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Short communication

Synthesis and in vitro microbiological evaluation of imidazo(4,5-b)pyridinylethoxypiperidones

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Abstract

A series of imidazo(4,5-b)pyridinylethoxypiperidones was designed, synthesized and characterized for evaluation of potential antibacterial activity against *Bacillus subtilis*, *Klebsiella pneumoniae, Escherichia coli, Staphylococcus aureus* and *Pseudomonas aeruginosa* and antifungal activity against *Candida albicans*-6, *Candida albicans*, *Aspergillus niger*, *Candida albicans-51* and *Aspergillus flavus*. Structure–activity relationship led to the conclusion that compound **39** exerted strong in vitro antibacterial activity against *Bacillus subtilis* and *Staphylococcus aureus* whereas compounds **38** and **39** displayed promising antifungal activity against *Aspergillus flavus*. The interesting antimicrobial profile of compound **39** led us to select this derivative for further development.

Keywords: Piperidin-4-one; Cyanoethylation; Imidazo(4,5-b)pyridine; Antibacterial activity; Antifungal activity

1. Introduction

Heterocyclic ring systems having piperidin-4-one nucleus have aroused great interest in the past and recent years due to their wide variety of biological properties such as antiviral [1], antitumor [1,2], anti inflammatory [3], central nervous system [4–9], local anaesthetic [5,10], anticancer [11], and antimicrobial activity [12] and their derivative piperidines are also biologically important and act as neurokinin receptor antagonists [13], analgesic and antihypertensive agents [14]. The importance of piperidin-4-one as intermediates in the synthesis of a variety of compounds of physiologically active has been reviewed by Prostakov and Gaivoronskaya [15]. The extensive studies undertaken in the past on 4-piperidones have their relation to the synthesis of drug [16]. The utility of substituents at second, third and sixth positions, particularly aromatic substituent at second and/or sixth positions with regard to is biological activity have been well documented by many workers [5,6,12,17]. Consequently, the establishment of general methods for the synthesis of piperidine derivatives has been the topic of considerable synthetic effort [18].

Compounds incorporating the imidazo(4,5-b)pyridine ring system can be considered as structural analogues of purines and have shown a diverse biological activity depending on the substituents of the heterocyclic ring. Their activity includes antibacterial [19], antimicrobial [20], mutagenic [21], antiphlogistic [22], fungicidal [23], pesticidal [24], antiviral [25], anticancer [26], antimitotic [27], antituberculostatic [28], antiallergic [29] and antihypertensive [30] actions. They have also been evaluated as antagonists of various biological receptors including angiotensin II [31], thromboxane A_2 [32] and platelet activating factor [33] from human neutrophil membranes and cardio vascular agents [34]. In view of these findings, we have attempted to incorporate both the biolabile components together to give a confined structure like title compound for evaluating its antimicrobial activity.

In the recent years we have been involved in the synthesis and chemistry of 2,6-diarylpiperidin-4-one derivatives with a

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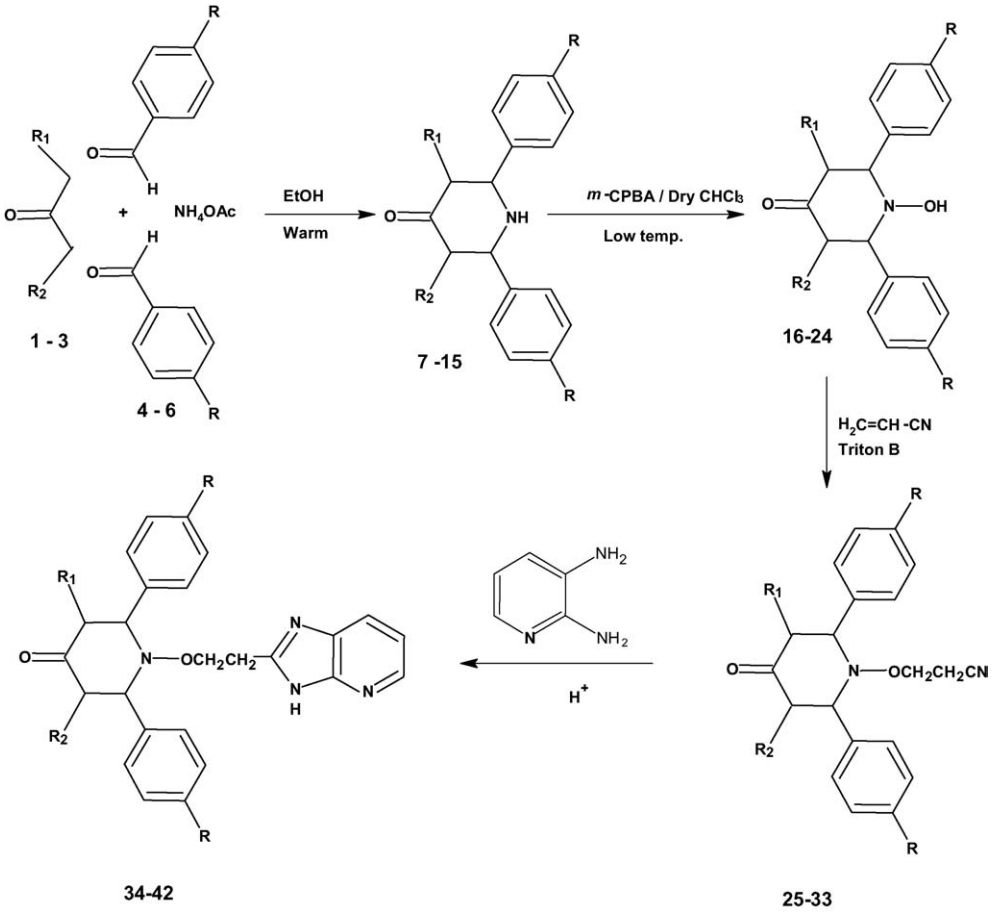
prospect to incorporate diverse bioactive heterocyclic nucleus intact for evaluating their antibacterial and antifungal significance and also as a reagent for effecting functional group inter conversion [34–44].

