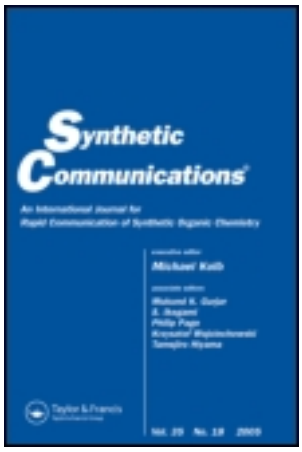


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

A Convenient Synthesis of Novel 1-[2-(Benzimidazol-2-yl)ethoxy]-2,6-diarylpiperidin-4-or

C. Ramalingan [a] , S. Balasubramanian [a] & S. Kabilan [a]

[a] Department of Chemistry , Annamalai University , Annamalainagar, 608 002, India

Published online: 21 Aug 2006.

To cite this article: C. Ramalingan , S. Balasubramanian & S. Kabilan (2004) A Convenient Synthesis of Novel 1-[2-(Benzimidazol-2-yl)ethoxy]-2,6-diarylpiperidin-4-ones, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 34:6, 1105-1116, DOI: 10.1081/SCC-120028643

To link to this article: http://dx.doi.org/10.1081/SCC-120028643

SYNTHETIC COMMUNICATIONS®
Vol. 34, No. 6, pp. 1105–1116, 2004

A Convenient Synthesis of Novel 1-[2-(Benzimidazol-2-yl)ethoxy]-2,6-diarylpiperidin-4-ones

C. Ramalingan, S. Balasubramanian, and S. Kabilan*

Department of Chemistry, Annamalai University, Annamalainagar, India

ABSTRACT

Upon the study of biological evaluation of benzazolylethoxypiperidones, an array of novel benzimidazolylethoxypiperidones were synthesized. 2,6-Diarylpiperidin-4-ones upon strategical *N*-hydroxylation, cyanoethylation followed by acid aided condensation with *o*-phenylenediamine afforded a convenient route to novel 1-[2-(benzimidazol-2-yl)ethoxy]-2,6-diarylpiperidin-4-ones.

Key Words: Cyanoethylation; Piperidine derivatives; Benzimidazole moiety, Synthetic compounds.

Substituted piperidin-4-ones are important synthetic intermediates for the preparation of various alkaloids and pharmaceuticals.[1] The piperidine

*Correspondence: S. Kabilan, Department of Chemistry, Annamalai University, Annamalainagar-608 002, India; E-mail: kabilan@satyam.net.in.

DOI: 10.1081/SCC-120028643 0039-7911 (Print); 1532-2432 (Online)

nucleus can also be frequently recognized in the structure of numerous naturally occurring alkaloids 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] Benzimidazole (1,3-dideazapurine) is an important nucleus which has been extensively used in medicinal chemistry, notable clinical examples being the antihistaminic astemizole and the antiulcerative omeprazole.[3] Benzimidazoles are marked for their anti-inflammatory,[4] macrofilaricidal,[5] antibiotic,[6] antiarrythemic,[6] anthelmintic,[7] antibacterial,[7] antifungal,[8] antihistaminic,[9] anticancer,[10] angiotension receptor antagonist,[11] potent and selective 5-HT_4 receptor antagonist,[12] antitumour[13] and antiviral[14] activities. 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.[15] 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.

