a normal chair conformation with equatorial orientation of the Ph ring and Me(C3) substituents. The coupling constant about C2–C3 bond ($J_{2ax,3ax}$) were considerably lower than that about the C5–C6 bond ($J_{6ax,5ax}$), due to the *gauche* interaction between the Ph group and the alkyl group of C2 and C3. Hence, the piperidine ring is flattened/distorted about the C2–C3 bond and hence the lower magnitude of $J_{2ax,3ax}$ relative to $J_{6ax,5ax}$. The chemical shift difference between the C5 carbon (33.88 ppm) and C3 carbon (49.51 ppm) arises due to $A^{1,3}$ interactions between the N–O and C5–H bonds. Thus, the C5 carbon signal was more shielded compared to C3 carbon. It was concluded that *O*-benzoyl group was *syn* to the C5 carbon.

*Single crystal XRD analysis of compounds **12** and **20***

The crystal data and refinement parameters for compounds **12**[24] and **20** are summarized in Table S-I of the Supplementary material. The ORTEP view of compounds **12** and **20** are shown in Figs. 1 and 2, respectively. In compound **12**, the piperidine ring (N1/C7–C11) adopts a chair conformation (the N1 and C9 atoms deviate from the best plane of C7/C8 and C10/C11 by 54.9(2)° and –47.7(2)°, respectively) with an equatorial orientation of the Ph rings and Me group substituted on the heterocyclic. The C–C=N bond angles are different (C8–C9=N2 = 126.54(19)° and C10–C9=N2 = 117.50(18)°) and the dihedral angle between the atoms C10–C9=N2–O1 is –177.16(19)°, showing that the molecule exists as the *E*-isomer.

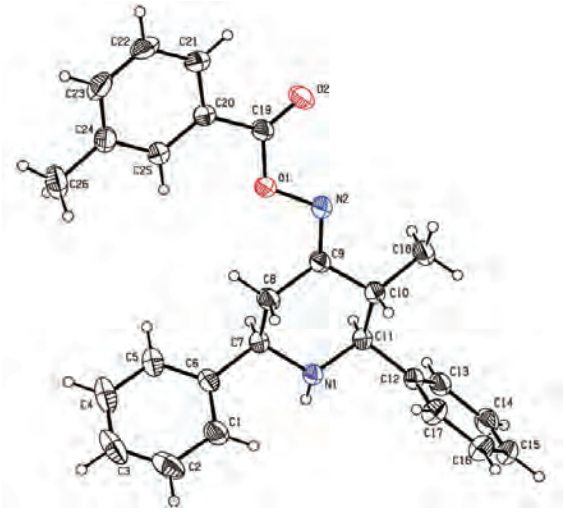


Fig. 1. The ORTEP view of compound **12** showing 30 % probability displacement ellipsoids.

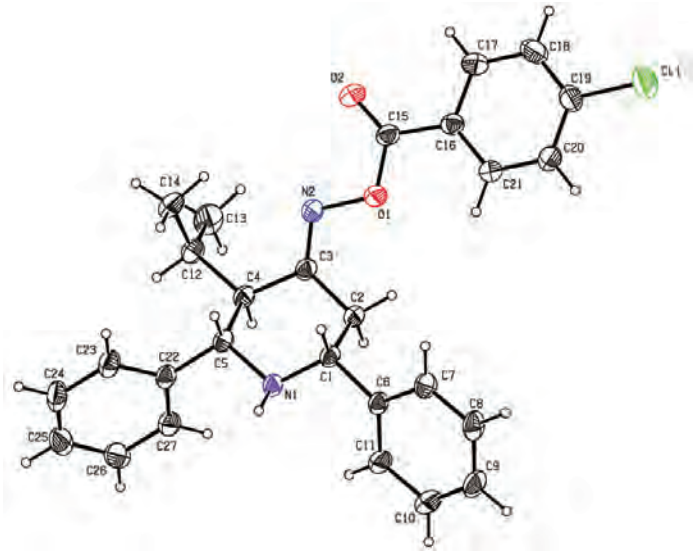


Fig. 2. The ORTEP view of compound **20** showing 50 % probability displacement ellipsoids.

In compound **20**, the piperidine ring (N1/C1–C5) also exists in a chair conformation with the ring atoms N1 and C3 deviating from the best plane of C1/C2 and C4/C5 by 66.77 and –62.22°, respectively. The Ph rings and the isopropyl group substituted on the heterocyclic ring are equatorially orientated. The bond angles of the C–C=N are different (C2–C3=N2 is 126.45° and C4–C3=N2 is 118.97°) and the molecule is found to exist in *E*-isomeric form as evidenced by the C2–C3=N2–O1 dihedral angle of 179.08°.

