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ORIGINAL ARTICLE

Synthesis and properties of novel alkoxy- and phenoxyalkyl ethers of secondary and tertiary ethynylpiperidin-4-ols possessing unusual analgesic, anti-bacterial, anti-spasmotic, and anti-allergic properties as well as low toxicity

Valentina K. Yu [a], Aissulu Zh. Kabdraissova [a], Kaldybay D. Praliyev [a], Svetlana N. Shin [b], K. Darrell Berlin [c,*]

[a] *Institute of Chemical Sciences, 106 Walikhanov Str., Almaty 050010, Kazakhstan*
[b] *Kazakh Research Institute of Veterinary, 2223 Raimbek Str., Almaty 050016, Kazakhstan*
[c] *Department of Chemistry, Oklahoma State University, Stillwater, OK 74078, United States*

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Abstract Methodology was developed to obtain a series of unusual alkoxy- and phenoxyalkyl ethers of secondary and tertiary ethynylpiperidin-4-ols representative examples of which were evaluated for analgesic, anti-bacterial, anti-spasmotic, and anti-allergic activity. Twenty-two new compounds were prepared and identified by elemental and spectra analyses. Etherification of 4-hydroxypiperidin-4-ols was accomplished via Williamson ether-type syntheses in dry DMF. Side reactions of the bromides used appeared to involve complex processes with DMF under a variety of conditions employed which led to modest yields of products. Since all target molecules were oils at room temperature, conversions to β-cyclodextrins were accomplished and served as vehicles for pharmacological screening. Several ethynyl-substituted agents displayed deep analgesic activity in the ''tail flick'' model although some alkoxy- and phenoxy ethers from secondary alcohols were less effective as analgesics (Table 1). Interestingly, LD50 values for the agents

* Corresponding author.
E-mail address: kdb@okstate.edu (K.D. Berlin).

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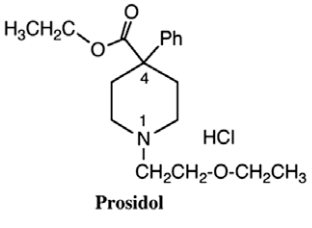
exceeded that of a number of clinical agents including Dimedrole, Klemastine, Lidocaine, No-spa, Tramal, Streptomycin, and Euphilline. Three representative examples of the agents (Table 2) exhibited moderate anti-bacterial action against *Escherichia coli*, *Salmonella chloerae suis*, *Salmonella typhimurium*, and *Staphylococcus aureus*, but did not exceed that of Streptomycin. The absence of the ethynyl ether group resulted in no anti-bacterial activity in several ethers. A few agents possessed anti-spasmotic ability, especially the ethers of 1-(2-ethoxyethyl)-4-ethynyl-4-hydroxypiperidines in various preparations (Table 3), and included the systems of acetylcholine-induced spasms, the histamine-induced spasms, and the calcium chloride-induced spasms. Two examples void of the ethynyl group were not effective as anti-spasmotic compounds. A small survey of five agents for anti-allergic properties (Table 4) revealed that two with ethynyl groups were similar in activity with Dimedrole but less than that of Klemastine in screens using acetylcholine and histamine systems. Overall, these families of piperidines possess a wide variety of important biological properties which require further exploration.

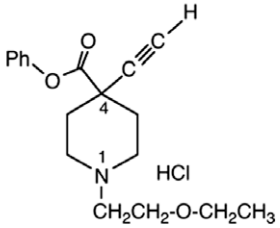
1. Introduction

The effect of ether linkages on useful biological activity in piperidine systems has not been fully recognized. Preliminary investigations revealed that such linkages in certain C-substituted and N-substituted piperidines conveyed medicinal properties which exceeded activities of a number of pharmacologically active pharmaceuticals (Praliyev and Yu, 2005). The major component required for high activity was the presence of the ether group. Two products from prior work exhibited a wide range of pharmacological actions and are currently in use (Praliyev et al., 1994, 1996). The two agents are the analgesic Prosidol (Praliyev et al., 1994) and the anesthetic/anti-arrhythmic Kazcaine (Praliyev et al., 1996).

In the current report, one objective was to alter the basic piperidine structure by the inclusion of additional ether linkages, particularly at C-4, while retaining the N-alkoxyalkyl group and an alkynyl group at C-4. Only a very few examples exist in the literature where selected 4-aryloxypiperidines are described with important biological activity (Puhakka et al., 1977; Lapa et al., 2005; Weis et al., 2003; Waldmeier et al., 1986; Patat et al., 1994; Mattson and Catt, 1995; Duggan et al., 1994).



Prosidol



Kazcaine

2. Experimental

Both ^{1}H and ^{13}C NMR spectra were recorded on a Varian-Mercury spectrometer operating at 300 MHz (1H) and 75 MHz (^{13}C), respectively, in $DCCl_3$ as solvent and HMDS as the internal standard. IR spectra were obtained as films on a Nicolet 5-700 FT-I unit. Elemental analyses were performed on a unit from CE-440 EAI Exeter Analytical, Inc. All chromatography employed weakly acidic alumina (Fluka, particle size was 0.05–0.15 mm). 1-Methyl-4-piperidin-4-one (**1**) (Prostavov and Gaivoronskaya, 1978; Chen and LeFevre, 1965) was purchased (Aldrich) and used directly. Members of **7** were prepared as described (Korablev et al., 1985).

2.1. General procedures for the preparation of alkoxyalkyl ethers of N-substituted piperidin-4-ols

To an ice-cooled solution of the required piperidin-4-ol (1.0 mol) in freshly distilled DMF (20 mmol) was added KOH (5.0 mol). The appropriate alkoxyalkyl bromide (1.0 mol) in DMF (15 mmol) was added dropwise at room temperature with stirring which was continued for 70–100 h. The product was extracted with hexane and then with benzene to remove the starting piperidin-4-ol. The organic solutions were dried ($MgSO_4$) and then were distilled under vacuum to yield the pure product. All starting materials were distilled.

2.2. General procedures for the preparation of phenoxyalkyl ethers of N-substituted piperidin-4-ols

To an ice-cooled solution of the required piperidin-4-ol (1.0 mol) in freshly distilled DMF (20 mmol) was added KOH (5.0 mol). The appropriate phenoxyalkyl bromide (1.0 mol) in DMF (15 mmol) was added dropwise at room temperature with stirring which was continued for 70–100 h. The remaining procedure was as above for the alkoxyalkyl ethers with the following exceptions. The final dried ($MgSO_4$) solution was evaporated, and the residual oil was chromatographed over alumina with hexane:dioxane (10:1) except where noted.

*2.2.1. 1-(2-Methoxyethyl)-4-piperidin-4-one (**2**)*

Oil, 17.70 g (45.3%); b.p. 98 °C/2 mm; R_f 0.82 (ether:hexane, 2:1); IR: 1720 (C═O), 1116 (COC) cm^{-1}; ^{13}C NMR ppm 41.1 (C-3/C-5), 53.7 (C-2/C-6), 56.8 (NCH_2), 58.9 (C-9), 70.4 (C-8), 208.9 (C-4). Anal. Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.28; H, 9.79; N, 8.93.

*2.2.2. 1-(2-Ethoxyethyl)-4-piperidin-4-one (**3**)*

Oil, 28.49 g (73.3%), b.p. 84–86 °C/2 mm; R_f 0.82 (ether:hexane, 2:1); IR (film) 1725 (C═O), 1120 (COC) cm^{-1}; ^{13}C NMR ppm 14.6 (C-10), 40.7 (C-3/C-5), 53.1 (C-2/C-6), 53.6

(NCH_2), 65.9 (C-9), 68.2 (C-8), 207.2 (C-4). Anal. Calcd for $C_9H_{17}NO_2$: C, 63.13; H, 10.01; N, 8.18. Found: C, 63.28; H, 10.31; N, 8.12.

