Synthesis and Biological Evaluation of Novel Benzimidazol/Benzoxazolylethoxypiperidone Oximes

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Some novel benzimidazol/benzoxazolylethoxypiperidone oximes were synthesized and their antibacterial activity against *Staphylococcus aureus* (NCIM-2492), *Bacillus subtilis* (NCIM-2439), *Escherichia coli* (NCIM-2345) and *Pseudomonas aeruginosa* (NCIM-2035) and antifungal activity against *Candida albicans* (NCIM-C27), *Candida*-6 (NCIM-C27), *Candida*-51 (NCIM-C27), *Aspergillus niger* (NCIM-590) and *Aspergillus flavus* (NCIM-539) have been evaluated. Compounds 26 and 27 exerted potent *in vitro* antibacterial activity against *Bacillus subtilis*, *Escherichia coli* and *Staphylococcus aureus* while compounds 26, 29 and 30 exhibited potent *in vitro* antifungal activity against *Candida albicans*, *Candida*-51, and *Aspergillus niger*.

Key words piperidin-4-one; cyanoethylation; benzazole; oxime; antibacterial activity; antifungal activity

Piperidines are an important group of heterocyclic compounds in the field of medicinal chemistry owing to the fact that these can frequently be recognized in the structure of numerous naturally occurring alkaloid and synthetic compounds with interesting biological and pharmacological properties. Piperidones were also reported to possess analgesic,[2,3] anti-inflammatory,[3] central nervous system (CNS),[4—8] local anaesthetic,[4,9] anticancer[10] and antimicrobial activity.[11] The earlier reports indicated that the significant biological activities of piperidones were associated with aromatic substituents at 2nd and/or 6th positions.[6,11] Oximes of the 2,6-disubstituted piperidones were also reported to exhibit antimicrobial,[12] analgesic,[13] local anaesthetic[13] and antifungal activity.[13]

The benzimidazole nucleus is widely accepted for its antiallergic and antiasthmatic activity[14,15] and its derivatives were found to possess diverse biological activities such as antiamoebic, microfilaricidal, antifungal and antiarylthemic.[16—22] It is well known that in the treatment of parasitic infection, substituted benzimidazoles, mebendazole and febendazole were found to be efficient.[23,24] Benzoxazole nucleus is also marked for its biological activity. 2-Substituted benzoxazoles have been shown to exert analgesic,[25] fungicidal, insecticidal, nematocidal,[26] potent protease inhibitory,[27] anticancer activities[28] and serve as topoisomerase I poisons.[29]

An essential part of the search for new leads in a drug designing programme is the synthesis of new molecules, which are novel yet resemble known biologically active molecules by virtue of the presence of some critical structural features. There are few small heterocyclic molecules, which act as highly functionalized scaffolds and are known pharmacophores of a number of biologically active and medicinally useful molecules.[30—32]

Aiming at extending our knowledge in structure–activity relationship, we considered that it was valuable to synthesis a system which unites biolabile piperidone oximes and benzimidazole and benzoxazole units respectively together to give a compact structure of benzimidazolylethoxypiperidone oximes and benzoxazolylethoxypiperidone oximes. The influence of some structural variations at different pharmacophoric groups in the synthesized compounds towards their biological activities was evaluated.

In the course of broad programme in developing biologically active molecules, we have recently reported the synthesis of 2,6-diarylpiperidin-4-one derivatives and evaluated their biological importance and also a reagent for effecting functional group interconversion.[33—42]

MATERIALS AND METHODS

The course of reaction and 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 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 analysis (C, H, and N) were carried out on a Carlo Erba Model 1106 and Perkin Elmer models 240 CHN analyzer. The results are within $\pm$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.

The general synthetic scheme of the novel compounds **25**—**30** is furnished in Fig. 1.

