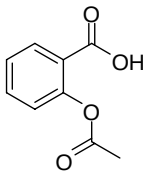
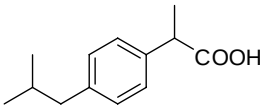
PART II : SYNTHESIS OF NAPHTHOL DERIVATIVES WITH ANTI-INFLAMMATORY ACTIVITY

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are drugs with analgesic (against minor pain and aches), antipyretic (against fever) and anti-inflammatory effects. Prominent members of this group of drugs include aspirin (**165**) and ibuprofen (**166**).

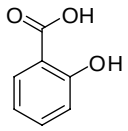


Aspirin, **165**



Ibuprofen, **166**

In 1829, the aspirin precursor, salicylic acid (**167**) was isolated from the folk remedy willow bark and NSAIDs have become an important part of the pharmaceutical treatment of pain at low doses and inflammation at higher doses.



Salicylic acid, **167**

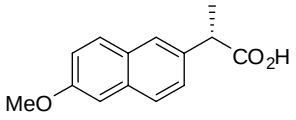
NSAIDs are usually indicated for the treatment of acute or chronic conditions such as pain and inflammation and their widespread has meant that that adverse effects of these relatively safe drugs have become increasingly prevalent. The two main adverse drug reactions (ADRs), associated with NSAIDs are gastrointestinal (GI) effects and renal effects. These effects are dose-dependent, and in many cases

severe enough to pose risks of ulcer perforation, upper gastrointestinal bleeding, and death, limiting the use of NSAID therapy.

Most NSAIDs act as non-selective inhibitors of the enzyme, cyclooxygenase, inhibiting to varying degrees both cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) isoenzymes. Cyclooxygenase catalyses the formation of various types of prostaglandins and thromboxane, from arachidonic acid, promoting inflammation, pain, and fever. However, only COX-1 produces prostaglandins that support platelets and protect the stomach lining. Nonsteroidal anti-inflammatory drugs block the COX enzymes and reduce prostaglandins throughout the body. As a consequence, ongoing inflammation, pain, and fever are reduced. Since the prostaglandins that protect the stomach and support the platelets and blood clotting also are reduced, NSAIDs can cause ulcers in the stomach and promote bleeding. NSAIDs differ in how strongly they inhibit COX-1 and, therefore, in their tendency to cause ulcers and promote bleeding.

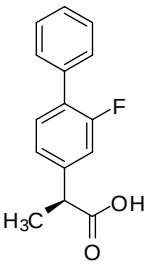
The discovery of COX-2 in 1991 by Xie *et al*. (Xie *et al*., 1991) raised the hope of developing an effective NSAID without the gastric problems, characteristic of these agents. It was thought that selective inhibition of COX-2 would result in anti-inflammatory action without disrupting the COX-1 gastroprotective prostaglandins.

COX-1 is a constitutively expressed enzyme with a "house-keeping" role in regulating many normal physiological processes. One of these is in the stomach lining, where prostaglandins serve a protective role, preventing the stomach mucosa from being eroded by its own acid. When non-selective COX-1/COX-2 inhibitors (such as aspirin, ibuprofen, and naproxen (**168**)) lower stomach prostaglandin levels, these protective effects are lost and ulcers of the stomach or duodenum and internal bleeding can result. COX-2 is an enzyme expressed in inflammation, and it is the inhibition of COX-2 that produces the desirable effects of NSAIDs.

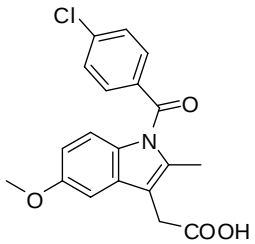


Naproxen, **168**

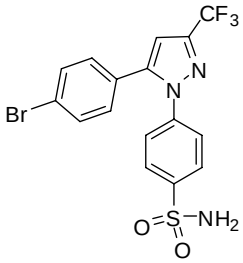
In 1996, Kurumbail *et al*. reported the structural basis for selective inhibition of COX-2 by anti-inflammatory agents such as flurbiprofen (**169**), indomethacin (**170**) and SC-558 (**171**) which is a highly selective COX-2 inhibitor.



Flurbiprofen, **169**

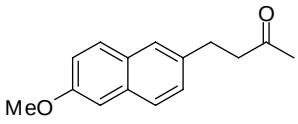


Indomethacin, **170**



SC-558, **171**

As some of NSAIDs such as naproxen and nabumetone (**172**) possess the naphthyl skeleton and naphthol derivatives are intermediates in the synthesis of naphthoquinone ester, it is advantageous to study the anti-inflammatory activity of naphthols.



Nabumetone, **172**

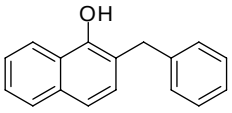
(*S*)-Naproxen is a nonsteroidal anti-inflammatory drug introduced to the market by Syntex in 1976. It showed less potent inhibition of COX-1 and COX-2 activity in blood with IC_{50} values of 32.01 and 28.19 μM, respectively. So, the ratio of inhibition concentration (IC_{50}) of naproxen for COX-2/COX-1 is 0.88. Nabumetone (4-(6-methoxy-2-napthalenyl)-2-butanone) is a novel nonacidic broad-spectrum anti-inflammatory, analgesic and antipyretic agent, discovered in 1985. It inhibits COX-1 and COX-2 with IC_{50} values of 33.57 and 20.83 μM, respectively. So,

the ratio of inhibition concentration (IC_{50}) of nabumetone for COX-2/COX-1 is 0.62. Thus naproxen and nabumetone are more COX-2 selective (Kolasa *et al*., 1997; Cryer *et al*., 1998).

Therefore, it is of interest to study the anti-inflammatory activity of naphthol derivatives and to develop more COX-2 selective drugs.

LITERATURE REVIEWS

In 1990, Batt *et al*. reported the synthesis, biological evaluation and structure-activity relationships of a series of 1-naphthol bearing carbon substituents at the 2-position. These compounds were found to be potent inhibitors of 5-lipoxygenase from RBL-1 cells and also inhibited bovine seminal vesicle cyclooxygenases. Especially, 2-benzyl-1-naphthol (DuP 654, **173**) showed a very attractive profile of topical anti-inflammatory activity (IC50 = 0.019 μM and is currently in clinical trials as a topically applied antipsoriatic agent.



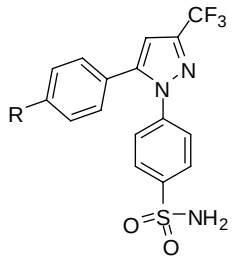
DuP 654, **173**

In 1997, Kolasa and co-workers reported using NSAIDs as orally bioavailable scaffolds to design selective 5-lipoxygenase (5-LO) inhibitors. Replacement of the NSAID carboxylic acid group with a *N*-hydroxyurea group provided congeners with selective 5-LO inhibitory activity. Each new *N*-hydroxyurea congener had individual characteristics which imparted differences in the amount of cyclooxygenase inhibitory activity retained and oral bioavailability observed in the rat.

In 1999, Llorens and co-workers studied molecular modeling on the two cyclooxygenase isozymes suggesting that the cavity at the mouth of the active site on the membrane domain may act as an actual binding site of COX ligands.

In 2000, Plount Price and Jorgensen reported the analysis of the binding affinities for celecoxib analogues (**174**) with COX-1 and COX-2 from docking experiments. The results reveal that steric hindrance restricts access of the ligand's substituents to some regions of the binding pocket and thus affects binding affinity. Furthermore, ligands which contain H-bonding functionality at the 4-position of the 5-

aryl ring are poor binders because H-bonds cannot be formed between the substituents and the surrounding protein residues.



Celecoxib analogues, **174**

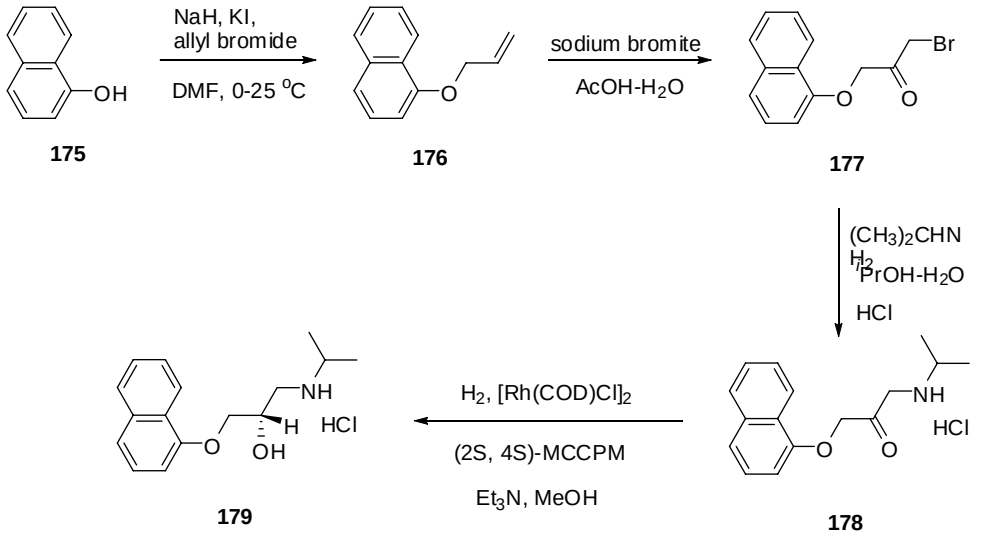
In the same year, Talanian *et al.* (Talanian *et al.*, 2000) reported using caspases as targets for anti-inflammatory and anti-apoptotic drugs. These enzymes had required roles in both processes and were widely considered promising targets for drug discovery. Much of the emphasis in caspase chemistry had been on development of novel electrophilic aspartic acid derivatives. Electrophilic moieties such as acyloxymethyl, aminomethyl and sulfonylaminomethyl were used in their caspase inhibitors and many of them were effective caspase-1 inhibitors.