2. Chemistry

Cyclic ketones normally undergo Baeyer–Villiger oxidation (oxygen insertion reaction) to yield lactones upon treatment with peracids [45]. When 2,6-diarylpiperidin-4-ones were subjected to Baeyer-Villiger type of reaction by using *meta* chloroperbenzoic acid (*m*-CPBA), 1-hydroxy-2,6-diarylpiperidin-4-ones resulted instead of lactones. On treatment with acrylonitrile, substituted tetrahydrothiopyran-4-ones containing active hydrogen underwent cyanoethylation yielding 3-[2-cyanoethoxy] derivatives [46]. In 1-hydroxy-2,6-diarylpiperidin-4-ones, there are active methylenic hydrogens at C_3 and C_5 positions. 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 [36,38–40] to afford 1-[2-cyanoethoxy]-2,6-diarylpiperidin-4-ones in good yields (60–74%) upon treatment with acrylonitrile in the presence of catalyst Triton B.

Usually, cyanoethylation [47] is a base catalyzed reaction and invariably requires an alkaline catalyst. But certain amines 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 into 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-diarylpiperdin-4-ones upon cyclocondensation with 2,3-diaminopyridine in acid medium afforded 1-[2-(imidazo(4,5-b)pyridin-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 associated potential broad-spectrum biological activity. The synthesis of imidazo(4,5-b)pyridinylethoxy piperidones **34–42** was achieved with a versatile and efficient synthetic route outlined in Scheme 1 and the analytical data are reproduced in Table 1.



Scheme 1.

Table 1
Analytical data for compounds **25**–**42**[a]

Entry	R1	R2	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	24	148–149
35	H	CH_3	H	26	105
36	CH_3	CH_3	H	30	123–124
37	H	H	Cl	23	100–101
38	H	CH_3	Cl	27	87
39	CH_3	CH_3	Cl	28	114
40	H	H	OCH_3	24	109
41	H	CH_3	OCH_3	27	130–131
42	CH_3	CH_3	OCH_3	25	90–91

[a] The micro-analysis values for C, H and N were within ± 0.4% of the theoretical values.

To percept structure–activity relationship well, numberings of the target compound are done and is shown below. Fig. 1.

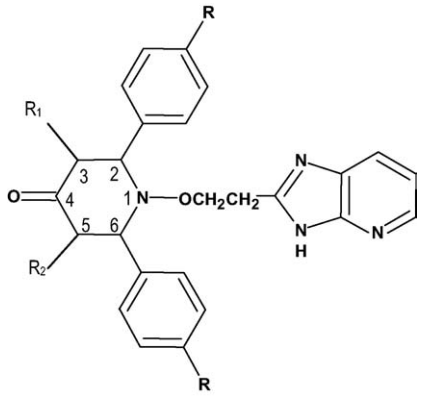


Fig. 1.

3. Pharmacology

3.1. In vitro antibacterial and antifungal activity

The in vitro activities of the compounds were tested in Sabourauds dextrose broth (SDB; Hi-media, Mumbai) for fungi and Nutrient broth (NB; Hi-media, Mumbai) for bacteria by the twofold serial dilution method [48]. The test compounds were dissolved in dimethylsulfoxide (DMSO) to obtain 1 mg ml^{-1} stock solutions. 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 24-h- to 7-day-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 ml^{-1}. The final inoculum size was 10^5 cfu ml^{-1} for antibacterial assay and 1.1–1. 5 × 10^2 cfu ml^{-1} for antifungal assay. Testing was performed at pH 7.4 ± 0.2. Exactly 0.2 ml of the solution of test compound was added to 1.8 ml of seeded broth to form the first dilution. One milliliter of this was diluted with a further 1 ml of the 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 and likewise solvent controls were also run simultaneously. 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. Penicillin G, streptomycin and amphotericin B were used as standards.