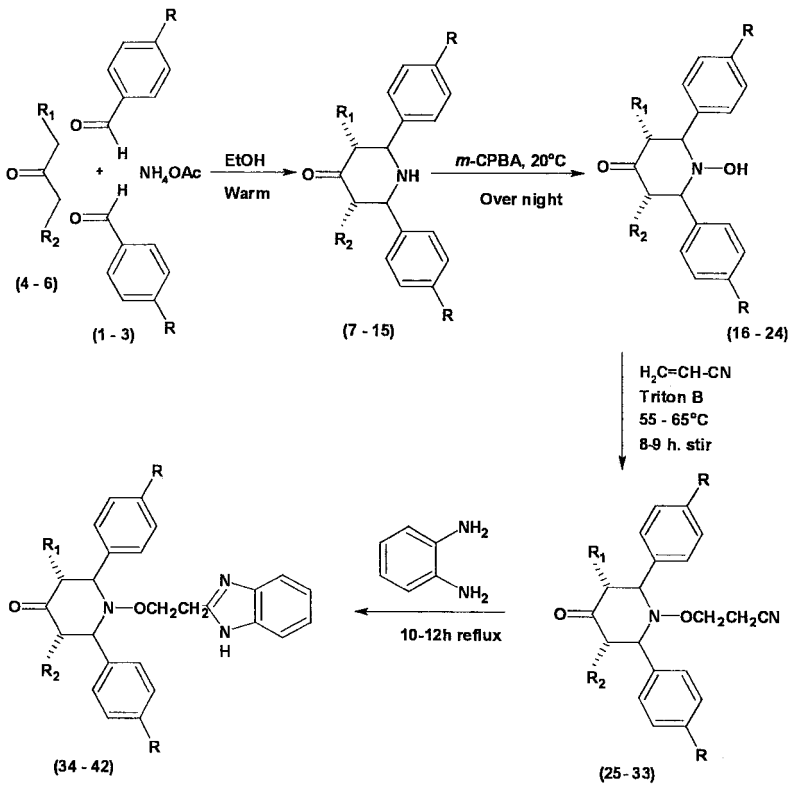
Recently, we exploited the synthesis of 2,6-diarylpiperidin-4-one derivatives with a view to incorporate various other bioactive heterocyclic nucleus intact for evaluation of their biological importance and also as a reagent for effecting functional group interconversion.[16]

Cyclic ketones normally undergo Baeyer–Villeger oxidation (oxygen insertion reaction) to yield lactones upon treatment with peracids.[17] 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[18] resulted instead of lactones. On treatment with acrylonitrile, substituted tetrahydrothiopyran-4-ones containing active hydrogen underwent cyanoethylation yielding 3-[2-cyanoethoxy]derivatives.[19] 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[20] 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[21] 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 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.

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

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*-phenylenediamine in acid medium resulted 1-[2-(benzimidazol-2-yl)ethoxy]-2,6-diarylpiperidin-4-ones in moderate yields (40%–62%). 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 Sch. 1 and Table 1, respectively. The spectral characterization data for the novel intermediates **25–33** are furnished in Table 2.



Scheme 1.

Marcel Dekker, Inc.
270 Madison Avenue, New York, New York 10016

Table 1. Analytical data for compounds **25**–**42**.

Entry	R_1	R_2	R	Yield (%)	M.P. (°C)	Elemental analysis C (%)	H (%)	N (%)
25	H	H	H	70	87	74.92	6.24	8.73
26	H	CH_3	H	74	76	75.39	6.57	8.37
27	CH_3	CH_3	H	69	92	75.81	6.89	8.04
28	H	H	Cl	65	71	61.79	4.63	7.23
29	H	CH_3	Cl	64	60	62.62	4.97	6.95
30	CH_3	CH_3	Cl	67	68	63.39	5.28	6.72
31	H	H	OCH_3	69	80	69.42	6.31	7.36
32	H	CH_3	OCH_3	70	73	69.96	6.58	7.10
33	CH_3	CH_3	OCH_3	63	62	70.46	6.85	6.87
34	H	H	H	60	128	75.93	5.98	10.16
35	H	CH_3	H	62	107–108	76.20	6.31	9.82
36	CH_3	CH_3	H	60	98	76.49	6.56	9.50
37	H	H	Cl	40	79	64.98	4.83	8.71
38	H	CH_3	Cl	35	92	65.58	5.04	8.48
39	CH_3	CH_3	Cl	35	71–72	66.14	5.28	8.24
40	H	H	OCH_3	52	113	71.27	6.15	8.90
41	H	CH_3	OCH_3	55	102–103	71.77	6.36	8.60
42	CH_3	CH_3	OCH_3	47	85–86	72.10	6.57	8.39

EXPERIMENTAL

The 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 acquisition system. Satisfactory microanalysis were obtained on Carlo Erba 1106 and Perkin Elmer models 240 CHN analyzer.

From the literature precedent,[22] 2,6-diarylpiperidin-4-ones (**7**–**15**) were prepared by the condensation of appropriate ketones, aldehydes, and ammonium acetate in 1 : 2 : 1 ratio.

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).

(*continued*)

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

Table 2. Continued.

Entry	Spectral characterization data
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).