In 2001, Dannhardt and Kiefer discussed the current status and future prospects of cyclooxygenase inhibitors. They described selective cyclooxygenase inhibitors involving inflammatory processes as being agents that inhibit COX-2 but not COX-1 as a new attractive therapeutic development and a major advance in the treatment of rheumatoid arthritis and osteoarthritis. In inflammatory processes, COX-2 seems to play a role in angiogenesis, colon cancer and Alzheimer's disease, based on the fact that it is expressed during these diseases. Moreover, they explained the benefits of specific and selective COX-2 inhibitors which are currently under discussion and offer a new perspective for further use of COX-2 inhibitors.

In 2005, Luo and co-workers discussed the mechanism of COX-2 inhibitor therapy and its role in the development of anti-inflammatory, analgesic and antipyretic drugs.

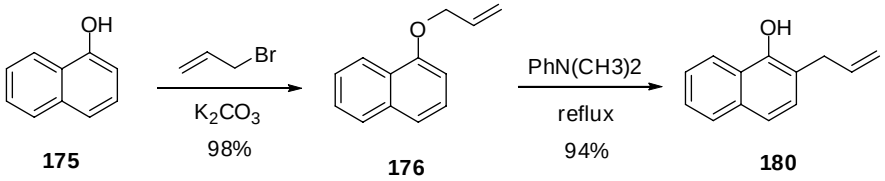
***O*-Allylation of naphthol and Claisen rearrangement**

In 1990, Takahashi *et al*. reported highly efficient asymmetric hydrogenation of 3-(aryloxy)-2-oxo-1-propylamine derivatives leading to a practical synthesis of (*S*)-1-amino-3-(aryloxy)-2-propanol derivatives, chiral *β*–adrenergic blocking agents (**Scheme 29**).



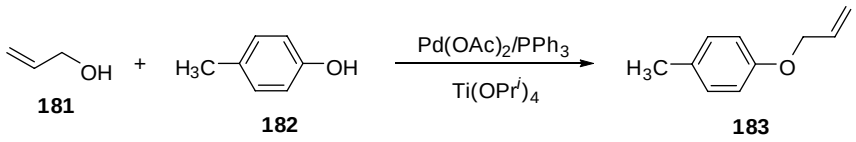
Scheme 29

In 1996, Reich *et al*. reported the synthesis of allyl naphthyl ether (**176**) from 1-naphthol (**175**) and Claisen rearrangement of this ether under reflux in *N*,*N*-dimethylaniline to provide allyl naphthol (**180**) (**Scheme 30**).



Scheme 30

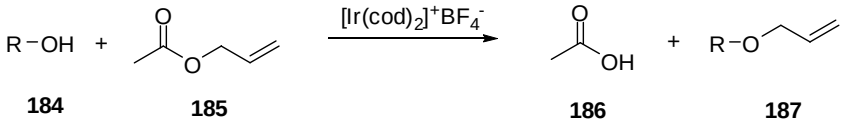
In 1997, Satoh and co-workers studied the palladium-catalyzed etherification of allyl alcohols using phenols in the presence of titanium (IV) isopropoxide (**Scheme 31**). The etherification gave the corresponding ethers in good yield .



181 **182** **183**

Scheme 31

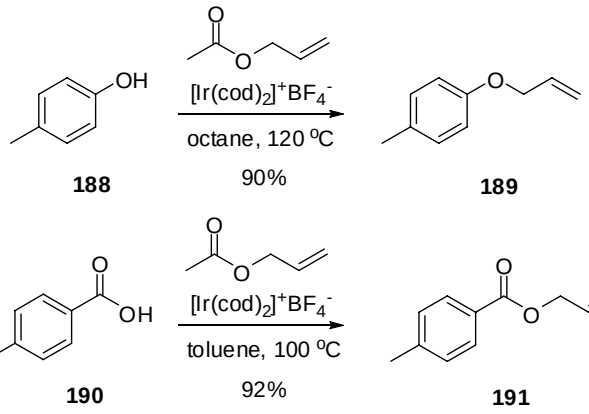
In 2001, Nakagawa *et al*. reported the allylation of alcohols and carboxylic acids with allyl acetate (**185**) using $[Ir(cod)_2]^+BF4^-$ complex as catalyst.(**Scheme 32**) Allyl ether and allyl ester products were obtained in good to quantitative yield. This complex also catalyzed the reaction of alkyl and aromatic amines with allyl acetate to give the corresponding allyl amines in fair to good yield.



184 **185** **186** **187**

Scheme 32

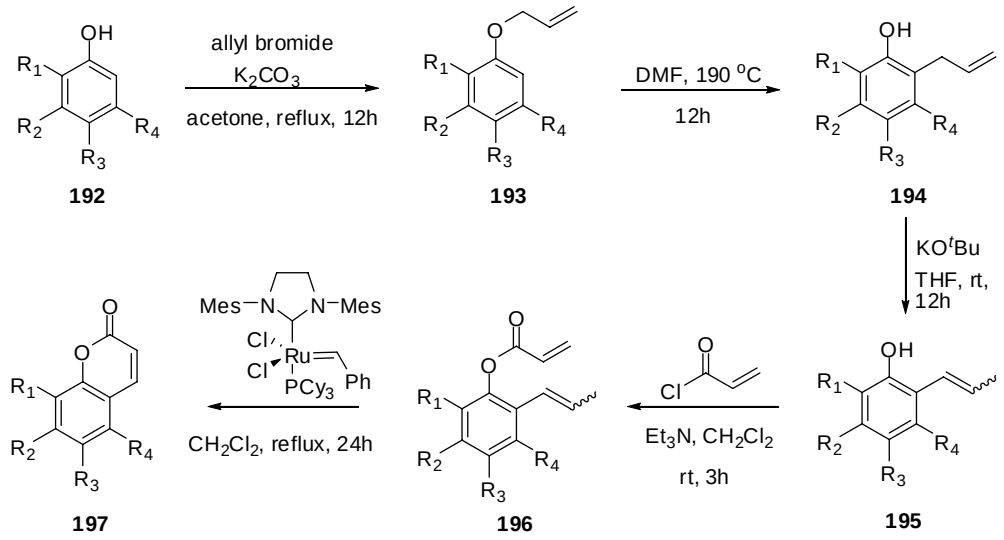
For example:



188 **189** **190** **191**

In 2003, Van and co-workers synthesized coumarins from phenolic substrates using ring-closing metathesis. This sequence involves *O*-allylation of phenols

followed by ortho-Claisen rearrangement, subsequent basic-induced isomerization, acylation and finally ring-closing metathesis with Grubb's and generation catalyst (**Scheme 33**).



Scheme 33

MATERIALS AND METHODS

Materials

Instrumentations

Melting points (m.p.) were determined on a Fisher John apparatus and MEI-TEMP capillary melting point apparatus at the Department of Chemistry, Kasetsart University and are incorrected.

The infrared (IR) spectra were recorded on a Perkin-Elmer 2000 Fourier transform infrared spectrophotometer at the Department of Chemistry, Faculty of Science, Kasetsart University.

Mass spectra (MS) were obtained on the GCMS-QP-5050A at Kasetsart Agricultural and Agro Industrial Product Improvement Institute (KAPI) and on AGILENT 1100 series LC/MSB TRAP at the Faculty of Science, Kasetsart University.

Proton nuclear magnetic resonance (^{1}H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded at 400 MHz on a VARIAN ^{UNITY} INOVA 400 MHz spectrometer at the Department of Chemistry, Kasetsart University. Chemical shifts (δ) are given in parts per million (ppm) downfield from tetramethylsilane (TMS) as internal standard. Coupling constants (J) are given in Hertz (Hz). Unless otherwise specified deuterochloroform ($CDCl_3$) was used as a solvent. The following abbreviations are used: s = singlet, d = doublet, q = quartet, quint = quintet, sext = sextet, sept = septet, m = multiplet, br s = broad singlet, dd = doublet of doublet, dt = doublet of triplet, td = triplet of doublet, qd = quartet of doublet, ddd = doublet of doublet of doublet.