4. Results and discussion

4.1. Structure–activity relationship results

4.1.1. Antibacterial activity

The synthesis of a series of these derivatives was carried out and the obtained compounds **34**–**42** were tested for their in vitro antibacterial activity against some Gram positive [*Staphylococcus aureus* NCIM-2492 and *Bacillus subtilis* NCIM-2439] and Gram negative [*Escherichia coli* NCIM-2345, *Klebsiella pneumoniae* (derived from Medical College, Annamalai University) and *Pseudomonas aeruginosa* NCIM-2035] bacter-

Table 2
In vitro antibacterial activity of compounds **34**–**42**

Entry	Minimum inhibitory concentration (MIC) in μg ml^{-1}				
	Bacillus subtilis	*Klebsiella pneumoniae*	*Escherichia coli*	*Staphylococcus aureus*	*Pseudomonas aeruginosa*
34	–	–	–	100	200
35	200	–	100	200	100
36	100	100	50	100	100
37	50	25	50	50	50
38	12.5	12.5	50	50	12.5
39	6.25	12.5	12.5	6.25	12.5
40	50	100	50	50	100
41	25	50	100	100	100
42	25	12.5	100	25	50
Penicillin G	25	12.5	50	12.5	50
Streptomycin	12.5	50	12.5	50	25

ia. Penicillin G and streptomycin were used as standard drugs whose minimum inhibitory concentration values are summarized in Table 2.

The antibacterial screening put in evidence that all the synthesized novel imidazo(4,5-b)pyridinylethoxypiperidones **34**–**42** exhibited a wide spectrum of antibacterial profile in vitro against the tested organisms except **34** against *B. subtilis*, *K. pneumoniae* only. Compounds **34**–**36** without any substituent at *para* position of aryl groups present at C_2 and C_6 of piperidone ring exerted moderate antibacterial activity in vitro at 50–200 μg ml^{-1} against *B. subtilis*, *E. coli*, *S. aureus* and *P. aeruginosa* with an exception of compound **34** against *B. subtilis* and *E. coli*. Among **34**–**36**, introduction of methyl group at C_3 position in **34** (compound **35**) improved the activity against *B. subtilis* and *E. coli* while against *S. aureus*, onefold decrease in activity was observed. From Table 2, it is obvious that introduction of another methyl group at C_5 in addition to C_3 in **34** (compound **36**) has appreciably enhanced the activity not only against *K. pneumoniae* but also against rest of the bacterial strains.

Introduction of chloro function at the *para* position of the aryl groups at C_2 and C_6 of **34** (compound **37**) produced antibacterial activity in the range of 6.25–50 μg ml^{-1} against all the tested bacterial strains. This introduction causes further increase (i.e. 50%) in activity against *B. subtilis, S. aureus* and *P. aeruginosa* except against *E. coli* whereas against *K. pneumonia* the activity was increased by 100%. Replacement of hydrogens at C_3 of heterocyclic ring in **37** by methyl group showed onefold increase in activity against *B. subtilis*, *K. pneumoniae* and *P. aeruginosa* except *E. coli* and *S. aureus* against which the activity did not change.

Introduction of one more methyl group at C_5 along with the C_3 methyl group in **37** (compound **39**) was in turn improved the activity by onefold against *B. subtilis* and *E. coli* while against *S. aureus* twofold increased activity was noted. But against *K. pneumoniae* and *P. aeruginosa*, the activity was retained as such without any further improvement.

Replacement of chloro moieties present at the *para* position of aryl groups which the nitrogen is flanked by in piperidone heterocyclic ring system through methoxy functionalities in **37** (compound **40**), the activity was suppressed against all the tested organisms. This decrease in activity was significant against *B. subtilis*, *K. pneumoniae, S. aureus* and *P. aeruginosa* whereas against *E. coli*, 50% decrease in activity was observed. Substitution of methyl group at C_3 position of the six-member heterocyclic ring showed 50% improved activity against *B. subtilis* and *K. pneumoniae* while against *E. coli* and *S. aureus* 50% decrease in activity was observed when compared to compound **40**. Introduction of another methyl group at C_5 of **40** (compound **42**) along with C_3 methyl group exerted 50% enhancement in activity against *K. pneumoniae* and *P. aeruginosa* whereas against *S. aureus*, 100% increase in activity was noted. Against *B. subtilis* and *E. coli*, the activity did not change by the introduction of another methyl group at C_5 in **41** (compound **42**).

