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Short communication

Synthesis and study of antibacterial and antifungal activities of novel 1-[2-(benzoxazol-2-yl)ethoxy]- 2,6-diarylpiperidin-4-ones

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Abstract

Some novel benzoxazolylethoxypiperidones have been synthesized and their antibacterial activity against streptococcus faecalis, bacillus subtilis, escherichia coli, staphylococcus aureus aand pseudomonas aeruginosa and antifungal activity against Candida-6, Candida albicans, Aspergillus niger, Candida-51 and Aspergillus flavus were evaluated. Compounds 37, 38 and 39 exerted potent in vitro antibacterial activity against Streptococcus faecalis while compounds 40 and 41 exhibited potent in vitro antifungal activity against Candida-51.

Keywords: Piperidin-4-one; Cyanoethylation; Benzoxazole; Antibacterial activity; Antifungal activity

1. Introduction

Substituted piperidin-4-ones are important synthetic intermediates for the preparation of various alkaloids and pharmaceuticals [1]. The piperidine nucleus can also be frequently recognized in the structure of numerous naturally occurring alkaloid and synthetic compounds with interesting biological and pharmacological properties. As a consequence, the development of general methods for the synthesis of piperidine derivatives has been the subject of considerable synthetic effort [2]. Benzoxazole nucleus is marked for its biological activity. 2-Substituted benzoxazoles were shown to exhibit analgesic [3], fungicidal, insecticidal, nematocidal [4], potent protease inhibitory [5], anticancer [6] activities and serve as topoisomerase I poisons [7].

An essential component of the search for new leads in a drug designing program is the synthesis of molecules, which are novel yet resemble known biologically active molecules by virtue of the presence of some critical structural features. Certain small heterocyclic molecules act as highly funtionalized scaffolds and are known pharmacophores of a number of biologically active and medicinally useful molecules [8]. In the interest of above, we planned to synthesize a system which combines these two biolabile components together to give a compact structure like title compounds.

Recently, we exploited the synthesis of 2,6-diarylpiperidin-4-one derivatives with a view to incorporate various other bioactive heterocyclic nucleus intact for evaluation of their biological importance and also as a reagent for effecting functional group interconversion [9-14].

2. Chemistry

Cyclic ketones normally undergo Baeyer-Villeger oxidation (oxygen insertion reaction) to yield lactones upon treatment with peracids [15]. When 2,6-diarylpiperidin-4-ones were subjected to Baeyer-Villeger type of reaction by using *m*-CPBA, 1-hydroxy-2,6-diarylpiperidin-4-ones [16] resulted instead of lactones. On treatment with acrylonitrile, substituted tetrahydrothiopyran-4-ones containing active hydrogen underwent cyanoethylation yielding 3-[2-cyanoethoxy] derivatives [17]. In 1-hydroxy-2,6-diarylpiperidin-4-ones, there are active methylenic hydrogens at C_3 and C_5. Hence expectation of cyanoethylation to occur at these positions besides at 1-hydroxyl group is quite normal. However in all the cases, specifically the 1-hydroxy group alone underwent cyanoethylation [18] to afford 1-(2-cyanoethoxy)-2,6-diarylpiperidin-4-one in good yields (60-74%) upon treatment with acrylonitrile in the presence of catalyst triton B. Usually cyanoethylation [19] is a base catalyzed reaction and invariably requires an alkaline catalyst. But certain amines

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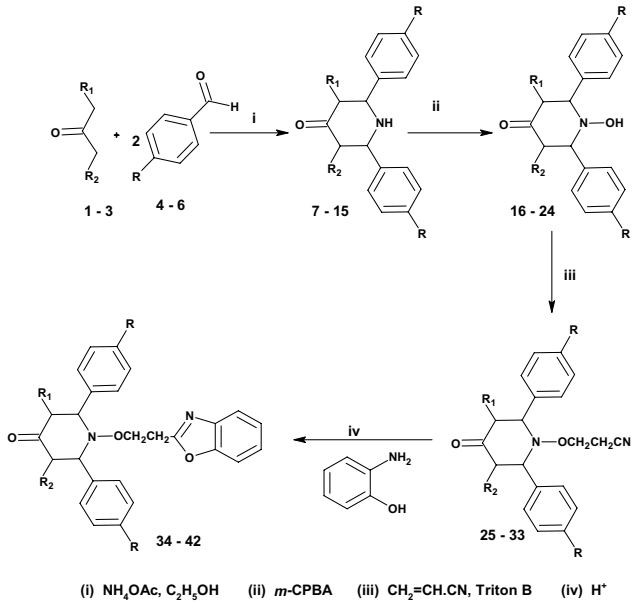

Scheme 1.

are quite exceptional. Oxides, hydroxides, alkoxides, alkali metal hydrides etc. are useful for this purpose. Solubility of the bases in organic solvents should be taken in to account. Mono or multiple cyanoethylation depends upon the proper choice of a catalyst with sufficient basicity to remove the labile proton from the compound undergoing cyanoethylation. Triton B is particularly employed here on account of its basicity and its solubility in organic media. Cyanoethylation requires cooling to avoid polymerization of acrylonitrile. Inert solvents like benzene, dioxane, acetonitrile or pyridine can be used to dissolve solid reactants or to moderate the reaction.

