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Enzyme-assisted kinetic resolution of novel 2-naphthol Mannich bases

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ABSTRACT

In an attempt to develop novel Selective Estrogen Receptor Modulators (SERMs) containing a chirality centre, simpler 1-((2-hydroxynaphthalen-1-yl)arylmethyl)piperidin-4-ol prototypes were synthesized as racemic mixtures via the Mannich reaction protocol from 2-naphthol, 4-piperidinol, and 10 different aromatic aldehydes. These 10 chiral Mannich bases were then resolved utilizing an enzyme-assisted chemo-, regio-, and enantioselective acetylation process. The enzyme (Novozyme 435®; Lipase B from *Candida Antarctica*) displayed exclusive chemo- and regioselectivity in acetylating the test compounds; the optical enrichment was also achieved as evidenced by measurement of the optical rotation of the mono-acetylated product and unreacted dihydroxy compound.

1. Introduction

Selective Estrogen Receptor Modulators (SERMs) function to block the action of estrogen by binding to estrogen receptors (ER_α or ER_β subtypes) in cells. SERMs are selective for various receptors throughout the body [1]. In some cases, a SERM may inhibit the effects of estrogen, by preventing estrogen molecules from binding to the receptor sites. In other cases, it may increase the effects by activating the estrogen receptor. The outcome of the SERM is determined by both the position of the specific ER to which it binds, as well as the ER subtype [2].

Current uses of SERMs include treatment of breast cancer and osteoporosis where ERs play an important role. Although all SERMs decrease the risk of breast cancer, the side effects of many of these drugs are dangerous [3]. For example, a drug may inhibit ERs in the breast, yet stimulate ERs in the uterus. These positive and negative effects associated with a particular SERM must be carefully weighed to ensure an advantageous result [4]. Tamoxifen is currently the most widely used SERM which inhibits the growth of estrogen receptor-positive breast cancer [2]. After a large number of experimental trials, it was first approved for use in the 1970s. This drug acts by binding to ERs in the breast, thereby blocking estrogen from doing so as well. This interference results in the deactivation of genes which stimulate cell proliferation. Tamoxifen can also be used to treat women who are currently healthy, yet who are at increased risk for developing breast cancer [5]. Although tamoxifen has shown extremely beneficial effects in the treatment of breast cancer, negative side effects have also been observed. While acting as an estrogen inhibitor in the breast, it also mimics the effect of estrogen in the uterus. This imitation effectively increases cell proliferation in uterine tissue and resultantly, the risk of developing uterine cancer [6]. Raloxifene is another SERM which appears to have a higher ratio of positive to negative effects. It was initially approved by the FDA in 1997 for the treatment of osteoporosis in postmenopausal women. Although not much information is available regarding the long term effects of this drug, it has been found to have beneficial effects on bone strength and LDL cholesterol levels, without increasing the risk for breast cancer development [7]. Preliminary trials have shown raloxifene to be just as effective at preventing breast cancer as tamoxifen [6,7]. The incidence of uterine cancer in these trials has also been substantially lower [6]. The only observable downfall of raloxifene is its apparent inability to reduce the incidence of noninvasive breast cancer, as does tamoxifen [8].

The generic structure of a prototypical potential SERM designed for our study is shown in Fig. 1, along with structures of estradiol and raloxifene for comparison. It is evident that it contains phenolic and alcoholic hydroxyl groups positioned appropriately to mimic estradiol. It also bears a dialkylaminoethoxyphenyl side chain found in clinical SERMs. Additionally, it has a chiral centre making its topology asymmetric and non-planar like estrogen. It is hypothesized that these features will render potent

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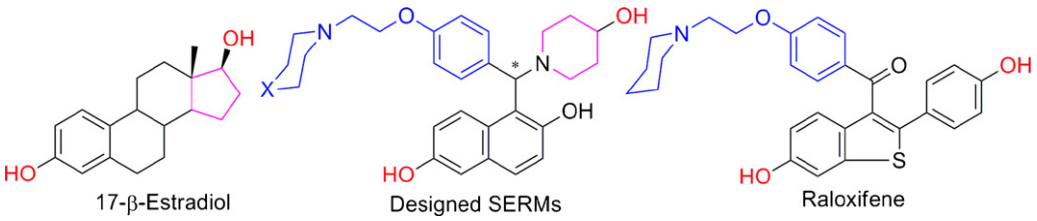


Fig. 1. Prototypical potential SERMs compared to 17-β-estradiol and raloxifene.

selective estrogen receptor modulatory activity to the designed molecules.

A number of challenges are presented when dealing with the synthesis of a chiral drug prototype. Regulatory agencies no longer approve racemic mixtures to be introduced in the market as drugs. It is a well established fact that desired pharmacological action is possessed by one enantiomer only and that the other enantiomer, in nearly all cases, is either inactive or toxic [9]. Since, our designed molecule has a chirality centre, we need either to synthesize it in enantiomerically pure form or to resolve the enantiomeric pair.

For the purpose of current research, we decided to develop a methodology to produce optically pure material on a simplified version of the designed molecule (Fig. 2). These compounds can be prepared in racemic form by performing a Mannich reaction among 2-naphthol, 4-piperidinol, and aromatic aldehydes. While the reaction appears to be relatively straightforward, it will produce the products as racemic mixtures. Given that these molecules contain two kinds of hydroxyl groups, we found them to be excellent candidates for enzyme-assisted enantioselection process utilizing a transesterification reaction [10,11].

Lipases and esterases are known to impart chemo-, regio-, and/or enantioselectivity in organic reactions performed under aqueous and organic solvent conditions at ambient temperature [10,11]. Numerous enzyme preparations are now commercially available for this purpose. We selected a versatile enzyme, Novozyme 435® (immobilized Lipase B from *Candida Antarctica*) [12] for our studies. If this endeavor is successful, it is hoped that the developed methodology can be easily applied to prepare designed SERMs (Fig. 1) in enantiomerically pure form.

We herein report successful synthesis of racemic 1-((2-hydroxynaphthalen-1-yl)(phenyl)methyl)piperidin-4-ol, simpler prototypes of designed SERMs, and their Novozyme-assisted kinetic resolution in chloroform. 1-((2-Hydroxynaphthalen-1-yl)-arylmethyl)piperidin-4-yl acetates were exclusively obtained confirming the chemo- and regioselective acetylation ability of Novozyme 435®; optical enrichment was also achieved as evident from the optical rotation values obtained for acetylated products and unreacted starting diols. All compounds studied in this investigation are new to chemical literature and have been completely characterized.

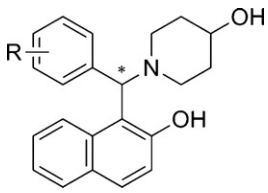


Fig. 2. 1-((2-Hydroxynaphthalen-1-yl)arylmethyl)piperidin-4-ols, simplified analogs of designed SERMs chosen for enantioselective synthesis as model examples.

2. Experimental

2.1. General

All reagents and solvents were used as supplied by commercial sources without further purification. Novozyme 435® was purchased from Sigma–Aldrich. Melting points were measured using a MEL-TEMP II apparatus. Precoated fluorescent silica gel TLC plates were used to monitor the progress of the reactions. IR spectra were recorded on a Nicolet MAGNA-IR 560 spectrophotometer. ^{1}H and ^{13}C NMR spectra were obtained by a Bruker AV300 spectrometer. Chemical shifts of the ^{1}H NMR spectra are reported in parts per million (ppm) downfield from tetramethylsilane. HRMS and EIMS mass spectra were recorded by Mr. Xiao Feng at Dalhousie University, Halifax, Nova Scotia. APD220 Polarimeter manufactured by Bellingham Stanley Ltd was used to obtain optical rotation values of the enantiomerically enriched samples. Yields of enantiomerically enriched products were calculated by assuming corresponding single enantiomer as 100% in the starting 1-((2-hydroxynaphthalen-1-yl)arylmethyl)-piperidin-4-ols.