4.1.2. Antifungal activity

The in vitro antifungal activity of compounds **34**–**42** were examined against the fungal strains viz., *Candida albicans-6* (NCIM-C27), *Candida albicans* (NCIM-C27), *Aspergillus niger* (NCIM-590), *Candida albicans-51* (NCIM-C27) and *Aspergillus flavus* (NCIM-539). Amphotericin B was used as standard drug whose minimum inhibitory concentration values are reproduced in Table 3.

The antibacterial profile of compounds **34**–**36** without any substituents at the *para* position of the aryl groups at C_2 and C_6 of the six-member heterocyclic moiety falls in the region of 50–200 μg ml^{-1} except **34** against *C. albicans-6, C. albicans* and *A. flavus* and **35** against *A. flavus* even at the high concentration of 200 μg ml^{-1}. Of these, the activity was rich in **35** compared to **34** due to the introduction of methyl group at C_3 position in **34** against *C. albicans-6* and *C. albicans* while against *A. flavus*, the activity was not improved. Introduction of another methyl group at C_5 position of the six-member heterocyclic moiety (compound **36**) enhanced the activity against *C. albicans* and *A. flavus* whereas against rest of the fungal strains, the activity did not change appreciably.

Due to the introduction of chloro functions at the *para* position of aryl groups which the nitrogen is flanked by in piperidone ring of **34** (compound **37**) significantly improved the antifungal activity against *C. albicans-6* while against *A. niger*, *C. albicans-51* and *A. flavus* only 50% increase in activity was observed. Replacement of hydrogen at C_3 in **37** (compound **38**) by methyl group improved the activity further by about 100% against *C. albicans*, *A. flavus* whereas against *C. albicans-51* activity was enhanced by 50%. Against *C. al-*

Table 3
In vitro antifungal activity of compounds **34**–**42**

Entry	Minimum inhibitory concentration (MIC) in μg ml^{-1}				
	Candida albicans-6	*Candida albicans*	*Aspergillus niger*	*Candida albicans-51*	*Aspergillus flavus*
34	–	–	200	100	–
35	200	100	100	50	–
36	200	50	100	50	50
37	12.5	50	50	25	25
38	50	12.5	50	12.5	6.25
39	50	25	12.5	12.5	6.25
40	25	50	100	100	50
41	50	25	50	25	12.5
42	12.5	25	50	50	12.5
Amphotericin B	25	25	50	25	50

bicans-6, onefold decreased activity was noted. Similarly, introduction of another methyl group at C_5 position of the six-member heterocyclic moiety (i.e. in **39**), onefold increase in activity was observed against *A. niger* while against *C. albicans*-6, *C. albicans-51* and *A. flavaus*, the activity remained unchanged compared to compound **38**. Moreover, against *C. albicans*, the activity was suppressed by 50% due to this methyl group modification.

Replacement of chloro moieties at the *para* positions of the aryl groups at C_2 and C_6 in **37** by methoxy functions caused a significant reduction in activity against all the tested fungal strains except *C. albicans-6* towards which activity was enhanced by 50% compared to compound **40**.

Compound **41** having methyl group at C_3 of heterocyclic ring instead of hydrogen exerted modest activity against *C. albicans*, *A. niger*, *C. albicans -51*, and *A. flavaus* while against *C. albicans-6* activity was suppressed. Besides, further methyl group modification at C_5 of compound **40** along with a methyl group at C_5 position, the activity did not alter against *C. albicans*, *A. niger* and *A. flavus* whereas against *C. albicans-6*, onefold increase in activity was noted. But towards *C. albicans-51*, activity was decreased by about 50% due to the second methyl group introduction.

5. Conclusion

A close examination of in vitro antibacterial and antifungal profile of variously substituted novel imidazo(4,5-b)pyridinylethoxypiperidones against the tested bacterial and fungal strains provide a better structure–activity correlate which is summarized below. Chloro and methoxy functions at the *para* position of the aryl moieties present at C_2 and C_6 of piperidone moiety along with or without methyl substituent at C_3 and C_3/C_5 positions play an important role in eliciting inhibition of all the bacteria and fungi assayed.

Of the novel nine compounds tested, those with C_3 and C_5 dimethyl groups along with a chloro functions at the *para* positions of the aryl moieties at C_2 and C_6 exerted the highest level of antibacterial activity against *B. subtilis* and *S. aureus* while against the fungal strain *A. flavus*, the compound with C_3 methyl and C_3, C_5 dimethyl groups showed striking influence in inhibiting the fungal growth. The MIC values of the target compounds indicated that the compound **39** is showing promising activity against *B. subtilis* and *S. aureus* when compared to both the standard drugs namely penicillin G and streptomycin. Similarly, the compounds **38** and **39** exhibited comparatively good activity than amphotericin B against *A. flavus*.