High resolution mass spectral data (HRMS) were measured at EPSRC National Mass Spectrometry Service Centre, Department of Chemistry, University of

Wales Swansea, UK and by LCP Micromass at the National Science and Technology Development Agency (NSTDA), Bangkok, THAILAND.

Elemental analyses were performed by the LECO CHNS-932 at the Faculty of Science, Kasetsart University.

Chromatographic systems

Thin-layer chromatography (TLC) on aluminum sheets with silica gel 60 F_{254} was used routinely for monitoring reaction progress. The chromatograms were visualized under ultraviolet light (254 nm).

Flash column chromatography was performed on silica gel (230-400 mesh, Merck 9385) according to the method of Still (1978).

Chemical reagents

All reagents and solvents were used as received from Merck, Fluka and Aldrich Chemical. Unless otherwise noted in the case of anhydrous condition, purifications were accomplished according to the standard procedure outlined in Vogel's Text Book of Practical Organic Chemistry (1989).

Dry reagents

Acetone was dried over Type 4A molecular sieves for 24 hours.

Benzene was dried over sodium wire for 24 hours.

Dichloromethane was dried over anhydrous calcium chloride for 24 hours then distilled from calcium hydride and stored over Type 3A molecular sieves.

Diethyl ether and tetrahydrofuran (THF) were dried over sodium metal and benzophenone under nitrogen atmosphere until the dark blue or purple colour persisted. The anhydrous ether was distilled immediately before use.

Dimethylformamide (DMF) was dried over Type 3A molecular sieve for 72 hours, followed by distillation under reduced pressure and stored over Type 3A molecular seives

Tissue culture components

All tissue culture components were purchased from Gibco BRL (Gaithersburg, MD). Aspirin and calcium ionophore A23187 were purchased from Sigma (St. Louis, MO). ^{3}H-PGE_2 was from NEN Life Science (Boston, MA) and anti-PGE_2 antibody was from the Upstate Biotechnology (Upstate, NY) or Sigma (St. Louis, MO).

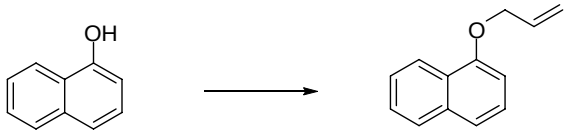
Methods

***O*-Allylation of naphthol**

General procedure:

A mixture of 1-naphthol (**175**) (3.42 mmol), allyl halide (4.10 mmol) and potassium carbonate (3.6 mmol) in acetone (10 mL) was refluxed for 3 hours. The reaction mixture was cooled to room temperature, filtered and the solids washed with acetone. The combined organic layers were concentrated in vacuo, diethyl ether (50 mL) added and the organic phase was washed with water (3×20 mL), dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated in vacuo.

1-Allyloxy-naphthalene (176) (Kongkathip *et al*., 2003)



175 **176**

Prepared by the general procedure from 1-naphthol (**175**) (0.439 g, 3.42 mmol), allyl bromide (0.33 mL, 4.1 mmol) and potassium carbonate (0.50 g, 3.6 mmol) in acetone (10 mL) at reflux over 3 hours. The residue was purified by flash column chromatography eluting with hexane to afford the product **176** (0.54 g, 86%) as a colourless oil (Reich, 1996).

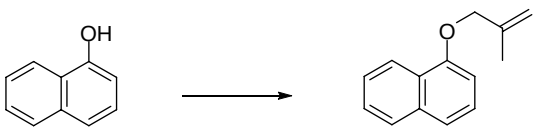
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 4.73 (d, *J*=5.0 Hz, 2H, OCH_2), 5.35 (dd, *J*=10.0 and 1.0 Hz, 1H, CH_2=CH), 5.55 (dd, *J*=17.0 and 1.0 Hz, 1H, CH_2=CH), 6.20 (m, 1H, -*CH*=CH_2), 6.82 (d, *J*=7.5 Hz, 1H, ArH), 7.38 (m, 1H, ArH), 7.45 (d, *J*=8.2 Hz, 1H, ArH), 7.50 (m, 2H, ArH), 7.80 (m, 1H, ArH), 8.35 (m, 1H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 69.59 (CH_2), 105.73 (CH_2), 118.01 (CH), 121.05 (CH), 122.77 (CH), 125.85 (CH), 126.46 (CH), 127.05 (C, CH), 128.12 (CH), 134.01 (CH), 135.22 (C), 154.99 (C).

FTIR (neat, cm^{-1}): 3055 (CH), 1580, 1508, 1400, 1269 (C=C), 1237, 1097 (C-O).

MS (EI), *m/z* (% relative intensity): 184 (M^+, 70), 143 (72), 113 (100).

1-(2-Methyl-allyloxy)-naphthalene (198) (Kongkathip *et al*., 2003)



175 **198**

Prepared by the general procedure from 1-naphthol (**175**) (0.51 g, 3.47 mmol), 3-chloro-2-methylprop-1-ene (0.40 mL, 4.17 mmol) and potassium carbonate (0.50 g, 3.47 mmol) in acetone (10 mL) at reflux over 20 hours. The residue was purified by flash column chromatography eluting with hexane to afford the product **198** (0.58 g, 84%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.00 (s, 3H, CH_3), 4.65 (s, 2H, OCH_2), 5.10 and 5.30 (2×s, 2×1H, CH_2=C), 6.86 (d, *J*=7.5 Hz, 1H, ArH), 7.40 (m, 1H, ArH), 7.48 (d, *J*=7.6 Hz, 1H, ArH), 7.54 (m, 2H, ArH), 7.85 (m, 1H, ArH), 8.39 (m, 1H, ArH).

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 19.54 (CH_3), 71.71 (CH_2), 104.93 (CH_2), 112.53 (CH), 120.25 (CH), 122.04 (CH), 125.12 (CH), 125.78 (CH), 126.32 (C, CH), 127.41 (CH), 134.48 (C), 140.89 (C), 154.34 (C).

FTIR (neat, cm^{-1}): 3054 (CH-aromatic), 2918 (CH_2), 1579, 1508, 1457, 1269 (C=C), 1235, 1101 (C-O).

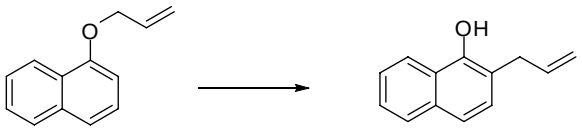
MS (EI), *m/z* (% relative intensity): 198 (M^+,77), 183 (56), 143 (63), 115 (100).

Claisen rearrangement of allyl naphthyl ether

General procedure:

The allyl ethers (**176** and **198**) (0.4 g) in *N,N*-dimethylformamide (4 mL) was heated for 6 hours at 180 ^{o}C. Then the reaction mixture was cooled to room temperature, water was added and the mixture was extracted with diethyl ether (3×20 mL). The combined organic layers were washed with water, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated in vacuo.

2-Allyl-naphthalen-1-ol (180) (Kongkathip *et al*., 2003)



176 **180**

Prepared by the general procedure from allyl ether **176** (0.391 g) in *N,N*-dimethylformamide (4 mL) at 180 ^{o}C over 6 hours. The residue was purified by flash column chromatography eluting with 2% dichloromethane-hexane to afford the product **180** (0.321 g, 82%) as a colourless oil (Reich, 1996).

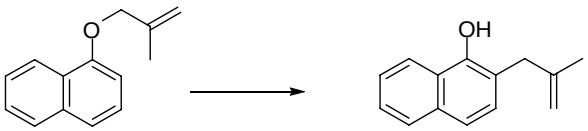
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.56 (d, 2H, *J*=6.2 Hz, CH_2), 5.23 (m, 2H, *CH_2*=CH), 5.54 (s, 1H, OH), 6.67 (m, 1H, CH_2=*CH*), 7.21 (d, *J*=8.3 Hz, 1H, ArH), 7.40 (d, *J*=8.3 Hz, 1H, ArH), 7.45 (m, 2H, ArH), 7.77 (m, 1H, ArH), 8.16 (m, 1H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 36.44 (CH_2), 117.68 (CH_2), 118.44 (C), 121.04 (CH), 122.00 (CH), 125.49 (C), 125.98 (CH), 126.45 (CH), 128.20 (CH), 129.12 (CH), 134.42 (C), 136.80 (CH), 150.23 (C).

FTIR (neat, cm^{-1}): 3509 (OH), 3057 (CH-aromatic), 1574, 1509, 1389 (C=C), 1265, 1075 (C-O).