Antimicrobial screening

All the synthesized compounds **8**–**22** were screened for their *in vitro* antimicrobial activity in nutrient broth (NB) for bacteria and Sabouraud dextrose broth (SDB) for fungi by the twofold serial dilution method. A standard procedure was adopted for the preparation of all test samples.[25] The minimum inhibitory concentration (MIC) values of the synthesized compounds **8**–**22** against bacterial strains *viz*. *Bacillus subtilis*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Escherichia coli* are compared with the those of ampicillin in Table IV and against fungal strains *viz*. *Penicillim chrysogenum*, *Trichoderma viride*, *Aspergillus niger* and *A. flavus* are compared with those of amphotericin-B in Table V.

Antibacterial activity

All the synthesized piperidin-4-one oxime esters exhibited a wide range of *in vitro* antibacterial activity from the highest concentration (200 μg mL^{-1}) to the lowest concentration (6.25 μg mL^{-1}) against all the tested organisms, except **8** that

TABLE IV. Antibacterial activity (*MIC* / μg mL^{-1}) of compounds **8**–**22**; –: no inhibition at 200 μg mL^{-1}

Cmpd.	Bacteria			
	B. subtilis	*S. aureus*	*P. aeruginosa*	*E. coli*
8	100	–	200	200
9	25	50	25	50
10	25	100	50	50
11	50	100	50	50
12	100	200	100	100
13	50	200	100	200
14	12.5	25	12.5	12.5
15	25	50	50	25
16	25	50	25	25
17	50	100	50	50
18	50	100	50	50
19	6.25	12.5	6.25	6.25
20	12.5	25	6.25	12.5
21	6.25	25	25	12.5
22	25	50	25	25
Ampicillin	12.5	50	25	25

TABLE V. Antifungal activity (*MIC* / μg mL^{-1}) of compounds **8**–**22**; – no inhibition at 200 μg mL^{-1}

Cmpd.	Fungi			
	P. chrysogenum	*T. viride*	*A. niger*	*A. flavus*
8	–	200	–	–
9	200	100	100	200
10	200	200	200	200
11	–	–	200	200
12	–	200	–	200
13	200	100	100	100
14	50	50	50	25
15	100	50	50	50
16	100	100	50	25
17	100	100	100	50
18	50	25	50	50
19	25	12.5	12.5	12.5
20	25	12.5	25	25
21	50	25	25	25
22	50	25	25	25
Amphotericin B	25	25	50	50

failed to inhibit the growth of *S. aureus* at the highest concentration (200 μg mL^{-1}). Compounds **9**–**11** recorded moderate activity against *S. aureus* (100 μg mL^{-1}) and improved activity against *B. subtilis*, *P. aeruginosa* and *E. coli*. However, compounds **8** and **12** showed weaker activity against *S. aureus*, *P. aeruginosa*

and *E. coli* at 200 μg mL^{-1}. On introducing an ethyl and/or isopropyl group at the 3rd position of the piperidine ring instead of a methyl group and replacing of *O*-benzoyl group in the oxime part of all the compounds registered better activity against all the strains. Several authors also documented that the 3-ethyl and/or 3-isopropyl substituted piperidin-4-one oxime derivatives exhibited outstanding antibacterial and antifungal activities.[26,27] The 3-ethyl substituted oxime esters **13**–**17** showed better activity against all the tested organisms compared to compounds **8**–**12**. Among these compounds, **14** registered greater activity (12.5–25 μg mL^{-1}) against all the tested organisms and compounds **15** and **16** recorded good activity against *B. subtilis* and *E. coli* at 25 μg mL^{-1}. Compound **17** showed moderate activity against *B. subtilis*, *P. aeruginosa* and *E. coli* at 50 μg mL^{-1} and compound **13** did not show any significant activity against *S. aureus* and *E. coli* even at the highest concentration (200 μg mL^{-1}). The presence of an isopropyl group at the 3rd position in compounds **18**–**22** showed better activity with *MIC* values of 6.25–12.5 μg mL^{-1} when compared with the other substituents (methyl or ethyl). Especially compound **19** registered greater activity against all the tested strains at lower concentrations (6.25–12.5 μg mL^{-1}) and compounds **20** and **21** also registered better activity (12.5–50.0 μg mL^{-1}) against all the tested organisms compared with **18** and **22** (25–100 μg mL^{-1}). From the above observations, it is obvious that the nicotinoyl-substituted oxime esters **14** and **19** recorded excellent activity among the substituted oxime esters. The chloro- and nitro-substituted oximes esters **15**, **16**, **20** and **21** also registered good activity.