1-Hydroxy-2,6-diphenylpiperidin-4-one[17] (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 allowed to stand at 20°C overnight. The mixture was diluted with chloroform and washed with 10% sodium bicarbonate solution. The chloroform layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification of the residue by silicagel column chromatography with 8 : 12 benzene-petroleum ether as element 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

Marcel Dekker, Inc.
270 Madison Avenue, New York, New York 10016

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. The mixture was stirred at 65°C–75°C for 9 hr during which time some of the solvent evaporated. After cooling, the resulting solution was poured over benzene : petroleum ether, 1 : 3 mixture. The solid thus obtained was recrystallized from methanol to afford **25**. The compounds **26–33** were prepared similarly.

1-[2-(Benzimidazol-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 *o*-phenylenediamine (0.005 mol), dilute hydrochloric acid (10 cc of conc. HCl in 100 cc of water) was added with constant shaking. Then the contents of the flask was allowed to reflux in an oil bath for 12 hr. After the addition of 50 mL of water into to reaction mass, it was filtered to remove impurities. To isolate **34** as a base, the acid solution was treated with strong ammonia (15 cc) and was poured into water. The precipitated base was recrystallized twice from ethanol. IR: cm^{-1} (KBr) 3256, 2942, 2930, 1705. Mass: m/z 411(M^+) (M.F.: $C_{26}H_{25}N_3O_2$), 320, 294, 280, 267, 250, 222, 208, 194, 163, 144, 117, 103 (100%), 91, 77, 65, 51. ^{1}H-NMR: δ 4.04 (dd, $^3J = 12.64$ Hz; 3.86 Hz, 2H, H_2, H_6), 2.61–2.85 (m, 6H, H_3, H_5, $-OCH_2-$ CH_2-), 7.27–7.49 (m, 14H, arylprotons), 3.86 (t, $J = 6.50$ Hz, 2H, $-OCH_2-$ CH_2-), 12.83 (br.s, 1H, NH). ^{13}C-NMR: δ 69.27 (C_2, C_6), 49.29 (C_3, C_5), 206.11 (C═O), 69.31 ($-OCH_2-CH_2-$), 19.86 ($-OCH_2-CH_2-$), 110.23, 115.01, 115.13, 120.99, 121.01, 127.78, 129.78, 130.72, 137.25 (aryl carbons), 141.73(C_2', C_6'), 157.15 (C_2 of benzimidazole moiety).

The compounds **35–42** were synthesised similarly.

1-[2-(Benzimidazol-2-yl)ethoxy]-2,6-diphenyl-3-methylpiperidin-4-one (35)

IR: cm^{-1} (KBr) 3250, 2942, 2807, 1695. Mass: m/z 425(M^+) (M.F.: $C_{27}H_{27}N_3O_2$), 294, 281, 264, 236, 222, 205, 177, 162, 144, 131, 118, 117, 105 (100%), 91, 77, 65, 51. ^{1}H-NMR: δ 4.02 (dd, $^3J = 13.03$ Hz; 3.36 Hz, 1H, H_6), 3.59(d, $^3J = 11.65$ Hz, 1H, H_2), 2.60–2.88 (m, 5H, H_3, H_5, $-OCH_2-CH_2-$), 7.28–7.48 (m, 14H, arylprotons), 3.85 (t, $J = 6.49$ Hz, 2H, $-OCH_2-CH_2-$), 0.80 (d, $J = 6.54$ Hz, 3H, CH_3), 12.85 (br.s, 1H, NH). ^{13}C-NMR: δ 75.80 (C_2), 69.58 (C_6), 49.12 (C_3), 48.77 (C_5), 207.55 (C═O), 69.32 ($-OCH_2-CH_2-$), 19.87 ($-OCH_2-CH_2-$), 110.20, 115.01, 115.14, 120.98, 121.05, 127.74,

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

127.71, 129.83, 130.59, 130.70, 137.27 (aryl carbons), 140.99 (C_2'), 141.83 (C_6'), 157.16 (C_2 of benzimidazole moiety), 10.60 (CH_3).