MS (EI), *m/z* (% relative intensity) : 184 (M^+, 100), 169 (32), 141 (45), 128 (63).

2-(2-Methyl-allyl)-naphthalen-1-ol (199) (Kongkathip *et al*., 2003)



198 **199**

Prepared by the general procedure from allyl ether **198** (0.322 g) in *N,N*-dimethylformamide (4 mL) at 180 ^{o}C over 6 hours. The residue was purified by flash column chromatography eluting with 2% dichloromethane-hexane to afford the product **199** (0.30 g, 93%) as a colourless oil (Krohn, 1996).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.80 (s, 3H, CH_3), 3.58 (s, 2H, CH_2), 5.03 (s, 2H, CH_2=C), 5.82 (s, 1H, OH), 7.24 (d, *J*=8.3 Hz, 1H, ArH), 7.42 (d, *J*=8.3 Hz, 1H, ArH), 7.50 (m, 2H, ArH), 7.80 (m, 1H, ArH), 8.22 (m, 1H, ArH).

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 22.01 (CH_3), 40.70 (CH_2), 112.80 (CH_2), 117.61 (C), 120.18 (CH), 121.58 (CH), 124.90 (C), 125.26 (CH), 125.81 (CH), 127.48 (CH), 128.99 (CH), 133.80 (C), 144.7 (C), 150.14 (C).

FTIR (neat, cm^{-1}): 3489 (OH), 3062 (CH-aromatic), 2914 (CH_2), 1657, 1575, 1441, 1387 (C=C), 1266, 1081 (C-O).

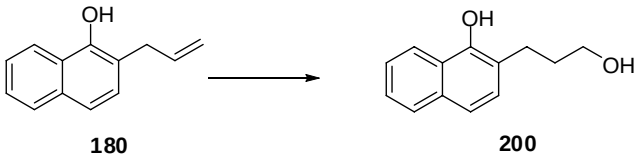
MS (EI), *m/z* (% relative intensity) : 198 (M^+, 70), 183 (63), 155 (52), 128 (100).

Hydroboration of alkenes

General procedure:

A 1M solution of borane in tetrahydrofuran (10.8 mmol) was added dropwise over 20 minutes to a stirred solution of alkene (**180** and **199**) (10.8 mmol) in anhydrous tetrahydrofuran (15 mL) at room temperature under nitrogen. After stirring at room temperature for 4 hours, water (1.1 mL) was added dropwise, followed by 3M NaOH (1.5 mL). Then hydrogen peroxide (40%, 1.5 mL) was added at such a rate that the temperature of the reaction mixture stayed between 30-50 ^{o}C. After the addition, stirring was continued for 4 hours at room temperature. Diethyl ether (15 mL) was added and the mixture washed with brine and water. The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated in vacuo.

2-(3-Hydroxy-propyl)-1-naphthalen-1-ol (200)



180 **200**

Compound **200** was synthesized by following the general procedure: a 1M solution of borane in tetrahydrofuran (10.8 mL, 10.8 mmol) was added dropwise over 20 minutes to a stirred solution of compound **180** (1.99 g, 10.8 mmol) in anhydrous tetrahydrofuran (15 mL) at room temperature under nitrogen. The reaction mixture was stirred to complete for 4 hours. The residue was purified by flash column chromatography eluting with 10 % ethyl acetate-hexane to afford the desired product **200** (1.62 g, 74%) as a colourless amorphous powder, m.p. 86-87 °C.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.95 (m, 2H, $CH_2CH_2CH_2$), 2.95 (t, J=6.4 Hz, 2H, CH_2Ar), 3.65 (t, J=5.7 Hz, 2H, OCH_2), 7.20 (d, J=8.3 Hz, 1H, ArH), 7.37 (d, J=8.3 Hz, 1H, ArH), 7.45 (m, 2H, ArH), 7.75 (dd, J=1.5 and 7.4 Hz, 1H, ArH), 8.25 (dd, J=1.5 and 8.9 Hz, 1H, ArH).

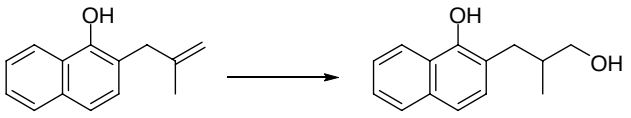
^{13}C NMR ($CDCl_3$, 75 MHz) δ: 25.04 (CH_2), 31.50 (CH_2), 60.49 (CH_2), 119.72 (C), 120.18 (CH), 122.25 (CH), 125.17 (CH), 125.40 (C), 125.61 (CH), 127.54 (CH), 128.82 (CH), 134.00 (C), 150.50 (C).

FTIR (KBr, cm^{-1}): 3481 (OH), 3141 (CH-aromatic), 2940 (CH_2), 1627, 1513, 1323 (C=C), 1272 (C-O).

MS (EI), *m/z* (% relative intensity) : 202 (M^+, 98), 184(99), 156 (69), 128 (100).

Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.41; H, 6.79 %.

2-(3-Hydroxy-2-methyl-propyl)-naphthalen-1-ol (201)



199 **201**

Compound **201** was synthesized by following the general procedure: a 1M solution of borane in tetrahydrofuran (10.7 mL, 10.7 mmol) was added dropwise over 20 minutes to a stirred solution of compound **199** (2.11 g, 10.7 mmol) in anhydrous tetrahydrofuran (15 mL) at room temperature under nitrogen. The reaction mixture was stirred to complete for 4 hours. The residue was purified by flash column chromatography eluting with 10 % ethyl acetate-hexane to afford the desired product **201** (2.21 g, 96%) as a colourless amorphous powder, m.p. 89-90^{o}C.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.08 (d, J=7.0 Hz, 3H, CH_3), 2.10 (m, 1H, CH), 2.40 (br s, 1H, OH), 2.90 (m, 2H, CH_2Ar), 3.38 (dd, J=6.9 and 10.3 Hz, 1H, OCH_2), 3.60 (dd, J=3.9 and 10.3 Hz, 1H, OCH_2), 7.21 (d, J=8.3 Hz, 1H, ArH), 7.40 (d, J=8.3 Hz, 1H, ArH), 7.48 (m, 2H, ArH), 7.80 (m, 1H, ArH), 8.15 (br s, 1H, OH), 8.30 (m, 1H, ArH).

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 17.50 (CH_3), 32.50 (CH_2), 34.58 (CH), 65.70 (CH_2), 118.30 (C), 119.53 (CH), 122.20 (CH), 125.11 (CH), 125.69 (C), 125.80 (CH), 127.48 (CH), 129.80 (CH), 133.79 (C), 150.54 (C).

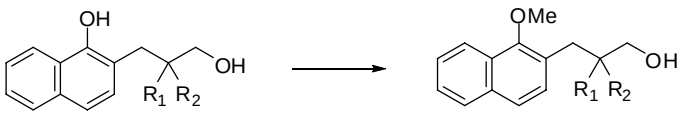
FTIR (KBr, cm^{-1}): 3376 (OH), 2953 (CH_2, CH_3), 1569, 1466, 1384, 1315 (C=C), 1267, 1016 (C-O).

MS (EI), *m/z* (% relative intensity) : 216 (M^+, 62), 198 (40), 183 (44), 157 (94), 128 (100).

Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.66; H, 7.43%.

Methylation of naphthols

General procedure:



200: $R_1 = R_2 = H$ **202**: $R_1 = R_2 = H$

201: $R_1 = H$; $R_2 = Me$ **203**: $R_1 = H$; $R_2 = Me$

98: $R_1 = R_2 = Me$ **206**: $R_1 = R_2 = Me$

A mixture of alcohol (**98, 200** or **201**)(1.0 mmol), methyl iodide (2.0 mmol) and potassium carbonate (2.0 mmol) in acetone (5 mL) was refluxed for 4 hours. Then the reaction mixtue was cooled to room temperature, filtered and washed with acetone. The filtrate was concentrated in vacuo, then diethyl ether was added and washed with water, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash column chromatography.

3-(1-Methoxy-naphthalen-2-yl)-propan-1-ol (202)

Prepared by the general procedure from naphthol **200** (0.2 g, 1.0 mmol), methyl iodide (0.12 mL, 2.0 mmol) and potassium carbonate (0.27 g, 2.0 mmol) in acetone (5 mL) at reflux over 4 hours. The residue was purified by flash column chromatography eluting with 10% ethyl acetate-hexane to afford the product (**202**) in quantitative yield (0.22 g) as a colourless oil.