2.2. General procedure for synthesis of 1-((2-hydroxynaphthalen-1-yl)arylmethyl)-piperidin-4-ols (**1a-j**)

To a mixture of 2-naphthol, 4-piperidinol and an appropriate aromatic aldehyde in ethanol, pTSA was added. The resulting mixture was refluxed and stirred for 72 h. During this time, the mixture appeared dark brown in color. Reaction progress was monitored by TLC. After the reaction proceeded to completion, ethanol was removed under reduced pressure and crude product was purified using column chromatography (1–4% MeOH/DCM as eluent).

2.2.1. 1-((2-Hydroxynaphthalen-1-yl)-(phenyl)methyl) piperidin-4-ol (**1a**)

White solid (34.6% yield); R_f 0.29 (5% MeOH/DCM); mp 218–220 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.48 (t, 2H, J = 9.9 Hz, CH_2), 1.77 (br s, 2H, CH_2), 2.24 (br s, 2H, CH_2), 2.54 (s, 1H, alcoholic OH), 2.87 and 3.59 (br s, 1H each, CH_2), 4.72 (s, 1H, CH), 5.30 (s, 1H, CH), 7.07 and 7.10 (m, 1H, ArH), 7.19–7.28 (m, 4H, ArH), 7.38 (m, 1H, ArH), 7.61 (d, 2H, J = 6.0 Hz, ArH), 7.72 (t, 2H, J = 8.4 Hz, ArH), 8.01 (d, 1H, J = 7.8 Hz, ArH), 13.80 (br s, 1H, phenolic OH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 35.02, 49.62, 66.01 (br), 70.61, 117.33, 120.49, 122.27, 123.18, 127.28, 128.58, 128.98, 129.46, 129.57 (2C), 129.91, 132.81, 141.21, 155.99. IR (KBr): ν_{max} 740, 746, 806, 813, 946, 1017, 1050, 1062, 1140, 1237, 1266, 1369, 1415, 1452, 1476, 1520, 1600, 1621, 2931, 3264 (OH) cm^{-1}. HRMS: calculated for $C_{22}H_{23}NO_2$: $[M]^+$ 333.1729; found $[M]^+$ 333.1733.

2.2.2. 1-((4-Fluorophenyl)(2-hydroxynaphthalen-1-yl)-methyl)piperidin-4-ol (**1b**)

Pale yellow solid (47.8%); R_f 0.21 (5% MeOH/DCM); mp 180–182 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26–1.29 (m, 4H, 2 × CH_2), 1.73–1.76 (m, 4H, 2 × CH_2), 1.97 (br s, 1H, alcoholic OH), 2.67 (s, 1H, CH), 5.12 (s, 1H, CH), 6.97 (t, 2H, J = 6.0 Hz, ArH), 7.17 (d,

1H, J = 8.7 Hz, ArH), 7.26 (t, 1H, J = 7.2 Hz, ArH), 7.40 (t, 1H, J = 6.0 Hz, ArH), 7.55 (br s, 2H, ArH), 7.72 (t, 2H, J = 9.0 Hz, ArH), 7.80 (d, 1H, J = 8.4 Hz, ArH), 13.50 (br s, 1H, phenolic OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 35.08, 49.74, 69.02 (br), 71.06, 116.30, 120.35, 121.27, 123.01, 126.99, 129.17, 129.41 (2C), 130.08, 131.10, 132.54, 135.88, 155.63, 161.12, 164.39. IR (KBr): ν_{max} 742, 798, 816, 837, 946, 1016, 1050, 1140, 1162, 1235, 1266, 1369, 1384, 1415, 1458, 1476, 1511, 1518, 1521, 1600, 1620, 2930, 2966, 3265 (OH) cm^{-1}. HRMS: calculated for $C_{22}H_{22}FNO_2$: $[M]^+$ 351.1634; found $[M]^+$ 351.1641.

2.2.3. 1-((4-Chlorophenyl)(2-hydroxynaphthalen-1-yl)methyl)-piperidin-4-ol (**1c**)

White solid (56.2%); R_f 0.48 (5% MeOH/DCM); mp 86–88 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.74–1.77 (m, 4H, 2 × CH_2), 1.98 (br s, 4H, 2 × CH_2), 2.24 (s, 1H, alcoholic OH), 2.71 (s, 1H, CH), 5.13 (br s, 1H, CH), 7.17–7.27 (m, 4H, ArH), 7.37–7.40 (m, 1H, ArH), 7.51–7.54 (m, 2H, ArH), 7.68–7.74 and 7.78–7.80 (2 m, 3H, ArH), 13.40 (br s, 1H, phenolic OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 34.86, 50.12, 71.11 (2C), 115.88, 120.31, 121.15, 123.05, 127.04, 129.18 (2C), 129.43 (2C), 130.21, 130.71, 132.48, 134.33, 138.45, 155.57. IR (KBr): ν_{max} 617, 705, 738, 831, 946, 1014, 1053, 1108, 1239, 1265, 1369, 1411, 1453, 1491, 1600, 1622, 3393 (OH) cm^{-1}. HRMS: calculated for $C_{22}H_{22}ClNO_2$: $[M]^+$ 367.1339; found $[M]^+$ 367.1340.

2.2.4. 1-((2-Hydroxynaphthalen-1-yl)(p-tolyl)methyl)-piperidin-4-ol (**1d**)

White solid (37.2%); R_f 0.20 (5% MeOH/DCM); mp 133–136 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.65–1.76 (m, 4H, 2 × CH_2), 1.96 (m, 4H, 2 × CH_2), 2.10 (s, 1H, alcoholic OH), 2.27 (s, 3H, CH_3), 2.70 (br s, 1H, CH), 5.12 (s, 1H, CH), 7.09 (d, 2H, J = 8.1 Hz, ArH), 7.17 (d, 1H, J = 9.0 Hz), 7.25 (m, 1H, ArH), 7.38 (t, 1H, J = 5.7 Hz, ArH), 7.46 (d, 1H, J = 7.5 Hz, ArH), 7.69 (t, 2H, J = 9.3 Hz, ArH), 7.84 (d, 1H, J = 8.4 Hz, ArH), 13.50 (br s, 1H, phenolic OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.47, 35.12, 49.94, 69.01 (br), 71.63, 116.60, 120.30, 121.50, 122.84, 126.84, 129.17, 129.30 (2C), 129.81, 132.71, 137.04, 138.16, 155.72. IR (KBr): ν_{max} 742, 818, 947, 1049, 1062, 1238, 1267, 1362, 1369, 1384, 1415, 1449, 1477, 1513, 1518, 1622, 2853, 2940, 3277 (OH) cm^{-1}. HRMS: calculated for $C_{23}H_{25}NO_2$: $[M]^+$ 347.1885; found $[M]^+$ 347.1881.