1-(2-Cyanoethoxy)-2,6-diarylpiperidin-4-ones upon condensation with *o*-aminophenol in acid medium resulted 1-[2-(benzoxazol-2-yl)ethoxy]-2,6-diarylpiperidin-4-ones in moderate yields. Formation of an iminoyl chloride from the cyanoethylated compound in the presence of HCl is presumed to be essential for the condensation. 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 25-42 are given in Scheme 1 and Table 1 respectively. The spectral characterization data for the novel intermediates 25-33 are furnished in Table 2.

3. Pharmacology

In vitro antibacterial and antifungal sensitivity

The in vitro activities of the compounds were tested in Sabourauds dextrose broth (SDB) for fungi and Nutrient broth (NB) for bacteria by the twofold serial dilution method [20]. The test compounds were dissolved in DMSO (dimethylsulphoxide) to obtain 1 mg/ml stock solutions. Seeded broth (broth containing microbial spores) was prepared in

Table 1
Analytical data of compounds 25-42

Entry	R_1	R_2	R	Yield (%)	m.p (°C)
25	H	H	H	70	87
26	H	CH_3	H	74	76
27	CH_3	CH_3	H	69	92
28	H	H	Cl	65	71
29	H	CH_3	Cl	64	60
30	CH_3	CH_3	Cl	67	68
31	H	H	OCH_3	69	80
32	H	CH_3	OCH_3	70	73
33	CH_3	CH_3	OCH_3	63	62
34	H	H	H	54	139
35	H	CH_3	H	58	95
36	CH_3	CH_3	H	55	116
37	H	H	Cl	32	88-89
38	H	CH_3	Cl	27	75-76
39	CH_3	CH_3	Cl	40	106
40	H	H	OCH_3	58	100
41	H	CH_3	OCH_3	50	119-120
42	CH_3	CH_3	OCH_3	50	81

NB from 24 h old bacterial cultures on nutrient agar at 37°C while fungal spores from 24 h - 7 days old Sabourauds agar 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 per ml. 0.2 ml of the solution of test compound was added to 1.8 ml of seeded broth to form the first dilution. One ml of this was diluted with a further 1 ml of the seeded broth to give the second dilution and so on till 6 such dilutions were obtained. A set of assay tubes containing only seeded broth was kept as control and likewise solvent controls were also run simultaneously. The tubes were incubated in BOD incubators at 37°C for bacteria and 28°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. Penicillin, Streptomycin and Amphotericin B were used as standards.

4. Results and Discussion

Structure activity relationship results

4.1. Antibacterial activity

All the synthesized novel benzoxazolylethoxypiperidones 34-42 were tested for their antibacterial activity in vitro against Bacillus subtilis, Streptococcus faecalis, Escherichia coli, Staphylococcus aureus and Pseudomonas aeruginosa. Penicillin and Streptomycin were used as standard drugs whose minimum inhibitory concentration (MIC) values were furnished in Table 3.

In general all the synthesized novel benzoxazolylethoxypiperidones exerted a wide range of modest in vitro antibacterial activity against all the tested organisms except 34-36 against S.aureus and B.subtilis and 34 against S.faecalis. The