Chemistry Cyclic ketones normally undergo Baeyer-Villiger oxidation (oxygen insertion reaction) to yield lactones upon treatment with peracids.[43—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, expec-

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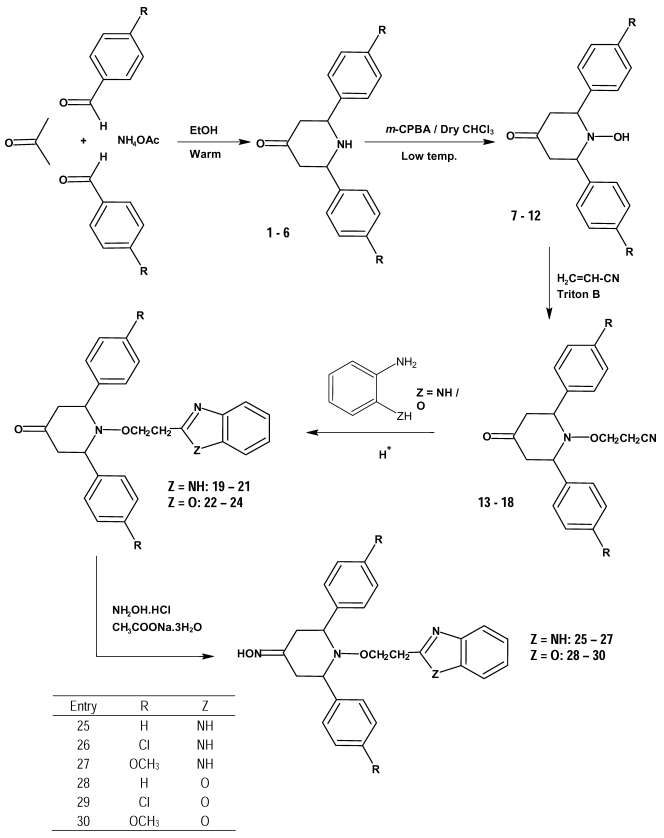

Entry	R	Z
25	H	NH
26	Cl	NH
27	OCH_3	NH
28	H	O
29	Cl	O
30	OCH_3	O

Fig. 1. Synthetic Scheme

tation 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[34,36—38] 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[47,48] 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.

2,6-Diarylpiperidin-4-ones (**1**—**6**) were prepared by the condensation of appropriate ketones, aldehydes and ammonium acetate in 1 : 2 : 1 ratio.[49]

1-Hydroxy-2,6-diphenylpiperidin-4-one (7) 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 for 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 sulphate and distilled off under reduced pressure. Purifications with silicagel column chromatography with 4 : 1 benzene–pet.ether (bp 40—60 °C) mixture yielded the product **7**. The compounds **8**—**12** were prepared similarly.

1-(2-Cyanoethoxy)-2,6-diphenylpiperidin-4-one (13) A mixture of 1-hydroxy-2,6-diphenylpiperidin-4-one **7** (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 **13**. The compounds **14**—**18** were prepared similarly.

1-[2-(Benzimidazol-2-yl)ethoxy]-2,6-diphenylpiperidin-4-one (19) To a mixture of 1-(2-cyanoethoxy)-2,6-diphenylpiperidin-4-one **13** (0.005 mol) and *o*-phenylenediamine (0.005 mol), dilute hydrochloric acid (10%) was added with constant shaking. The content of the flask was refluxed on an oil-bath for 12 h. After the addition of 50 ml of water to the reaction mass, it was filtered to remove impurities. To isolate product as a base, the acid solution was treated with aqueous ammonia (15 ml) and then poured into water. The precipitated compound **19** was recrystallized twice from ethanol. The compounds **20** and **21** were prepared similarly.