*2.2.3. 1-Methylpiperidin-4-ol (**4**)*
Oil, 8.34 g (82.0%); R_f 0.18 (hexane:dioxane, 2:1); IR: 3240 cm^{-1} (OH); ^1H NMR δ 1.52–1.64 (m, 2H, H-3_{ax}, H-5_{ax}), 1.82–1.87 (m, 2H, H-3_{eq}, H-5_{eq}), 2.08 (bt, 2H, H-2_{ax}, H-6_{ax}, J = 10.2 Hz), 2.22 (s, 3H, NCH_3), 2.69–2.73 (m, 2H, H-2_{eq}, H-6_{eq}), 3.59 (m, 1H, H-4); ^{13}C NMR ppm 34.2 (C-3/C-5), 45.9 (NCH_3), 53.4 (C-2/C-6), 66.7 (C-4). Anal. Calcd for $C_6H_{13}NO$: C, 62.57; H, 11.38; N, 12.16. Found: C, 62.58; H, 11.38; N, 11.36 (Hennion and O'Shea, 1958).

*2.2.4. 1-(2-Methoxyethyl) piperidin-4-ol (**5**)*
Oil, 4.78 g (94.0%); R_f 0.24 (hexane:dioxane, 2:1); IR: 3605 cm^{-1} (OH), 1115 cm^{-1} (COC); ^1H NMR δ 1.46–1.58 (m, 2H, H-3_{ax}, H-5_{ax}), 1.76–1.81 (m, 2H, H-3_{eq}, H-5_{eq}), 2.08 (ddd, 2H, H-2_{ax}, H-6_{ax}, J = 12.6 Hz, 2.7 Hz), 2.47 (t, 2H, NCH_2), 2.69–2.76 (m, 2H, H-2_{eq}, H-6_{eq}), 3.25 (s, 3H, H-9), 3.42 (t, 2H, H-8), 3.56 (m, 1H, H-4); ^{13}C NMR ppm 34.2 (C-3/C-5), 51.6 (C-2/C-6), 57.6 (NCH_2), 58.8 (C-9), 67.5 (C-4), 70.3 (C-8). Anal. Calcd for $C_8H_{17}NO_2$: C, 60.35; H, 10.76; N, 8.80. Found: C, 60.42; H, 10.79; N, 8.93.

*2.2.5. 1-(2-Ethoxyethyl)piperidin-4-ol (**6**)*
Oil, 17.76 g (95.2%); R_f 0.32 (hexane:dioxane, 2:1); IR: 3617 cm^{-1} (OH), 1125 cm^{-1} (COC); ^1H NMR δ 1.18 (t, 3H, H-10), 1.54–1.66 (m, 2H, H-3_{ax}, H-5_{ax}), 1.85–1.91 (m, 2H, H-3_{eq}, H-5_{eq}), 2.21 (ddd, 2H, H-2_{ax}, H-6_{ax}, J = 11.7 Hz, 1.8 Hz), 2.58 (t, 2H, NCH_2), 2.80–2.86 (m, 2H, H-2_{eq}, H-6_{eq}), 3.48 (q, 2H, H-9), 3.55 (t, 2H, H-8), 3.65 (m, 1H, H-4); ^{13}C NMR ppm 15.1 (C-10), 34.0 (C-3/C-5), 51.6 (C-2/C-6), 57.6 (NCH_2), 66.4 (C-9), 67.2 (C-4), 68.4 (C-8). Anal. Calcd for $C_9H_{19}NO_2$: C, 62.39; H, 11.05; N, 8.08. Found: C, 62.51; H, 11.27; N, 7.90.

*2.2.6. 1-(2-Ethoxyethyl)-4-ethynyl-piperidin-4-ol (**8**)*
20.17 g (88.3%); m.p. 81–82 °C; R_f 0,21 (hexane:dioxane, 2:1); IR: 3580 (OH), 3300 (≡CH), 2107 (C≡C), 1110 cm^{-1} (COC); ^1H NMR δ 1.18 (t, 3H, H-10), 1.80-1.97 (m, 4H, H-3_{ax}, H-5_{ax}, H-3_{eq}, H-5_{eq}), 2.46 (ddd, 2H, H-2_{ax}, H-6_{ax}, J = 11.4 Hz, 3.0 Hz), 2.50 (s, 1H, ≡CH), 2.60 (t, 2H, NCH_2), 2.73 (m, 2H, H-2_{eq}, H-6_{eq}), 3.48 (q, 2H, H-9), 3.56 (t, 2H, H-8), 3.71 (bs, H, 4-OH); ^{13}C NMR ppm 14.8 (C-10), 38.5 (C-3/C-5), 50.1 (C-2/C-6), 57.0 (NCH_2), 65.6 (C-4), 66.0 (C-9), 67.9 (C-8), 72.4 (≡CH), 87.0 (≡C). Anal. Calcd for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71; N, 7.10. Found: C, 67.01; H, 9.58; N, 7.33.

*2.2.7. 4-(2-Methoxyethoxy)-1-methylpiperidine (**9**)*
Oil, 0.34 g (22.3%); R_f 0.17 (hexane:dioxane, 2:1); IR: 1112 cm^{-1} (COC); ^1H NMR δ 1.57–1.69 (m, 2H, H-3_{ax}, H-5_{ax}), 1.87–1.93 (m, 2H, H-3_{eq}, H-5_{eq}), 2.07 (ddd, 2H, H-2_{ax}, H-6_{ax}, J = 12.0 Hz, 2.7 Hz), 2.24 (s, 3H, NCH_3), 2.68–2.72 (m, 2H, H-2_{eq}, H-6_{eq}), 3.31 (m, 1H, H-4), 3.37 (s, 3H, $OCH_2CH_2OCH_3$), 3.52 (t, 2H, $OCH_2CH_2OCH_3$), 3.59 (t, 2H, $OCH_2CH_2OCH_3$); ^{13}C NMR ppm 31.3 (C-3/C-5) 46.1 (NCH_3), 53.5 (C-2/C-6), 59.0 ($OCH_2CH_2OCH_3$), 67.1 ($OCH_2CH_2OCH_3$), 72.2 ($OCH_2CH_2OCH_3$), 75.2 (C-4). Anal. Calcd for $C_9H_{19}NO_2$: C, 62.39; H, 11.05; N, 8.08. Found: C, 62.44; H, 10.96; N, 8.22.

*2.2.8. 4-(2-Methoxyethoxy)-1-(2-methoxyethyl)piperidine (**10**)*
Oil, 0.23 g (16.9%); R_f 0.53 (hexane:dioxane, 2:1); IR: 1108 cm^{-1} (COC); ^1H NMR δ 1.58–1.70 (m, 2H, H-3_{ax}, H-5_{ax}), 1.86–1.93 (m, 2H, H-3_{eq}, H-5_{eq}), 2.14 (ddd, 2H, H-2_{ax}, H-6_{ax}, J = 12.2 Hz, 2.4 Hz), 2.54 (t, 2H, NCH_2), 2.76–2.83 (m, 2H, H-2_{eq}, H-6_{eq}), 3.30 (m, 1H, H-4), 3.33 (s, 3H, H-9), 3.37 (s, 3H, $OCH_2CH_2OCH_3$), 3.48 (t, 2H, H-8), 3.52 (t, 2H, $OCH_2CH_2OCH_3$), 3.59 (t, 2H, $OCH_2CH_2OCH_3$); ^{13}C NMR ppm 31.1 (C-3/C-5), 51.7 (C-2/C-6), 57.8 (NCH_2), 58.8 (C-9), 59.0 ($OCH_2CH_2OCH_3$), 67.0 ($OCH_2CH_2OCH_3$), 70.4 (C-8), 72.2 ($OCH_2CH_2OCH_3$), 75.6 (C-4). Anal. Calcd for $C_{11}H_{23}NO_3$: C, 60.80; H, 10.67; N, 6.45. Found: C, 60.80; H, 10.66; N, 6.19.