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.87 (m, 2H, $CH_2CH_2CH_2$), 2.20 (br s, 1H, OH), 2.87 (t, J=7.2 Hz, 2H, CH_2Ar), 3.53 (t, J=6.0 Hz, 2H, OCH_2), 3.89 (s, 3H, OCH_3), 7.25 (d, J=8.4 Hz, 1H, ArH), 7.43 (m, 2H, ArH), 7.53 (d, J=8.4 Hz, 1H, ArH), 7.76 (d, J=7.7 Hz, 1H, ArH), 8.02 (d, J=8.2 Hz, 1H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 26.12 (CH_2), 33.91 (CH_2), 62.00 (CH_3), 62.84 (CH_2), 122.55 (CH), 125.09 (CH), 126.16 (CH), 126.66 (CH), 128.43 (C), 128.65 (CH), 128.86 (CH), 130.19 (C), 134.47 (C), 153.97 (C).

FTIR (neat, cm^{-1}): 3380 (OH), 2937 (CH_2), 1572, 1446, 1371 (C=C), 1241, 1085, 1056 (C-O).

MS (EI), *m/z* (% relative intensity) : 216 (M^+, 100), 171 (79), 156 (40), 128 (60).

Anal. Calcd for $C_{14}H_{16}O_2$: C,77.75; H, 7.46. Found: C, 77.47; H, 7.64.

3-(1-Methoxy-naphthalen-2-yl)-2-methyl-propan-1-ol (203)

Prepared by the general procedure from naphthol **201** (0.22 g, 1.0 mmol), methyl iodide (0.23 mL, 2.0 mmol) and potassium carbonate (0.25 g, 2.0 mmol) in acetone (10 mL) at reflux over 4 hours. The residue, purified by flash column chromatography eluting with 10 % ethyl acetate-hexane, provided the product (**203**) in quantitative yield (0.23 g) as a colourless oil.

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.93 (d, *J*=6.8 Hz, 3H, CH_3), 1.94 (m, 1H, CH), 2.32 (br s, 1H, OH), 2.65 (m, 1H, CH_2), 2.81 (m, 1H, CH_2), 3.30 (m, 2H, OCH_2), 3.85 (s, 3H, OCH_3), 7.20 (d, *J*=8.4 Hz, 1H, ArH), 7.40 (m, 2H, ArH), 7.49 (d, *J*=8.4 Hz, 1H, ArH), 7.73 (d, *J*=7.8 Hz, 1H, ArH), 7.98 (d, *J*=8.3 Hz, 1H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 17.75 (CH_3), 33.47 (CH_2), 37.75 (CH), 62.79 (CH_3), 66.90 (CH_2), 122.58 (CH), 124.86 (CH), 126.19 (CH), 126.65 (CH), 128.33 (C), 128.64 (CH), 129.57 (C), 129.15 (CH), 134.54 (C), 154.13 (C).

FTIR (neat, cm^{-1}): 3400 (OH), 2952 (CH_2, CH_3), 1462, 1370 (C=C), 1258, 1035 (C-O).

MS (EI), *m/z* (% relative intensity) : 230 (M^+, 50), 171 (100), 156 (44), 128 (69).

Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.32; H, 7.92.

3-(1-Methoxy-naphthalen-2-yl)-2,2-dimethyl-propan-1-ol (206)

Prepared by the general procedure from naphthol **98** (0.22 g, 1.0 mmol), methyl iodide (0.24 mL, 2.0 mmol) and potassium carbonate (0.26 g, 2.0 mmol) in acetone (10 mL) at reflux over 4 hours. The residue, purified by flash column chromatography eluting with 5 % ethyl acetate-hexane, yielded the product (**206**) (0.229 g, 98%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.94 (s, 6H, 2×CH_3), 2.71 (s, 2H, CH_2), 2.99 (s, 2H, OCH_2), 3.11 (br s, 1H, OH), 3.91 (s, 3H, OCH_3), 7.22 (d, *J*=8.4 Hz, 1H, ArH), 7.46 (m, 2H, ArH), 7.53 (d, *J*=8.4 Hz, 1H, ArH), 7.79 (m, 1H, ArH), 8.02 (m, 1H, ArH).

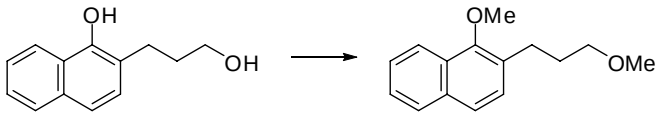
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 25.77 (2×CH_3), 38.21 (C), 38.75 (CH_2), 62.79 (CH_3), 70.03 (CH_2), 122.62 (CH), 124.41 (CH), 126.32 (CH), 126.68 (CH), 127.82 (C), 128.00 (C), 128.62 (CH), 131.08 (CH), 134.71 (C), 154.31 (C).

FTIR (neat, cm^{-1}): 3437 (OH), 2953 (CH_2, CH_3), 1466, 1371 (C=C), 1080, 1045 (C-O).

MS (EI), *m/z* (% relative intensity): 244 (M^+, 52), 171 (100), 156 (29), 128(47).

Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.72, H, 8.09.

1-Methoxy-2-(3-methoxy-propyl)-naphthalene (204)



200 **204**

To a stirred suspension of sodium hydride (0.14 g, 6 mmol) in dry tetrahydrofuran (THF) (5 mL), a solution of alcohol **200** (156) (0.2 g, 1 mmol) in dry THF (5 mL) was added dropwise. After refluxing for 3 hours, the reaction mixture was cooled to room temperature and quenched with water, then extracted with diethyl ether (3×50 mL). The combined organic phase was washed with water, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash column chromatography eluting with 2% ethyl acetate-hexane to afford the dimethoxy product (**204**) (93%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.00 (m, 2H, CH_2), 2.92 (t, J=7.7 Hz, 2H, CH_2), 3.40 (s, 3H, OCH_3), 3.48 (t, J=6.4 Hz, 2H, OCH_2), 3.97 (s, 3H, OCH_3), 7.37 (d, J=8.4 Hz, 1H, ArH), 7.47 (m, 1H, ArH), 7.53 (m, 1H, ArH), 7.61 (d, J=8.4 Hz, 1H, ArH), 7.85 (m, 1H, ArH), 8.12 (m, 1H, ArH).

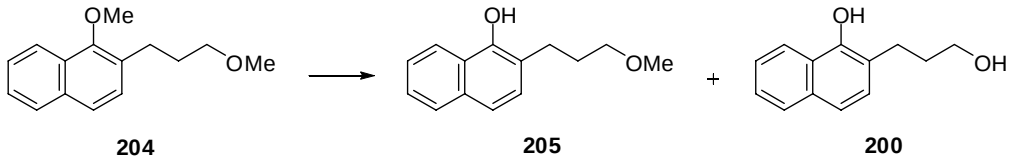
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 26.89 (CH_2), 31.27 (CH_2), 59.21 (CH_2), 62.64 (CH_3), 72.88 (CH_3), 122.62 (CH), 124.62 (CH), 126.03 (CH), 126.49 (CH), 128.58 (CH), 128.72 (C), 128.88 (CH), 130.79 (C), 134.39 (C), 154.04 (C).

FTIR (neat, cm^{-1}): 2931(CH_2), 1572, 1450, 1372 (C=C), 1243, 1116 (C-O).

MS (EI), *m/z* (% relative intensity) : 230 (M^+, 71), 171 (30), 141 (30), 57 (100).

HRMS calcd for $C_{15}H_{18}O_2$ [M+Na] 253.1204, found 253.1201.

2-(3-Methoxy-propyl)-naphthalen-1-ol (205)



204 **205** **200**

To a solution of compound **204** (0.2 g, 0.9 mmol) in dry dichloromethane (20 mL) at 0 ^{o}C, boron tribromide (0.3 mL, 3.5 mmol) was added dropwise and the solution was stirred for 1 hour at 0 °C, then water was added and extracted with dichloromethane (3×50 mL). The organic phase was washed with water, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash column chromatography eluting with 2 % ethyl acetate-hexane to afford the desired product (**205**) (84.6 mg, 45%) as the major product (a brown oil) and the minor product (**200**) (44.0 mg, 25%) as a colourless solid, m.p. 86-87 ^{o}C.

Spectroscopic data for compound **205**

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.00 (m, 2H, CH_2), 2.92 (t, J=6.4 Hz, 2H, CH_2), 3.39 (t, J=6.4 Hz, 2H, OCH_2), 3.49 (s, 3H, OCH_3), 7.22 (d, J=8.3 Hz, 1H, ArH), 7.40 (d, J=8.3 Hz, 1H, ArH), 7.48 (m, 2H, ArH), 7.79 (m, 1H, ArH), 7.94 (s, 1H, OH), 8.33 (m, 1H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 26.00 (CH_2), 29.91 (CH_2), 59.13 (CH_2), 70.40 (CH_3), 120.05(C), 120.48(CH), 122.99(CH), 125.60(CH), 125.94(C), 126.18(CH), 127.90(CH), 129.28 (CH), 134.25(C), 151.07 (C).

FTIR (neat, cm^{-1}): 3290 (OH), 2932 (CH_2, CH_3), 1662, 1574, 1463, 1387 (C=C), 1265, 1105 (C-O).