1-[2-(Benzoxazol-2-yl)ethoxy]-2,6-diphenylpiperidin-4-one (22) A mixture of 1-(2-cyanoethoxy)-2,6-diphenylpiperidin-4-one **16** (0.005 mol), *o*-aminophenol (0.005 mol) and dilute hydrochloric acid (10%) was taken in a 250 ml round bottom flask and was allowed to reflux on an oil-bath for 18 h. After cooling, the content in the flask was leached with 100 ml of diethyl ether and the separated ether extract was washed with five 25 ml portions of sodium hydroxide (4 N) solution. The ether layer was separated, dried over calcium chloride and freed of ether by distillation. The solid obtained was recrystallized twice from ethanol to yield the product **22**. The compounds **23** and **24** were prepared similarly.

1-[2-(Benzimidazol-2-yl)ethoxy]-2,6-diphenylpiperidin-4-one Oxime (25) 1-[2-(Benzimidazol-2-yl)ethoxy]-2,6-diphenylpiperidin-4-one **19** (0.05 mol), sodium acetate trihydrate (0.15 mol) and hydroxylamine hydrochloride (0.06 mol) were refluxed for 30 min in ethanol medium. After refluxing, the mixture was poured into ice water. The solid obtained was filtered and recrystallized from ethanol to afford 1-[2-(benzimidazol-2-yl)ethoxy]-2,6-diphenylpiperidin-4-one oxime **25**.

^{1}H-NMR ($CDCl_3$) δ: 3.91 (1H, H_{2a}, dd, ^3J=11.45 Hz; 2.91 Hz); 3.80—3.86 (3H, H_{6a}, $O\underline{C}H_2CH_2$, m); 3.47 (1H, H_{5e}, d, J=8.00 Hz); 2.52—2.73 (4H, H_{3a}, H_{3e}, $OCH_2\underline{C}H_2$, m); 2.29 (1H, H_{5a}, d, J=8.00 Hz); 7.28—7.49 (14H, aryl protons, m); 8.01 (1H, NOH, s). ^{13}C-NMR ($CDCl_3$) δ: 70.173 (C_2); 68.873 (C_6); 41.288 (C_3); 34.287 (C_5); 157.108 (C_4); 158.146 (C_b); 19.868 ($OCH_2\underline{C}H_2$); 69.310 ($O\underline{C}H_2CH_2$); 110.198, 115.008, 115.138, 120.976, 121.056, 127.742, 129.710, 129.828, 130.592, 130.698, 137.268, 140.985, 141.827 (aryl carbons). IR (KBr) (cm^{-1}): 3728 (N–OH), 3254 (N–H), 2940, 2930, 2854, 2762 (C–H), 1664 (C=N), 1592, 1569, 1490, 1422, 1400, 1370, 1345, 1328, 1308, 1291, 1240, 1156, 1124, 1070, 1030, 948, 901, 852, 816, 782, 750, 693, 660, 605, 516, 497, 466. Mass *m*/*z*: 426 (M^+), 252, 239, 222,

208, 194, 144, 131, 117, 103 (100%), 91, 77, 65, 51. Melting point: 159 °C. Yield (%): 64. *Anal.* Calcd for $C_{26}H_{26}N_4O_2$: C, 73.22; H, 6.15; N, 13.14. Found: C, 72.96; H, 6.16; N, 13.11.

The compounds **26**—**30** were synthesized similarly.

