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Original Article

Synthesis and Evaluation of Novel Furfurylidene Derivatives of 2, 6-Diphenyl Piperidin-4-one as Antifungal Agents

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ABSTRACT

The antifungal activity of α, β-unsaturated carbonyl compounds has been recognized generally due to their ability to react with sulfhydryl containing system of fungi essential for normal metabolism.In view of this, number of enones and related compounds were synthesized and evaluated for the antifungal properties. In the present investigation, a series of some novel furfurylidene derivatives of 2,6-diphenyl piperidin-4-one have been synthesized. All compounds were prepared by Claisen-Schmidt condensation between piperidin-4-one derivatives and furfuraldehyde in the basic medium; led to formation of furfurylidene derivatives. *N*-aryl sulphonyl and benzoyl derivatives were prepared by reacting furfurylidene piperidin-4-one with aryl sulphonyl chloride and benzoyl chloride. The newly synthesized compounds were found to havepractical yield in range of 68-96% with high purity and their characterization was done using M.P., TLC, FTIR and ^{1}HNMR spectral analysis.All these newly synthesized compounds were then evaluated for their *in-vitro* antifungal activity against *Candida albicans* and *Aspergillus niger* fungal strains in which most of the compounds showed potent activity. The present results may be used as key step for the construction of novel chemical entities with better pharmacological profiles than standard drugs.

Keywords: α,β-unsaturated carbonyl compounds, 2,6-diphenyl piperidin-4-one, furfuraldehyde, benzoyl chloride, furfurylidene derivatives, antifungal activity.

INTRODUCTION

Despite the growing list of antimicrobial agents including polyenes, allyl amines, azole derivatives, fluoropyrimidines and thiocarbamates; their clinical use has been limited by their relatively high risk of toxicity, insufficiencies in their antimicrobial activity and/or pharmacokinetic deficiencies. These observations foregrounded the emergent need to develop safe, efficacious, and non-toxic antimycotics that can be administered orally as well as parenterally.[1–3] Heterocyclic compounds carrying piperidine skeleton are attractive targets of organic synthesis owing to their pharmacological activity and their wide occurrence in nature,[4–6] Specifically, piperidine based chemical entities with aryl substituents at carbons 2 and 6 of the piperidine ring have been documented as potent antimicrobial agents.[7–15]

It is known that clinically useful azole antifungal drugs such as miconazole, econazole and oxiconazole have an o-benzyl structural unit in addition to azole and aryl moieties. Particularly, oxiconazole has an oximino unit, which is connected to O-benzyl, C-aryl, and C-azole groups. Recently, various oxiconazole-related antifungal chemical entities (ACE), which possessa benzyl unit linked to oximino moiety with different substituents including chromone scaffold have been reported.[16,17] Furthermore, synthesis of novel chemical entities, which were still in resemblance with bioactive molecules by virtue of the presence of some critical structural features, is an essential component of the search for new leads in drug designing programs.

The principle aim of the research is discovery of novel antifungal agents which act by alkylating mechanism. The currently available antineoplastic agents act by alkylating of cellular nucleophile by interaction with nucleic acid, so they produce mutagenic and carcinogenic effects.[18,19] In contrast various α,β-unsaturated ketones reacts preferentially or exclusively with thiols but not with amino or hydroxyl groups of nucleic acids.[20,21] As the thiols are not a part of nucleic acid structure, hence these compounds may be free from the problems like mutagenicity or carcinogenicity.[21,22] Recently the antineoplastic properties of various 1, 3-diaryl-2-propene-1-ones have been reviewed. These 3, 5 bis (arylidene) piperidene-4-one derivatives contain 1, 5-diaryl-3-oxo-1, 4-pentadinenyl pharma-cophore; which has been considered to interact at a complimentary binding site and permitting two successive alkylation of thiol to occur. The predicted binding mechanism of drug with thiol is as in **Figure-1**.[23]

There is imperative need for novel antifungal agents different in their structures and mode of action from those currently available in market and which contributes to number of side effects. It has already proved that the number of α, β-unsaturated ketones exhibit prominent antifungal effect. The antifungal activity of α,β-unsaturated carbonyl compounds has been recognized generally due to their ability to react with sulfhydryl containing system essential for normal metabolism of fungi.[24] The attachment of N-acyl group to the nitrogen of piperidone leads to increase in activity by many folds. Dimmock *et al* proposed that this increased activity is due to binding of molecule to two sites that are primary site A and second auxiliary site B as shown in **Figure-2**.