2.2.5. 1-((2-Hydroxynaphthalen-1-yl)(4-methoxyphenyl)-methyl)piperidin-4-ol (**1e**)

White solid (85.0%); R_f 0.23 (5% MeOH/DCM); mp 234–237 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.91 and 1.29 (s, 1H each, CH_2), 1.78 (br s, 2H, CH_2), 1.98 (s, 4H, 2 × CH_2), 2.74 (s, 1H, alcoholic OH), 3.74 (s, 3H, OCH_3), 5.12 (s, 1H, CH), 6.81 (d, 2H, J = 8.1 Hz, ArH), 7.19–7.28 (m, 2H, ArH), 7.39 (t, 1H, J = 6.0 Hz, ArH), 7.49 (d, 2H, J = 7.5 Hz, ArH), 7.70 (t, 2H, J = 9.0 Hz, ArH), 7.82 (d, 1H, J = 9.0 Hz, ArH), 13.42 (br s, 1H, phenolic OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 35.45, 49.62, 55.57, 69.08 (br), 71.22, 114.57, 116.66, 120.30, 121.46, 122.83, 126.82, 129.30, 129.77, 130.55, 132.07, 132.64, 155.64, 159.65. IR (KBr): ν_{max} 528, 743, 815, 829, 839, 947, 1015, 1049, 1061, 1095, 1144, 1238, 1267, 1361, 1370, 1410, 1450, 1466, 1475, 1491, 1519, 1623, 2853, 2945, 3277 cm^{-1}. HRMS: calculated for $C_{23}H_{25}NO_3$: $[M]^+$ 363.1834; found $[M]^+$ 363.1821.

2.2.6. 1-((3,4-Dichlorophenyl)(2-hydroxynaphthalen-1-yl)-methyl)piperidin-4-ol (**1f**)

White solid (6.5%); R_f 0.36 (5% MeOH/DCM); mp 128–131 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.73 (br s, 4H, 2 × CH_2), 1.95 (br s, 4H, 2 × CH_2), 2.72 (s, 1H, alcoholic OH), 5.16 (br s, 1H, CH), 5.31 (s, 1H, CH), 7.12–7.69 (m, 5H, ArH), 7.72–7.79 (m, 4H, ArH), 13.01 (br s, 1H, phenolic OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 34.81, 49.35, 70.75 (2C), 115.41, 120.39, 120.96, 123.16, 127.19, 128.51, 129.19, 129.50, 130.42, 131.18 (2C), 132.37, 132.61, 133.25, 140.37, 155.67. IR (KBr): ν_{max} 737, 819, 947, 1032, 1053, 1141, 1238, 1266, 1330, 1368, 1414, 1453, 1467, 1521, 1600, 1622, 2941, 3403 (OH) cm^{-1}. HRMS: calculated for $C_{22}H_{21}Cl_2NO_2$: $[M]^+$ 401.0949; found $[M]^+$ 401.1028.

2.2.7. 1-((2-Hydroxynaphthalen-1-yl)(3,4-dimethoxyphenyl)-methyl)piperidin-4-ol (**1g**)

Pale brown solid (25.7%); R_f 0.39 (5% MeOH/DCM); mp 185–187 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.78 (s, 4H, 2 × CH_2), 1.99 (s, 4H, 2 × CH_2), 2.80 (s, 1H, alcoholic OH), 3.79 and 3.81 (2s, 6H, 2 × OCH_3), 3.83 (s, 1H, CH), 5.31 (s, 1H, CH), 6.76 (d, 1H, J = 6.0 Hz, ArH), 7.12 (br s, 1H, ArH), 7.19 (br s, 1H, ArH), 7.25–7.28 (m, 2H, ArH), 7.40 (m, 1H, ArH), 7.67–7.73 (m, 2H, ArH), 7.83–7.86 (m, 1H, ArH), 13.11 (br s, 1H, phenolic OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 35.04, 49.84, 56.20, 56.30, 71.60 (2C), 111.43, 116.58, 118.55, 120.25, 121.47, 122.10, 122.88, 126.84, 129.17, 129.32, 129.86, 132.52, 132.68, 149.22, 149.68, 155.67. IR (KBr): ν_{max} 748, 815, 1025, 1053, 1148, 1240, 1260, 1341, 1364, 1384, 1420, 1451, 1465, 1515, 1601, 1621, 2835, 2935, 3422 (OH) cm^{-1}. HRMS: calculated for $C_{24}H_{27}NO_4$: $[M]^+$ 393.1940; found $[M]^+$ 393.1919.

2.2.8. 1-((Benzo[d][1,3]dioxol-5-yl)(2-hydroxynaphthalen-1-yl)methyl)piperidin-4-ol (**1h**)

Pale brown solid (60.1%); R_f 0.48 (5% MeOH/DCM); mp 117–120 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.64–1.76 (m, 2H, CH_2), 1.97 (br s, 2H, CH_2), 2.19 (s, 1H, alcoholic OH), 2.73 (br s, 1H, CH), 3.29 and 3.70 (br s, 2H each, CH_2), 5.04 (s, 1H, CH), 5.85 and 5.91 (2s, 2H, ArH), 6.71 (d, 2H, J = 15.6 Hz), 7.00 (br s, 1H, ArH), 7.10–7.18 (m, 2H, ArH), 7.25 (t, 1H, J = 7.5 Hz, ArH), 7.39 (t, 1H, J = 7.2 Hz, ArH), 7.70 (t, 2H, J = 8.1 Hz, ArH), 7.81 (d, 1H, J = 8.4 Hz, ArH), 13.50 (s, 1H, phenolic OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 35.30, 49.86, 52.70, 69.21, 71.60, 101.51, 108.45, 116.38, 120.36, 121.43, 122.89 (2C), 126.87, 129.13, 129.33, 129.90, 132.61, 133.79, 147.74, 148.52, 155.66. IR (KBr): ν_{max} 739, 816, 935, 1039, 1101, 1247, 1267, 1368, 1415, 1441. 1466. 1487, 1501, 1621, 3273 (OH) cm^{-1}. EIMS: m/z (% int.): 378 (M^+, 9), 277 (100), 259 (5), 247 (10), 219 (10).

2.2.9. 1-((2-Hydroxynaphthalen-1-yl)(pyridin-4-yl)-methyl)piperidin-4-ol (**1i**)

Rust-colored solid (18.3%); R_f 0.50 (5% MeOH/DCM); mp 165–168 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26 (t, 2H, J = 6.0 Hz, CH_2), 1.70 (br s, 2H, CH_2), 1.95 (br s, 2H, CH_2), 2.05 (s, 1H, alcoholic OH), 2.25 and 2.70 (2 br s, 1H each, CH_2), 4.09–4.16 (m, 1H, CH), 5.11 (s, 1H, CH), 7.15 (m, 1H, ArH), 7.26 (t, 1H, J = 6.0 Hz, ArH), 7.41 (t, 1H, J = 6.3 Hz, ArH), 7.53 (d, 2H, J = 4.5 Hz, ArH), 7.71 (t, 2H, J = 8.4 Hz, ArH), 7.79 (d, 1H, J = 8.4 Hz, ArH), 8.48 (d, 2H, J = 4.5 Hz, ArH), phenolic OH not visible. ^{13}C NMR (75 MHz, $CDCl_3$): δ 34.62, 49.98, 67.51 (br), 70.73, 115.01, 120.30, 120.87, 123.19, 124.10, 127.20, 129.16, 129.53, 130.56, 132.37, 149.16, 150.63, 155.81. IR (KBr): ν_{max} 739, 817, 947, 1064, 1237, 1267, 1370, 1414, 1519, 1600, 1621, 3352 (OH) cm^{-1}. HRMS: calculated for $C_{21}H_{22}N_2O_2$: $[M]^+$ 334.1681; found $[M]^+$ 334.1683.