1-[2-(Benzimidazol-2-yl)ethoxy]-2,6-bis(*p*-chlorophenyl)piperidin-4-one Oxime (26) ^{1}H-NMR ($CDCl_3$) δ: 3.94 (1H, H_{2a}, dd, ^3J=11.46 Hz; 2.91 Hz,); 3.81—3.88 (3H, H_{6a}, $O\underline{C}H_2CH_2$, m); 3.46 (1H, H_{5e}, d, J=8.00 Hz); 2.51—2.74 (4H, H_{3a}, H_{3e}, $OCH_2\underline{C}H_2$, m); 2.28 (1H, H_{5a}, d, J=8.15 Hz); 7.18—7.50 (12H, aryl protons, m); 8.02 (1H, NOH, s). ^{13}C-NMR ($CDCl_3$) δ: 69.783 (C_2); 68.285 (C_6); 41.163 (C_3); 34.062 (C_5); 155.909 (C_4); 158.201 (C_b); 19.871 ($OCH_2\underline{C}H_2$); 69.321 ($O\underline{C}H_2CH_2$); 110.212, 115.010, 115.142, 120.999, 121.089, 129.375, 129.380, 129.862, 129.998, 134.741, 134.901, 137.269, 139.102, 139.970 (aryl carbons). IR (KBr) (cm^{-1}): 3725 (N–OH), 3222 (N–H), 2946, 2925, 2850, 2791 (C–H), 1666 (C=N), 1623, 1574, 1488, 1416, 1374, 1322, 1320, 1315, 1282, 1160, 1126, 1062, 1007, 947, 895, 841, 824, 765, 743, 688, 671, 517, 492, 471. Mass (*m*/*z*): 494 (M^+), 320, 307, 290, 276, 262, 182, 169, 155, 145, 137, 117, 111, 91, 75, 65, 53 (100%), 50. Melting point: 128 °C. Yield (%): 50. *Anal.* Calcd for $C_{26}H_{24}N_4O_2Cl_2$: C, 63.04; H, 4.88; N, 11.31; Found: C, 62.94; H, 4.9; N, 11.33.

1-[2-(Benzimidazol-2-yl)ethoxy]-2,6-bis(*p*-methoxyphenyl)piperidin-4-one Oxime (27) ^{1}H-NMR ($CDCl_3$) δ: 3.93 (1H, H_{2a}, dd, ^3J=11.45 Hz; 2.99 Hz); 3.79—3.87 (9H, H_{6a}, aryl OCH_3, $O\underline{C}H_2CH_2$, m); 3.44 (1H, H_{5e}, d, J=8.00 Hz); 2.49—2.73 (4H, H_{3a}, H_{3e}, $OCH_2\underline{C}H_2$, m); 2.26 (1H, H_{5a}, d, J=8.01 Hz); 6.87, 7.26—7.51 (4H, 8H, aryl protons); 8.00 (1H, NOH, s). ^{13}C-NMR ($CDCl_3$) δ: 69.828 (C_2); 68.427 (C_6); 41.485 (C_3); 34.386 (C_5); 156.712 (C_4); 158.341 (C_b); 19.844 ($OCH_2\underline{C}H_2$); 69.402 ($O\underline{C}H_2CH_2$); 110.201, 114.894, 114.972, 114.980, 120.990, 120.996, 132.991, 133.110, 135.127, 135.833, 137.348, 158.562, 158.956 (aryl carbons); 55.182 (aryl OCH_3). IR (KBr) (cm^{-1}): 3718 (N–OH), 3233 (N–H), 2940, 2928, 2831, 2786 (C–H), 1664 (C=N), 1635, 1570, 1462, 1438, 1380, 1361, 1314, 1250, 1193, 1136, 1028, 920, 851, 796, 789, 740, 650, 524, 507, 441. Mass (*m*/*z*): 486 (M^+), 312, 299, 282, 268, 254, 178, 163, 151, 144, 133, 117, 107, 91, 75, 65, 53 (100%), 50. Melting point: 145 °C. Yield (%): 56. *Anal.* Calcd for $C_{28}H_{30}N_4O_4$: C, 69.12; H, 6.22; N, 11.52. Found: C, 68.85; H, 6.19; N, 11.54.