Antifungal activity

The synthesized compounds **8**–**22** were also screened for their *in vitro* antifungal activity against the tested organisms. Compounds **8** and **12** showed no significant inhibition of *P. chrysogenum*, *A. niger* and *A. flavus* even at the highest concentration of 200 μg mL^{-1}, nor did compound **11** against *P. chrysogenum* and *T. viride*. Compounds **9**, **10** and **13** showed weak activity against *A. flavus* and *P. chrysogenum* at 200 μg mL^{-1}. Replacement of the methyl group by ethyl and/or isopropyl led to significant activity against all the tested organisms. Compound **14** registered better activity against *T. viride*, *P. chrysogenum* and *A. niger* at 50 μg mL^{-1} and compound **15** also showed better activity against *T. viride*, *A. flavus* and *A. niger*. Compounds **16** and **17** exhibited moderate activity against *P. chrysogenum*, *T. viride* with *MIC* value of 100 μg mL^{-1}. Compound **18** showed good activity against *P. chrysogenum*, *A. flavus* and *A. niger* and improved activity against *T. viride* at 25 μg mL^{-1}. Introduction of nicotinoyl and/or an electron-withdrawing group (chloro or nitro) at the oxime part increased the activity of compounds **19** and **20** against *T. viride*, *A. niger* and *A. flavus* at 12.5–25 μg mL^{-1}, of compounds **21** and **22** against *P. chrysogenum*, *T. viride* and *A. niger* at 25–50 μg mL^{-1}. An isopropyl group at the 3rd position of the piperidine ring

resulted in greater activity against all the tested organisms (12.5–50 μg mL^{-1}), when compared with the other compounds.

CONCLUSIONS

In summary, the $POCl_3$ and pyridine system was described as an *in situ* activating agent for direct piperidin-4-one oxime ester formation in the reaction between aromatic acids and piperidin-4-one oximes. The present method is practically efficient, involves shorter reaction times, simple purification procedures and is economic for the synthesis of piperidin-4-one oxime esters. From XRD crystallographic results, it was shown that the piperidine rings of compounds **12** and **20** adopt chair confirmations with equatorial orientation of the aryl groups. Based on the antimicrobial studies, it was proved that piperidin-4-one oxime esters show better activities against standard strains than ampicillin and amphotericin-B. In particular, nicotinoyl oximes **14** and **19** showed excellent antibacterial as well as antifungal activities in comparison with the other oxime esters.

SUPPLEMENTARY MATERIAL

Analytical and spectral data of the synthesized compounds and the crystal data and structural refinement of compounds **12** and **20** are available electronically from http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

ИЗВОД

СИНТЕЗА, СТРУКТУРНА КАРАКТЕРИЗАЦИЈА И ИСПИТИВАЊЕ АНТИМИКРОБНЕ АКТИВНОСТИ НОВИХ ЕСТАРА ПИПЕРИДИН-4-ОН-ОКСИМА

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Синтетисано је петнаест нових, биолошки активних, естара пиперидин-4-он-оксима естара **8**–**22** у добром приносу. Једињења су добијена реакцијом непосредно припремљених алканоил-хлорида, добијених из одговарајућих карбоксилних киселина и $POCl_3$, са пиперидин-4-он-оксимима. Структура добијених деривата утврђена је FTIR, NMR (1D и 2D) и масеном спектралном анализом. Структура деривата недвосмислено је потврђена XRD анализом монокристала једињења **12** и **20**. Испитана је *in vitro* антибактеријска и антифунгална активност свих синтетисаних деривата. Значајан број ових једињења показује добру активност према *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Trichoderma viride* и *Aspergillus flavus*.

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REFERENCES

1. a) S. Jegham, G. DeFoase, T. Purcell, J. Sehoernaker, US Patent 5,280,030 (1994); b) M. J. Schneider, *Alkaloids: Chemical and Biological Perspectives*; S. W. Pelletier, Ed., Pergamon, Oxford, 1996; c) A. P. Kozikowski, G. L. Araldi, J. Boja, W. M. Meil, K. M. Johnson, J. L. Flippen-Anderson, C. George, E. Saiah, *J. Med. Chem.* **41** (1998) 1962; d) S. S. Hadida-Ruah, H. M. Binch, M. P. DeNinno, L. T. D. Fanning, B. A. Frieman, P. D. J. Grootenhuis, N. Hilgraf, P. Joshi, E. A. Kallel, M. T. Miller, J. Pontillo, A. Silina, U. J. Sheth, D. J. Hurley, V. Arumugam, US Patent 2012/0264749 A1 (2012)