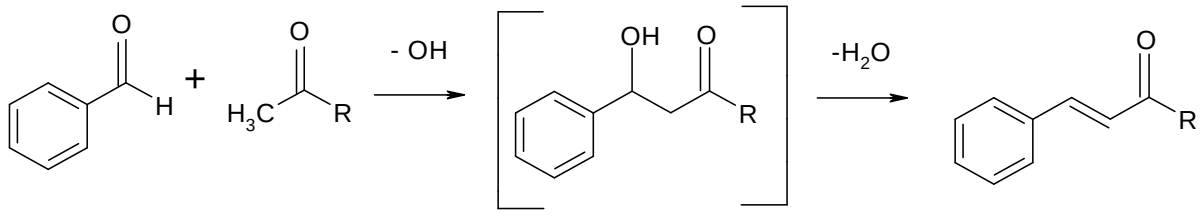
While reviewing literature we came to know that very few synthetic piperidin-4-one derivatives have been reported. In view of this, number of enones and related compounds were synthesized and evaluated for their antifungal properties. Mechanism of this addition has also been studied.[25,26]

The reported compounds having α, β-unsaturated carbonyl group and hence shows antifungal activity.

Mechanism of Synthesis

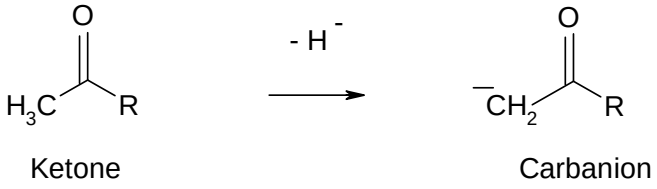
Claisen-Schmidt Reaction

Aromatic aldehydes condense with ketones in presence of aqueous alkali to form α, β-unsaturated ketones.



In the first step formation of nucleophilic, mesomerically stabilized α-carbanion (the enolate ion) of ketone take place by the action of base. After that condensation of carbanion of ketone with aromatic aldehyde take place to form hydroxyketone and lastly dehydration of the hydroxyketone leads to formation of conjugated unsaturated carbonyl compounds.[27,28]

Step 1-



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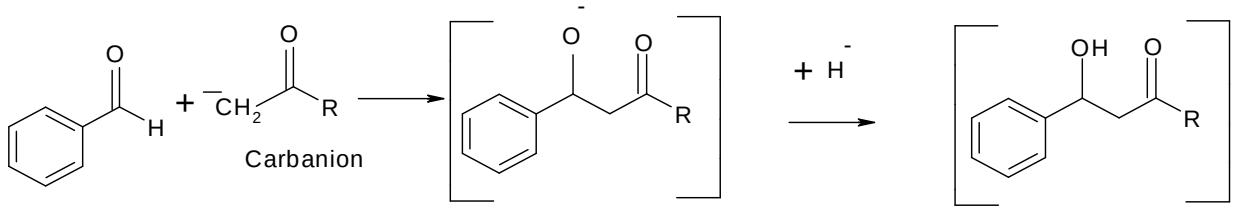

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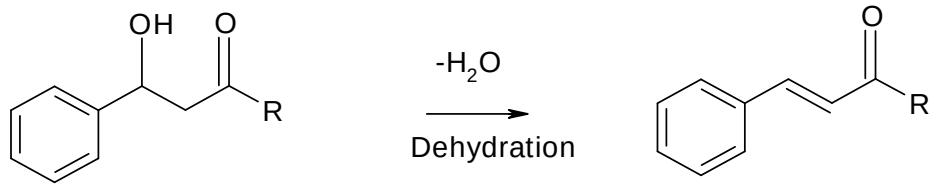

Similarly, it is predicted that piperidine-4-one formation also has same type of mechanism like (Figure 3)

MATERIALS AND METHODS

All the chemicals, reagents and solvents used were of analytical grade and were obtained from S. D. Fine Chem. Ltd., Mumbai and E-Merck Ltd., Mumbai. Melting points were determined by open capillary method and are uncorrected. The IR spectra in KBr were recorded on Shimadzu Spectrophotometer and ^{1}H NMR spectra were recorded in DMSO on Avance 300 MHz Spectrometer using TMS as internal standard. The chemical shift values are expressed in part per million (ppm) downfield from the internal standard and signals are quoted as s (singlet), d (doublet), t (triplet) and m (multiplet). Purity of the compounds is checked by TLC plates (Merck) using benzene and ethyl acetate as an eluent (6:4 v/v).