The high efficacy exhibited by the compounds **38** and **39** clearly reveals that the methyl group modification is essential at C_3 and C_5 in addition to chloro substitution at the *para* position of aryl moieties at C_2 and C_6 of heterocyclic ring moiety. The effect of methyl group substitution on structure–activity relationship may perhaps be due to an effect on stereochemical preferences on the piperidone ring which could influence their antimicrobial properties. Thus, in future, this class of novel imidazo(4,5-b)pyridinylethoxypiperidones may be used as templates to generate better drugs to *fight* bacterial and fungal infections.

6. Experimental

The course of reaction and the purity were ascertained by performing TLC. Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded in Perkin-Elmer 297 spectrophotometer with 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 tetramethyl silane (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 acquisition system. Elemental analyses (C, H and N) were carried out on a Carlo Erba Model 1106 and Perkin Elmer models 240 CHN analyzer. The results are within ± 0.4% of the theoretical values.

Unless otherwise stated, all the starting materials and reagents were of high grade, purchased from Aldrich, Fluka and Merck. All the solvents were distilled prior to use.

From the literature precedent [49] 2,6-diarylpiperidin-4-ones **7–15** were prepared by the condensation of appropriate ketones, aldehydes and ammonium acetate in 1:2:1 ratio.

*6.1. 1-Hydroxy-2,6-diphenylpiperidin-4-one (**16**)*

A solution of 2,6-diphenylpiperidin-4-one **1** (0.005 mol) and *m*-CPBA (0.005 mol) in 40 ml of dry chloroform was stirred for 15 min at 0 °C and kept aside overnight at 20 °C. Then the mixture was extracted with chloroform and washed well with 10% sodium bicarbonate solution. The chloroform layer was dried over anhydrous sodium sulfate and distilled off under reduced pressure. Purifications with silicagel column chromatography with 4:1 benzene/pet. ether (b.p. 40–60 °C) mixture yielded the product **16**. The compounds **17–24** were prepared similarly.

*6.2. 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 a 100 ml round-bottom flask and cooled in an ice-bath. A few crystals of resorcinol were added followed by drop-wise addition of Triton B with shaking. Then, the contents were stirred for 9 h at 65–75 °C and concentrated. After cooling, the resulting solution was poured over 1:3 benzene/pet. ether mixture. The solid obtained was recrystallized from methanol to afford the product **25**. The compounds **26–33** were prepared similarly.

*6.3. 1-[2-(Imidazo(4,5-b)pyridin-2-yl)ethoxy]-2,6-diphenylpiperidin-4-one (**34**)*

To a mixture of 1-(2-cyanoethoxy)-2,6-diphenylpiperidin-4-one **25** (0.005 mol) and 2,3-diaminopyridine (0.005 mol), dilute hydrochloric acid (10%) was added with constant shaking. The contents of the flask were refluxed on an oil bath. After the completion of reaction, 50 ml of water was added to the reaction mass. Later this was filtered to remove impurities. To isolate the product as a base, the acid solution was treated with aqueous ammonia (15 ml) and then poured into water. The precipitated compound **34** was recrystallized twice from ethanol.

IR (KBr) (cm^{-1}): 3259 (N–H), 3025, 3010, 2947, 2934, 2858, 2766 (C–H), 1708 (C=O), 1591, 1561, 1499, 1352, 1318, 1298, 1246, 1155, 1128, 1038, 908, 862, 820, 784, 758, 730, 697, 669, 603, 519, 490; Mass (*m/z*): 412 (M^+), 280, 250, 222, 208, 194, 145, 132, 118, 103(100%), 91, 77, 65, 55, 51; ^{1}H-NMR (δ ppm): 4.05 (dd, ^3J = 12.65 Hz; 3.81 Hz, 2H, H_{2a}, H_{6a}), 2.61–2.84 (m, 6H, $H_{3a,3e}$; $H_{5a,5e}$, –$OCH_2\underline{CH_2}$–), 3.93 (t, J = 6.51 Hz; 2H, –$O\underline{CH_2}CH_2$–), 7.28–7.49 (m, 13H, aryl protons), ^{13}C-NMR (δ ppm): 69.262 (C_2, C_6), 49.341 (C_3, C_5); 206.060 ($\underline{C}$=O), 141.739 (C_2' and C_6'), 114.289, 118.943, 119.058, 127.791, 129.773, 130.710, 133.105, 143.120 (aryl carbons), 162.614 (C_B), 67.533 (–$O\underline{C}H_2CH_2$–), 27.630 (–$OCH_2\underline{C}H_2$–).

The compounds **35–42** were also synthesized similarly.