1-[2-(Benzoxazol-2-yl)ethoxy]-2,6-diphenylpiperidin-4-one Oxime (28) ^{1}H-NMR ($CDCl_3$) δ: 3.91 (1H, H_{2a}, dd, ^3J=11.48 Hz; 2.99 Hz); 3.84—3.87 (3H, H_{6a}, $O\underline{C}H_2CH_2$, m); 3.46 (1H, H_{5e}, d, J=8.02 Hz); 2.50—2.74 (4H, H_{3a}, H_{3e}, $OCH_2\underline{C}H_2$, m); 2.28 (1H, H_{5a}, d, J=8.53 Hz); 7.28—7.48 (14H, aryl protons, m); 8.02 (1H, NOH, s). ^{13}C-NMR ($CDCl_3$) δ: 70.162 (C_2); 68.863 (C_6); 41.312 (C_3); 34.317 (C_5); 157.051 (C_4); 163.604 (C_b); 27.648 ($OCH_2\underline{C}H_2$); 67.572 ($O\underline{C}H_2CH_2$); 109.758, 114.194, 118.938, 119.101, 127.754, 129.712, 129.820, 130.603, 130.714, 133.112, 140.979, 141.820, 143.134 (aryl carbons). IR (KBr) (cm^{-1}): 3720 (N–OH), 2922, 2850, 2765 (C–H), 1658 (C=N), 1600, 1455, 1428, 1390, 1372, 1346, 1286, 1254, 1236, 1154, 1103, 1077, 1033, 941, 902, 853, 785, 746, 687, 654, 602, 516, 500, 470. Mass (*m*/*z*): 427 (M^+), 252, 239, 222, 208, 194, 145, 132, 118, 103 (100%), 91, 77, 65, 55, 51. Melting point: 161 °C. Yield (%): 57. *Anal.* Calcd for $C_{26}H_{25}N_3O_3$: C, 73.05; H, 5.9; N, 9.83. Found: C, 75.20; H, 5.88; N, 9.85.

1-[2-(Benzoxazol-2-yl)ethoxy]-2,6-bis(*p*-chlorophenyl)-piperidin-4-one Oxime (29) ^{1}H-NMR ($CDCl_3$) δ: 3.94 (1H, H_{2a}, dd, ^3J=11.45 Hz; 2.91 Hz); 3.84—3.89 (3H, H_{6a}, $O\underline{C}H_2CH_2$, m); 3.46 (1H, H_{5e}, d, J=8.06 Hz); 2.52—2.75 (4H, H_{3a}, H_{3e}, $OCH_2\underline{C}H_2$, m); 2.29 (1H, H_{5a}, d, J=8.26 Hz); 7.13—7.43 (12H, aryl protons, m); 8.03 (1H, NOH, s). ^{13}C-NMR ($CDCl_3$) δ: 69.770 (C_2); 68.272 (C_6); 41.186 (C_3); 34.085 (C_5); 155.862 (C_4); 163.613 (C_b); 27.644 ($OCH_2\underline{C}H_2$); 67.575 ($O\underline{C}H_2CH_2$); 109.768, 114.204, 118.976, 119.156, 129.361, 129.373, 129.883, 130.004, 133.120, 134.753, 134.922, 139.094, 139.953, 143.354 (aryl carbons). IR (KBr) (cm^{-1}): 3724 (N–OH), 2926, 2840, 2794, (C–H), 1664 (C=N), 1627, 1490, 1407, 1370, 1321, 1279, 1264, 1235, 1227, 1128, 1115, 1042, 1003, 952, 893, 820, 736, 690, 514, 488, 476. Mass (*m*/*z*): 495 (M^+), 320, 307, 290, 276, 262, 182, 169, 146, 137, 132, 118, 111, 91, 75, 65, 53 (100%), 50. Melting point: 112—113 °C. Yield (%): 38. *Anal.* Calcd for $C_{26}H_{23}N_3O_3Cl_2$: C, 62.91; H, 4.67; N, 8.47. Found: C, 62.63; H, 4.65; N, 8.46.