2.2.10. 1-((2-Hydroxynaphthalen-1-yl)(pyridin-2-yl)-methyl)piperidin-4-ol (**1j**)

Pale brown solid (17.6%); R_f 0.32 (5% MeOH/DCM); mp 184–186 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.56 (br s, 2H, CH_2), 1.76 (br s, 2H, CH_2), 2.25 (m, 2H, CH_2), 2.82 (s, 1H, alcoholic OH), 3.60 (s, 2H, CH_2), 4.73 (s, 1H, CH), 5.39 (s, 1H, CH), 7.05 (d, 1H, J = 9.0 Hz, ArH), 7.22 (t, 2H, J = 6.0 Hz, ArH), 7.39 (t, 1H, J = 6.0 Hz, ArH), 7.63–7.75 (m, 4H, ArH), 8.09 (d, 1H, J = 8.7 Hz, ArH), 8.50 (d, 1H, J = 3.9 Hz), phenolic OH not visible. ^{13}C NMR (75 MHz, $CDCl_3$): δ 34.98, 49.70, 72.47 (2C), 115.79, 120.42, 122.35, 123.21, 123.66, 123.76, 127.38, 128.86, 129.45, 130.14, 132.96, 138.19, 150.01, 156.19, 160.56. IR (KBr): ν_{max} 743, 751, 773, 815, 947, 1020, 1053, 1140, 1173, 1241, 1271, 1350, 1370, 1416, 1431, 1458, 1468, 1476, 1521, 1566, 1586, 1600, 1623, 2933, 2967, 3043, 3254 (OH) cm^{-1}.

HRMS: calculated for $C_{21}H_{22}N_2O_2$: $[M]^+$ 334.1681; found $[M]^+$ 334.1677.

2.3. Resolution of 1-((2-hydroxynaphthalen-1-yl)arylmethyl)-piperidin-4-ols (**1a-j**)

To a solution of racemic (2-(hydroxynaphthalen-1-yl)arylmethyl)piperidin-4-ol and vinyl acetate in chloroform, Novozyme 435® was added and the reaction mixture was shaken for 3–5 days. Thin layer chromatography was used to determine the extent of the reaction. Amount of compound acetylated was judged based on intensity of TLC spot. After 50% conversion (TLC estimate) of the starting material to acetylated product, reaction was stopped by filtering off the enzyme and subsequently washing with chloroform. The chloroform layer was concentrated to give an oily liquid. Enzyme was recovered and used for subsequent reactions. The optically enriched acetate and unreacted hydroxyl compounds were separated using column chromatography (0–5% MeOH/DCM as eluent).

2.4. Acetylated 2-naphthol Mannich base products (**+/−2a-j**)

2.4.1. 1-((2-Hydroxynaphthalen-1-yl)-(phenyl)methyl)-piperidin-4-yl acetate (**+2a**)

White solid (92.4%); R_f 0.63 (5% MeOH/DCM); mp 201–206 °C; $[\alpha]_D$ +30.00 (25 °C, DCM). ^{1}H NMR (300 MHz, DMSO): δ 1.67 (2H, br s, CH_2), 1.87 and 1.99 (m, 4H, 2 × CH_2), 2.08 (s, 3H, $OCOCH_3$), 2.5 and 3.3 (br s, 1H, CH_2), 4.80 (br s, 1H, CH), 5.15 (s, 1H, CH), 7.18 (d, 1H, J = 9.0 Hz, ArH), 7.22–7.32 (m, 4H, ArH), 7.39 (t, 1H, J = 7.8 Hz, ArH), 7.58 and 7.60 (2 br s, 2H, ArH), 7.71 (t, 2H, J = 9.0 Hz, ArH), 7.86 (d, 1H, J = 8.4 Hz, ArH), 13.55 (br s, 1H, phenolic OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.68, 31.28, 49.79, 70.01 (br), 71.96, 116.27, 120.29, 121.44, 122.90, 126.87, 128.49, 129.16, 129.31 (3C), 129.96, 132.68, 139.91, 155.67, 170.83. IR (KBr): ν_{max} 741, 746, 806, 813, 846, 1018, 1051, 1063, 1140, 1237, 1266, 1369, 1415, 1452, 1465, 1477, 1520, 1600, 1621, 2931, 3267 (OH) cm^{-1}. HRMS: calculated for $C_{24}H_{25}NO_3$: $[M]^+$ 375.1834; found $[M]^+$ 375.1842.

2.4.2. 1-((4-Fluorophenyl)(2-hydroxynaphthalen-1-yl)methyl)-piperidin-4-yl acetate (**+2b**)

Pale yellow solid (74.4%); R_f 0.45 (5% MeOH/DCM); mp 83–87 °C; $[\alpha]_D$ +10.75 (25 °C, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.88 (br s, 4H, 2 × CH_2), 2.02 (br s, 4H, 2 × CH_2), 2.09 (s, 3H, $OCOCH_3$), 2.65 (br s, 1H, CH), 5.14 (s, 1H, CH), 7.01 (m, 2H, ArH), 7.19 (d, 2H, J = 8.7 Hz, ArH), 7.27 (t, 1H, J = 6.5 Hz, ArH), 7.41 (t, 2H, J = 7.5 Hz, ArH), 7.56 (br s, 2H, ArH), 7.73 (t, 2H, J = 9.0 Hz, ArH), 7.82 (d, 1H, J = 8.4 Hz, ArH), 13.35 (br s, 1H, phenolic OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.67, 30.13, 49.75, 52.33, 71.07, 116.15, 120.34, 121.26, 123.04, 127.01, 129.21, 129.42, 130.14, 131.07, 132.54, 135.76, 155.56 (2C), 161.15, 164.43, 170.83. IR (KBr): ν_{max} 745, 838, 947, 1040, 1159, 1236, 1364, 1384, 1414, 1453, 1457, 1466, 1508, 1517, 1521, 1601, 1623, 1730, 1735, 2955, 3443, 3447 (OH) cm^{-1}. HRMS: calculated for $C_{24}H_{24}FNO_3$: $[M]^+$ 393.1740; found $[M]^+$ 393.1731.

2.4.3. 1-((4-Chlorophenyl)(2-hydroxynaphthalen-1-yl)methyl)-piperidin-4-yl acetate (**+2c**)

Light yellow solid (45.0%); R_f 0.83 (5% MeOH/DCM); mp 65–68 °C; $[\alpha]_D$ +10.29 (25 °C, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.88 (br s, 2H, CH_2), 2.01 (br s, 2H, CH_2), 2.09 (s, 3H, $OCOCH_3$), 2.70 and 3.40 (2 br s, 2H each, CH_2), 4.80 and 5.14 (2s, 1H each, CH), 7.18 (d, 1H, J = 7.5 Hz, ArH), 7.27 (d, 3H, J = 6.6 Hz, ArH), 7.41 (t, 1H, J = 7.8 Hz, ArH), 7.52 (br s, 2H, ArH), 7.73–7.82 (m, 3H, ArH), 13.25 (br s, 1H, phenolic OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.68, 31.30, 49.79, 71.08 (2C), 120.46, 121.24, 123.14, 127.01, 129.28, 129.39, 129.53 (2C), 130.15, 130.72 (2C), 132.45, 134.35, 138.51, 155.77, 170.81. IR (KBr): ν_{max} 705, 739, 817, 835, 947, 1015, 1040, 1092, 1116, 1239, 1309, 1364, 1412, 1454, 1466, 1475, 1491, 1522, 1600, 1622, 1732, 2959, 3325 (OH) cm^{-1}. HRMS: calculated for $C_{24}H_{24}ClNO_3$: $[M]^+$ 409.1445; found $[M]^+$ 409.1450.