1-[2-(Benzimidazol-2-yl)ethoxy]-2,6-diphenyl-3,5-dimethylpiperidin-4-one (36)

IR: cm^{-1} (KBr) 3258, 2932, 2848, 1698. Mass: m/z 439 (M^+) (M.F.: $C_{28}H_{29}N_3O_2$), 308, 295, 278, 250, 173, 144, 121, 118, 117, 103 (100%), 91, 84, 77, 59, 56, 51. ^{1}H-NMR: δ 3.62 (d, $^3J = 11.66$ Hz, 2H, H_2, H_6), 2.82–2.88 (m, 2H, H_3, H_5), 2.72 (t, $J = 6.52$ Hz, 2H, $-OCH_2-CH_2-$), 7.27–7.54 (m, 14H, arylprotons), 3.86 (t, $J = 6.50$ Hz, 2H, $-OCH_2-CH_2-$), 0.81 (d, $J = 6.58$ Hz, 6H, CH_3), 12.92 (br.s, 1H, NH). ^{13}C-NMR: δ 76.03 (C_2, C_6), 49.42 (C_3, C_5), 209.21 (C═O), 69.32 ($-OCH_2-CH_2-$), 19.87 ($-OCH_2-CH_2-$), 110.19, 115.02, 115.14, 120.99, 121.03, 127.85, 129.80, 130.66, 137.24 (aryl carbons), 141.10 (C_2', C_6'), 157.14 (C_2 of benzimidazole moiety), 10.98 (CH_3).

1-[2-(Benzimidazol-2-yl)ethoxy]-2,6-*bis*(*p*-chlorophenyl)piperidin-4-one (37)

IR: cm^{-1} (KBr) 3224, 2927, 2792, 1708. Mass: m/z 479 (M^+) (M.F.: $C_{26}H_{23}N_3O_2Cl_2$), 388, 362, 348, 335, 318, 290, 276, 262, 197, 167, 145, 137, 117, 111, 91, 75, 65, 53 (100%), 50. ^{1}H-NMR: δ 4.07 (dd, $^3J = 12.64$ Hz; 3.87 Hz, 2H, H_2, H_6), 2.60–2.89 (m, 6H, H_3, H_5, $-OCH_2-CH_2-$), 7.29–7.53 (m, 12H, arylprotons), 3.86 (t, $J = 6.50$ Hz, 2H, $-OCH_2-CH_2-$), 12.89 (br.s, 1H, NH). ^{13}C-NMR: δ 68.48 (C_2,C_6), 48.96 (C_3, C_5), 205.11 (C═O), 69.32 ($-OCH_2-CH_2-$), 19.88 ($-OCH_2-CH_2-$), 110.24, 115.03, 115.14, 120.99, 121.05, 129.01, 129.99, 137.27 (aryl carbons), 134.92 (C_2''', C_6'''), 139.88 (C_2', C_6'), 157.20 (C_2 of benzimidazole moiety).

1-[2-(Benzimidazol-2-yl)ethoxy]-2,6-*bis*(*p*-chlorophenyl)-3-methylpiperidin-4-one (38)

IR: cm^{-1} (KBr) 3220, 2961, 2857, 2728, 1694. Mass: m/z 493 (M^+) (M.F.: $C_{27}H_{25}N_3O_2Cl_2$), 362, 349, 332, 304, 290, 239, 211, 196, 165, 152, 145, 139, 131, 117, 111, 91, 75, 53 (100%), 50. ^{1}H-NMR: δ 4.06 (dd, $^3J = 13.02$ Hz; 3.36 Hz, 1H, H_6), 3.68 (d, $^3J = 11.64$ Hz, 1H, H_2), 2.61–2.90 (m, 5H, H_3, H_5, $-OCH_2-CH_2-$), 7.18–7.51 (m, 12H, arylprotons), 3.86 (t, $J = 6.50$ Hz, 2H, $-OCH_2-CH_2$), 0.79(d, $J = 6.58$ Hz, 3H, CH_3), 12.85

Marcel Dekker, Inc.
270 Madison Avenue, New York, New York 10016

(br.s, 1H, NH). ^{13}C-NMR: δ 75.00 (C_2), 68.86 (C_6), 48.82 (C_3), 48.46 (C_5), 206.24 (C═O), 69.33 ($-OCH_2-CH_2-$), 19.88 ($-OCH_2-CH_2-$), 110.21, 115.01, 115.14, 121.00, 121.10, 129.37, 129.38, 129.86, 129.99, 137.30 (aryl carbons), 134.74 (C_2'''), 134.90 (C_6'''), 139.10 (C_2'), 139.97 (C_6'), 157.16 (C_2 of benzimidazole moiety), 10.70 (CH_3).