Table 2
Spectral characterization data for compounds 25 – 33

Entry	Spectral characterization data
25	Mass: m/z 320(M^+) (M.F. $C_{20}H_{20}O_2N_2$), 294, 280, 267, 250, 222, 208, 194, 163, 91, 77(100%), 65, 53, 51. ^{1}H-NMR: δ 2.58-2.81 (m, 6H, H_3, H_5, OCH_2CH_2), 3.75(t, 2H, OCH_2CH_2), 4.01 (dd, 2H, H_2, H_6), 7.25-7.46(m, 10H, aryl protons). ^{13}C-NMR: δ 19.623 (OCH_2CH_2), 51.078(C_3, C_5), 65.314 (C_2, C_6), 70.123 (OCH_2CH_2), 124.310(C≡N), 124.862, 126.537, 127.131, 146.810(aryl carbons), 206.310 (C=O).
26	Mass: m/z 334(M^+) (M.F. $C_{21}H_{22}O_2N_2$), 294, 281, 264, 222, 177, 131, 118, 105, 91, 77(100%), 65, 53, 51. ^{1}H-NMR: δ 0.81 (d, 3H, CH_3), 2.57-2.84 (m, 5H, H_3, H_5, OCH_2CH_2), 3.57(d, 1H, H_2), 3.74(t, 2H, OCH_2CH_2), 3.95 (dd, 1H, H_6), 7.28-7.48(m, 10H, aryl protons). ^{13}C-NMR: δ 10.604(CH_3 at 3), 19.629 (OCH_2CH_2), 50.908(C_3) 51.592(C_5), 65.625(C_6), 70.131(OCH_2CH_2), 71.136(C_2), 124.324(C≡N), 124.642 126.312, 126.463, 127.192, 127.560, 139.958, 149.548 (aryl carbons), 207.712 (C=O).
27	Mass: m/z 348(M^+) (M.F. $C_{22}H_{24}O_2N_2$), 308, 298, 278, 144, 121, 84, 77(100%), 59, 56, 53. ^{1}H-NMR: δ 0.82 (d, 6H, CH_3), 2.59 (t, 2H, OCH_2CH_2), 2.71-2.78(m, 2H, H_3, H_5), 3.60(d, 2H, H_2, H_6), 3.77(t, 2H, OCH_2CH_2), 7.27-7.53(m, 10H, aryl protons). ^{13}C-NMR: δ 10.981(CH_3 at 3), 19.627(OCH_2CH_2), 51.210(C_3, C_5), 70.123 (OCH_2CH_2), 71.326 (C_2, C_6), 124.298(C≡N), 124.936, 126.692, 127.252, 147.821(aryl carbons), 209.448 (C=O).
28	Mass: m/z 388(M^+) (M.F. $C_{20}H_{18}O_2N_2Cl_2$), 362, 348, 338, 290, 276, 197, 137, 111, 75, 65, 53(100%), 50. ^{1}H-NMR: δ 2.58-2.84 (m, 6H, H_3, H_5, OCH_2CH_2), 3.76(t, 2H, OCH_2CH_2), 4.04 (dd, 2H, H_2, H_6), 7.30, 7.36(2d, 8H, aryl protons). ^{13}C-NMR: δ 19.663 (OCH_2CH_2), 51.325(C_3, C_5), 64.524(C_2, C_6), 70.129 (OCH_2CH_2), 124.410(C≡N), 128.054, 128.203, 133.106, 146.538(aryl carbons), 204.982 (C=O).
29	Mass: m/z 402(M^+) (M.F. $C_{21}H_{20}O_2N_2Cl_2$), 362, 349, 304, 290, 239, 196, 152, 139, 111, 75, 65, 53(100%), 50. ^{1}H-NMR: δ 0.78 (d, 3H, CH_3), 2.59-2.87 (m, 5H, H_3, H_5, OCH_2CH_2), 3.64(d, 1H, H_2), 3.76(t, 2H, OCH_2CH_2), 4.03(dd, 1H, H_6), 7.32-7.45(m, 8H, aryl protons). ^{13}C-NMR: δ 10.712(CH_3 at 3), 19.674 (OCH_2CH_2), 51.165(C_3) 51.842(C_5), 64.825(C_6), 70.141(OCH_2CH_2), 70.524(C_2), 124.372(C≡N), 127.186, 128.652, 128.783, 131.243, 131.980, 133.924, 138.911, 146.392 (aryl carbons), 206.204 (C=O).
30	Mass: m/z 416(M^+) (M.F. $C_{22}H_{22}O_2N_2Cl_2$), 376, 363, 318, 207, 183, 155, 111, 91, 84, 75, 65, 53(100%), 50. ^{1}H-NMR: δ 0.79 (d, 6H, CH_3), 2.61 (t, 2H, OCH_2CH_2), 2.73-2.88(m, 2H, H_3, H_5), 3.62(d, 2H, H_2, H_6), 3.75(t, 2H, OCH_2CH_2), 7.33, 7.39(2d, 8H, aryl protons). ^{13}C-NMR: δ 10.870(CH_3 at 3), 19.668(OCH_2CH_2), 51.462(C_3, C_5), 70.133(OCH_2CH_2), 70.526(C_2, C_6), 124.640(C≡N), 128.216, 128.386, 133.192, 146.738(aryl carbons), 208.196 (C=O).
31	Mass: m/z 380(M^+) (M.F. $C_{22}H_{24}O_4N_2$), 340, 327, 282, 254, 193, 133, 107, 75, 65, 53(100%). ^{1}H-NMR: δ 2.50-2.79 (m, 6H, H_3, H_5, OCH_2CH_2), 3.76(t, 2H, OCH_2CH_2), 3.81(s, 6H, aryl OCH_3), 4.03(dd, 2H, H_2, H_6), 6.89, 7.34(2d, 8H, aryl protons). ^{13}C-NMR: δ 19.638(OCH_2CH_2), 50.981(C_3, C_5), 54.314(aryl OCH_3), 64.669(C_2, C_6), 70.160(OCH_2CH_2), 124.432(C≡N), 115.532, 127.841, 141.897, 157.874(aryl carbons), 206.194 (C=O).
32	Mass: m/z 394(M^+) (M.F. $C_{23}H_{26}O_4N_2$), 354, 341, 296, 207, 192, 148, 107, 75, 65, 53(100%), 50. ^{1}H-NMR: δ 0.79 (d, 3H, CH_3), 2.51-2.81 (m, 5H, H_3, H_5, OCH_2CH_2), 3.62(d, 1H, H_2), 3.76(t, 2H, OCH_2CH_2), 3.81(s, 6H, aryl OCH_3), 4.03(dd, 1H, H_6), 6.84-6.86, 7.35-7.37(m, 8H, aryl protons). ^{13}C-NMR: δ 10.608(CH_3 at 3), 19.667(OCH_2CH_2), 50.810(C_3) 51.497(C_5), 54.423(aryl OCH_3), 64.980(C_6), 70.172(OCH_2CH_2), 70.548(C_2), 124.278(C≡N), 114.380, 115.786, 128.016, 130.943, 134.723, 141.598, 157.271, 159.216(aryl carbons), 207.792(C=O).
33	Mass: m/z 408(M^+) (M.F. $C_{24}H_{28}O_4N_2$), 368, 355, 310, 204, 151, 133, 107, 84, 75, 59, 53(100%), 50. ^{1}H-NMR: δ 0.81 (d, 6H, CH_3), 2.61 (t, 2H, OCH_2CH_2), 2.70-2.87(m, 2H, H_3, H_5), 3.62(d, 2H, H_2, H_6), 3.77(t, 2H, OCH_2CH_2), 3.82(s, 6H, aryl OCH_3), 6.89, 7.36(2d, 8H, aryl protons). ^{13}C-NMR: δ 10.897(CH_3 at 3), 19.693(OCH_2CH_2), 51.117(C_3, C_5), 54.562(aryl OCH_3), 70.166(OCH_2CH_2), 71.196(C_2, C_6), 124.512(C≡N), 115.386, 127.792, 141.898, 158.486(aryl carbons), 207.430 (C=O).

compounds 34-36 without any substituents at the para position of the aryl groups at C_2 and C_6 positions of the six membered heterocyclic moiety did not exhibit in vitro antibacterial activity even at the maximum concentration of 200μg/ml against S. aureus and B. subtilis. Of these 34-36, introduction of methyl group at C_3 position of the six membered heterocyclic moiety (35) improved the activity compared to 34 against P.aeruginosa and S.faecalis while the activity did not change appreciably against E.coli. There was no further improvement in the activity when another methyl group was substituted at the C_5 position of the six membered heterocyclic ring as well (36) compared to 35 against these organisms.