2.4.4. 1-((2-Hydroxynaphthalen-1-yl)(p-tolyl)methyl)-piperidin-4-yl acetate (**+2d**)

Orange solid (64.1%); R_f 0.41 (5% MeOH/DCM); mp 106–109 °C; $[\alpha]_D$ +26.90 (25 °C, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.86 (br s, 4H, 2 × CH_2), 1.98–2.00 (m, 4H, 2 × CH_2), 2.08 (s, 3H, $OCOCH_3$), 2.28 (s, 3H, CH_3), 5.11 and 5.30 (2s, 1H each, CH), 7.10 (d, 2H, J = 7.8 Hz, ArH), 7.18 (d, 1H, J = 7.8 Hz, ArH), 7.24 (t, 1H, J = 7.2 Hz, ArH), 7.39 (t, 1H, J = 8.1 Hz, ArH), 7.47 (d, 2H, J = 7.5 Hz, ArH), 7.70 (t, 1H, J = 9.3 Hz, ArH), 7.86 (d, 1H, J = 8.4 Hz, ArH), 13.40 (br s, 1H, phenolic OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.46, 21.69, 31.22, 49.73, 71.64 (2C), 116.42, 120.26, 121.46, 121.90, 122.87, 126.84, 129.17, 129.29, 129.86, 132.67, 136.87, 138.24, 155.61, 170.86. IR (KBr): ν_{max} 745, 817, 947, 1039, 1236, 1364, 1384, 1414, 1453, 1457, 1466, 1513, 1518, 1522, 1600, 1621, 1719, 1730, 1735, 2923, 3450 (OH) cm^{-1}. HRMS: calculated for $C_{25}H_{27}NO_3$: $[M]^+$ 389.1991; found $[M]^+$ 389.2000.

2.4.5. 1-((2-Hydroxynaphthalen-1-yl)(4-methoxyphenyl) methyl)-piperidin-4-yl acetate (**+2e**)

Yellow viscous liquid (41.0%); R_f 0.42 (5% MeOH/DCM); $[\alpha]_D$ +21.00 (25 °C, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.98 (br s, 4H, 2 × CH_2) 2.01 (br s, 2H, CH_2), 2.09 (s, 3H, $OCOCH_3$), 2.50 and 3.20 (2 br s, 1H each, CH_2), 3.73 (s, 3H, OCH_3), 5.15 and 5.29 (s, 1H each, CH), 6.81 (d, 2H, J = 8.7 Hz, ArH), 7.19 (d, 1H, J = 9.0 Hz, ArH), 7.23–7.28 (m, 1H, ArH), 7.43 (m, 1H, ArH), 7.49 (d, 2H, J = 8.4 Hz, ArH), 7.71 (t, 2H, J = 9.3 Hz, ArH), 7.84 (d, 1H, J = 8.4 Hz, ArH), 13.50 (br s, 1H, phenolic OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.69, 31.27, 49.69, 55.57, 71.24 (2C), 114.67, 116.54, 120.29, 121.48, 122.90, 126.87, 129.18, 129.32, 129.85, 130.55, 131.90, 132.65, 155.57, 159.72, 170.86. IR (KBr): ν_{max} 705, 732, 758, 781, 817, 835, 879, 909, 947, 1015, 1041, 1060, 1092, 1117, 1143, 1156, 1179, 1242, 1310, 1336, 1365, 1412, 1454, 1466, 1475, 1491, 1521, 1583, 1600, 1623, 1732, 2958, 3070 (OH) cm^{-1}. HRMS: calculated for $C_{25}H_{27}NO_4$: $[M]^+$ 405.4862; found $[M]^+$ 405.4862.

2.4.6. 1-((3,4-Dichlorophenyl)(2-hydroxynaphthalen-1-yl)-methyl)piperidin-4-yl acetate (**+2f**)

Orange solid (87.3%); R_f 0.82 (5% MeOH/DCM); mp 109–111 °C; $[\alpha]_D$ +12.89 (25 °C, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.86–1.89 (m, 2H, CH_2), 1.96 (br s, 2H, CH_2), 2.08 (s, 3H, $OCOCH_3$), 2.65 and 3.37 (2 br s, 4H, CH_2), 5.13 and 5.31 (2s, 1H each, CH), 7.20–7.49 (m, 5H, ArH), 7.70–7.79 (m, 4H, ArH), 13.01 (br s, 1H, phenolic OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.68, 31.14, 49.89, 70.76 (2C), 115.27, 120.38, 120.95, 123.21, 127.22, 127.90, 128.64, 129.22, 129.52, 130.49, 131.16, 132.36, 132.70, 133.27, 140.21, 155.59, 170.81. IR (KBr): ν_{max} 737, 820, 892, 948, 1040, 1092, 1118, 1133, 1238, 1332, 1365, 1415, 1455, 1467, 1520, 1600, 1622, 1733, 2961, 3442 (OH) cm^{-1}. HRMS: calculated for $C_{24}H_{23}Cl_2NO_3$: $[M]^+$ 443.1055; found $[M]^+$ 443.1076.

2.4.7. 1-((2-Hydroxynaphthalen-1-yl)(3,4-dimethoxyphenyl)-methyl)piperidin-4-yl acetate (**+2g**)

Brown solid (29.0%); R_f 0.32 (5% MeOH/DCM); mp 184–185 °C; $[\alpha]_D$ +15.63 (25 °C, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.88 (br s, 4H, 2 × CH_2), 2.01–2.07 (m, 4H, 2 × CH_2), 2.09 (s, 1H, $OCOCH_3$), 3.78 and 3.82 (2s, 6H, 2 × OCH_3), 5.10 and 5.24 (2s, 1H each, CH), 6.74 (d, 1H, J = 8.1 Hz, ArH), 7.10–7.26 (m, 4H, ArH), 7.40 (t, 1H, J = 7.8 Hz, ArH), 7.70 (t, 2H, J = 7.4 Hz, ArH), 7.87 (d, 1H, J = 8.7 Hz, ArH), phenolic OH not visible. ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.71, 31.19, 49.68, 52.48, 56.16, 56.28, 71.59, 110.96, 111.40, 120.25, 120.37, 121.50, 122.97, 126.92 (2C), 129.36 (2C), 129.95, 132.30, 132.67, 149.24, 149.58, 155.56, 170.97. IR (KBr): ν_{max} 736, 770, 822, 947,

1039, 1118, 1143, 1181, 1237, 1259, 1365, 1416, 1454, 1465, 1516, 1600, 1622, 1732, 2835, 2957, 3056 (OH) cm^{-1}. HRMS: calculated for $C_{26}H_{29}NO_5$: $[M]^+$ 435.2045; found $[M]^+$ 435.2048.