*2.2.9. 1-(2-Ethoxyethyl)-4-(2-methoxyethoxy)piperidine (**11**)*
Oil, 0.20 (13.3%); R_f 0.57 (hexane:dioxane, 2:1); IR: 1108 cm^{-1} (COC); ^1H NMR δ 1.18 (t, 3H, H-10); 1.57–1.68 (m, 2H, H-3_{ax}, H-5_{ax}), 1.87–1.92 (m, 2H, H-3_{eq}, H-5_{eq}), 2.15 (ddd, 2H, H-2_{ax}, H-6_{ax}, J = 12.2 Hz, 2.4 Hz), 2.55 (t, 2H, NCH_2), 2.78–2.84 (m, 2H, H-2_{eq}, H-6_{eq}), 3.32 (m, 1H, H-4), 3.37 (s, 3H, $OCH_2CH_2OCH_3$), 3.48 (q, 2H, H-9), 3.51 (t, 2H, H-8), 3.53 (t, 2H, $OCH_2CH_2OCH_3$), 3.59 (t, 2H, $OCH_2CH_2OCH_3$); ^{13}C NMR ppm 15.1 (C-10), 31.1 (C-3/C-5), 51.7 (C-2/C-6), 57.7 (NCH_2), 59.0 ($OCH_2CH_2OCH_3$), 66.4 (C-9), 67.0 ($OCH_2CH_2OCH_3$), 68.3 (C-8), 72.2 ($OCH_2CH_2OCH_3$), 75.5 (C-4). Anal. Calcd for $C_{12}H_{25}NO_3$: C, 62.30; H, 10.89; N, 6.05. Found: C, 62.33; H, 10.86; N, 6.30.

*2.2.10. 4-(2-Ethoxyethoxy)-1-methylpiperidine (**12**)*
Oil, 0.28 g (16.9%); R_f 0.27 (hexane:dioxane, 2:1); IR: 1104 cm^{-1} (COC); ^1H NMR δ 1.19 (t, 3H, $OCH_2CH_2OCH_2CH_3$); 1.57–1.68 (m, 2H, H-3_{ax}, H-5_{ax}), 1.86–1.92 (m, 2H, H-3_{eq}, H-5_{eq}), 2.07 (ddd, 2H, H-2_{ax}, H-6_{ax}, J = 12.0 Hz, 2.1 Hz), 2.24 (s, 3H, NCH_3), 2.67–2.72 (m, 2H, H-2_{eq}, H-6_{eq}), 3.31 (m, 1H, H-4), 3.52 (q, 2H, $OCH_2CH_2OCH_2CH_3$), 3.56 (t, $OCH_2CH_2OCH_2CH_3$), 3.59 (t, 2H, $OCH_2CH_2OCH_2CH_3$); ^{13}C NMR ppm 15.1 ($OCH_2CH_2OCH_2CH_3$), 31.3 (C-3/C-5), 46.2 (NCH_3), 53.5 (C-2/C-6), 66.6 ($OCH_2CH_2OCH_2CH_3$), 67.2 ($OCH_2CH_2OCH_2CH_3$), 70.1 ($OCH_2CH_2OCH_2CH_3$), 75.2 (C-4). Anal. Calcd for $C_{10}H_{21}NO_2$: C, 64.13; H, 11.30; N, 7.48. Found: C, 64.20; N, 11.24; N, 7.59.

*2.2.11. 4-(2-Ethoxyethoxy)-1-(2-methoxyethyl)piperidine (**13**)*
Oil, 0.22 g (15.2%); R_f 0.65 (hexane:dioxane, 2:1); IR: 1120 cm^{-1} (COC); ^1H NMR δ 1.19 (t, 3H, $OCH_2CH_2OCH_2CH_3$), 1.57–1.69 (m, 2H, H-3_{ax}, H-5_{ax}), 1.86–1.93 (m, 2H, H-3_{eq}, H-5_{eq}), 2.14 (ddd, 2H, H-2_{ax}, H-6_{ax}, J = 12.0 Hz, 2.7 Hz), 2.54 (t, 2H, NCH_2), 2.77–2.81 (m, 2H, 2_{eq}, H-6_{eq}), 3.31 (m, 1H, H-4), 3.33 (s, 3H, H-9), 3.48 (t, 2H, H-8), 3.52 (q, 2H, $OCH_2CH_2OCH_2CH_3$), 3.56 (t, 2H, $OCH_2CH_2OCH_2CH_3$), 3.58 (t, 2H, $OCH_2CH_2OCH_2CH_3$); ^{13}C NMR ppm 15.2 $OCH_2CH_2OCH_2CH_3$, 31.1(C-3/C-5), 51.7 (C-2/C-6), 57.8 (NCH_2), 58.8 (C-9), 66.6 ($OCH_2CH_2OCH_2CH_3$), 67.2 ($OCH_2CH_2OCH_2CH_3$), 70.1 ($OCH_2CH_2OCH_2CH_3$), 70.5 (C-8), 75.5 (C-4). Anal. Calcd for $C_{12}H_{25}NO_3$: C, 62.30; H, 10.89; N, 6.05. Found: C, 62.30; H, 10.87; N, 6.04.

*2.2.12. 4-(2-Ethoxyethoxy)-1-(2-ethoxyethyl)piperidine (**14**)*
Oil, 0.78 g (18.4%); R_f 0.68 (hexane:dioxane, 2:1); IR: 1112 cm^{-1} (COC); ^1H NMR δ 1.18 (t, 3H, H-10), 1.19 (t, 3H,

$OCH_2CH_2OCH_2CH_3$), 1.56–1.68 (m, 2H, H-3_{ax}, H-5_{ax}), 1.86-1.93 (m, 2H, H-3_{eq}, H-5_{eq}), 2.15 (ddd, 2H, H-2_{ax}, H-6_{ax}, J = 12.2 Hz, 2.4 Hz), 2.55 (t, 2H, NCH_2), 2.77-2.83 (m, 2H, H-2_{eq}, H-6_{eq}), 3.32 (m, 1H, H-4), 3.48 (q, 2H, H-9), 3.51 (t, 2H, H-8), 3.52 (q, 2H, $OCH_2CH_2OCH_2CH_3$), 3.56 (t, 2H, $OCH_2CH_2OCH_2CH_3$), 3.58 (t, 2H, $OCH_2CH_2OCH_2CH_3$); ^{13}C NMR ppm 15.2 (C-10 and $OCH_2CH_2OCH_2CH_3$), 31.2 (C-3/C-5), 51.8 (C-2/C-6), 57.8 (NCH_2), 66.4 (C-9), 66.6 ($OCH_2CH_2OCH_2CH_3$), 67.1 ($OCH_2CH_2OCH_2CH_3$), 68.4 (C-8), 70,1 ($OCH_2CH_2OCH_2CH_3$), 75.5 (C-4). Anal. Calcd for $C_{13}H_{27}NO_3$: C, 63.64; H, 11.09; N, 5.71. Found: C, 63.51; H, 11.03; N, 5.60.

*2.2.13. 4-(3-Phenoxypropoxy)-1-methylpiperidine (**15**)*
Oil, 0.76 g (35.1%); R_f 0.18 (hexane:dioxane, 5:1); IR: 3064 (Ar-H), 1104 (COC), 752, 696 cm^{-1}; ^{1}H NMR δ 1.54–1.65 (m, 2H, H-3_{ax}, H-5_{ax}), 1.82–1.88 (m, 2H, H-3_{eq}, H-5_{eq}), 2.00 (m, 2H, $OCH_2CH_2CH_2OPh$), 2.08 (bt, H-2_{ax}, H-6_{ax}, J = 9.9 Hz), 2.21 (s, 3H, NCH_3), 2.63 (bs, 2H, H-2_{eq}, H-6_{eq}), 3.27 (m, 1H, H-4), 3.59 (t, 2H, $OCH_2CH_2CH_2OPh$), 4.03 (t, 2H, $OCH_2CH_2CH_2OPh$), 6.86–7.28 (m, 5H, Ar-H); ^{13}C NMR ppm 29.9 ($OCH_2CH_2CH_2OPh$), 31.1 (C-3/C-5), 46.1 (NCH_3), 53.1 (C-2/C-6), 64.1 ($OCH_2CH_2CH_2OPh$), 64.6 ($OCH_2CH_2CH_2OPh$), 74.3 (C-4), 114.4 (Ar-C), 120.5 (Ar-C), 129.4 (Ar-C), 158.9 (ArC-O). Anal. Calcd for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30; N, 5.62. Found: C, 72.20; H, 9.10; N, 5.59.