1-[2-(Benzoxazol-2-yl)ethoxy]-2,6-bis(*p*-methoxyphenyl)piperidin-4-one Oxime (30) ^{1}H-NMR ($CDCl_3$) δ: 3.93 (1H, H_{2a}, dd, ^3J=11.49 Hz; 2.92 Hz); 3.81—3.87 (9H, H_{6a}, aryl OCH_3, $O\underline{C}H_2CH_2$, m); 3.46 (1H, H_{5e}, d, J=8.02 Hz); 2.50—2.74 (4H, H_{3a}, H_{3e}, $OCH_2\underline{C}H_2$, m); 2.27 (1H, H_{5a}, d, J=8.31 Hz); 6.90, 7.27—7.50 (4H, 8H, aryl protons); 8.01 (1H, NOH, s). ^{13}C-NMR ($CDCl_3$) δ: 69.812 (C_2); 68.411 (C_6); 41.501 (C_3); 34.402 (C_5); 156.664 (C_4); 163.610 (C_b); 27.676 ($OCH_2\underline{C}H_2$); 67.612 ($O\underline{C}H_2CH_2$); 109.743, 114.102, 114.645, 114.879, 118.768, 118.936, 132.999, 133.126, 135.132, 135.847, 143.380, 158.569, 158.940 (aryl carbons); 55.187 (aryl OCH_3). IR (KBr) (cm^{-1}): 3717 (N–OH), 2925, 2851, 2784 (C–H), 1662 (C=N), 1639, 1464, 1376, 1365, 1528, 1234, 1191, 1134, 1042, 1023, 924, 857, 800, 742, 651, 600, 523, 512. Mass (*m*/*z*): 487 (M^+), 312, 299, 282, 268, 254, 178, 163, 147, 145, 132, 118, 107, 92, 75, 65, 53 (100%), 50. Melting point: 126 °C. Yield (%): 56. *Anal.* Calcd for $C_{28}H_{29}N_3O_5$: C, 68.98; H, 6.0; N, 8.62. Found: C, 69.12; H, 5.88; N, 8.6.

To comprehend structure–activity relationship well, numberings of the target compound is shown in Fig. 2.

PHARMACOLOGY

The bacterial strains *Staphylococcus aureus* (NCIM-2492), *Bacillus subtilis* (NCIM-2439), *Escherichia coli* (NCIM-2345), *Pseudomonas aeruginosa* (NCIM-2035), and antifungal strains *Candida albicans* (NCIM-C27), *Candida*-6 (NCIM-C27), *Candida*-51 (NCIM-C27), *Aspergillus niger*

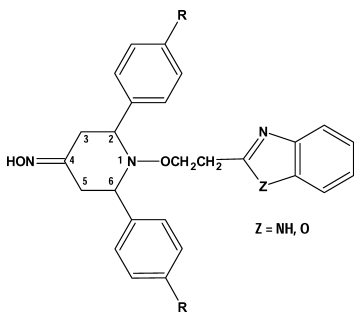

Fig. 2. Structure of Target Compound

(NCIM-590), *Aspergillus flavus* (NCIM-539) are procured from National Chemical Laboratory, Pune, India.

***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 two-fold serial dilution method.[50] The test compounds were dissolved in DMSO (dimethylsulphoxide) to obtain 1 mg/ml 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—7 d old Sabourauds agar (Hi-media, Mumbai) 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 10^2—10^5 cfu/ml. The final inoculum size was 10^5 cfu/ml for antibacterial assay and 1.1—1.5×10^2 cfu/ml for antifungal assay. Testing was performed at pH 7.4±0.2. 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 dilution were obtained. A set of assay tubes containing only inoculated 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, streptomycin and amphotericin B were used as standards.

RESULTS AND DISCUSSION

Structure–Activity Relationship Results. Antibacterial Activity All the synthesized novel benzimidazol/benzoxazolylethoxypiperidone oximes were evaluated *in vitro* for their activity to inhibit the growth of bacterial strains *viz. Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeruginosa*. Penicillin and streptomycin were used as standard drugs whose minimum inhibitory concentration (MIC) values are given in Table 1. To get clear comprehension over antibacterial activity of the synthesized compounds, these were compared with that of their proceeding compounds having keto functionality as reported by Ramalingan *et al*.[35,38]

Unlike the compounds having keto functional group, the present series of compounds **25**—**30**, with oxime substitution in place of keto group (compounds **25**—**30**) seems to play a vital role in the antibacterial activity against all the tested organisms. The compounds (with keto functionality) which failed to show activity, exhibited moderate activity against *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Bacillus subtilis* at a MIC ranging from 100—200 μg/ml due to oximation (compounds **25**, **28**). Compound **25** significantly inhibits *Staphylococcus aureus* and *Bacillus subtilis* bacterial strains at a MIC of 50 μg/ml. Likewise, compound **28** also exhibited a higher activity against *Pseudomonas aeruginosa* and recorded the same MIC.