2. S. O. Thorberg, S. Berg, J. Lundstrom, B. Pettersson, A. Wijkstrom, D. Sanchez, P. Lindberg, J. L. G. Nilsson, *J. Med. Chem.* **30** (1987) 2008
3. G. Xu, A. Kannan, T. L. Hartman, H. Wargo, K. Watson, J. A. Turpin, R. W. Buckheit Jr., A. A. Johnson, Y. Pommier, M. Cushman, *Bioorg. Med. Chem.* **10** (2002) 2807
4. P. Lagisetty, P. Vilekar, K. Sahoo, S. Anant, V. Awasthi, *Bioorg. Med. Chem*. **18** (2010) 6109
5. D. Cheng, S. Valente, S. Castellano, G. Sbardella, R. D. Santo, R. Costi, M. T. Bedford, A. Mai, *J. Med. Chem*. **54** (2011) 4928
6. A. M. Katsori, M. Chatzopoulou, K. Dimas, C. Kontogiorgis, A. Patsilinakos, T. Trangas, D. Hadjipavlou-Litina, *Eur. J. Med. Chem.* **46** (2011) 2722
7. S. T. Harini, H. V. Kumar, J. Rangaswamy, N. Naik, *Bioorg. Med. Chem. Lett*. **22** (2012) 7588
8. J. P. Michael, *Nat. Prod. Rep*. **5** (2003) 476
9. a) D. J. Lauffer, M. R. Pavia, H. Tecle, A. J. Thomas, European Patent 445,731, A1 (1991); b) I. Damljanovic, M. Vukicevic, R. D. Vukicevic, *Monatsh. Chem*. **137** (2006) 301; c) P. Politzer, J. S. Murray, *The Chemistry of Hydroxylamines, Oximes and Hydroxamic Acids*, Wiley, Chichester, 2009
10. D. A. Bachovchin, M. R. Wolfe, K. Masuda, S. J. Brown, T. P. Spicer, V. Fernandez-Vega, P. Chase, P. S. Hodder, H. Rosen, B. F. Cravatt, *Bioorg. Med. Chem. Lett*. **20** (2010) 2254
11. G. Surkau, K. J. Bohm, K. Muller, H. Prinz, *Eur. J. Med. Chem*. **45** (2010) 3354
12. A. Karakurt, M. A. Alagoz, B. Sayoglu, U. Calis, S. Dalkara, *Eur. J. Med. Chem*. **57** (2012) 275
13. X. H. Liu, L. Pan, C. X. Tan, J. Q. Weng, B. L. Wang, Z. M. Li, *Pest. Biochem. Physiol*. **101** (2011) 143
14. K. Kunimoto, J. Tanabe, H. Kura, H. Oka, M. Ohwa, US Patent 7 189 489 B2 (2007)
15. R. R. Hwu, S. C. Tsay, S. C. Hong, M. H. Hsu, C. F. Liu, S. S. P. Chou, *Bioconjugate Chem*. **24** (2013) 1778
16. J. Otera, J. Nishikido, *Esterification: Methods, Reactions and Applications*, 2nd ed., Wiley-VCH, Weinheim, 2010
17. B. Neises, W. Steglich, *Angew. Chem. Int. Ed. Engl*. **17** (1978) 522
18. O. Mitsunobu, M. Eguchi, *Bull. Chem. Soc. Jpn.* **44** (1971) 3427
19. A. K. Adak, *Synlett* (2004) 1651
20. J. McNulty, R. Vemula, V. Krishnamoorthy, A. Robertson, *Tetrahedron* **68** (2012) 5415
21. F. Effenberger, G. Konig, H. Klenk, *Angew. Chem., Int. Ed. Engl.* **17** (1978) 695
22. a) C. R. Noller, V. Baliah, *J. Am. Chem. Soc.* **70** (1948) 3853; b) K. Gokula Krishnan, R. Sivakumar, V. Thanikachalam, *Can. Chem. Trans*. **2** (2014) 353
23. a) K. Pandiarajan, R. T. Sabapathy Mohan, M. U. Hasan, *Magn. Reson. Chem*. **24** (1986) 312; b) E. Abele, R. Abele, O. Dzenitis, E. Lukevics, *Chem. Heterocycl. Compd. (N.Y., NY, U.S.)* **39** (2003) 3
24. V. Kathiravan, K. Gokula Krishnan, T. Mohandas, V. Thanikachalam, P. Sakthivel, *Acta Crystallogr*., *E* **70** (2014) o883
25. M. L. Dhar, M. M. Dhar, B. N. Dhawan, B. N. Mehrotra, C. Ray, *Indian J. Exp. Biol*. **6** (1968) 232
26. P. Parthiban, S. Balasubramanian, G. Aridoss, S. Kabilan, *Med. Chem. Res*. **14** (2005) 523
27. P. Parthiban, G. Aridoss, P. Rathika, V. Ramkumar, S. Kabilan, *Bioorg. Med. Chem. Lett*. **19** (2009) 2981.