*2.2.14. 4-(3-Phenoxypropoxy)-1-(2-methoxyethyl)piperidine (**16**)*
Oil, 0.51 g (27.7%); R_f (hexane:dioxane, 5:1); IR: 3040 (Ar-H), 1116 (COC), 756, 696 cm^{-1}; ^{1}H NMR δ 1.55–1.66 (m, 2H, H-3_{ax}, H-5_{ax}), 1.82–1.90 (m, 2H, H-3_{eq}, H-5_{eq}), 2.00 (m, 2H, $OCH_2CH_2CH_2OPh$), 2.14 (ddd, 2H, H-2_{ax}, H-6_{ax}, J = 11.4 Hz, 2.4 Hz), 2.50 (t, 2H, NCH_2), 2.71–2.75 (m, 2H, H-2_{eq}, H-6_{eq}), 3.28 (m, 1H, H-4), 3.31 (s, 3H, H-9), 3.45 (t, 2H, H-8), 3.59 (t, 2H, $OCH_2CH_2CH_2OPh$), 4.03 (t, 2H, $OCH_2CH_2CH_2OPh$), 6.86–7.27 (m, 5H, Ar-H); ^{13}C NMR ppm 30.0 ($OCH_2CH_2CH_2OPh$), 31.1 (C-3/C-5), 51.5 (C-2/C-6), 57.8 (NCH_2), 58.8 (C-9), 64.0 ($OCH_2CH_2CH_2OPh$), 64.7 ($OCH_2CH_2CH_2OPh$), 70.4 (C-8), 74.9 (C-4), 114.4 (Ar-C), 120.5 (Ar-C), 129.4 (Ar-C), 159.0 (Ar*C*-O). Anal. Calcd for $C_{17}H_{27}NO_3$: C, 69.59; H, 9.28; N, 4.77. Found: C, 69.36; H, 9.51; N, 5.03.

*2.2.15. 4-(2-Phenoxyethoxy)-1-(2-ethoxyethyl)piperidine (**17**)*
Oil, 0.45 g (16.7%); R_f 0.30 (hexane:dioxane, 5:1); IR: 2944 (Ar-H), 1116 (COC), 760, 696 cm^{-1}; ^{1}H NMR δ 1.18 (t, 3H, H-10), 1.58–1.70 (m, 2H, H-3_{ax}, H-5_{ax}), 1.87–1.92 (m, 2H, H-3_{eq}, H-5_{eq}), 2.17 (ddd, H-2_{ax}, H-6_{ax}, J = 12.0 Hz, 2.7 Hz), 2.54 (t, 2H, NCH_2), 2.77–2.80 (m, 2H, H-2_{eq}, H-6_{eq}), 3.39 (m, 1H, H-4), 3.46 (q, 2H, H-9), 3.52 (t, 2H, H-8), 3.77 (t, 2H, OCH_2CH_2OPh), 4.08 (t, 2H, OCH_2CH_2OPh), 6.88–7.27 (m, 5H, Ar-H); ^{13}C NMR ppm 15.1 (C-10), 31.2 (C-3/C-5), 51.6 (C-2/-C-6), 57.8 (NCH_2), 66.2 (C-9), 66.4 (OCH_2CH_2OPh), 67.5 (OCH_2CH_2OPh), 68.4 (C-8), 75.5 (C-4), 114.6 (Ar-C), 120.7 (Ar-C), 129.3 (Ar-C), 158.8 (ArC-O). Anal. Calcd for $C_{17}H_{27}NO_3$: C, 69.59; H, 9.27; N, 4.78. Found: C, 69.62; H, 9.58; N, 4.83.

*2.2.16. 4-(3-Phenoxypropoxy)-1-(2-ethoxyethyl)piperidine (**18**)*
Oil, 0.37 g (12.8%); R_f 0.32 (hexane:dioxane, 5:1); IR: 3040 (Ar-H), 1108 (COC), 752, 696 cm^{-1}; ^{1}H NMR δ 1.18 (t, 3H, H-10), 1.53–1.65 (m, 2H, H-3_{ax}, H-5_{ax}), 1.83–1.90 (m, 2H, H-3_{eq}, H-5_{eq}), 2.01 (m, $OCH_2CH_2CH_2OPh$), 2.16 (ddd, 2H, H-2_{ax}, H-6_{ax}, J = 11.9 Hz, 2.4 Hz), 2.53 (t, 2H, NCH_2), 2.72–2.78 (m, 2H, H-2_{eq}, H-6_{eq}), 3.28 (m, 1H, H-4), 3.47 (q, 2H, H-9), 3.52 (t, 2H, H-8), 3.60 (t, 2H, $OCH_2CH_2CH_2OPh$), 4.05 (t, 2H, $OCH_2CH_2CH_2OPh$), 6.86–7.29 (m, 5H, Ar-H); ^{13}C NMR ppm 15.1 (C-10), 30.0 ($OCH_2CH_2CH_2OPh$), 31.2 (C-3/C-5), 51.7 (C-2/C-6), 57.8 (NCH_2), 64.1 ($OCH_2CH_2CH_2OPh$), 64.7 ($OCH_2CH_2CH_2OPh$), 66.4 (C-9), 68.3 (C-8), 75.5 (C-4), 114.5 (Ar-C), 120.5 (Ar-C), 129.4 (Ar-C), 159.0 (ArC-O). Anal. Calcd for $C_{18}H_{29}NO_3$: C, 70.32; H, 9.51; N, 4.56. Found: C, 70.26; H, 9.50; N, 4.74.

*2.2.17. 4-(2-Methoxyethoxy)-4-ethynyl-1-methylpiperidine (**19**)*
Oil, 2.06 g (36.3%); R_f 0.52 (hexane:dioxane, 2:1); IR: 3246 (≡CH), 2103 (C≡C), 1089 (COC) cm^{-1}; ^{1}H NMR δ 1.82–1.99 (m, 4H, H-3_{ax}, H-5_{ax}, H-3_{eq}, H-5_{eq}), 2.27 (s, 3H, NCH_3), 2.35 (ddd, 2H, H-2_{ax}, H-6_{ax}, J = 11.7 Hz, 3.0 Hz), 2.50 (s, 1H, ≡CH), 2.59 (bs, 2H, H-2_{eq}, H-6_{eq}), 3.38 (s, 3H, $OCH_2CH_2OCH_3$), 3.55 (t, 2H, $OCH_2CH_2OCH_3$), 3.71 (t, 2H, $OCH_2CH_2OCH_3$); ^{13}C NMR ppm 36.5 (C-3/C-5), 45.9 (NCH_3), 52.0 (C-2/C-6), 59.0 ($OCH_2CH_2OCH_3$), 62.7 ($OCH_2CH_2OCH_3$), 71.4 (C-4), 72.0 ($OCH_2CH_2OCH_3$), 74.5 (≡CH), 84.4 (C≡). Anal. Calcd for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71; N, 7.10. Found: C, 67.01; H, 9.70; N, 6.86.