MS (EI), *m/z* (% relative intensity) : 216 (M^+, 63), 184 (100), 156 (59), 128 (50).

HRMS calcd for $C_{14}H_{16}O_2$ [M+Na] 239.1048, found 239.2046.

Spectroscopic data for compound **200**

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.95 (m, 2H, CH_2), 2.95 (t, *J*=6.4 Hz, 2H, CH_2), 3.65 (t, *J*=5.7 Hz, 2H, OCH_2), 7.20 (d, *J*=8.3 Hz, 1H, ArH), 7.37 (d, 1H, *J*=8.3 Hz, ArH), 7.45 (m, 2H, ArH), 7.75 (dd, *J*=7.4 and 1.5 Hz, 1H, ArH), 8.25 (dd, *J*=8.9 and 1.5 Hz, 1H, ArH).

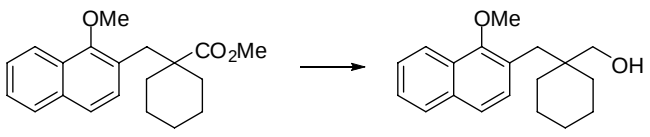
^{13}C NMR ($CDCl_3$, 75 MHz) δ: 25.04 (CH_2), 31.50 (CH_2), 60.49 (CH_2), 119.72 (C), 120.18 (CH), 122.25 (CH), 125.17 (CH), 125.40 (C), 125.61 (CH), 127.54 (CH), 128.82 (CH), 134.00 (C), 150.50 (C).

FTIR (KBr, cm^{-1}): 3481 (OH), 3141 (CH-aromatic), 2940 (CH_2), 1627, 1513, 1323 (C=C), 1272 (C-O).

MS (EI), *m/z* (% relative intensity) : 202 (M^+, 98), 184(99), 156 (69), 128 (100).

Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.41; H, 6.79.

(1-((1-Methoxynaphthalen-2-yl)methyl)cyclohexyl)methanol (210)



125 **210**

A solution of ester **125** (150 mg, 0.48 mmol) in dry diethyl ether (2 mL) was added dropwise to a stirred and ice-cooled suspension of lithium aluminium hydride (54.0 mg, 0.48 mmol) in dry diethyl ether (3 mL). After stirring for 2 hours at room temperature, the reaction mixture was quenched with ethyl acetate and water, then

extracted with diethyl ether (3×30 mL). The combined organic phases were washed with water and brine, filtered and concentrated in vacuo. The crude residue was purified by flash column chromatography eluting with 5% ethyl acetate-hexane to afford the desired product **210** (104 mg, 76%) as a colourless solid, m.p. 89-90 ºC.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.28-1.60 (m, 10H, $(CH_2)_5$), 2.73 (s, 2H, CH_2Ar), 3.03 (s, 2H, CH_2OH), 3.88 (s, 3H, $ArOCH_3$), 7.19 (d, 1H, *J*=8.4 Hz, ArH), 7.41 (m, 2H, ArH), 7.48 (d, 1H, *J*=8.4 Hz, ArH), 7.75 (m, 1H, ArH), 7.98 (m, 1H, ArH).

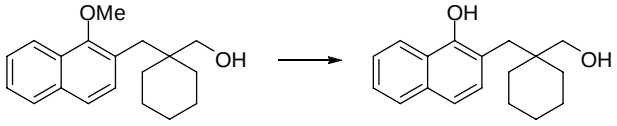
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 21.81 (2×CH_2), 26.64 (CH_2), 33.26 (2×CH_2), 35.50 (CH_2), 39.78 (C), 62.23 (CH_2), 66.75 (CH_3), 121.96 (CH), 123.79 (CH), 125.67 (CH), 126.05 (CH), 126.96 (C), 127.31 (C), 127.94 (CH), 130.14 (CH), 134.04 (C), 153.75 (C).

FTIR (KBr, cm^{-1}): 3532 (OH), 3051 (CH-aromatic), 2926, 2847 (CH_2, CH_3), 1597, 1455, 1371, 1265, (C=C), 1072, 1038 (C-O).

MS (EI), *m/z* (% relative intensity): 284 (M^+, 21), 172 (100), 157 (26), 141 (25), 142 (9), 128 (30), 115 (22), 95 (32).

HRMS: calcd for $C_{19}H_{24}O_2$ [M+Na] 307.1674, found 307.1669.

2-((1-(Hydroxymethyl)cyclohexyl)methyl)naphthalen-1-ol (127)



210 **127**

1 M Boron tribromide in dichloromethane (141 µL, 0.14 mmol) was added dropwise to a stirred solution of the methyl ether **210** (40 mg, 0.14 mmol) in dry

dichloromethane (3 mL) at 0ºC and the solution was stirred for 1 h at the same temperature. Then water was added and extracted with dichloromethane (3×10 mL). The combined organic phases were washed with water, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash column chromatography eluting with 5% ethyl acetate-hexane to give the desired product **127** (34 mg, 89%) as a colourless amorphous powder, m.p. 126-127 ºC.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.30-1.65 (m, 10H, $(CH_2)_5$), 2.78 (s, 2H, CH_2Ar), 3.31 (s, 2H, CH_2OH), 7.11 (d, J=8.4 Hz, 1H, ArH), 7.26 (d, J=8.4Hz, 1H, ArH), 7.38 (m, 2H, ArH), 7.69 (m, 1H, ArH), 8.25 (m, 1H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 21.64 (2×CH_2), 26.47 (CH_2), 33.16 (2×CH_2), 35.50 (CH_2), 38.81 (C), 67.43 (CH_2), 117.22 (C), 118.84 (CH), 122.52 (CH), 124.85 (CH), 125.54 (C), 125.59 (CH), 127.12 (CH), 130.45 (CH), 133.62 (C), 151.20 (C).

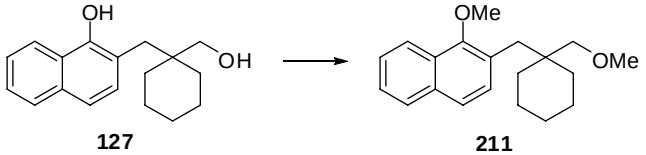
FTIR (KBr, cm^{-1}): 3413 (OH), 3047 (CH-aromatic), 2922, 2856 (CH_2, CH_3), 1570, 1457, 1376, 1273 (C=C), 1072, 1015 (C-O).

MS (EI), *m/z* (% relative intensity): 270 (M^+, 11), 253 (26), 239 (5), 169 (3), 157 (100), 129 (22).

HRMS: calcd for $C_{18}H_{22}O_2$ [M+H] 271.1698, found 271.1699.

Anal. Calcd. for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 80.00, H, 8.20.

1-Methoxy-2-((1-(methoxymethyl)cyclohexyl)methyl)naphthalene (211)



127 **211**

A solution of alcohol **127** (50 mg, 0.19 mmol) in dry THF (1mL) was added dropwise to a stirred suspension of sodium hydride (60% in mineral oil)(22.2 mg, 0.56 mmol) in dry THF (2 mL). Then methyl iodide (35 µL, 0.56 mmol) was added dropwise to the reaction mixture. After refluxing for 6 h, the reaction mixture was cooled to room temperature and quenched with water, then extracted with diethyl ether (3×15 mL). The combined organic layers were washed with brine and water, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash column chromatography eluting with 5% dichloromethane-hexane to yield the desired product **211** (45 mg, 82%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.30-1.55 (m, 10H, $(CH_2)_5$), 2.76 (s, 2H, CH_2Ar), 3.02 (s, 2H, CH_2OCH_3), 3.29 (s, 2H, CH_2OCH_3), 3.82 (s, 3H, $ArOCH_3$), 7.26 (d, *J*=8.5 Hz, 1H, ArH), 7.38 (m, 2H, ArH), 7.43 (d, *J*=8.5 Hz, 1H, ArH), 7.74 (m, 1H, ArH), 8.01 (m, 1H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 21.94 ($2\times CH_2$), 26.32 (CH_2), 32.97 ($2\times CH_2$), 36.60 (CH_2), 39.20 (C), 58.82 (CH_3), 61.53 (CH_3), 77.00 (CH_2), 122.23 (CH), 122.97 (CH), 125.32 (CH), 125.57 (CH), 127.50 (C), 127.81 (CH), 127.96 (C), 130.83 (CH), 133.92 (C), 154.59 (C).

FTIR (neat, cm^{-1}): 3052 (CH-aromatic), 2926, 2850 (CH_2, CH_3), 1572, 1451, 1370, 1259 (C=C), 1197, 1112 (C-O).

MS (EI), *m/z* (% relative intensity): 298 (M^+, 15), 267 (38), 171 (100), 156 (4), 128 (3).