*2.4.8. 1-((Benzo[d][1,3]dioxol-5-yl)(2-hydroxynaphthalen-1-yl)-methyl)piperidin-4-yl acetate (+**2h**)*

White solid (90.9%); R_f 0.81 (5% MeOH/DCM); mp 110–113 °C; $[\alpha]_D$ +3.20 (25 °C, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.89 (br s, 2H, CH_2), 2.03 (br s, 2H, CH_2), 2.09 (s, 3H, $OCOCH_3$), 2.76 and 3.35 (br s, 2H each, CH_2), 5.08 and 5.28 (s, 1H each, CH), 5.89 (s, 2H, OCH_2O), 6.72 (d, 1H, J = 7.8 Hz, ArH), 7.04 (d, 1H, J = 6.6 Hz, ArH), 7.14–7.29 (m, 3H, ArH), 7.42 (t, 1H, J = 7.2 Hz, ArH), 7.72 (t, 2H, J = 9.0 Hz, ArH), 7.85 (d, 1H, J = 8.4 Hz, ArH), phenolic OH not visible. ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.74, 31.38, 39.66, 52.48, 69.88, 71.61, 101.58, 108.67, 116.24, 120.38, 121.47, 123.01 (2C), 126.97, 129.19, 129.39, 130.02, 132.62, 133.58, 147.84, 148.66, 155.57, 170.91. IR (KBr): ν_{max} 819, 1027, 1142, 1235, 1260, 1364, 1384, 1415, 1420, 1452, 1457, 1466, 1513, 1517, 1522, 1600, 1624, 1719, 1730, 1735, 1740, 2932, 3447 (OH) cm^{-1}. HRMS: calculated for $C_{25}H_{25}NO_5$: $[M]^+$ 419.1732; found $[M]^+$ 419.1735.

*2.4.9. 1-((2-Hydroxynaphthalen-1-yl)(pyridin-4-yl)methyl)-piperidin-4-yl acetate (−**2i**)*

Pale brown solid (98.2%); R_f 0.63 (5% MeOH/DCM); mp 174–176 °C; $[\alpha]_D$ −4.62 (25 °C, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.87 (br s, 2H, CH_2), 2.01 (br s, 2H, CH_2), 2.07 (s, 3H, $OCOCH_3$), 2.39 and 2.70 (2 br s, 4H, CH_2), 5.13 (br s, 1H, CH), 5.30 (s, 1H, CH), 7.16 (d, 1H, J = 8.7 Hz, ArH), 7.27 (br s, 1H, ArH), 7.41 (d, 1H, J = 7.5 Hz, ArH), 7.55 (s, 2H, ArH), 7.70 (d, 2H, J = 8.1 Hz, ArH), 7.82 (d, 1H, J = 8.1 Hz, ArH), 8.54 (s, 2H, ArH), 13.01 (s, 1H, phenolic OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.65, 31.02, 49.92, 70.74 (2C), 114.82, 120.28, 120.87, 123.26, 124.04, 127.25, 129.21, 129.55, 130.65, 132.35, 148.95, 150.70, 155.70, 170.76. IR (KBr): ν_{max} 739, 817, 948, 1041, 1237, 1330, 1265, 1414, 1453, 1466, 1474, 1521, 1595, 1621, 1735, 2963, 3053 (OH) cm^{-1}. HRMS: calculated for $C_{23}H_{24}N_2O_3$: $[M]^+$ 376.1787; found $[M]^+$ 376.1793.

*2.4.10. 1-((2-Hydroxynaphthalen-1-yl)(pyridin-2-yl)methyl)-piperidin-4-yl acetate (−**2j**)*

Orange solid (85.7%); R_f 0.58 (5% MeOH/DCM); mp 176–179 °C; $[\alpha]_D$ −7.07 (25 °C, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.82–2.01 (m, 4H, 2 × CH_2), 2.19 (s, 3H, $OCOCH_3$), 2.30 and 2.60 (2 br s, 4H, CH_2), 4.90 (s, 1H, CH), 5.47 (s, 1H, CH), 7.16 (d, 2H, J = 8.4 Hz, ArH), 7.27 (d, 2H, J = 6.6 Hz, ArH), 7.41 (m, 1H, ArH), 7.58 (m, 1H, ArH), 7.65–7.73 (m, 2H, ArH), 8.04 (d, 1H, J = 8.4 Hz, ArH), 8.57 (d, 1H, J = 8.4 Hz, ArH), 13.35 (br s, 1H, phenolic OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.70, 31.00, 31.34, 49.53, 73.60, 115.07, 120.24, 122.06, 123.11, 123.34, 123.75, 127.08, 129.05, 129.12, 130.29, 132.94, 137.89, 149.24, 155.83, 159.90, 170.87. IR (KBr): ν_{max} 749, 817, 947, 1040, 1089, 1239, 1365, 1416, 1434, 1454, 1467, 1588, 1600, 1622, 1732, 2962, 3052 (OH) cm^{-1}. HRMS: calculated for $C_{23}H_{24}N_2O_3$: $[M]^+$ 376.1787; found $[M]^+$ 376.1793.

*2.5. Unreacted enantiomerically enriched 2-naphthol Mannich bases (−/+**1a-j**)*

The spectroscopic data (^{1}H and ^{13}C NMR), IR, UV and MS of these compounds were identical to those reported for racemates in the earlier section.

*2.5.1. 1-((2-Hydroxynaphthalen-1-yl)(phenyl)methyl)-piperidin-4-ol (−**1a**)*

White solid (97.2%); R_f 0.29 (5% MeOH/DCM); mp 205–208 °C; $[\alpha]_D$ −10.66 (25 °C, MeOH).

*2.5.2. 1-((4-Fluorophenyl)(2-hydroxynaphthalen-1-yl)methyl)-piperidin-4-ol (−**1b**)*

Pale yellow solid (74.2%); R_f 0.21 (5% MeOH/DCM); mp 170–173 °C; $[\alpha]_D$ −4.80 (25 °C, MeOH).

*2.5.3. 1-((4-Chlorophenyl)(2-hydroxynaphthalen-1-yl)methyl)-piperidin-4-ol (−**1c**)*

Pale yellow solid (70.0%); R_f 0.48 (5% MeOH/DCM); mp 84–86 °C; $[\alpha]_D$ −26.04 (25 °C, MeOH).

*2.5.4. 1-((2-Hydroxynaphthalen-1-yl)(p-tolyl)methyl)-piperidin-4-ol (−**1d**)*

White solid (74.2%); R_f 0.20 (5% MeOH/DCM); mp 130–133 °C; $[\alpha]_D$ −7.14 (25 °C, MeOH).

*2.5.5. 1-((2-Hydroxynaphthalen-1-yl)(4-methoxyphenyl) methyl)-piperidin-4-ol (−**1e**)*

White solid (57.1%); R_f 0.23 (5% MeOH/DCM); mp 130–133 °C; $[\alpha]_D$ −10.55 (25 °C, MeOH).

*2.5.6. 1-((3,4-Dichlorophenyl)(2-hydroxynaphthalen-1-yl) methyl)-piperidin-4-ol (−**1f**)*

White solid (84.0%); R_f 0.36 (5% MeOH/DCM); mp 128–131 °C; $[\alpha]_D$ −14.58 (25 °C, MeOH).

*2.5.7. 1-((2-Hydroxynaphthalen-1-yl)(3,4-dimethoxyphenyl) methyl)-piperidin-4-ol (−**1g**)*

Pale brown solid (88.0%); R_f 0.39 (5% MeOH/DCM); mp 187–189 °C; $[\alpha]_D$ −46.89 (25 °C, MeOH).

*2.5.8. 1-((Benzo[d][1,3]dioxol-5-yl)(2-hydroxynaphthalen-1-yl)-methyl)piperidin-4-ol (−**1h**)*

Pale brown solid (92.0%); R_f 0.48 (5% MeOH/DCM); mp 118–120 °C; $[\alpha]_D$ −3.63 (25 °C, MeOH).