Experimental Section

The derivatives of 2, 6- diphenyl piperidine-4-one (1, 2, 2a, 2b and 2c as shown in **Figure 4**) were synthesized.

For synthesis of 2, 6-diphenyl piperidin-4-one[28]

Ammonium acetate (7.7 gm, 100mmol), benzaldehyde (21.2 ml, 200mmol) andacetone (14.5ml, 200mmol) were dissolved in 95% ethanol (20ml), the solution was heated on a hot plate with gentle swirling until color of mixture changed to orange. The mixture was cooled under running tap water and poured into ether (100ml). The ether insoluble 2, 4, 6, 8-tetraphenyl-3, 7 diazabicyclo nanan-9-one (M.P. 234-236^{0}C) was filtered off and concentrated HCl (14ml) was added to the filtrate. The precipitated 2,6-diphenyl piperidin-4-one hydrochloride was collected by filtration and recrystallized from ethanol and then dry ether was added until turbidity appeared in the cold solution. The hydrochloride (M.P. 215-216^{0}C) was dispersed in acetone (50ml) and concentrated aqueous ammonia was added dropwise until a clear solution obtained. The clear solution was then poured into crushed ice and the solid precipitate was collected and recrystallized from ethanol (M.P. 102-105^{0}C).

For synthesis of furfurylidene-piperidin-4-one derivatives[28]

A mixture of piperidin-4-one (0.01mole) and the appropriate aldehyde (0.02mole) in alcoholic NaOH (50ml, 10%) was stirred at room temperature. The reaction was monitored using TLC. After completion of reaction, the separated solid was filtered and recrystallized from suitable solvents.

RESULTS AND DISCUSSION

In the present work various furfurylidene derivatives of 2, 6-diphenyl piperidin-4-one (1, 2, 2a, 2b, 2c) were prepared by Claisen-Schmidth condensation between piperidin-4-one derivatives and furfuraldehyde in basic medium. *N*-aryl sulphonyl and benzoyl derivatives were prepared by reacting furfurylidene piperidin-4-one with aryl sulphonyl chloride and benzoyl chloride respectively. The structures of newly synthesized compounds have been confirmed by IR and ^{1}H-NMR. The analytical data obtained (**Table No. 1 and 2**) revealed that the compounds were isometrically pure. Yield of synthesized derivatives was appreciable in range of 68-96%. The absorption of olifenic protons in the ^{1}H-NMR spectra were located at 7.5 to 8 ppm, which is indicative of compound possessing the *E*-configuration. For the corresponding *Z*-isomer, these protons would be predicted to be located at higher field. The ^{1}H-NMR spectra of all synthesized products showed that all arylidene protons were found above the 7.8 ppm, piperidyl in between 5.0-6.0 ppm and broad peak of NH in the region of 1.6-2.3 ppm; whereas furfuryl protons overlapped with aryl protons.

Synthesized derivatives were also evaluated for their *in-vitro* antifungal activity

against two fungal strains (*Candida albicans* and *Aspergillus niger*) measured as minimum inhibitory concentration (MIC, µg/ml). Fluconazole and DMSO were used as standard and control respectively. The data for biological evaluation by using Cup and Plate Method at 50 µg/ml concentration is furnished in **Table No. 3**. The antifungal data indicates that *Candida albicans* and *Aspergillus niger* were sensitive to these compounds. All compounds reflected more antifungal activity against *C. albicans*, where as *A. niger* depicted less sensitivity. 2, 6 diphenyl piperidin-4-one analogs showed more potency than piperidin-4-one analogs. The antifungal activity results depicted that analog **2a** have more activity as compare to all other analogs.