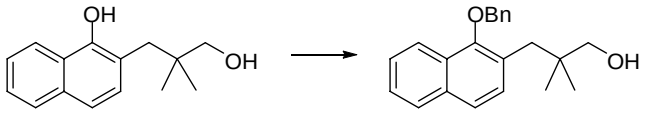
HRMS: calcd for $C_{20}H_{26}O_2$ [M+H] 299.2011, found 299.2013.

Benzylation of naphthol

General procedure:

A mixture of naphthol **98** or **127** (1.0 mmol), potassium carbonate (2.0 mmol) and benzyl chloride (2.0 mmol) in acetone (25 mL) was stirred under refluxing for 5-24 h. After that the reaction mixture was cooled to room temperature, water was added to the mixture and then extracted with diethyl ether (3×25 mL). The combined organic layers were washed with water, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo.

3-(1-Benzyloxy-naphthalen-2-yl)-2,2-dimethyl-propan-1-ol (207)



98 **207**

Prepared by the general procedure from naphthol **98** (0.5 g, 2.2 mmol), potassium carbonate (0.6 g, 4.3 mmol) and benzyl chloride (0.5 mL, 4.3 mmol) in acetone (10 mL) at reflux over 5 h. The residue was purified by flash column chromatography eluting with 8% ethyl acetate-hexane to afford the product **207** (0.66 g, 95%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.00 (s, 6H, 2×CH_3), 2.78 (s, 2H, CH_2), 3.05 (d, J=7.0 Hz, 2H, OCH_2), 3.41 (t, J=7.0 Hz, 1H, OH), 5.08 (s, 2H, OCH_2Ph), 7.34 (d, J=8.4 Hz, 1H, ArH), 7.43-7.62 (m, 7H, ArH), 7.65 (d, J=8.4 Hz, 1H, ArH), 7.91 (m, 1H, ArH), 8.18 (m, 1H, ArH).

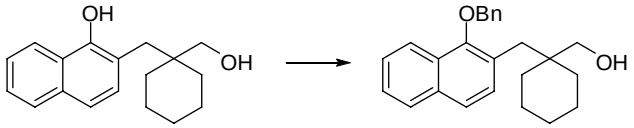
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 25.75 (2×CH_3), 38.21 (C), 39.05 (CH_2), 69.92 (CH_2), 77.56 (CH_2), 122.64 (CH), 124.57 (CH), 126.38 (CH), 126.79 (CH), 128.17 (C), 128.43 (C), 128.71 (CH), 128.86 (2×CH), 129.31 (CH), 129.55 (2×CH), 131.10 (CH), 134.75 (C), 136.96 (C), 153.04 (C).

FTIR (neat, cm^{-1}): 3447 (OH), 3059 (CH-aromatic), 2956, 2868 (CH_2, CH_3), 1501, 1467, 1361 (C=C), 1231, 1181, 1077, 1044 (C-O).

MS (EI), *m/z* (% relative intensity): 320 (M^+, 4), 212 (5), 157 (16), 128 (11), 91 (100).

HRMS calcd for $C_{22}H_{24}O_2$ [M+H] 321.1849, found 321.1851

(1-((1-(Benzyloxy)naphthalen-2-yl)methyl)cyclohexyl)methanol (212)



127 **212**

Prepared by the general procedure from naphthol **127** (0.25 g, 0.93 mmol), potassium carbonate (0.19 g, 1.39 mmol) and benzyl chloride (0.16 mL, 1.39 mmol) in acetone (25 mL) at reflux over 24 h.The residue was purified by flash column chromatography eluting with 10% CH_2Cl_2-hexane to yield the desired product **212** (0.30 g, 91%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.25-1.46 (m, 10H, $(CH_2)_5$), 2.70 (s, 2H, CH_2Ar), 3.00 (s, 2H, CH_2OH), 4.95 (s, 2H, OCH_2Ph), 7.22 (d, *J*=8.5 Hz, 1H, ArH), 7.30-7.49 (m, 7H, ArH), 7.51 (d, *J*=8.5 Hz, 1H, ArH), 7.78 (dd, *J*=1.0 and 8.4 Hz, 1H, ArH), 8.05 (dd, *J*=1.0 and 8.4 Hz, 1H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 22.46 (2×CH_2), 27.26 (CH_2), 33.87 (2×CH_2), 36.65 (CH_2), 40.39 (C), 67.01 (CH_2), 77.74 (CH_2), 122.62 (CH), 124.61 (CH), 126.39 (CH), 126.83 (CH), 128.11 (C), 128.20 (C), 128.69 (CH), 128.94 (2×CH), 129.38 (CH), 129.59 (2×CH), 130.81 (CH), 134.69 (C), 136.79 (C), 153.09 (C).

FTIR (neat, cm^{-1}): 3531 (OH), 3049 (CH-aromatic), 2924, 2845 (CH_2, CH_3), 1452, 1384, 1356 (C=C), 1177, 1069, 1041 (C-O).

MS (EI), *m/z* (% relative intensity): 360 (M^+, 44), 359 (97), 343 (22), 341 (59), 247 (100), 169 (10), 128 (5).

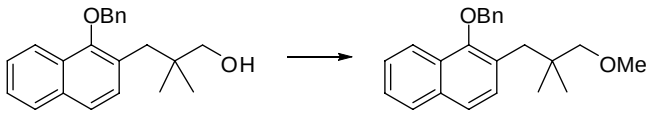
HRMS: calcd for $C_{25}H_{28}O_2$ [M+H] 361.2167, found 361.2168.

Methylation of alkyl alcohol

General procedure:

A solution of alcohol **207** or **212** (1.0 mmol) in dry THF (2 mL) was added dropwise to a stirred suspension of sodium hydride (6.0 mmol) in dry THF (4 mL). Then methyl iodide (6.0 mmol) was added dropwise to the reaction mixture. After refluxing for 5 h, the reaction mixture was cooled to room temperature and quenched with water, then extracted with diethyl ether (3×15 mL). The combined organic layers were washed with brine and water, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo.

1-Benzyloxy-2-(3-methoxy-2,2-dimethyl-propyl)-naphthalene (208)



207 **208**

Compound **208** was synthesized by following the general procedure: a solution of alcohol **207** (0.26 g, 0.8 mmol) in dry THF (4 mL) was added dropwise to a stirred suspension of sodium hydride (0.12 g, 4.8 mmol) in dry THF (6 mL). Then methyl iodide (0.31 mL, 4.8 mmol) was added dropwise to the reaction mixture. The mixture was stirred for 5 hours. The residue was purified by flash column

chromatography eluting with 10% CH_2Cl_2-hexane to afford the desired product **208** (0.25 g, 94%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.00 (s, 6H, 2×CH_3), 2.85 (s, 2H, CH_2Ar), 3.11 (s, 2H, OCH_2), 3.41 (s, 3H, OCH_3), 5.05 (s, 2H, OCH_2Ph), 7.38 (d, *J*=8.4 Hz, 1H, ArH), 7.45 (m, 1H, ArH), 7.51 (m, 4H, ArH), 7.64 (m, 3H, ArH), 7.90 (m, 1H, ArH), 8.17 (m, 1H, ArH).

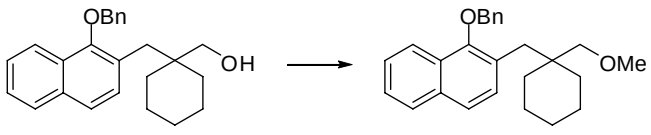
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 25.54 (2×CH_3), 37.73 (C), 39.31 (CH_2), 59.72 (CH_2), 76.39 (CH_2), 82.06 (CH_3), 122.90 (CH), 123.92 (CH), 126.08 (CH), 126.38 (CH), 128.22 (2×CH), 128.55 (2×CH), 128.79 (2×C), 129.18 (2×CH), 131.17 (CH), 134.63 (C), 138.44 (C), 153.81 (C).

FTIR (neat, cm^{-1}): 3058 (CH-aromatic), 2959, 2868 (CH_2, CH_3), 1457, 1361 (C=C), 1183, 1109 (C-O).

MS (EI), *m/z* (% relative intensity) : 334 (M^+, 4), 212 (22), 157 (20), 128 (13), 91 (100).

HRMS calcd for $C_{23}H_{26}O_2$ [M+H 335.2006, found 335.2006.