Table 3
In vitro antibacterial activity of compounds 34-42

Entry	Minimum inhibitory concentration (MIC) in μg/ml				
	B.subtilis	S.faecalis	E.coli	S.aureus	P.aeruginosa
34	-	-	200	-	100
35	-	200	200	-	50
36	-	200	200	-	50
37	25	12.5	100	100	25
38	50	6.25	100	100	25
39	50	12.5	100	50	25
40	200	50	25	200	50
41	200	25	12.5	100	25
42	200	25	25	200	50
penicillin	25	25	50	12.5	50
streptomycin	12.5	12.5	12.5	50	25

'-' no inhibition at 200 μg/ml

Replacement of hydrogen present at the para position of the aryl moieties at C_2 and C_6 positions of the six membered heterocyclic ring by a chloro function in 34 (i.e., in 37) showed activity in the range of 12.50 μg/ml to 100 μg/ml against all the tested organisms. Introduction of methyl group at C_3 in 37 (i.e., in 38) did not exhibit appreciable change in the activity against S.aureus, E.coli and P.aeruginosa whereas activity reduced against B.subtilis. Against S. faecalis, the activity was enhanced by this introduction compared to 37. But the introduction of another methyl group at C_5 position of the six membered heterocyclic ring in 37 (i.e., in 39) exhibited similar activity against B.subtilis, E.coli and P.aeruginosa while against S.faecalis and S.aureus activity reduced compared to 38.

Due to the introduction of methoxy groups at the para position of the aryl groups at C_2 and C_6 positions of the six membered heterocyclic moiety in the place of chloro functions in 37 (i.e., in 40), the activity was suppressed against all

Table 4
In vitro antifungal activity of compounds 34-42

Entry	Minimum inhibitory concentration (MIC) in μg/ml against fungi				
	Candida-6	C. albicans	A. niger	Candida-51	A. flavus
34	200	100	50	100	200
35	200	50	50	100	-
36	200	100	50	100	-
37	100	50	12.5	25	50
38	50	25	25	50	100
39	100	50	25	50	50
40	50	50	50	12.5	50
41	25	50	25	12.5	25
42	25	50	50	25	50
Amphotericin B	25	25	50	25	50

'-' no inhibition at 200 μg/ml

the tested organisms except E.coli against which activity enhanced by this introduction compared to 37. Replacement of hydrogen at C_3 position of the six membered heterocyclic moiety by a methyl group in 40 (i.e., in 41) did not improve the activity against B.subtilis while against S.aureus, E.coli, P.aeruginosa and S.faecalis, the activity was enhanced compared to 40. Similarly, the replacement of a another hydrogen at C_5 as well by a methyl group (42) exhibited no appreciable change in the activity compared to 41 against B.subtilis and S.faecalis. The activity was reduced compared to the same against rest of the organisms tested viz., P.aeruginosa, E.coli and S.aureus.

4.2. Antifungal activity

The in vitro antifungal activity of the novel compounds 34-42 was studied against the fungal strains viz., Candida–6, Candida albicans, Aspergillus niger, Candida-51 and Aspergillus flavus. Amphotericin-B was used as a standard drug whose minimum inhibitory concentration (MIC) values were furnished in Table 4.

The compounds 34-36 without any substituents at the para position of the aryl groups present at the C_2 and C_6 positions of the six membered heterocyclic moiety exerted modest antifungal activity in the range of 50 μg/ml to 200 μg/ml against all the tested organisms except 35 and 36 against A. flavus, which did not exhibit antifungal activity even at the maximum concentration of 200 μg/ml. Of 34-36, replacement of one of the hydrogens at C_3 position of the six membered heterocyclic moiety by a methyl group (i.e., in 35) increased the activity against C. albicans, while against Candida-6, Candida-51 and A. niger no appreciable change in the activity was resulted compared to 34 by this introduction. Introduction of another methyl group at C_5 position of the six membered heterocyclic moiety (i.e., in 36) did not improve the activity appreciably against Candida-6, Candida-51 and A. niger while activity reduced by this introduction against C.albicans compared to 35. Against A. flavus, the compound 34 showed activity at 200 μg/ml whereas the activity disappeared at the maximum concentration of 200μg/ml by the introduction of methyl group at C_3 (i.e., in 35) and methyl groups at C_3 and C_5 (i.e., in 36).

Due to the replacement of hydrogens at the para position of the aryl groups at C_2 and C_6 positions of the six membered heterocyclic moiety (34) by chloro functions (i.e., in 37), activity enhanced compared to 34 against all the tested organisms. Introduction of methyl group at C_3 position of the six membered heterocyclic moiety in 37 (i.e., in 38) increased the activity against C.albicans, Candida-6 while against Candida-51, A. niger and A. flavus, the activity suppressed by this introduction compared to 37. Similarly, due to the introduction of another methyl group at C_5 position of the six membered heterocyclic moiety (i.e., in 39), activity reduced against C. albicans, Candida-6 and activity enhanced against A. flavus. Against Candida-51 and A. niger, this introduction did not improve the activity compared to 38.