CONCLUSION

Several furfurylidene-piperidin-4-one derivatives were synthesized and their characterization was done using M.P., TLC, FTIR and ^{1}HNMR. The synthesized derivatives were found to be isometrically pure and the investigation has revealed that all derivatives exhibit significant activity against *C. albicans* and *A. niger* fungal strains. In particular compound 2a depicted prominent antifungal activity. Hence the novel substituted furfurylidene derivatives may have promising applications in mycosis and other fungal infections and may become first step which lead to a new path in fungal therapy.

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Table 1. Physical Data of Synthesized Derivatives

Sr. No.	Entry of Compound	Mole. Formula (Mole. Wt.)	M.P. (^{0}C)	Yield (%)	R_f Value [Solvent System]
1	1	$C_{24}H_{23}NO_2$ (357.44)	110	68	0.76 [Chloroform]
2	2	$C_{27}H_{21}NO_3$ (407.46)	200	96.28	0.93 [Chloroform]
3	2a	$C_{33}H_{25}NO_5S$ (547.62)	206-208	92	0.95 [Hexane]
4	2b	$C_{34}H_{27}NO_5S$ (561.65)	194	90	0.53 [Chloroform]
5	2c	$C_{34}H_{25}NO_4$(511.57)	60-65	84	0.63 [Chloroform]

Table 2. Analytical Data of Synthesized Derivatives

Sr. No.	Entry of Compound	^{1}H-NMR	IR
1	1	δ-6.6-7.4 (m, 14H, arylidine H, aryi H, furfuryl H), δ- 4.5 (s, 1H, 2-piperidyl H), δ- 4.15 (d, 1H, 6-piperidyl H), δ- 3.0 (m, 1H, 5-piperidyl H), δ -1.5 (m, 2H, -CH2-), δ-0.9 (t, 3H, methyl H), δ-2.2 (br, 1H, NH).	Ali.CH=1455.07 Ar.CH=1433.22 C=O=1702.53 R-O-R=1296.15 NH=1321,3304
2	2	δ-7.85 (S, 2H, arylidine H), δ-6.5-7.6 (M, 16H, aryl & furfuryl H),δ- 5.644 (S 2H, piperidyl H), δ-2.0 (br, 1H, NH)	Ali.CH=1463.20 Ar.CH=3023.94 C=O=1749.60 R-O-R=1240.28 NH=1300.7,3303
	2a	δ-7.6-7.7 (S, 2H, arylidine H), δ-6.8-7.3 (M, 15H, aryl) , δ-6.4-6.6 (M, 4H, furfuryl H), δ- 7.5 (d, 2H, furfuyl H), δ- 5.644 (S 2H, piperidyl H).	Ali.CH=2981 Ar.CH=3025 C=O=1725 tert. N=1680 Sulphonamide=1300
4	2b	δ-7.6-7.7 (s, 2H, arylidine H), δ-6.8-7.4 (m, 15H, aryl) , δ-6.4-6.6 (M, 4H, furfuryl H), δ- 7.5 (d, 2H, furfuyl H), δ- 5.644 (S 2H, piperidyl H)., δ-2.4 (S 3H, methyl).	Ali.CH=2830 Ar.CH=3032 C=O=1728 tert. N=1650 Sulphonamide=1330
5	2c	δ-7.6-7.7 (S, 2H, arylidine H), δ-6.8-7.3 (M, 15H, aryl), δ-6.4-6.6 (M, 4H, furfuryl H), δ- 7.5 (d, 2H, furfuyl H), δ- 5.644 (S 2H, piperidyl H).	Ali.CH=2950 Ar.CH=3040 C=O=1725 tert. N=1660

Table 3. Antifungal activity data

Sr. No	Entry of Compound	*Against Candida albicans	*Against Aspergillus niger
1	1	12	12
2	2	18	16
3	2a	19	18
4	2b	16	16
5	2c	18	16
6	Fluconazole	23	22

*Zone of inhibition at 50µg/ml in mm.