*2.2.18. 4-(2-Ethoxyethoxy)-4-ethynyl-1-methylpiperidine (**20**)*
Oil, 2.55 g (42.0%); R_f 0.85 (hexane:dioxane, 2:1); IR: 3246 (≡CH), 2103 (C≡C), 1093 (COC) cm^{-1}; ^{1}H NMR δ 1.19 (t, 3H, $OCH_2CH_2OCH_2CH_3$), 1.81–1.99 (m, 4H, H-3_{ax}, H-5_{ax}, H-3_{eq}, H-5_{eq}), 2.26 (s, 3H, NCH_3), 2.35 (ddd, 2H, H-2_{ax}, H-6_{ax}, J = 11.4 Hz, 2.7 Hz), 2.50 (s, 1H, ≡CH), 2.59 (bs, 2H, H-2_{eq}, H-6_{eq}), 3.54 (q, 2H, $OCH_2CH_2OCH_2CH_3$), 3.59 (t, 2H, $OCH_2CH_2OCH_2CH_3$), 3.71 (t, 2H, $OCH_2CH_2OCH_2CH_3$); ^{13}C NMR ppm 15.2 ($OCH_2CH_2OCH_2CH_3$), 36.5 (C-3/C-5), 45.9 (NCH_3), 51.9 (C-2/C-6), 62.8 ($OCH_2CH_2OCH_2CH_3$), 66.5 ($OCH_2CH_2OCH_2CH_3$), 69.8 ($OCH_2CH_2OCH_2CH_3$), 71.3 (C-4), 74.5 (≡CH), 84.3 (C≡). Anal. Calcd for $C_{12}H_{21}NO_2$: C, 68.21; H, 10.02; N, 6.63. Found: C, 68.08; H, 10.02; N, 6.87.

*2.2.19. 4-(2-Methoxyethoxy)-4-ethynyl-1-(2-ethoxyethyl) piperidine (**21**)*
Oil, 7.58 g (38.3%); R_f 0.61 (hexane:dioxane, 2:1); IR: 3246 (≡CH), 2104 (C≡C), 1089 (COC) cm^{-1}; ^{1}H NMR δ 1.14 (t, 3H, H-10), 1.77–1.95 (m, 4H, H-3_{ax}, H-5_{ax}, H-3_{eq}, H-5_{eq}), 2.40 (ddd, 2H, H-2_{ax}, H-6_{ax}, J = 12.0 Hz, 3.2 Hz), 2.45 (s, 1H, ≡CH), 2.54 (t, 2H, NCH_2), 2.64 (bs, 2H, H-2_{eq}, H-6_{eq}), 3.33 (s, 3H, $OCH_2CH_2OCH_3$), 3.44 (q, 2H, H-9), 3.49 (t, 2H, H-8), 3.51 (t, 2H, $OCH_2CH_2OCH_3$), 3.67 (t, 2H, $OCH_2CH_2OCH_3$); ^{13}C NMR ppm 15.2 (C-10), 36.3 (C-3/C-5), 50.4 (C-2/C-6), 57.7 (NCH_2), 59.1 ($OCH_2CH_2OCH_3$), 62.7 ($OCH_2CH_2OCH_3$), 66.5 (C-9), 68.4 (C-8), 71.8 (C-4), 72.1 ($OCH_2CH_2OCH_3$), 74.6 (≡CH), 84.4 (C≡). Anal. Calcd for $C_{14}H_{25}NO_3$: C, 65.85; H, 9.87; N, 5.49. Found: C, 65.85; H, 9.82; N, 5.64.

*2.2.20. 4-(2-Ethoxyethoxy)-4-ethynyl-1-(2-ethoxyethyl) piperidine (**22**)*
Oil, 5.45 g (26.6%); R_f 0.91 (hexane:dioxane, 2:1); IR: 3246 (≡CH), 2104 (C≡C), 1094 (COC) cm^{-1}; ^{1}H NMR δ 1.13 (t, 3H, H-10), 1.14 (t, 3H, OCH_2CH_2 OCH_2CH_3), 1.77–1.94 (m, 4H, H-3_{ax}, H-5_{ax}, H-3_{eq}, H-5_{eq}), 2.40 (ddd, 2H, H-2_{ax}, H-6_{ax},

J = 11.1 Hz, 2.7 Hz), 2.44 (s, 1H, ≡CH), 2.53 (t, 2H, NCH_2), 2.64 (bs, 2H, H-2_{eq}, H-6_{eq}), 3.43 (q, 2H, H-9), 3.48 (q, 2H, $OCH_2CH_2OCH_2CH_3$), 3.49 (t, 2H, H-8), 3.54 (t, 2H, OCH_2-$CH_2OCH_2CH_3$), 3.66 (t, 2H, $OCH_2CH_2OCH_2CH_3$); ^{13}C NMR ppm 15.2 (C-10), 15.3 ($OCH_2CH_2OCH_2CH_3$), 36.3 (C-3/C-5), 50.3 (C-2/C-6), 57.7 (NCH_2), 62.8 (OCH_2-$CH_2OCH_2CH_3$), 66.5 (C-9), 66.7 ($OCH_2CH_2OCH_2CH_3$), 68.4 (C-8), 69.9 ($OCH_2CH_2OCH_2CH_3$), 71.7 (C-4), 74.5 (≡CH), 84.4 (C≡). Anal. Calcd for $C_{15}H_{27}NO_3$: C, 66.88; H, 10.10; N, 5.20. Found: C, 66.61; H, 9.94; N, 5.16.

*2.2.21. 4-(2-Phenoxyethoxy)-4-ethynyl-1-methylpiperidine (**23**)*
Oil, 1.79 g (13.7%); R_f 0,26 (hexane:dioxane, 5:1); IR: 3288 (≡CH) 3063 (Ar-H), 2104 (C≡C), 1098 (COC), 755, 692 cm^{-1}; ^{1}H NMR δ 1.85–2.00 (m, 4H, H-3_{ax}, H-5_{ax}, H-3_{eq}, H-5_{eq}), 2.25 (s, 3H, NCH_3), 2.35 (bt, 2H, H-2_{ax}, H-6_{ax}, J = 8.4 Hz), 2.51 (s, 1H, ≡CH), 2.56 (bs, 2H, H-2_{eq}, H-6_{eq}), 3.89 (t, 2H, OCH_2CH_2OPh), 4.11 (t, 2H, OCH_2CH_2OPh), 6.88–7.28 (m, 5H, Ar-H); ^{13}C NMR 36.4 (C-3/C-5), 45.9 (NCH_3), 51.8 (C-2/C-6), 61.9 (t, OCH_2CH_2OPh), 67.1 (OCH_2-CH_2OPh), 71.3 (C-4), 74.6 (≡CH), 84.5 (C≡), 114.6 (Ar-C), 120.7 (Ar-C), 129.3 (Ar-C), 158.7 (ArC-O). Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C,74.15; H, 8.15; N, 5.67.

*2.2.22. 4-(3-Phenoxypropoxy)-4-ethynyl-1-methylpiperidine (**24**)*
Oil, 0.92 g (18.8%); R_f 0,27 (hexane:dioxane, 5:1); IR: 3292 (≡CH), 3063 (Ar-H), 2104 (C≡C), 1086 (COC), 754, 692 cm^{-1}; ^{1}H NMR δ 1.82–1.97 (m, 4H, H-3_{ax}, H-5_{ax}, H-3_{eq}, H-5_{eq}), 2.03 (m, 2H, $OCH_2CH_2CH_2OPh$), 2.21 (s, 3H, NCH_3), 2.33 (bt, 2H, H-2_{ax}, H-6_{ax} J = 9.6 Hz), 2.42 (s, 1H, ≡CH), 2.51 (bs, 2H, 2-H_{eq}, 6-H_{eq}), 3.72 (t, 2H, $OCH_2CH_2CH_2OPh$), 4.04 (t, 2H, $OCH_2CH_2CH_2OPh$), 6.85–7.28 (m, 5H, Ar-H); ^{13}C NMR ppm 29.8 ($OCH_2CH_2CH_2OPh$), 36.4 (C-3/C-5), 45.9 (NCH_3), 51.8 (C-2/C-6), 59.5 ($OCH_2CH_2CH_2OPh$), 64.6 ($OCH_2CH_2CH_2OPh$), 70.9 (C-4), 74.2 (≡CH), 84.5 (C≡), 114.4 (Ar-C), 120.4 (Ar-C), 129.3 (Ar-C), 158.9 (ArC-O). Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.71; H, 8.48; N, 5.01.