*2.5.9. 1-((2-Hydroxynaphthalen-1-yl)(pyridin-4-yl)methyl)-piperidin-4-ol (+**1i**)*

Rust-colored solid (78.4%); R_f 0.50 (5% MeOH/DCM); mp 170–173 °C; $[\alpha]_D$ +5.83 (25 °C, MeOH).

*2.5.10. 1-((2-Hydroxynaphthalen-1-yl)(pyridin-2-yl)methyl)-piperidin-4-ol (+**1j**)*

Pale brown solid (88.6%); R_f 0.32 (5% MeOH/DCM); mp 181–183 °C; $[\alpha]_D$ +5.92 (25 °C, MeOH).

2.6. X-ray crystallography

Crystals of compound (−)-**1c** were grown from a saturated dichloromethane–methanol (1:1) solution. A colorless block crystal having approximate dimensions of 0.36 mm × 0.28 mm × 0.19 mm was mounted on a glass fiber. All measurements were made on a Rigaku RAXIS RAPID imaging plate area detector with graphite monochromated Mo-Kα radiation.

The data were collected at a temperature of −150 ± 1 °C to a maximum 2θ value of 145.1°. The structure was solved by direct methods [13] and expanded using Fourier techniques [14]. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined isotropically. Neutral atom scattering factors were taken from Cromer and Weber [15]. Anomalous dispersion effects were included in F_{calc} [16]; the values for $\Delta f'$ and $\Delta f''$ were those of Creagh and McAuley [17]. The values for the mass attenuation coefficients are those of Creagh and Hubbell [18]. All calculations were performed using the CrystalStructure [19,20] crystallographic software package.

The crystallographic data collection parameters are presented in Table 2. The full details of the structure have been deposited with the Cambridge Structural Database (CCDC # 700816).

3. Results and discussion

Mannich reactions were carried out using 10 aromatic aldehydes to produce 10 different 2-naphthol Mannich bases namely, 1-((2-hydroxynaphthalen-1-yl)arylmethyl)piperidin-4-ols (**1a-j**, Scheme 1). 2-Naphthol, the aromatic aldehyde and 4-piperidinol were reacted in equimolar ratio in the presence of *p*-toluenesulfonic acid (pTSA) in refluxing ethanol. Products were purified by column chromatography or recrystallization and characterized by spectroscopic means. We invariably observed broad peaks in ^{1}H and ^{13}C NMR spectra owing to molecular dynamics commonly exhibited by piperidine derivatives [21]. The methine C attached to –OH group was sometimes not observed even after ~21 000 scans (overnight) on 300 MHz NMR. This phenomenon has also been noted previously on structurally related compounds [22].

Mannich bases have in fact been synthesized with an enantiomeric excess in the past from enantiomerically enriched starting materials [23]. In present investigation, we elected to employ kinetic resolution of racemic Mannich bases using an appropriate enzyme to catalyze selective acylation. These chiral molecules contain a phenolic and a secondary aliphatic hydroxyl group and are therefore candidates for chemo- (alcoholic vs. phenolic –OH), regio- (two –OH groups at different locations) as well as enantioselection (*d* vs. *l* stereoisomers).

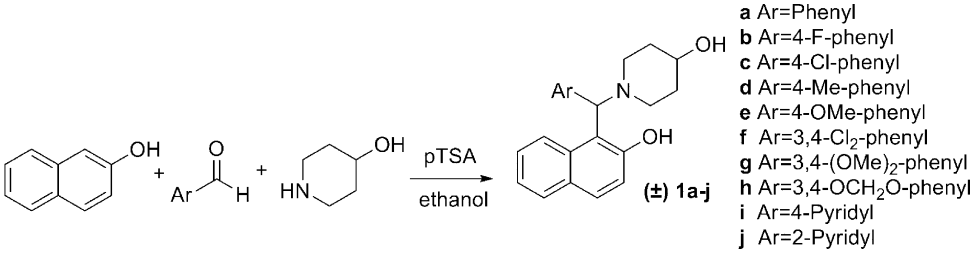
The synthesized 1-((2-hydroxynaphthalen-1-yl)arylmethyl) piperidin-4-ols (±**1a-j)** were subjected to acetylation (using vinyl acetate as an acetyl group donor) under enzyme-assisted kinetic resolution conditions at ambient temperature in chloroform (Scheme 2). The enzyme reaction time varied from 72 to 120 h. While the acetylation can potentially happen on either or both of the hydroxyl groups, acetylation was selectively expected at the alcoholic hydroxyl group based on previous precedence [24]. Although chloroform is not a solvent of choice for enzyme-assisted reactions (acetone, ethers, cyclic ethers, hexane, toluene, etc. are commonly used) [12] the insolubility of the starting materials dictated its selection. The progress of the reaction was monitored by TLC and the reaction was stopped after visual inspection of the TLC indicated ~50% conversion to the product. Since it was assumed that the process would be highly enantioselective, any acetylated product formed was expected to be highly enantiomerically enriched and therefore a crude estimation of the reaction progress was considered reasonable. The unreacted hydroxyl compounds and acetylated compounds were then separated via column chromatography.

Table 1
Specific rotations, $[\alpha]_D$ of 1-((2-hydroxynaphthalen-1-yl)arylmethyl)piperidin-4-yl acetates (**2a-j**) and unreacted 1-((2-hydroxynaphthalen-1-yl)arylmethyl)piperidin-4-ols (**1a-j**).

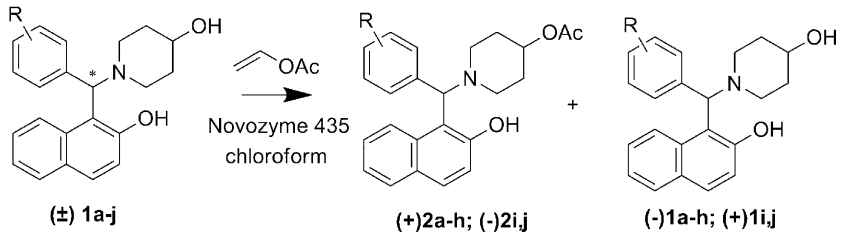
R	**2a-j**		Unreacted **1a-j**	
	Compd. ID	$[\alpha]_D$	Compd. ID	$[\alpha]_D$
Phenyl	**+2a**	+30.0	**−1a**	−10.66
4-Fluorophenyl	**+2b**	+10.75	**−1b**	−4.80
4-Chlorophenyl	**+2c**	+10.29	**−1c**	−26.04
4-Methylphenyl	**+2d**	+26.90	**−1d**	−7.14
4-Methoxyphenyl	**+2e**	+21.00	**−1e**	−10.55
3,4-Dichlorophenyl	**+2f**	+12.89	**−1f**	−14.58
3,4-Dimethoxyphenyl	**+2g**	+15.63	**−1g**	−46.89
3,4-Dioxolphenyl	**+2h**	+3.20	**−1h**	−3.63
4-Pyridyl	**−2i**	−4.62	**+1i**	+5.83
2-Pyridyl	**−2j**	−7.07	**+1j**	+5.92

Spectroscopic characterization of all acetylated products led to their characterization as 1-((2-hydroxynaphthalen-1-yl)arylmethyl)piperidin-4-yl acetates (**2a-j**) where the acetyl group was chemo- and regioselectively delivered onto the piperidinol hydroxyl group exclusively. ^{1}H NMR of the acetylated compounds showed a broad peak in the δ 10–14 range characteristic of the phenolic hydroxyl engaged in hydrogen-bonding (with piperidine N). Novozyme 435® is also known to acylate phenolic hydroxyl groups [25]; the selective acylation of piperidinol hydroxyl over the aromatic hydroxyl may be due to difficulty experienced by the enzyme in acetylating the H-bonded and sterically hindered phenolic hydroxyl group or due to chemoselective preference of the enzyme to acylate alcoholic hydroxyl group [26].