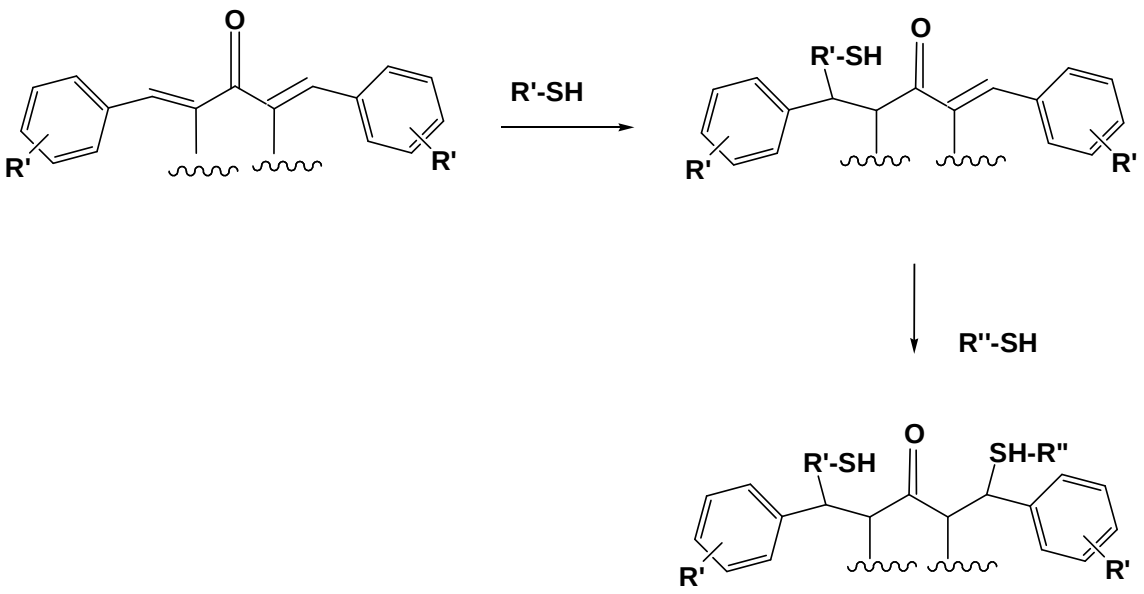

Figure 1. Predicted mode of binding of 4-piperidone with thiols

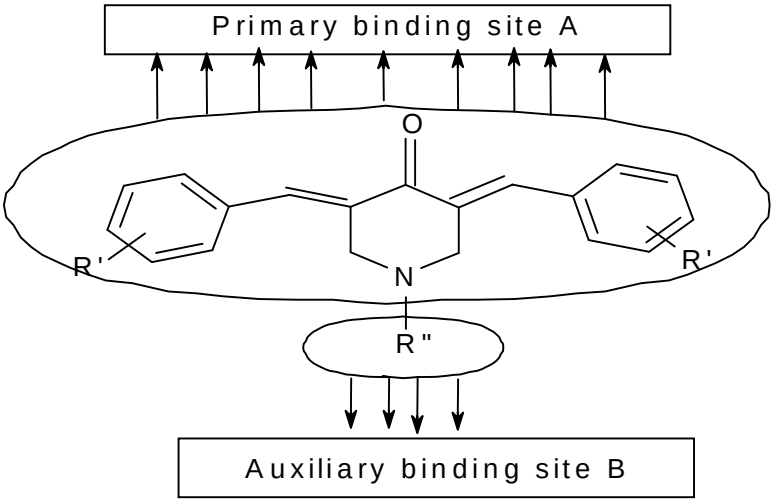

Figure 2. Observed binding mode of piperidone derivatives with binding sites