*2.2.23. 4-(2-Phenoxyethoxy)-4-ethynyl-1-(2-ethoxyethyl)piperidine (**25**)*
Oil, 470 g (19.5%); R_f 0,44 (hexane:dioxane, 5:1); IR: 3286 (≡CH) 3063 (Ar-H), 2104 (C≡C), 1101 (COC), 755, 692 cm^{-1}; ^{1}H NMR δ 1.18 (t, 3H, H-10), 1.83–2.00 (m, 4H, H-3_{ax}, H-5_{ax}, H-3_{eq}, H-5_{eq}), 2.44 (ddd, 2H, H-2_{ax}, H-6_{ax}, J = 11.1 Hz, 3.0 Hz), 2.51 (s, 1H, ≡CH), 2.57 (t, 2H, NCH_2), 2.66 (bs, 2H, H-2_{eq}, H-6_{eq}), 3.47 (q, 2H, H-9), 3.52 (t, 2H, H-8), 3.89 (t, 2H, OCH_2CH_2OPh), 4.11 (t, 2H, OCH_2-CH_2OPh), 6.88-7.28 (m, 5H, Ar-H); ^{13}C NMR ppm 15.1 (C-10), 36.2 (C-3/C-5), 50.1 (C-2/C-6), 57.6 (NCH_2), 61.9 (OCH_2CH_2OPh), 66.3 (C-9), 67.1 (OCH_2CH_2OPh), 68.3 (C-8), 71.7 (C-4), 74.6 (≡CH), 84.2 (C≡), 114.6 (Ar-C), 120.7 (Ar-C), 129.3 (Ar-C), 158.8 (ArC-O). Anal. Calcd for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41. Found: C, 71.63; H, 8.56: N, 4.56.

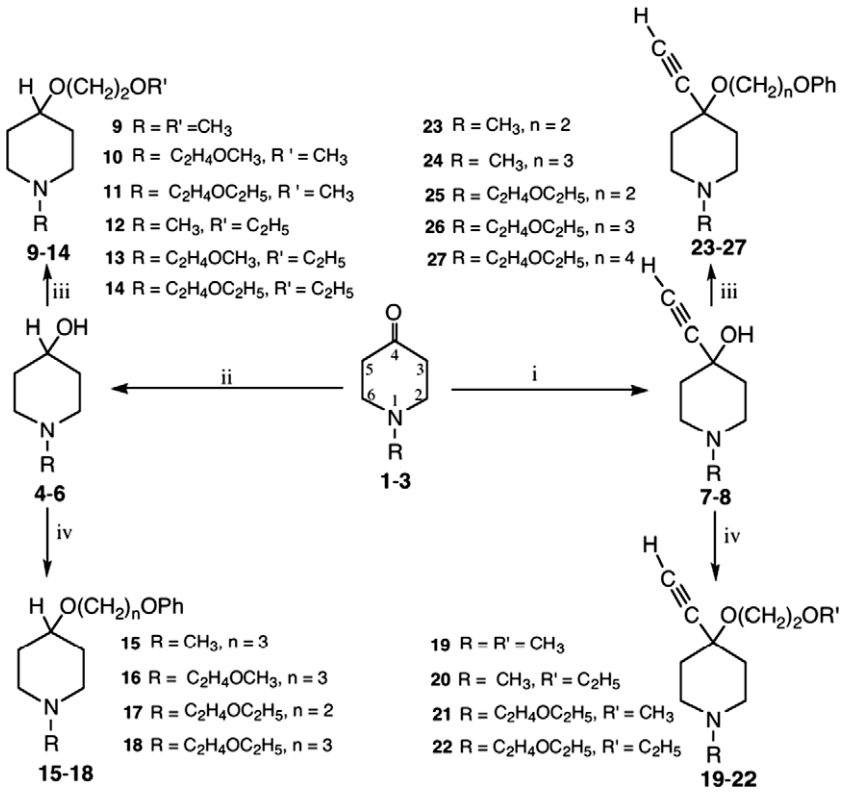
*2.2.24. 4-(3-Phenoxypropoxy)-4-ethynyl-1-(2-ethoxyethyl)piperidine (**26**)*
Oil, 7.64 g (45.5%); R_f 0.50 (hexane:dioxane, 5:1); IR: 3290 (≡CH), 3063 (Ar-H), 2100 (C≡C), 1086 cm^{-1} (COC), 755, 692 cm^{-1}; ^{1}H NMR δ 1.17 (t, 3H, H-10), 1.78–1.97 (m, 4H, H-3_{ax}, H-5_{ax}, H-3_{eq}, H-5_{eq}), 2.02 (m, 2H, $OCH_2CH_2CH_2OPh$), 2.41 (s, 1H, ≡CH), 2.42 (bt, 2H, H-2_{ax}, H-6_{ax}, J = 7.8 Hz), 2.52 (t, 2H, NCH_2), 2.60 (bs, 2H, H-2_{eq}, H-6_{eq}), 3.45 (q, 2H, H-9), 3.49 (t, 2H, H-8), 3.72 (t, 2H, $OCH_2CH_2CH_2OPh$), 4.04 (t, 2H, $OCH_2CH_2CH_2OPh$), 6.86–7.28 (m, 5H, Ar-H); ^{13}C NMR ppm 15.1 (C-10), 29.9 ($OCH_2CH_2CH_2OPh$), 36.3 (C-3/C-5), 50.2 (C-2/C-6), 57.6 (NCH_2), 59.4 (OCH_2CH_2-CH_2OPh), 64.6 ($OCH_2CH_2CH_2OPh$), 66.3 (C-9), 68.3 (C-8), 71.2 (C-4), 74.1 (≡CH), 84.5 (C≡), 114.4 (Ar-C), 120.4 (Ar-C), 129.3 (Ar-C), 159.0 (ArC-O). Anal. Calcd for $C_{20}H_{29}NO_3$: C, 72.47; H, 8.82; N, 4.23. Found: C, 72.46; H. 8.81; N, 4.46.

*2.2.25. 4-(4-Phenoxybutoxy)-4-ethynyl-1-(2-ethoxyethyl)piperidine (**27**)*
Oil, 10.32 g (45.5%); R_f 0.49 (hexane:dioxane, 5:1); IR: 3290 (≡CH), 3062 (Ar-H), 2102 (C≡C), 1086 (COC), 755, 692 cm^{-1}; ^{1}H NMR δ 1.26 (t, 3H, H-10), 1.79–2.02 (m 8H, H-3_{ax}, H-5_{ax}, H-3_{eq}, H-5_{eq}, $OCH_2CH_2CH_2CH_2OPh$), 2.53 (bt, 2H, H-2_{ax}, H-6_{ax}, J = 10.0 Hz), 2.54 (s, 1H, ≡CH), 2.65 (t, 2H, NCH_2), 2.73 (bs, 2H, H-2_{eq}, H-6_{eq}), 3.55 (q, 2H, H-9), 3.61 (t, 2H, H-8), 3.68 (t, 2H, $OCH_2CH_2CH_2CH_2OPh$), 4.05 (t, 2H, $OCH_2CH_2CH_2CH_2OPh$), 6.94–7.36 (m, 5H, Ar-H); ^{13}C NMR ppm 15.1 (C-10), 26.2 ($OCH_2CH_2CH_2$-CH_2OPh), 26.6 ($OCH_2CH_2CH_2CH_2OPh$), 36.3 (C-3/C-5), 50.2 (C-2/C-6), 57.6 (NCH_2), 62.5 ($OCH_2CH_2CH_2CH_2OPh$), 66.3 (C-9), 67.5 ($OCH_2CH_2CH_2CH_2OPh$), 68.3 (C-8), 71.2 (C-4), 74.1 (≡H), 84.7 (C≡), 114.4 (Ar-C), 120.4 (Ar-C), 129.3 (Ar-C), 159.0 (ArC-O). Anal. Calcd for $C_{21}H_{31}NO_3$: C, 73.01; H, 9.04; N, 4.05. Found: C, 72.79; H, 9.12; N, 4.07.