Introduction of methoxy functions at the para position of the aryl groups at C_2 and C_6 positions of the six membered heterocyclic ring in the place of chloromoieties in 37 (i.e., in 40) did not change the activity against C. albicans and A. flavus. But against Candida-6 and Candida-51, the activity was improved due to this introduction compared to 37. Against A. niger, the activity suppressed due to the introduction of methoxy groups. Of 40-42, the activity of 41 was remained unchanged against C. albicans and Candida-51 even when one of the hydrogens at C_3 position of the six membered heterocyclic moiety was replaced by a methyl group. Against Candida-6, A. niger and A. flavus, the activity of compound 41 was enhanced due to the introduction of methyl group compared to 40. Similarly, due to the introduction of another methyl group at the C_5 position of the six membered heterocyclic ring, the activity of 42 did not change against C. albicans and Candida-6 while activity reduced against rest of the organisms viz., Candida-51, As. niger and As. flavus compared to 41.

5. Conclusion

An examination of the in vitro antibacterial and antifungal activity profile of variety of substituted novel benzoxazolylethoxypiperidones against the bacterial strains viz., Bacillus subtilis, Streptococcus faecalis, Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa and the fungal strains viz., Candida–6, Candida albicans, Aspergillus niger, Candida-51, Aspergillus flavus respectively provide a structure activity correlate, which may be summarised as follows. The compounds with chloro or methoxy functions at the para position of the aryl moieties at C_2 and C_6 positions of the six membered heterocyclic moiety along with / without methyl substituents at C_3/C_5 and C_5 positions play an important role in eliciting biological response. Specifically of the novel benzoxazolylethoxypiperidones tested, the compounds with chloro function at the para position of the aryl moieties at C_2 and C_6 positions along with the methyl group at C_3 position of the six membered heterocyclic moiety

exhibited good activity against S.faecalis. The novel benzoxazolylethoxypiperidone with chloro moieties at the para position of the aryl groups at C_2 and C_6 positions of the six membered heterocyclic ring and the benzoxazolylethoxypiperidone with methoxy functions at the para position of the aryl groups present at the C_2 and C_6 positions along with / without methyl substituent at C_3 position of the six membered heterocyclic moiety exerted good antifungal activity against As.niger and Candida-51. Thus, in future this class of novel benzoxazolylethoxypiperidones may be used as templates to generate better drugs to combat bacterial and fungal infections.

6. Experimental

TLC was performed to access the reactions and purity of products. Melting points were recorded in open capillaries and were uncorrected. IR spectra were recorded in Perkin - Elmer 297 spectrophotometer in KBr pellets and only noteworthy absorption levels (reciprocal centimeter) are listed. ^{1}H - NMR spectra were recorded at 400 MHz on Bruker amx 400 MHz spectrophotometer in $CDCl_3$ using TMS as internal standard and ^{13}C-NMR spectra were recorded at 100 MHz on Bruker amx 400 MHz spectrophotometer in $CDCl_3$. Mass spectra were recorded on a VG analytical 7070E instrument equipped with VG 11-250 data acquision system. Satisfactory microanalysis were obtained on Carlo Erba 1106 and Perkin Elmer models 240 CHN analyzer.

From the literature precedent [21], 2,6-diarylpiperidin-4-ones 7-15 were prepared by the condensation of appropriate ketones, aldehydes and ammonium acetate in 1:2:1 ratio.

1-Hydroxy-2,6-diphenylpiperidin-4-one 16: A solution of 2,6-diphenylpiperidin-4-one 7 (0.005 mol) and *m*-CPBA (0.005 mol) in 40 ml of chloroform was stirred for 15 min. and kept aside for overnight at 20°C. Then the mixture was extracted with chloroform and washed with 10% sodium bicarbonate solution. The chloroform layer was dried over anhydrous sodium sulphate and distilled off under reduced pressure. Purifications with silicagel column chromatography with 8:2 benzene:pet-ether (bp40-60) mixture yielded the product 16. The compounds 17-24 were prepared similarly.

1-(2-Cyanoethoxy)-2,6-diphenylpiperidin-4-one 25: A mixture of 1-hydroxy-2,6-diphenylpiperidin-4-one 16 (0.005 mol) and acrylonitrile (0.005 mol) in 50 ml of 1,4-dioxane was taken in 100 ml round bottom flask and cooled in an ice bath. A few crystals of resorcinol were added followed by dropwise addition of triton B (5 ml) with shaking. Then the content was stirred under warm for 9 h. at 65-75°C and was concentrated. After cooling, the resulting solution was poured over benzene:pet-ether 1:3 mixture for extraction. The solid thus obtained from the extract after removal of solvents at reduced pressure was recrystallised from methanol to afford 25. The compounds 26-33 were prepared similarly.

1-[2-(Benzoxazol-2-yl)ethoxy]-2,6-diphenylpiperidin-4-one 34. A mixture of 1-[2-cyanoethoxy]-2,6-diphenylpiperidin-4-one 13 (0.005 mole), *o*-aminophenol (0.005 mole) and dilute hydrochloric acid (10cc of Con. HCl in 100cc of water) was taken in a 250ml round bottom flask and was allowed to reflux in an oil bath for 18 h. After cooling, the contents in the flask were leached with 100cc of diethylether and the separated ether extract was washed with five 25cc portions of 4N sodium hydroxide solution. The ether layer was separated, dried with calcium chloride and freed of ether by distillation. The solid thus obtained was recrystallised twice from ethanol.