*6.4. 1-[2-(Imidazo(4,5-b)pyridin-2-yl)ethoxy]-2,6-dipheny-3-methylpiperidin-4-one (**35**)*

IR (KBr) (cm^{-1}): 3252 (N–H), 3027, 3014, 2965, 2944, 2927, 2866, 2803 (C–H), 1696 (C=O), 2359, 2190, 1940, 1899, 1585, 1576, 1494, 1437, 1331, 1310, 1288, 1228, 1139, 1099, 1060, 943, 938, 912, 898, 856, 835, 824, 792, 734, 688, 628, 582, 541 Mass (*m/z*): 426 (M^+), 294, 281, 239, 162, 145, 133, 118, 103 (100%), 91, 77, 69, 65, 51; ^{1}H-NMR (δ ppm): 4.05 (dd, ^3J = 13.01 Hz; 3.30 Hz, 1H, H_{6a}), 3.61 (d, ^3J = 11.60 Hz, 1H, H_{2a}), 2.61–2.9 (m, 5H, H_{3a}, H $_{5a,\ 5e}$ and –OCH_2 $\underline{CH_2}$–), 3.91 (t, J = 6.50 Hz, 2H, –O $\underline{CH_2}CH_2$–), 7.30–7.50 (m, 13H, aryl protons), 0.82 (d, J = 6.6 Hz, 3H, –CH_3 at C_3); ^{13}C-NMR (δ ppm): 75.767 (C_2), 69.570 (C_6), 49.152 (C_3), 48.787 (C_5), 207.488 (C=O), 140.979 (C_2'), 141.820 (C_6'), 114.204, 118.938, 119.101, 127.743, 129.712, 129.820, 130.601, 130.714, 133.110, 143.140 (aryl carbons), 162.638 (C_B), 67.600 (–$O\underline{C}H_2CH_2$–), 27.730 (–$OCH_2\underline{C}H_2$–), 10.629 (–CH_3 at C_3).

*6.5. 1-[2-(Imidazo(4,5-b)pyridin-2-yl)ethoxy]-2,6-diphenyl-3,5-dimethylpiperidin-4-one (**36**)*

IR (KBr) (cm^{-1}): 3259 (N–H), 3028, 3016, 2966, 2925, 2848, 2815 (C–H), 1699 (C=O), 2361, 1607, 1582, 1480, 1461, 1441, 1381, 1338, 1324, 1272, 1191, 1142, 1099, 1011, 990, 926, 870, 823, 799, 769, 736, 679, 627, 559, 477, 451; Mass (*m/z*): 440 (M^+), 322,295, 190, 177, 146, 132, 118, 103 (100%), 100, 77, 56, 51; ^{1}H-NMR (δ ppm): 3.61 (d, ^3J = 11.62 Hz; 2H, $H_{2a,}$ H_{6a}), 2.82–2.91 (m, 2H, H_{3a}, H_{5a}), 2.69 (t, J = 6.50 Hz, 2H, –$OCH_2\underline{CH_2}$–), 3.91 (t, J = 6.50 Hz, 2H, –$O\underline{CH_2}CH_2$–), 7.28–7.55 (m, 13H, aryl protons), 0.82 (d, J=6.60 Hz, 6H, CH_3 at C_3 and C_5); ^{13}C-NMR (δ ppm): 76.025 (C_2 and C_6); 49.477 (C_3 and C_5); 209.192 (C=O), 141.120 (C_2' and C_6'), 114.257, 118.940, 119.097, 127.854, 129.794, 130.676, 133.112, 143.163 (aryl carbons), 67.608 (–$O\underline{C}H_2CH_2$–), 27.712 (–$OCH_2\underline{C}H_2$–), 10.976 (–CH_3 at C_3 and C_5).

*6.6. 1-[2-(Imidazo(4,5-b)pyridin-2-yl)ethoxy]-2,6-bis(p-chlorophenyl)piperidin-4-one (**37**)*

IR (KBr) (cm^{-1}): 3226 (N–H); 3026, 3008, 2928, 2842, 2798 (C–H), 1705 (C=O), 1632, 1584, 1492, 1431, 1419, 1366, 1335, 1311, 1326, 1293, 1171, 1135, 1055, 1017, 958, 888, 853, 756, 740, 698. 680, 679, 528, 499; Mass (*m/z*): 480 (M^+), 348, 335, 318, 290, 276, 166, 146, 137, 132, 118, 111, 75, 53 (100%), 50; ^{1}H-NMR (δ ppm): 4.08 (dd, ^3J = 12.60 Hz; 3.80 Hz, 2H, H_{2a}, H_{6a}), 2.60–2.89 (m, 6H, $H_{3a,\ 3e,}$ $H_{5a,\ 5e,}$ –$OCH_2\underline{CH_2}$–), 3.92 (t, J = 6.51 Hz, 2H, –$O\underline{CH_2}CH_2$–), 7.34–7.62 (m, 11H, aryl protons); ^{13}C-NMR (δ ppm) : 68.470 (C_2 and C_6), 48.992 (C_3 and C_5), 205.007 (C=O), 139.892 (C_2' and C_6'), 134.932 (C_2'''' and C_6''''), 114.290, 118.984, 119.080, 129.124, 129.963, 133.139, 143.347 (aryl carbons), 162.633 (C_B), 67.541 (–$O\underline{C}H_2CH_2$–), 27.634 (–$OCH_2\underline{C}H_2$–).