3. Results and discussion

The chemistry required is outlined in Scheme 1. Reduction of key starting piperidin-4-ones **1**–**3** to the piperidin-4-ols **4**–**6** was straightforward (Yu and MES, 2002). Ethynylation of **1** and **3** to members of **7**, **8** was also accomplished in a relatively facile manner (Fomicheva et al., 1998). Etherification of **4**–**6** and **7**, **8** gave members of **9**–**14** and **19**–**22**, respectively, with the process being enhanced by the addition of powdered KOH to freshly distilled DMF at ice temperatures. This was followed by the dropwise addition of the corresponding alkoxyethyl bromide dissolved in dry DMF. Stirring was continued at room temperature over 70–100 h. These mild conditions gave **9**–**14** and **19**–**22** in yields ranging from 13.3% to 22.3% and 26.6–42.0%, respectively. The positive aspect of the procedure was the easy workup which required only a simple evaporation of solvent. Treatment of **4**–**6** and **7**, **8** with phenoxyalkyl bromides under similar conditions led to **15**–**18** and **23**–**27** in yields of 12.8–35.0% and 13.7–45.5%, respectively. Purification of products was readily achieved by flash chromatography over Al_2O_3 using hexane:dioxane. Side reactions accompanied the above procedures and appeared to involve interactions of the bromides with DMF, especially with phenoxyalkyl bromides. Multiple variations in conditions did not alter the results, with the highest yields being as recorded above. Surprisingly, nearly all of the products were oils.

Confirmations of the structures of **9**–**27** were realized by both elemental and NMR analyses. The NMR spectra for all members of **9**–**27** revealed a multiplet for H-2 and H-3 ring protons, implying that the systems were dynamic under the conditions employed. Signals for H-4 in alkoxyalkyl ethers



Scheme 1 (i) Ethyne, KOH, NH_3 (liquid); (ii) $NaBH_4$, *i*-Pr: 60°; (iii) KOH, R′OCH_2CH_2Br, DMF, RT; and (iv) KOH, $PhO(CH_2)_nBr$, DMF, RT.

of secondary alcohols **9**–**14**, appeared upfield by 0.26–0.35 ppm compared to that in the starting piperidin-4-ols **4**–**6**. It is likely that H-4 is in an axial position to a major extent with the large alkylalkoxy group in an equatorial arrangement. The corresponding H-4 in **17**, for example, is 0.26 ppm upfield from that in **6** while **15**, **16**, and **18** exhibited a range of upfield shifts of 0.28–0.37 ppm compared to the corresponding signals in **4**–**6**. Interestingly, the ^{13}C NMR analysis of C-4 in ethers **9**–**18** derived from secondary alcohols **4**–**6** and ethers of ethynylpiperidin-4-ole **19**–**27** from **7**, **8** had downfield shifts of 7.4–8.5 ppm and 5.6–6.2 ppm, respectively, compared to those in **4**–**6** and **7**, **8**. However, signals for C-3 and C-5 in these systems were shifted upfield by 2.9–3.1 ppm and 2.2–2.3 ppm, respectively. Obviously the large groups at C-4 in the target molecules influence electron density around C-3 and C-5. No substantial changes in chemical shifts were noted for C-2 and C-6 in these derivatives.

It was decided that the oils would be converted to solid complexes with β-cyclodextrine [β-CD] for pharmacological screening. The ability of β-CD to serve as drug carriers resides in certain properties, namely high stability, a sufficiently large diameter of the interstice, and a good tolerance of various drug forms by organisms (Chayka et al., 1990). Our tests were performed on non-pedigreed white mice and rats of both sexes possessing a mass range of 17–23 g. The biological activity and toxicity of the synthetic compounds were compared to the corresponding properties of selected medicinal preparations as standards (see Tables 1–3).

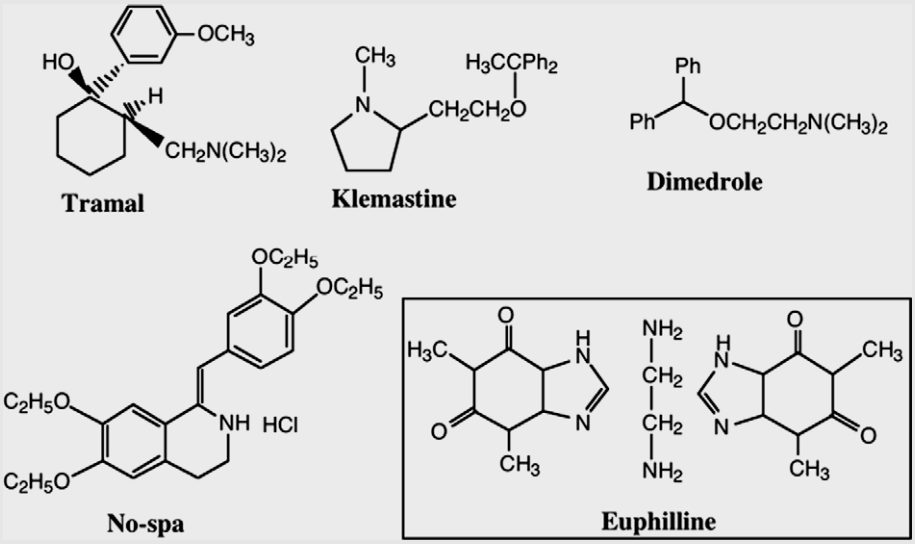
The LD50 values for the test compounds had a range of 500–1500 mg/kg as assessed following intra-peritoneal introduction to the mice. In contrast, the standards displayed LD50 values as follows: Tramal (175 g/kg), No-spa (66 mg/kg), Dimedrole (144 mg/kg), Lidocaine (95 mg/kg), Klemastine (154 mg/kg), Euphilline (240 mg/kg), and Streptomycin (213 mg/kg) (Krylov, 2001). Other data are included in Table 1. Consequently, the compounds prepared have quite low toxicity compared to the clinically employed standards.

Representative examples of the agents were screened for a variety of biological activities. To assess analgesic activity, the well known ''Tail-flick'' model was utilized via a focused infrared ray on rat tails. Observed analgesic activities for selected compounds are shown in Table 1. The data revealed that alkoxy- and phenoxyalkyl ethers **11**, **14**, **17**, and **18** from secondary alcohols **6** did not possess useful analgesic activity. The best results were noted with the ethynyl analogs, namely methoxylethyl ether **21** and aromatic ethers of *N*-ethoxylethyl-4-ethynylpiperidin-4-ols **25**–**27**. In terms of a common analgesic effect, the latter agents were 2.4–3.0 times more effective than Tramal. The range of common analgesia action was 180–221 min for **21** and **25**–**27** whereas the corresponding duration of action for Tramal was 75 min. In addition, Tramal did not produce a deep analgesic effect. A number of aromatic ethers generated deep analgesic effects such as observed for **27** [160 min], **26** [135 min], and **25** [70 min]. The ethers from *N*-methyl-4-ethynylpipeirdin-4-ols **19**,**23**, and **24** were of no effect or of modest effect for a deep analgesic result than the *N*-ethoxyethyl derivatives. Interestingly, the 4-ethoxylethyl-4-ethynyl-substituted compound **20** exhibited a deep analgesic effect of 170 min and a common analgesic effect of 240 min.

Table 1 Analgesic activity and acute toxicity of selected members of the ether-containing piperidines.

Compound	Latent period (min)	Duration of deep analgesia (min)	Duration of common analgesia (min)	LD50 (mg/kg)
11	No effect			> 800
14	No effect			> 800
17	30	–	45.3 (± 7.9)	> 1500
18	5	–	33.3 (± 6.7)	> 1500
19	No effect			> 800
20	5	170.0 (± 12.3)	240	> 1500
21	5	80.0 (± 17.32)	221.67 (± 6.45)	> 800
22	5	–	66.7 (± 11.21)	> 800
23	No effect			529.3 (± 13.4)
24	5	30.0 (± 12.3)	135.3 (± 9.8)	> 1500
25	5	70.0 (± 6.1)	180	> 800
26	5	135.3 (± 12.4)	183.3 (± 17.1)	> 800
27	5	160.0 (± 41.1)	210.0 (± 0.0)	580 (± 68.90)
Tramal	5	–	75.0 (± 9.1)	175 (± 30.15)
Klemastine				154 (± 12.1)
Dimedrole				144.51 (± 7.98)
Lidocaine				95 (± 13.1)
No-spa				66 (± 12.10)
Euphillinea				240 (± 17.21)
Streptomycin				213.8 (± 22.61)

Euphilline is a 4:1 mixture of theophylline:1,2-ethanediamine.