Substitution of chloro functionalities at the *para* position of phenyl rings present at C_2 and C_6 of the heterocyclic moiety in **25** and **28** (compounds **26**, **29**) enhanced antibacterial activity remarkably.

Table 1. *In Vitro* Antibacterial Activity of Compounds **25**—**30**

Compound	Minimum inhibitory concentration (MIC) in μg/ml			
	Staphylococcus aureus	*Bacillus subtilis*	*Escherichia coli*	*Pseudomonas aeruginosa*
25	50	50	100	200
26	25	12.5	12.5	25
27	12.5	25	50	25
28	200	200	100	50
29	50	25	50	25
30	100	100	25	50
Penicillin	12.5	25	50	50
Streptomycin	50	12.5	12.5	25

In the case of benzimidazole derivative having *para* chloro substituent (compound **26**) showed 2—4 fold increase in activity against *Bacillus subtilis*, *Escherichia coli* and *Pseudomonas aeruginosa* while only 50% improvement was observed against *Staphylococcus aureus*. Moreover, in benzoxazole derivative (compound **29**) 2—3 fold enhancement was observed against *Staphylococcus aureus*, *Bacillus subtilis* whereas against *Escherichia coli* and *Pseudomonas aeruginosa* one fold increase in activity was noted. In general, the *para* substituted compounds **26** and **29** expressed higher activity against the tested organisms when compared to unsubstituted compounds **25** and **28**.

Replacement of chloro functionalities present at the *para* position of phenyl groups by methoxy groups in **26** and **29** (compounds **27**, **30**) suppressed the activity against all the tested organisms except *Staphylococcus aureus* and *Escherichia coli* against which activity was improved due to this replacement in compounds **26** and **29** respectively.

But, when compared to compound having keto functionality at C_4, the antibacterial activity of the oximated compound **27** was increased by 50% towards the tested bacterial strains and lies in the range of 12.5—50 μg/ml. Similarly compound **30** exerted the same trend in activity except against *Escherichia coli* and *Pseudomonas aeruginosa* for which the activity did not change appreciably.

Antifungal Activity The *in vitro* antifungal activity of the novel compounds **25**—**30** was studied against the fungal strains *viz. Candida albicans*, *Candida*-6, *Candida*-51, *Aspergillus niger* and *Aspergillus flavus*. Amphotericin B was used as standard drug whose minimum inhibitory concentration (MIC) values are furnished in Table 2.

To mark the superiority of the synthesized compounds **25**—**30** with oxime functionality towards antifungal activity, the results are compared with the results[35,38] of compounds having keto functional group instead of oxime at C_4 of the heterocyclic ring moiety.

The compound **25** yielded by the oximation of the corresponding compound possessing keto group (which failed to exert *in vitro* antifungal activity even at a maximum concentration of 200 μg/ml towards *Aspergillus niger* and *Aspergillus flavus*) exhibited well pronounced activity against *Candida*-51, *Aspergillus niger* and *Aspergillus flavus* in the range of 50—100 μg/ml whereas against *Candida*-6, the activity was not improved appreciably. Likewise the antifungal activity of compound **28** was also significantly enhanced against *Candida*-6, *Candida*-51 and *Aspergillus flavus* while

Table 2. *In Vitro* Antifungal Activity of Compounds **25**—**30**

Compound	Minimum inhibitory concentration (MIC) in μg/ml				
	Candida albicans	*Candida*-6	*Candida*-51	*Aspergillus niger*	*Aspergillus flavus*
25	200	100	50	100	50
26	12.5	25	12.5	50	25
27	25	25	25	50	25
28	100	100	50	50	100
29	50	50	25	12.5	50
30	50	25	12.5	50	25
Amphotericin B	25	25	25	50	50

against *Candida albicans* and *Aspergillus flavus*, oximation has no effect and the antifungal potency of the parent compounds having keto function was retained as such.