*6.7. 1-[2-(Imidazo(4,5-b)pyridin-2-yl)ethoxy]-2,6-bis(p-chlorophenyl)-3-methylpiperidin-4-one (**38**)*

IR (KBr) (cm^{-1}): 3222 (N–H), 3028, 3013, 2966, 2934, 2853, 2728 (C–H), 1695 (C=O), 2973, 1952, 1826, 1641, 1591, 1580, 1496, 1377, 1382, 1324, 1316, 1279, 1228, 1142, 1118, 1053, 1021, 961, 942, 923, 888, 860, 760, 752, 700, 684, 661, 544, 487; Mass (*m/z*): 494(M^+), 362, 349, 332, 307, 262, 196, 180, 155, 146, 137, 133, 118, 111, 75, 69, 53 (100%), 50; ^{1}H-NMR (δ ppm): 4.07 (dd, ^3J = 13.00 Hz; 3.30 Hz, 1H, H_{6a}), 3.68 (d, ^3J = 11.60 Hz; 1H, H_{2a}), 2.63–2.93 (m, 5H, H_{3a}, $H_{5a,5e,}$ –$OCH_2\underline{CH_2}$–), 3.92 (t, J = 6.5 Hz, 2H, –$O\underline{CH_2}CH_2$–), 7.12–7.46 (m, 11H, aryl protons), 0.80 (d, J = 6.54 Hz, 3H, CH_3 at C_3), ^{13}C-NMR (δ ppm): 74.970 (C_2), 68.858 (C_6), 48.856 (C_3), 48.490 (C_5), 206.226 (C=O), 139.953 (C_6'), 139.094 (C_2'), 134.948 (C_6''''), 134.753 (C_2''''), 114.202, 118.976, 119.162, 129.361, 129.373, 129.883, 133.004, 133.120, 143.333 (aryl carbons), 162.633 (C_B), 67.614 (–$O\underline{C}H_2CH_2$–), 27.739 (–$OCH_2\underline{C}H_2$–), 10.676 (–CH_3 at C_3).

*6.8. 1-[2-(Imidazo(4,5-b)pyridin-2-yl)ethoxy]-2,6-bis(p-chlorophenyl)-3,5-dimethyl piperidin-4-one (**39**)*

IR (KBr) (cm^{-1}): 3219 (N–H), 3024, 3014, 2958, 2930, 2845, 2798 (C–H), 1697 (C=O), 2347, 1618, 1600, 1583, 1475, 1440, 1363, 1331, 1186, 1150, 1089, 1021, 982, 931, 889, 815, 761,

740, 701, 650, 540, 523, 489; Mass (*m/z*): 508 (M^+), 390, 363, 334, 211, 193, 180, 152, 146, 132, 118, 111, 100, 91, 75, 53 (100%), 50; ^{1}H-NMR (δ ppm): 3.64 (d, ^3J = 11.62 Hz; 2H, H_{2a}, H_{6a}), 2.80–2.89 (m, 2H, H_{3a} and H_{5a}), 2.70 (t, J = 6.51 Hz, 2H, –$OCH_2\underline{C}H_2$–), 3.91 (t, J = 6.50 Hz, 2H, –$O\underline{C}H_2CH_2$–), 7.31–7.54 (m, 11H, aryl protons), 0.80 (d, J = 6.52 Hz, 6H, CH_3 at C_3 and C_5); ^{13}C-NMR (δ ppm): 75.283 (C_2 and C_6), 49.210 (C_3 and C_5), 208.162 (C=O), 139.143 (C_2' and C_6'), 134.841 (C_2'''' and C_6''''), 114.239, 118.943, 119.162, 129.290, 129.819, 133.029, 143.359 (aryl carbons), 162.635 (C_B), 67.633 (–$O\underline{C}H_2CH_2$–), 27.709 (–$OCH_2\underline{C}H_2$–), 10.876 (–CH_3 at C_3 and C_5).

6.9. 1-[2-(Imidazo(4,5-b)pyridin-2-yl)ethoxy]-2,6-bis(p-methoxyphenyl)piperidin-4-one (**40**)