IR:cm^{-1}(KBr) 2924.1, 2850.6, 2767.2,(C-H Stretching), 1706.4(C=O Stretching). Other characteristic bands are 1600.3, 1456.7, 1429.3, 1392.3, 1374.7, 1347.6, 1287.1, 1255.3, 1237.8, 1155.4, 1104.9, 1076.2, 1035.4, 945.3, 904.7, 856.4, 788.2, 748.9, 689.1, 658.2, 604.8, 518.6, 500.7, 472.1. Mass:m/z 412(M^+) (M.F : $C_{26}H_{24}N_2O_3$), 280, 267, 250, 222, 208, 194, 167, 145, 132, 118, 103 (100%), 91.77, 65, 55, 51. ^{1}H NMR:δ 4.04(dd, ^{3}J=12.64Hz; 3.86Hz; 2H) H_2 and H_6, 2.60-2.85(m, 6H) H_3, H_5 and –OCH_2-CH_2-, 7.29-7.49(m, 14H) aryl protons, 3.93(t, J=6.50 Hz; 2H)–OCH_2-CH_2-. ^{13}C NMR:δ 69.262(C_2, C_4), 49.312(C_3, C_5), 206.050(C=O), 67.573(–OCH_2- CH_2-), 27.647 (–OCH_2-CH_2-), 109.738, 114.284, 118.943, 119.058, 127.798, 129.773, 130.731, 133.105, 143.134(aryl carbons), 141.739(C_2' and C_6'), 162.605(C_2 of benzoxazole moiety).

The compounds 35-42 were synthesised similarly.

1-[2-(Benzoxazol-2-yl)ethoxy]-2,6-diphenyl-3-methylpiperidin-4-one 35. IR:cm^{-1}(KBr) 2965.7, 2938.2, 2856.5, 2805.3(C-H Stretching), 1696.5(C=O Stretching). Other characteristic bands are 2352.8, 1952.1, 1813.2, 1589.3, 1488.2, 1449.7, 1368.2, 1335.1, 1269.3, 1251.7, 1229.4, 1198.2, 1131.9, 1089.8, 1024.2, 951.2, 930.7, 913.4, 871.8, 841.5, 834.6, 748.3, 686.9, 670.2, 635.0, 593.3, 551.8, 526.4. Mass:m/z 426(M^+), (M.F : $C_{27}H_{26}N_2O_3$), 294, 281, 264, 239, 172, 162, 145, 132, 118, 103(100%), 91, 77, 69, 65, 51. ^{1}H NMR:δ 4.02(dd, ^{3}J=13.03Hz; 3.36Hz, 2H) H_6, 3.60(d, ^{3}J=11.65Hz, 1H)H_2, 2.60-2.88(m, 5H) H_3, H_5 and –OCH_2-CH_2-, 7.28-7.48(m, 14H) aryl protons, 3.92(t, J=6.49 Hz, 2H) –OCH_2-CH_2-, 0.81(d, J=6.58Hz, 3H) CH_3. ^{13}C NMR:δ 75.767(C_2), 69.570(C_6), 49.140(C_3), 48.787(C_5), 207.498(C=O), 67.608(–OCH_2-CH_2-), 27.718(–OCH_2-CH_2-), 109.757, 114.194, 118.938, 119.101, 127.754, 129.712, 129.820, 130.601, 130.714, 133.110, 143.137(aryl carbons), 140.979(C_2'), 141.820(C_6'), 162.618(C_2 of benzoxazole moiety), 10.589(CH_3).

1-[2-(Benzoxazol-2-yl)ethoxy]-2,6-diphenyl-3,5-dimethylpiperidin-4-one 36 IR:cm^{-1}(KBr) 2965.2, 2923.3, 2876.4, 2847.4, 2813.3(C-H Stretching), 1697.7(C=O Stretching). Other characteristic bands are 2354.9, 1596.7, 1485.4, 1433.9, 1375.2, 1349.4, 1260.5, 1195.0, 1088.3, 1041.9, 1022.4, 980.0, 927.3, 882.1, 787.2, 760.7, 691.3, 673.2, 623.0, 554.3, 513.2. Mass: m/z 440(M^+), (M.F: $C_{28}H_{28}N_2O_3$), 322, 295, 266, 190, 177, 159, 146, 132, 118, 103(100%), 100, 77, 69, 56, 51. ^{1}H NMR:δ 3.62(d,

^{3}J=11.66Hz, 2H) H_2 and H_6, 2.83-2.88(m, 2H) H_3 and H_5, 2.71(t, J=6.52Hz, 2H) –OCH_2-CH_2-, 7.29-7.50(m, 14H) aryl protons, 3.92(t, J=6.50Hz, 2H) –OCH_2-CH_2-, 0.81(d, J=6.62Hz, 6H) CH_3. ^{13}C NMR:δ 76.025(C_2,C_6), 49.440(C_3 and C_5), 209.169(C=O), 67.609(–OCH_2-CH_2-), 27.684(–OCH_2-CH_2-), 109.746, 114.257, 118.940, 119.097, 127.854, 129.791, 130.676, 133.107, 143.140(aryl carbons), 141.120(C_2',C_6'), 162.620(C_2 of benzoxazole moiety), 10.968(CH_3).