1-[2-(Benzimidazol-2-yl)ethoxy]-2,6-*bis*(*p*-chlorophenyl)-3,5-dimethyl piperidin-4-one (39)

IR: cm^{-1} (KBr) 3217, 2958, 2841, 2798, 1695. Mass: m/z 507 (M^+) (M.F.: $C_{28}H_{27}N_3O_2Cl_2$), 376, 363, 346, 318, 207, 183, 155, 145, 137, 117, 111, 91, 75, 59, 53 (100%), 50. ^{1}H-NMR: δ 3.65 (d, $^3J = 11.66$ Hz, 2H, H_2, H_6), 2.83–2.89 (m, 2H H_3, H_5), 2.73 (t, $J = 6.53$ Hz, 2H, $-OCH_2-CH_2-$), 7.31–7.53 (m, 12H, arylprotons), 3.86 (t, $J = 6.49$ Hz, 2H, $-OCH_2-CH_2-$), 0.80 (d, $J = 6.61$ Hz, 6H, CH_3), 12.96 (br.s, 1H, NH). ^{13}C-NMR: δ 75.29 (C_2, C_6), 49.18 (C_3, C_5), 208.23 (C═O), 69.30 ($-OCH_2-CH_2-$), 19.87 ($-OCH_2-CH_2-$), 110.20, 115.02, 115.15, 121.00, 121.04, 129.24, 129.84, 137.25 (aryl carbons), 134.82 (C_2''', C_6'''), 139.12 (C_2', C_6'), 157.58 (C_2 of benzimidazole moiety), 10.87 (CH_3).

1-[2-(Benzimidazol-2-yl)ethoxy]-2,6-*bis*(*p*-methoxyphenyl)piperidin-4-one (40)

IR: cm^{-1} (KBr) 3235, 2942, 2830, 2787, 1704. Mass: m/z 471(M^+) (M.F.: $C_{28}H_{29}N_3O_4$), 380, 354, 340, 327, 310, 282, 268, 254, 193, 167, 144, 133, 117, 107, 91, 75, 65, 53 (100%), 50. ^{1}H-NMR: δ 4.06 (dd, $^3J = 12.65$ Hz; 3.85 Hz, 2H, H_2, H_6), 2.58–2.84 (m, 6H, H_3, H_5, $-OCH_2-CH_2-$), 6.88; 7.21–7.52 (d, 4H; m, 8H, arylprotons), 3.85 (t, $J = 6.52$ Hz, 2H, $-OCH_2-CH_2-$), 3.81 (s, 6H, OCH_3), 12.83 (br.s, 1H, NH). ^{13}C-NMR: δ 68.63 (C_2, C_6), 49.38 (C_3, C_5), 206.20 (C═O), 69.40 ($-OCH_2-CH_2-$), 19.84 ($-OCH_2-CH_2-$), 110.28, 114.50, 115.06, 115.20, 120.06, 121.10, 132.99, 137.34 (aryl carbons), 158.81 (C_2''', C_6'''), 135.55 (C_2', C_6'), 157.34 (C_2 of benzimidazole moiety), 55.01 (OCH_3).

1-[2-(Benzimidazol-2-yl)ethoxy]-2,6-*bis*(*p*-methoxyphenyl)-3-methyl piperidin-4-one (41)

IR: cm^{-1} (KBr) 3238, 2950, 2847, 1699. Mass: m/z 485 (M^+) (M.F.: $C_{29}H_{31}N_3O_4$), 354, 341, 324, 296, 282, 265, 207, 192, 161, 148, 131, 117, 107,

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

91, 75, 65, 53 (100%), 50. ^{1}H-NMR: δ 4.05 (dd, $^{3}J = 12.99$ Hz: 3.33 Hz, 1H, H_6), 3.66 (d, $^{3}J = 11.67$ Hz, 1H, H_2), 2.58–2.87 (m, 5H, H_3, H_5, $-OCH_2-CH_2-$), 6.87; 7.26–7.51 (d, 4H; m, 8H, arylprotons), 3.85 (t, $J = 6.52$ Hz, 2H, $-OCH_2-CH_2-$), 3.80 (s, 6H, OCH_3), 0.80 (d, $J = 6.54$ Hz, 3H, CH_3), 12.75 (br.s, 1H, NH). ^{13}C-NMR: δ 75.18 (C_2), 69.00 (C_6), 49.21 (C_3), 48.88 (C_5), 207.42 (C═O), 69.43 ($-OCH_2-CH_2-$), 19.87 ($-OCH_2-CH_2-$), 110.20, 114.89, 114.97, 114.98, 120.99, 121.00, 132.98, 133.11, 137.35 (aryl carbons), 158.56 (C_2'''), 158.95 (C_6''''), 135.13 (C_2'), 135.83 (C_6'), 157.16 (C_2 of benzimidazole moiety), 10.61 (CH_3).