Due to the introduction of chloro functionalities at the *para* position of the aryl groups at C_2 and C_6 of **25** and **28** (compounds **26**, **29**) instead of hydrogens, the MIC for the tested organisms decreased by about 50% and lies in the range of 12.5—50 μg/ml whereas for unsubstituted compounds, MIC ranges from 50 to 200 μg/ml. In fact, 2—8 fold increase in antifungal efficacy pertaining to compound **26** was observed particularly against *Candida*-51, *Candida*-6 and *Candida albicans* compared to **25** whereas in the case of compound **29**, only one fold increase in activity was observed against all the tested strains with respect to compound **28**.

From the observation it is obvious that oximation has significant role in enhancing the antifungal activity of the compounds having keto functional group.

Furthermore, introduction of methoxy functionalities in place of hydrogen present at the *para* position of phenyl groups at C_2 and C_6 of compounds **25** and **28** (compounds **27**, **30**) have registered a marked improvement in antifungal activity against all the tested organisms except to compound **30** which exerted the same activity of the compound having unsubstitution at aryl groups against *Aspergillus niger*.

In fact, unlike chlorine substituted compound (compound **29**), the methoxy substituted compound (compound **30**) exerted one fold increase in activity against *Candida*-6 and *Aspergillus flavus* while against rest of the tested organisms, no change in activity was noted compared to the corresponding ketones.

CONCLUSION

A close examination of the *in vitro* antibacterial and antifungal activity profile of variety of substituted novel benzimidazol/benzoxazolylethoxypiperidone oximes against the bacterial strains *viz.*, *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli* and *Pseudomonas aeruginosa* and the fungal strains *viz.*, *Candida albicans*, *Candida*-6, *Candida*-51, *Aspergillus niger* and *Aspergillus flavus* respectively provide a better structure–activity correlate, which may be summarized as follows.

In the present series of compounds, oximation of keto group at C_4 of heterocyclic moiety seems to play a vital role in the antibacterial activity against *Escherichia coli* and antifungal activity against *Aspergillus flavus*. The above said activity for the respective organisms are significantly higher for oximes (compounds **25**—**30**) than the corresponding ketones. Oximation of benzimidazol/benzoxazolylethoxypiperidones changes requisite characteristics needed for exhibiting better structure–activity correlate. Since, the oxime functionality carries a labile proton, which may in turn a key for suitably tailoring the properties of the compounds in terms of solubility, penetration and binding.

The pharmacological screening studies put evidence that benzimidazolylethoxy piperidone oximes are proved to be superior in exerting a marked antibacterial and antifungal profile than the corresponding benzoxazolylethoxypiperidone oximes. Furthermore, both the set of compounds with chloro functions at the *para* position of the aryl moieties at C_2 and C_6 positions exhibited an elevated antibacterial and antifungal activity than the corresponding methoxy substituted and unsubstituted compounds. Indeed, these chloro substituted compounds showed a promising biological potency when compared to the standard drug.

Moreover, all the tested compounds expressed a remarkable activity against *Escherichia coli* and *Candida*-51.

Thus, in future, this class of novel benzimidazol/benzoxazolylethoxypiperidone oximes may be used as templates to generate better drugs to combat bacterial and fungal infections. Although much facinating biological activity of benzazole nucleus is already known, further explorations are sure to uncover even more interesting and useful activities. It is quite remarkable that benzazole nucleus is finding general acceptance as an essential pharmacophoric group. It is also anticipated that benzazole core will continue to find increasing place in future drugs.

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