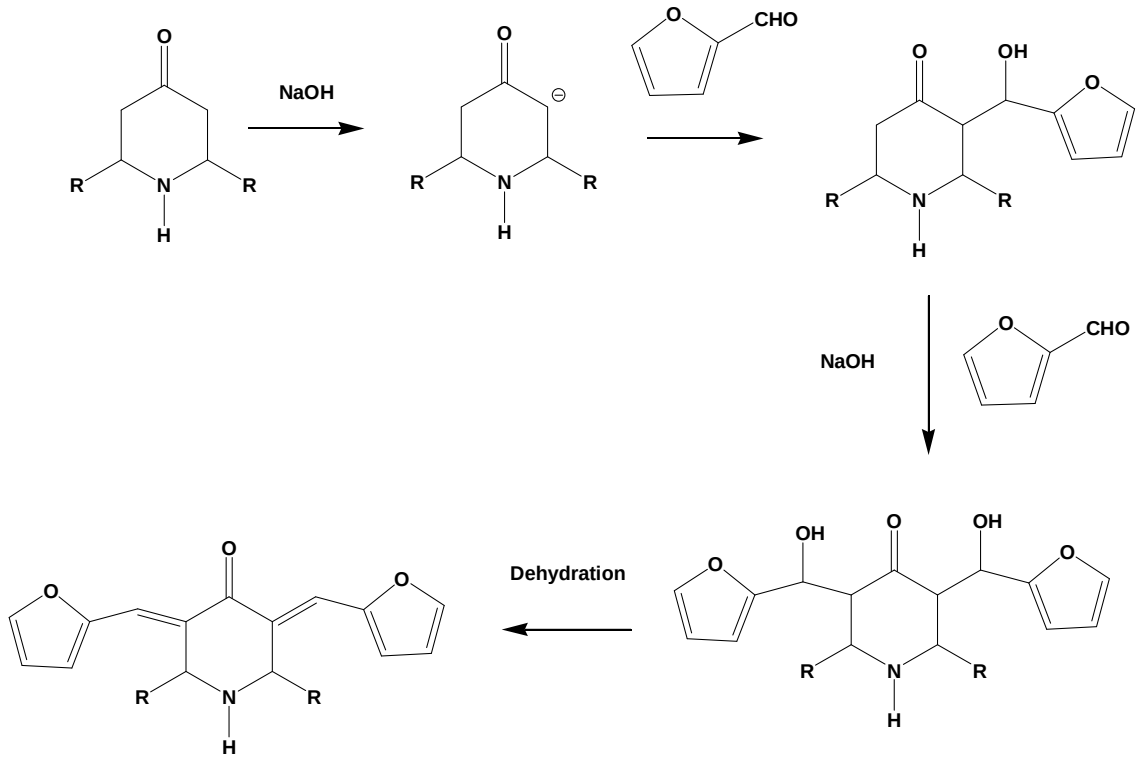

Figure 3. Predicted mechanism of 3, 5-bis (furfurylidene) 2, 6 diphenyl piperidine-4-one formation

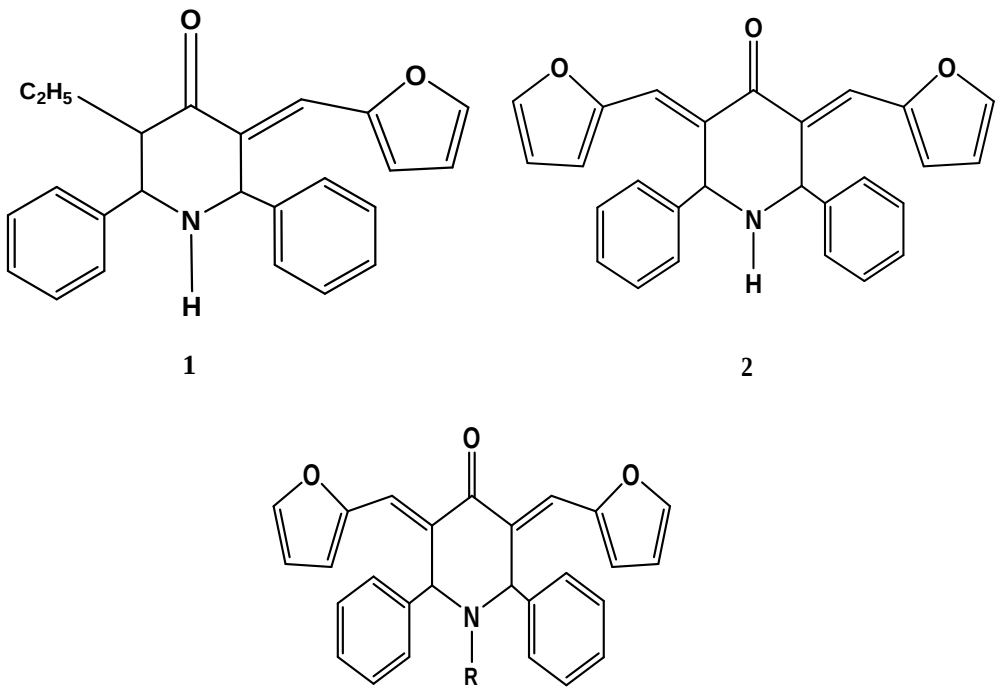

Figure 4. Synthesized furfurylidene derivatives of 2, 6-diphenyl piperidin-4-one