1-[2-(Benzimidazol-2-yl)ethoxy]-2,6-*bis*(*p*-methoxyphenyl)-3,5-dimethyl piperidin-4-one (42)

IR: cm^{-1} (KBr) 3227, 2927, 2848, 1697. Mass: m/z 499 (M^+) (M.F.: $C_{30}H_{33}N_3O_4$), 368, 355, 338, 310, 204, 179, 151, 145, 133, 117, 107, 91, 84, 75, 53 (100%), 50. ^{1}H-NMR: δ 3.64 (d, $^{3}J = 11.69$ Hz, 2H, H_2, H_6), 2.81–2.87 (m, 2H, H_3, H_5), 2.72 (t, $J = 6.51$ Hz, 2H, $-OCH_2-CH_2-$), 6.87; 7.25–7.51 (d, 4H; m, 8H, arylprotons), 3.86 (t, $J = 6.50$ Hz, 2H, $-OCH_2-CH_2-$), 3.81 (s, 6H, OCH_3), 12.94 (br.s, 1H, NH), 0.81 (d, $J = 6.57$ Hz, 6H, CH_3). ^{13}C-NMR: δ 75.46 (C_2, C_6), 49.54 (C_3, C_5), 209.43 (C═O), 69.31 ($-OCH_2-CH_2-$), 19.89 ($-OCH_2-CH_2-$), 110.00, 114.13, 114.97, 115.00, 120.98, 120.99, 133.20, 137.25 (aryl carbons), 158.88 (C_2''', C_6''''), 135.11 (C_2', C_6'), 157.56 (C_2 of benzimidazole moiety), 55.21 (OCH_3), 10.97 (CH_3).

ACKNOWLEDGMENT

The authors are grateful to Prof. K. Pandiarajan, Head, Department of Chemistry, Annamalai University for providing needed facilities. One of the authors, S.K., is grateful to University Grants Commission, New Delhi for financial support. SB wishes to thank Council of Scientific & Industrial Research, New Delhi for the award of Senior Research Fellowship.

REFERENCES

1. (a) Angle, S.R.; Breitenbucher, J.G. *Studies in Natural Products Chemistry, Stereoselective Synthesis*; Atta-ur-Rahman, Ed.; Elsevier: New York, 1995; Vol. 16, Part J, 453–502; (b) Grishina, G.V.; Gaidarova, E.L.; Zefirov, N.S. Chem. Heterocycl. Compd. **1994**, *30*,