Optical rotations of the compounds **2a-j** and the unreacted diols **1a-j** confirmed the reciprocal enantiomeric enrichment (Table 1). Using a polarimeter, it was determined that acetylation led to a product with non-zero optical rotation. This was reciprocated by the corresponding unreacted, optically enriched hydroxyl enantiomer which showed an opposite optical rotation value. This



Scheme 1. Synthesis of racemic 2-naphthol Mannich bases, 1-((2-hydroxynaphthalen-1-yl)arylmethyl)piperidin-4-ols (±**1a-j**).



Scheme 2. Enantioselective enzyme-assisted acetylation of 1-((2-hydroxynaphthalen-1-yl)arylmethyl)piperidin-4-ols (**1a-j**).

Table 2
Crystallographic data collection parameters for **1c**.

Parameter	
Empirical formula	$C_{22}H_{22}NO_2Cl$
Formula weight	367.87
Crystal color, habit	Colorless, block
Crystal dimension (mm^3)	$0.36 \times 0.28 \times 0.19$
$F(0\,0\,0)$	776
Crystal system	Monoclinic
Space group	$P2_1/n$ (#14)
Z	4
a (Å)	9.6254(4)
b (Å)	17.3965(15)
c (Å)	11.2215(9)
β (°)	102.503(3)
V (Å^3)	1834.5(2)
d_{calc} ($g\,cm^{-3}$)	1.332
Temperature (K)	123
Radiation	Mo-Kα ($\lambda = 0.71070$ Å)
μ (cm^{-1})	2.241
Total reflections	61 271
Observed reflections ($F_o > 4\sigma(F_o)$)	29 374
No. of variables	323
R_{int}	0.023
θ_{max} (°)	45
S (GoF) on F^2	0.989
R_1 ($I > 3\sigma(I)$)[a]	0.0368
wR_2 (all data)[b]	0.0451
Largest diff. peak and hole (e Å^{-3})	0.53 and −0.35

[a] $R_1 = \sum ||F_o| - |F_c|| / \sum |F_o|$.

[b] $wR_2 = [\sum w(|F_o| - |F_c|)^2 / \sum wF_o^2]^{1/2}$ where w is Chebychev polynomial with 3 parameters 8.3157, 1.5359, 6.3603.

established the enantioselectivity of Novozyme 435® in the present investigation.

In the case of 4-pyridyl (**1i**, **2i**) and 2-pyridyl (**1j**, **2j**) substituted compounds, the signs of optical rotation of the enzyme reaction products were reversed. The acetylated enantiomers showed negative values of optical rotation, whereas the unreacted hydroxyl compounds gave positive values. Although this may seem inconsistent with the enantioselectivity of the enzyme, it may still be in agreement. The sign of optical rotation is not indicative of absolute stereochemistry (i.e. *R* or *S*). Thus, the apparent sign switching may not be representative of a subsequent change in enantioselectivity. Also, it should be noted that 2-pyridyl substituted compound (**1j**, **2j**) will have an opposite stereochemical notation (*R*/*S*) in comparison with the rest of the molecules in the series in same stereochemical orientation due to altered priority sequence when Cahn–Ingold–Prelog rule is applied.

After separating the enantiomerically enriched pairs in derivatized and underivatized forms, we decided to ascertain the optical purities. Our efforts to determine enantiomeric excess (*ee*) by NMR utilizing chiral shift reagents ((+)-Eu(hfc)$_3$ and (+)-Eu(tfc)$_3$) failed owing to the molecular dynamics displayed by the molecules (*vide supra*). Also, we were unable to resolve the peaks of enantiomeric pairs on chiral HPLC. Subsequently, we elected to take our chances and determine the absolute stereochemistry of one representative enantiomerically enriched compound through X-ray crystallography. We were able to obtain crystals of enantiomerically enriched unreacted 1-((4-chlorophenyl)(2-hydroxynaphthalen-1-yl)methyl)piperidin-4-ol (−)-**1c**. We subjected this molecule to X-ray crystallographic studies and were able to resolve the molecular structure (Fig. 3). The crystal structure clearly shows the H-bonding of the phenolic –OH with the piperidinol N as acceptor. Unfortunately, in regards to the absolute stereochemistry, it turned out that the molecules crystallized in centrosymmetric crystal lattice with an inversion centre and that the crystal studied was racemic. Preferential crystallization of thermodynamically more stable racemate crystal from a solution of enantiomerically

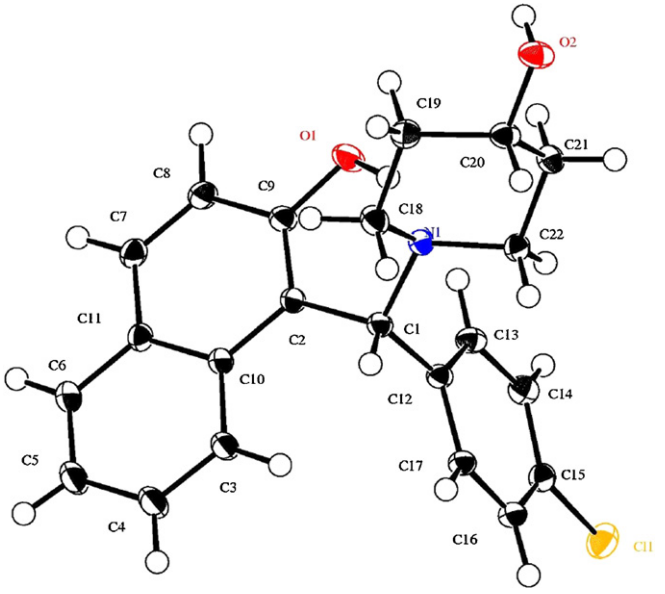


Fig. 3. ORTEP diagram of compound **1c**.

enriched sample is facile and relatively common [27]. After the preferential crystallization of all or nearly all racemate, the residual enantiopure material may or may not crystallize. In our case, we inadvertently pooled the rest of the material following crystal sampling and were not left with any enantiopure material to repeat X-ray crystallography without a significant undertaking.

4. Conclusion

The purpose of this research is to design a method for the synthesis of novel potential SERMs. To achieve this, enantioselective synthesis of structurally simpler analogs of designed potential SERMs was investigated. The Mannich reaction was used to synthesize 2-naphthol Mannich bases using 2-naphthol, 4-piperidinol, and 10 different aromatic aldehydes. These 10 chiral Mannich bases were then kinetically resolved using an enzyme-assisted chemo-, regio-, and enantioselective acetylation process in an organic solvent. While acyl transfer occurred with exclusive chemo- and regioselectivity, the optical enrichment was also achieved as evidenced by non-zero optical rotations of the mono-acetylated products and unreacted dihydroxy compounds. We have successfully established the chemistry to synthesize and resolve the enantiomeric pairs which will be applied in future synthesis of designed SERMs. We will attempt to establish the enantiomeric excess of the designed SERMs employing other strategies such as derivatization to disrupt H-bonding prior to chiral HPLC and shift reagent-promoted NMR analysis.

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