1-[2-(Benzoxazol-2-yl)ethoxy]-2,6-*bis*(*p*-chlorophenyl) piperidin-4-one 37 IR:cm^{-1}(KBr) 2927.1, 2841.7, 2796.2(C-H Stretching), 1704.8 (C=O Stretching). Other characteristic bands are 1628.7, 1492.2, 1409.3, 1371.3, 1323.4, 1280.8, 1265.3, 1237.7, 1129.1, 1116.9, 1044.5, 1005.3, 954.7, 895.2, 820.8, 740.3, 690.8, 518.1, 490.9, 475.9. Mass:m/z 480(M^+), (M.F : $C_{26}H_{22}N_2O_3Cl_2$), 348, 335, 318, 290, 276, 262, 194, 166, 146, 137, 132, 118, 111, 75, 53(100%), 50. ^{1}H NMR:δ 4.07(dd, ^{3}J=12.64Hz; 3.87Hz, 2H) H_2 and H_6, 2.60-2.86(m, 6H) H_3, H_5 and –OCH_2-CH_2-, 7.31-7.58(m, 12H) aryl protons, 3.92(t, J=6.50 Hz; 2H) –OCH_2-CH_2-.^{13}C NMR:δ 68.470(C_2, C_6), 48.986(C_3, C_5), 205.062(C=O), 67.576(–OCH_2- CH_2-), 27.642 (–OCH_2-CH_2-), 109.750, 114.290, 118.984, 119.080, 129.130, 129.963, 133.124, 143.347(aryl carbons), 134.932(C_2'''' and C_6''''), 139.892 ($C_2'$and C_6'), 162.614(C_2 of benzoxazole moiety).

1-[2-(Benzoxazol-2-yl)ethoxy]-2,6-*bis*(*p*-chlorophenyl) –3-methylpiperidin-4-one 38. IR:cm^{-1}(KBr) 2964.7, 2931.7, 2852.4, 2726.9(C-H Stretching), 1694.9(C=O Stretching). Other characteristic bands are 2363.3, 1945.0, 1820.1, 1633.2, 1586.1, 1492.1, 1380.2, 1304.4, 1258.3, 1221.9, 1139.2, 1110.7, 1039.5, 1009.9, 948.2, 918.7, 898.1, 866.6, 773.1, 689.7, 633.4, 563.8, 499.9. Mass:m/z 494(M^+), (M.F : $C_{27}H_{24}N_2O_3Cl_2$), 362, 349, 332, 307, 262, 196, 180, 166, 155, 146, 137, 118, 111, 75, 69, 53(100%), 50. ^{1}H NMR:δ 4.06(dd, ^{3}J=13.02Hz; 3.36Hz, 1H) H_6, 3.69 (d, ^{3}J=11.64Hz, 1H) H_2, 2.61-2.90(m, 5H) H_3, H_5 and –OCH_2-CH_2-, 7.13-7.43(m, 12H) aryl protons, 3.93(t, J=6.50Hz, 2H) –OCH_2-CH_2, 0.79(d, J=6.54Hz, 3H) CH_3. ^{13}C NMR:δ 74.970(C_2), 68.842(C_6), 48.856(C_3) 48.476(C_5), 206.211(C=O), 67.614(–OCH_2-CH_2-), 27.702(–OCH_2-CH_2-), 109.768, 114.202, 118.976, 119.154, 129.361, 129.373, 129.883, 130.004, 133.120, 143.354(aryl carbons), 139.094(C_2'), 139.953(C_6'), 134.753(C_2''''), 134.920(C_6''''), 162.627(C_2 of benzoxazole moiety), 10.681(CH_3).

1-[2-(Benzoxazol-2-yl)ethoxy]-2,6-*bis*(*p*-chlorophenyl) –3,5-dimethylpiperidin-4-one 39 IR:cm^{-1}(KBr) 2957.7, 2929.9, 2844.1, 2796.7(C-H Stretching), 1696.5(C=O Stretching). Other characteristic bands are 2355.2, 1651.1, 1585.3, 1478.0, 1410.5, 1373.7, 1319.6, 1268.7, 1198.9, 1080.0, 1048.6, 1006.3, 975.3, 883.7, 824.9, 697.4, 645.2, 560.0. Mass:m/z 390(M-118), (M.F: $C_{28}H_{26}N_2O_3Cl_2$), 363, 334, 224, 211, 193, 180, 165, 152, 146, 132, 118, 111, 100, 91, 75, 53(100%), 50. ^{1}H NMR:δ 3.65 (d, ^{3}J=11.66Hz, 2H) H_2 and H_6, 2.83-2.89(m, 2H) H_3 and H_5, 2.71(t, J=6.53Hz, 2H) –OCH_2-CH_2-, 7.31-7.52(m, 12H) aryl protons, 3.92(t, J=6.49Hz, 2H) –OCH_2-CH_2-, 0.80(d, J=6.57Hz, 6H) CH_3. ^{13}C NMR:δ 75.283(C_2,C_6), 49.201(C_3,C_5), 208.176(C=O), 67.628(–OCH_2-CH_2-), 27.699(–OCH_2-CH_2-), 109.784, 114.222, 118.943, 119.162, 129.290, 129.820, 133.018, 143.359(aryl carbons), 134.841(C_2'''',C_6''''), 139.130(C_2',C_6'), 162.648(C_2 of benzoxazole moiety), 10.865(CH_3).