1401; (c) Wang, C.-L.; Wuorola, M.A. Org. Prep. Proced. Int. **1992**, *24*, 585.
2. (a) Takahata, H.; Ouchi, H.; Ichionose, M.; Nemoto, H. Org. Lett. **2002**, *4* (20), 3459; (b) Davis, F.A.; Chao, B.; Rao, A. Org. Lett. **2001**, *3*, 3169; (c) Honda, T.; Kimura, M. Org. Lett. **2000**, *2*, 3925; (d) Wilkinson, T.; Stehle, N.W.; Beak, P. Org. Lett. **2000**, *2* (2), 155; (e) Ojima, I.; Vidal, E.S. J. Org. Chem. **1998**, *63*, 7999; (f) Amat, M.; Hidalgo, J.; Llor, N.; Bosch, J. Tetrahedron: Asymmetry **1998**, *9*, 2419.
3. (a) Ritcher, J.E. Am. J. Gastroenterol. **1997**, *92*, 34; (b) Al. Muhaimeed, H.J. J. Int. Med. Res. **1997**, *25*, 175.
4. Evans, D.; Kicks, T.A.; Williamson, W.R.N.; Dawson, N.V.; Meacocok, S.C.R.; Kitchen, E.A. Eur. J. Med. Chem. **1996**, *31*, 635.
5. Ojha, V.; Singh, J.; Bhakuni, D.S.; Singh, S.; Chatterjee, R.K. Indian J. Chem. **1991**, *30B*, 324.
6. Asobo, P.F.; Wahe, H.; Mabafor, J.T.; Nkengfack, A.E.; Fomum, Z.T.; Sopbue, E.F.; Döpp, D. J. Chem. Soc., Perkin Trans. **2001**, *1*, 457.
7. (a) Shetgiri, N.P.; Kokitkar, S.V. Indian J. Chem. **2001**, *40B*, 163; (b) Habib, N.S.; Soliman, R.; Ashour, F.A.; El. Taiebi, M. Pharmazie **1997**, *52*, 844; (c) Salluja, S.; Zou, R.; Drach, J.C.; Townsend, L.B. J. Med. Chem. **1996**, *39*, 881; (d) Townsend, L.B.; Wise, D.S. Parasitol. Today **1990**, *6*, 106.
8. (a) Göker, H.; Kus, G.; Boykin, D.W.; Yildiz, S.; Altanlar, N. Bioorg. Med. Chem. **2002**, *10*, 2589; (b) Göker, H.; Tuncbilek, M.; Suzen, S.; Kus, C.; Altanlar, N. Arch. Pharm. Pharm. Med. Chem. **2001**, *334*, 138.
9. Göker, H.; Kilicigil, G.A.; Tuncbilek, M.; Kus, C.; Ertan, R.; Kendi, E.; Ozbey, S.; Fort, M.; Garcia, C.; Farre, A.J. Heterocycles **1999**, *51*, 2561.
10. Kumar, D.; Jacob, M.R.; Reynolds, M.B.; Kerwin, S.M. Bioorg. Med. Chem. **2002**, *10*, 3997.
11. Kubo, K.; Indada, Y.; Kohara, Y.; Sugiures, Y.; Mamiojima; Itoh, K.; Furukawa, Y.; Nighiugaky, K.; Takehiko. J. Med. Chem. **1993**, *36* (12), 1772.
12. Rodriguez, M.L.L.; Benhamu, B.; Viso, A.; Morcillo, M.J.; Murcia, M.; Orensanz, L.; Alfaro, M.J.; Martin, M.I. Bioorg. Med. Chem. **1999**, *7*, 2271.
13. Sharma, S.; Abuzar, S. Prog. Drug. Res. **1983**, *27*, 85.
14. Garuti, L.; Roberti, M.; Malagoli, M.; Rossi, T.; Castelli, M. Bioorg. Med. Chem. Lett. **2000**, *10*, 2193.
15. (a) Silverman, R.B. *Organic Chemistry of Drug Design and Drug Action*; Academic Press Inc: San Diego, 1992; (b) Thompson, L.A.; Ellman, J.A. Chem. Rev. **1996**, *96*, 555.
16. (a) Balsubramanian, S.; Ramalingan, C.; Kabilan, S. Synth. Commun. **2003**, *33* (17), 2979; (b) Ramalingan, C.; Balasubramanian, S.; Kabilan, S.

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

Synth. Commun. **2003**, *33* (9), 1443; (c) Balasubramanian, S.; Ramalingan, C.; Kabilan, S. Indian J. Chem. **2002**, *41B*, 2402; (d) Ramalingan, C.; Balasubramanian, S.; Kabilan, S.; Vasudevan, M. Med. Chem. Res. **2003**, *12* (1), 26; (e) Ramalingan, C.; Balasubramanian, S.; Kabilan, S. Heterocycl. Commun. (Communicated).

17. (a) Hudlicky, M. *Oxidations in Organic Chemistry*; American Chemical Society: Washington, 1990; 186; (b) Krow, G.R. Tetrahedron **1981**, *37*, 2697.
18. Sughanya, V. Ph.D. Thesis, Annamalai University; 1999.
19. Tokmurzin, KI.Kh.; Kozyren, V.V.; Sharifkanov, A.Sh. Chim. Geterotsikl. Soedin. **1982**, *10*, 1342.
20. Ramalingan, C. Ph.D. Thesis, Annamalai University; 2002.
21. (a) Bruson, H.A. *Organic Reactions*; Bachmann, W.E., Fieser, L.F., Blatt, A.H., Johnson, J.R., Eds.; Cyanoethylation, John Wiley & Sons: New York, 1949; Vol. 5, Chap. 2, 79–135; (b) Szabolajos; Gyoergy, K.; Alaios, K.; Pal, K.; Csabc, S. Heterocycles **1995**, *40* (1), 155.
22. Noller, C.R.; Baliah, V. J. Am. Chem. Soc. **1948**, *70*, 3853.

Received in India September 11, 2003