The ethers of 1-(2-ethoxyethyl)-4-ethynyl-4-hydroxypiperidines **21**, **22**, **25**, and **26** did not possess useful anti-bacterial activity (Table 2). These agents did not inhibit growth of gram-positive (*Staphylococcus aureus*) and gram-negative (*Escherichia coli*, *Salmonella cholerae suis*, and *Salmonella typhimurium*) microorganisms on meat-peptone broth. However, the phenoxybutoxy-containing system **27** did exhibit some moderate anti-bacterial action as did ethoxyethyl and phenoxypropyl ethers **20** and **24**, respectively, but less than did Streptomycin. The absence of the ethynyl group resulted in a poor ability to inhibit the bacteria as seen for **11**, **14**, **17**, and **18**. The small increase in length of the side chain in **24** had a dramatic positive effect on activity as compared to **23**. In general, an overall observation regarding anti-bacterial ability was that the *N*-methyl-containing family displayed slightly better activity then did the *N*-ethoxyethyl derivatives as viewed by data for **19**, **20**, and **24** versus **17**, **25**, and **27**, respectively, with the exception of **27** against *E. coli*.

Anti-spasmolitic activity (Table 3) was evaluated on isolated segments of mouse intestine with an artificial spasm being initiated by the addition of acetylcholine, histamine, and/or calcium chloride. The data are given in Table 3. 15 ethers of 1-(2-ethoxyethyl)-4-ethynyl-4-hydroxy-piperidines **21**, **22**, **26**, and **27** expressed anti-spasmotic activity in the various preparations employed. Specifically, alkoxyalkyl ethers **21** and **22**

Table 2 Anti-bacterial activity of the piperidine-containing ethers after 48 h of incubation in meat-peptone broth (bacteria growth in 1:1000).[a]

Compound	*Escherichia coli*	*Salmonella cholerae suis*	*Salmonella typhimurium*	*Staphylococcus aureus*
11	4	4	4	4
14	4	4	4	4
17	3	3	3	4
18	4	4	4	4
19	3	4	4	4
20	3	3	2	2
21	4	4	4	4
22	4	4	4	4
23	4	4	4	3
24	2	2	2	3
25	3	4	4	4
26	4	4	4	4
27	1	3	2	2
Streptomycin	0	0	0	0
Control (inoculation void of any preparation)	4	4	4	4

[a] Maximum turbidity related to maximum growth of microorganisms = 4. Absence of growth of microorganisms, maximum medium transparency = 0.

inhibited the acetylcholine-induced spasm while ethoxyethyl ether **22** also completely blocked the histamine-induced spasm in mouse intestine. The phenoxy-substituted ether **27** was very inhibitory to a calcium chloride-spasm. Ethers **11** and **14** void of an ethynl group were not effective. Results with the synthetic compounds were compared to the five standard preparations as outlined in Table 3.

To assess anti-allergic ability of the compounds, membrane-stable activity was studied via observance of indirect degranulation of fat cells [IDFC] (Methodical Instructions on Evaluation of Allergic Properties of Pharmacological Drugs, 1988). The biological activity was compared with that of Dimedrole and Klemastine [Histamine-1 blocking and anti-allergic action, respectively]. The pharmacological testing using methoxyethyl, ethoxyethyl, and phenoxypropyl ethers **21**, **22**, and **26**, respectively, derived from 1-(2-ethoxyethyl)-4-ethynyl-4-hydroxy- piperidines **8** was accomplished using the stable membrane model of degranulated fat cells from rats. Activity was noted with **22** which displayed ability comparable to that of the standard Dimedrole. Surprisingly, the phenoxypropyl derivative **26** surpassed Dimedrole in anti-allergic activity and in toxicity with respect to the model of degranulation of fat cells of the rat. However, the activity of **26** was less than that of Klemastine as seen in Table 4 containing data of some selected compounds. The smaller the value for the index of degranulation of fat cells (IDFC) the greater the anti-allergic induced activity by the agent. Interestingly, the systems **11** and **14** void of the ethynl group did not exhibit useful anti-allergic activity. It is apparent that very small changes in the structures induce sharp alterations in properties of this group of compounds. These observed activities prompt additional efforts to explore this novel family of heterocycles with potentially useful and wide ranging medicinal properties.

Table 3 Anti-spasmotic activity of selected piperidine-containing ethers [change in length (mm) of an isolated piece of intestine after stimulation when attached to isolated organs] (Kuzdenbayeva et al., 2000).

Compound	Clonus of intestine[a]	Clonus of intestine[b]	Clonus of intestine[c]	Clonus of intestine[d]
11	0	4.0	4.0	NA
14	0	4.0	4.0	NA
21	2	0.0	2.0	NA
22	0	0.0	0.0	NA
26	0	1.0	2.0	NA
27	0	1.0	NA	0.0
No-spa	0	0.0	0.0	0.0
Euphilline	0	0.0	0.0	0.0
Acetylcholine		5.0		
Histamine			4.3	
$CaCl_2$				2.5 ± 0.1

NA = not available.
[a] After the introduction of a preparation.
[b] In the presence of a preparation and acetyl choline.
[c] In the presence of a preparation and histamine.
[d] In the presence of a preparation and with a 10% solution of $CaCl_2$.

Since piperidines and many derivatives have been investigated with respect to conformational analysis, a few brief comments are in order for the derivatives discussed herein. In conformationally locked systems, ^{13}C NMR analysis has clear demonstrated that an *N*-methyl bond is essentially 99% equatorial (Crowley et al., 1977; Appleton et al., 1977; Delpuech, 1977). Consequently, it is reasonable that the piperidine systems in our work are also effectively locked systems with all large groups bonded to the ring in equatorial arrangements. It is also well known (Hennion and O'Shea, 1958) in cyclohexyl systems that the addition of sodium acetylide to 4-*t*-butylcyclohexanone results in the ethyne group in an axial position and the hydroxyl group in the equatorial position. The linear ethyne group apparently offers only small 3,5-interactions with axial C–H bonds. Thus, the ethynyl functions in the molecules prepared in our study are most likely in axial positions in a locked six-membered ring.

Table 4 Activity of piperidine-containing ethers and standards on stable membrane preparations – an examination of anti-allergic activity.

Compound	Index of degranulation of fat cells after the introduction of 0.03 ml of a 0.01% acetylcholine	Index of degranulation of fat cells after the introduction of 0.03 ml of a 0.01% histimime
11	NA	2.2 (±0.009)
14	NA	2.0 (±0.011)
21	2.0 (±0.001)	1.9 (±0.0005)
22	1.7 (±0.001)	1.5 (±0.001)
26	NA	1.0 (±0.01)
Histamine	NA	3.0 (±0)
Acetylcholine	3.0 (±0)	NA
Dimedrole	NA	1.374 (±0.01)
Klemastine	NA	0.14 (±0.005)

Index of degranulation relates to degranulation of fat cells which is a quantitative comparative measure of the expression of granules ejected by standard allergic agents (histamine or acetylcholine) from fall cells (Methodical Instructions on Evaluation of Allergic Properties of Pharmacological Drugs, 1988).
NA = not available.

4. Conclusions

A series of secondary- and tertiary-substituted piperidin-4-ols containing ethoxy groups have been prepared and exhibit wide ranging biological properties which include activities such as analgesic, anti-bacterial, anti-spasmotic, and anti-allergic. High LD50 values clearly indicate the compounds to be of low toxicity, an important quality for future evaluations. The presence of an ethynyl group at C-4 in N-ether-substituted piperidine markedly enhanced the analgesic activity of several agents. The presence of alkoxy and phenoxy ether linking groups at C-4 of the piperidines also contributed to the biological action of the substituted piperidines.

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