1-[2-(Benzoxazol-2-yl)ethoxy]-2,6-bis(p-methoxyphenyl)-3,5-dimethylpiperidin-4-one 40. IR:cm^{-1}(KBr) 2926.7, 2853.2, 2786.9(C-H Stretching), 1706.8(C=O Stretching). Other characteristic bands are 1639.2, 1465.7, 1378.9, 1366.5, 1259.1, 1236.4, 1189.3, 1137.9, 1040.4, 1025.3, 925.0, 856.4, 800.9, 744.7, 652.1, 602.9, 524.3, 510.7. Mass: m/z 472(M^+), (M.F : $C_{28}H_{28}N_2O_5$), 354, 327, 310, 282, 268, 254, 194, 162, 147, 145, 132, 118, 107, 75, 65, 55, 53(100%), 50. ^{1}H NMR:δ 4.06(dd, ^{3}J=12.65Hz; 3.85Hz, 2H) H_2 and H_6, 2.59-2.84(m, 6H) H_3, H_5 and –OCH_2-CH_2-, 6.90(d, 4H) and 7.34-7.55(m, 8H) aryl protons, 3.92(t, J=6.52Hz, 2H) –OCH_2-CH_2-, 3.81(s, 6H) OCH_3. ^{13}C NMR:δ 68.612(C_2, C_6), 49.401(C_3, C_5), 206.164(C=O), 67.614(–OCH_2- CH_2-), 27.674(–OCH_2-CH_2-), 109.785, 114.342, 114.490, 118.974, 119.005, 133.019, 133.148, 143.358(aryl carbons), 158.800(C_2'''' and C_6''''), 135.571 (C_2' and C_6'), 162.598(C_2 of benzoxazole moiety), 55.107(OCH_3).

1-[2-(Benzoxazol-2-yl)ethoxy]-2,6-*bis*(*p*-methoxyphenyl)-3-methylpiperidin-4-one 41 IR:cm^{-1}(KBr) 2937.9, 2837.7(C-H Stretching), 1698.7(C=O Stretching). Other characteristic bands are 2360.4, 2340.3, 1580.4, 1451.7, 1376.8, 1349.9, 1256.3, 1242.7, 1177.6, 1035.7, 1020.0, 932.6, 890.2, 842.2, 791.7, 656.5, 640.7, 535.1, 450.9. Mass:m/z 486(M^+), (M.F : $C_{29}H_{30}N_2O_5$), 354, 341, 324, 299, 254, 192, 176, 162, 148, 145, 133, 118, 107, 75, 69, 65, 53(100%), 50. ^{1}H NMR:δ 4.05(dd, ^{3}J=12.99Hz; 3.33Hz, 1H) H_6, 3.66(d, ^{3}J=11.67Hz, 1H) H_2, 2.59-2.87(m, 5H) H_3, H_5 and –OCH_2-CH_2-, 6.89(4H) and 7.27-7.50(m, 8H) aryl protons, 3.92(t, J=6.52Hz, 2H) –OCH_2-CH_2-, 3.80(s, 6H) OCH_3, 0.80(d, J=6.58Hz, 3H) CH_3. ^{13}C NMR:δ 75.169(C_2), 68.985(C_6), 49.229(C_3) 48.892(C_5), 207.387(C=O), 67.768 (–OCH_2-CH_2-), 27.654(–OCH_2-CH_2-), 109.742, 114.102, 114.648, 114.879, 118.768, 118.980, 132.999, 133.121, 143.380(aryl carbons), 135.132(C_2'), 135.847(C_6'), 158.569(C_2''''), 158.940(C_6''''), 162.504(C_2 of benzoxazole moiety) 55.188(OCH_3), 10.598(CH_3).

1-[2-(Benzoxazol-2-yl)ethoxy]-2,6-*bis*(*p*-methoxyphenyl)-3,5-dimethylpiperidin-4-one 42. IR:cm^{-1}(KBr) 2930.4, 2839.2(C-H Stretching), 1698.6(C=O Stretching). Other characteristic bands are 2351.7, 2337.4, 1580.2, 1504.8, 1344.3, 1301.5, 1257.8, 1234.7, 1076.1, 1040.8, 1033.6, 827.9, 791.4, 660.2, 537.6, 473.1. Mass:m/z 500(M^+), (M.F : $C_{30}H_{32}N_2O_5$), 382, 355, 326, 220, 207, 189, 176, 161, 146, 132, 118, 107, 100, 75, 69, 53(100%), 50. ^{1}H NMR:δ 3.64(d, ^{3}J=11.69Hz, 2H) H_2 and H_6, 2.81-2.86(m, 2H) H_3 and H_5 2.70(t, J=6.50Hz, 2H) –OCH_2-CH_2-, 6.88(4H) and 7.36-7.49(m, 8H) aryl protons, 3.92(t, J=6.50Hz, 2H) –OCH_2-CH_2-, 3.80(s, 6H) OCH_3, 0.81d, J=6.53Hz, 6H) CH_3. ^{13}C NMR:δ 75.476(C_2,C_6), 49.548(C_3,C_5), 209.399(C=O),

67.704(–OCH_2-CH_2-), 27.689 (–OCH_2-CH_2-), 109.788, 114.235, 114.528, 118.864, 119.005, 133.002, 133.226, 143.347(aryl carbons), 158.880(C_2'''',C_6''''), 135.127(C_2',C_6'), 162.602(C_2 of benzoxazole moiety), 55.201(OCH_3), 10.960(CH_3).

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