IR (KBr) (cm^{-1}): 3237 (N–H), 3028, 3013, 2928, 2855, 2788 (C–H), 1707 (C=O), 1645, 1579, 1472, 1445, 1371, 1355, 1322, 1258, 1185, 1143, 1038, 931, 790, 738, 700, 650, 644, 535, 509, 450; Mass (*m/z*): 472 (M^+), 354, 327, 310, 282, 254, 162, 147, 145, 132, 118, 107, 75, 65, 55, 53 (100%), 50, 43; ^{1}H-NMR (δ ppm) : 4.06 (dd, ^3J = 12.60 Hz; 3.8 Hz, 2H, $H_{2a,}$ H_{6a}), 2.57–2.85 (m, 6H, $H_{3a,3e}$; $H_{5a,5e}$; –$OCH_2\underline{C}H_2$–), 3.93 (t, J = 6.54 Hz 2H, –$O\underline{C}H_2CH_2$–), 6.88 (d,4H) and 7.34–7.59 (m, 7H, aryl protons), 3.81 (s, 6H, –OCH_3), ^{13}C-NMR (δ ppm): 68.612 (C_2 and C_6), 49.395 (C_3 and C_5); 206.177 (C=O), 158.806 (C_2'''' and C_6''''), 135.571 (C_2' and C_6'), 114.342, 114.490; 118.974, 119.011, 133.019, 133.148, 143.362 (aryl carbons), 162.598 (C_B), 67.620 (–$O\underline{C}H_2CH_2$–), 27.688 (–$OCH_2\underline{C}H_2$–), 55.113 (–OCH_3).

6.10. 1-[2-(Imidazo(4,5-b)pyridin-2-yl)ethoxy]-2,6-bis(p-methoxyphenyl)-3-methylpiperidin-4-one (**41**)

IR (KBr) (cm^{-1}): 3239 (N–H), 3028, 3016, 2939, 2836 (C–H), 1699 (C=O), 2367, 2335, 1591, 1560, 1500, 1460, 1365, 1335, 1310, 1245, 1170, 1035, 940, 849, 725, 700, 672, 645, 540, 475; Mass (*m/z*): 486 (M^+), 354, 341, 324, 299, 176, 148, 145, 133, 118, 107, 75, 69, 65, 53 (100%), 50; ^{1}H-NMR (δ ppm): 4.06 (dd, ^3J = 13.00 Hz; 3.30 Hz 1H, H_{6a}), 3.67 (d, ^3J = 11.61 Hz; 1H, H_{2a}), 2.55–2.88 (m, 5H, H_{3a}, $H_{5a,5e}$; –$OCH_2\underline{C}H_2$–), 3.93 (t, J = 6.54 Hz, 2H, –$O\underline{C}H_2CH_2$–), 6.90 (4H) and 7.28–7.51(m,7H, aryl protons), 3.80 (s, 6H, –OCH_3), 0.81 (d, J = 6.58 Hz, 3H, CH_3 at C_3), ^{13}C-NMR (δ ppm): 75.169 (C_2), 68.979 (C_6), 49.233 (C_3), 48.892 (C_5), 207.391 (C=O), 135.847 (C_6'), 135.134 (C_2'), 158.940 (C_6''''), 158.573 (C_2''''), 114.102, 114.648, 114.879, 118.768, 118.988, 132.999, 133.121, 143.380 (aryl carbons), 162.508 (C_B), 67.768 (–$O\underline{C}H_2CH_2$–), 27.650 (–$OCH_2\underline{C}H_2$–), 55.188 (–OCH_3), 10.614 (–CH_3 at C_3).

6.11. 1-[2-(Imidazo(4,5-b)pyridin-2-yl)ethoxy]-2,6-bis(p-methoxyphenyl)-3,5-dimethyl piperidin-4-one (**42**)

IR (KBr) (cm^{-1}): 3229 (N–H), 3029, 3014, 2932, 2841(C–H), 1699 (C=O), 2361, 2345, 1595, 1560, 1500, 1461, 1355, 1319, 1290, 1244, 1081, 1042, 841, 790, 735, 655, 540, 480, 450; Mass (*m/z*): 500 (M^+), 382, 355, 220, 207, 189, 176, 161, 146, 132, 118, 107, 100, 75, 53(100%), 50; ^{1}H-NMR(δ ppm): 3.63 (d, ^3J = 11.65 Hz; 2H, H_{2a}, H_{6a}), 2.79–2.86 (m, 2H, H_{3a} and H_{5a}), 2.69 (t, J = 6.49 Hz, 2H, –$OCH_2\underline{C}H_2$–), 3.93 (t, 6.52 Hz, 2H, –$O\underline{C}H_2CH_2$–), 6.88 (4H) and 7.35–7.49 (m, 7H, aryl protons), 3.80 (s, 6H, –OCH_3), 0.81 (d, J = 6.55 Hz, 6H, CH_3 at C_3 and C_5), ^{13}C-NMR (δ ppm): 75.476 (C_2 and C_6); 49.538 (C_3 and C_5), 209.419 (C=O), 158.882 (C_2'''' and C_6''''), 135.127 (C_2' and C_6'), 114.235, 114.528, 118.864, 119.014, 133.002, 133.226, 143.343 (aryl carbons), 162.611 (C_B), 67.704 (–$O\underline{C}H_2CH_2$–), 27.677 (–$OCH_2\underline{C}H_2$–), 55. 213(–OCH_3), 10.957 (–CH_3 at C_3 and C_5).

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