1-(Benzyloxy)-2-((1-(methoxymethyl)cyclohexyl)methyl)naphthalene (213)



212 **213**

Compound **213** was synthesized by following the general procedure: a solution of alcohol **212** (0.10 g, 0.28 mmol) in dry THF (2 mL) was added dropwise to a stirred suspension of sodium hydride (67 mg, 1.68 mmol) in dry THF (4 mL). Then methyl iodide (0.10 mL, 1.68 mmol) was added dropwise to the reaction

mixture. The mixture was stirred for 5 hours. The residue was purified by flash column chromatography eluting with 3% ethyl acetate-hexane to provide the desired product **213** (71 mg, 68%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.25-1.60 (m, 10H, $(CH_2)_5$), 2.85 (s, 2H, CH_2Ar), 3.13 (s, 2H, CH_2OCH_3), 3.35 (s, 3H, OCH_3), 5.00 (s, 2H, OCH_2Ph), 7.37 (d, J=8.4 Hz, 1H, ArH), 7.42 (m, 1H, ArH), 7.42-7.51 (m, 4H, ArH), 7.57-7.60 (m, 3H, ArH), 7.85 (m, 1H, ArH), 8.13 (m, 1H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 22.52 ($2\times CH_2$), 26.90 (CH_2), 30.35(CH_2), 33.48 ($2\times CH_2$), 37.44 (CH_2), 39.89 (C), 59.54 (CH_3), 76.66 (CH_2), 122.93 (CH), 123.81 (CH), 126.04 (CH), 126.33 (CH), 128.55 (3×CH), 128.61(CH), 128.64, (C) 128.71 (C), 129.16 (2×CH), 131.38 (CH), 134.58 (C), 138.31 (C), 153.99 (C).

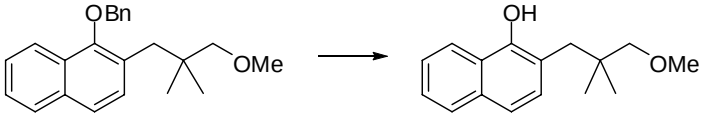
FTIR (neat, cm^{-1}): 3060 (CH-aromatic), 2924, 2852, 2807 (CH_2, CH_3), 1578, 1452, 1359, 1258 (C=C), 1183, 1111 (C-O).

MS (EI), *m/z* (% relative intensity): 374 (M^+, 78), 342 (19), 247 (100), 128 (2), 169 (16).

HRMS: calcd for $C_{26}H_{30}O_2$ [M+H] 375.2324, found 375.2329.

Debenzylation of naphthyl benzyl ether

2-(3-Methoxy-2,2-dimethyl-propyl)-naphthalen-1-ol (209)



208 **209**

To a mixture of compound **208** (0.12 g, 0.37 mmol), potassium iodide (0.18 g, 1.1 mmol) in acetonitrile (6 ml), trimethylsilylchloride (0.14 ml, 1.1 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 1 hour. After that water was added to the reaction mixture and extracted with diethyl ether (3×30 ml). The combined organic phases were washed with saturated sodium hydrogen carbonate and water, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash column chromatography eluting with 5% CH_2Cl_2-hexane to afford the desired product (**209**) (78 mg, 87%) as a colourless solid, m.p. 67-68^oC.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.10 (s, 6H, 2×CH_3), 2.78 (s, 2H, CH_2Ar), 3.00 (s, 2H, OCH_2), 3.50 (s, 3H, OCH_3), 7.18 (d, *J*=8.3 Hz, 1H, ArH), 7.35 (d, *J*=8.3 Hz, 1H, ArH), 7.48 (m, 2H, ArH), 7.79 (m, 1H, ArH), 8.36 (m, 1H, ArH), 8.55 (s, 1H, OH).

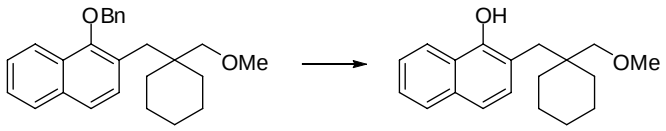
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 26.35 (2×CH_3), 36.84 (C), 39.52 (CH_2), 59.81 (CH_2), 79.96 (CH_3), 117.91 (C), 119.30 (CH), 123.25 (CH), 125.41 (CH), 125.91 (C), 126.25 (CH), 127.79 (CH), 131.43 (CH), 134.28 (C), 151.75 (C).

FTIR (KBr, cm^{-1}): 3229 (OH), 2951 (CH_2, CH_3), 1569, 1456, 1386, 1290 (C=C), 1083 (C-O).

MS (EI), *m/z* (% relative intensity) : 244 (M^+, 35), 212 (35), 157 (100), 128 (78) 87 (46).

HRMS calcd for $C_{16}H_{20}O_2$ [M+Na] 267.1361, found 267.1359.

2-((1-(Methoxymethyl)cyclohexyl)methyl)naphthalen-1-ol (214)



213 **214**

A mixture of benzyl ether **213** (40 mg, 0.11 mmol) and 10% Palladium-charcoal (11.4 mg, 10 mol%) in ethanol (2 mL) was stirred at room temperature for 24 h. Then the reaction mixture was filtered through celite and washed with ethyl acetate. The filtrate was concentrated in vacuo. The residue was purified by flash column chromatography eluting with 0.5% ethyl acetate-hexane to afford the desired product **214** (24.2 mg, 80%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.40-1.60 (m, 10H, $(CH_2)_5$), 2.81 (s, 2H, CH_2Ar), 3.10 (s, 2H, CH_2OCH_3), 3.48 (s, 3H, OCH_3), 7.17 (d, J=8.4 Hz, 1H, ArH), 7.32 (d, J=8.4 Hz, 1H, ArH), 7.46 (m, 2H, ArH), 7.77 (m, 1H, ArH), 8.35 (m, 1H, ArH), 8.63 (s, 1H, OH).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 22.37 (2×CH_2), 27.14 (CH_2), 34.29 (2×CH_2), 36.93 (CH_2), 39.14 (C), 59.91 (CH_3), 78.09 (CH_2), 117.62 (C), 119.22 (CH), 123.28 (CH), 125.38 (CH), 125.99 (C), 126.21 (CH), 127.76 (CH), 131.13 (CH), 134.26 (C), 152.02 (C).

FTIR (neat, cm^{-1}): 3268 (OH), 3047 (CH-aromatic), 2927, 2848 (CH_2, CH_3), 1572, 1454, 1387, 1299 (C=C), 1084 (C-O).

MS (EI), *m/z* (% relative intensity): 284 (M^+, 7), 247 (100), 247 (100), 168 (10), 157 (47), 141 (21).

HRMS calcd for $C_{19}H_{24}O_2$ [M+H] 285.1854, found 285.1857.

Anti-COX (PGHS) assay (Kirtikara *et al.*, 1998, 2001)

Immortalized mouse PGHS-1 (PGHS-$1^{-/-}$) and PGHS-2 (PGHS-$2^{-/-}$) null cells were seeded at 1×10^5 cell/mL in complete Dubelcco's Modified Eagle Medium (DMEM) supplemented with non essential amino acids (0.1 mM), glutamine (292 mg/L), ascorbic acid (50 mg/L) and 10% FCS in 96-well (83 μL/well) flat-bottomed tissue culture plates. The cells were incubated at 37 ^{o}C in a humidified incubator with 5% CO_2 for 72h. The cells were then washed with DMEM medium without FCS and preincubated for 30 min with 83 μL serum-free DMEM medium containing vehicle or drug. Aspirin or the test compounds were dissolved and serially diluted in ethanol or DMSO before they were added to the medium. The final concentrations of ethanol and DMSO were 1% and 0.1%, respectively. Following the preincubation period, the medium was removed and the cells were immediately treated with serum-free medium containing vehicle or drug and 2 μM A23187 for 30 min. Medium samples were then collected from the wells and analyzed for PGE_2 concentration by RIA as previously described. The test compounds were first screened at 10^{-5} g/mL. IC_{50} values were further determined for samples (10^{-5} g/mL) that show inhibitory effect on PGE_2 production. Aspirin, which was found to have PGHS-1 and PGHS-2 IC_{50} values of 0.014±0.008 and 0.058±0.053 mg/mL, respectively was employed as a nonselective COX-2 inhibitor.

Molecular docking

Crystal structure (1eqh and 1c×2) from Brookhaven Protein Data Bank (http://www.rcsb.org/pdb/) provided enzyme structures and binding site information for COX-2 complexed with SC-588 (Kurumbail *et al.*, 1996) and COX-1 bound to flurbiprofen (Selinsky *et al.*, 2001, Picot *et al*., 1994) as reference structures. Initial structures of naphthol derivatives were generated by molecular modeling software Sybyl 6.8. (Sybyl version 6.7, 2000) The geometries of these compounds were subsequently optimized using the semi-empirical parameter AM1.

Binding conformations of naphthol derivatives with COX-2 and COX-1 were analyzed by the program AutoDock 3.0.5 using the Lamarckian genetic algorithm (LGA) in conjunction with an empirical force field to calculate ligand free energy of binding. (Morris *et al*., 1998) Kollman-all-atom charges were assigned to enzyme electrostatic contributions whereas Gasteiger-Hückel charges were assigned to all ligands. (Weiner *et al*., 1984, Purcell *et al*., 1967) All calculations were performed by representing the enzyme affinity by a 90×90×90 grid box of 0.25 Å grid spacing.

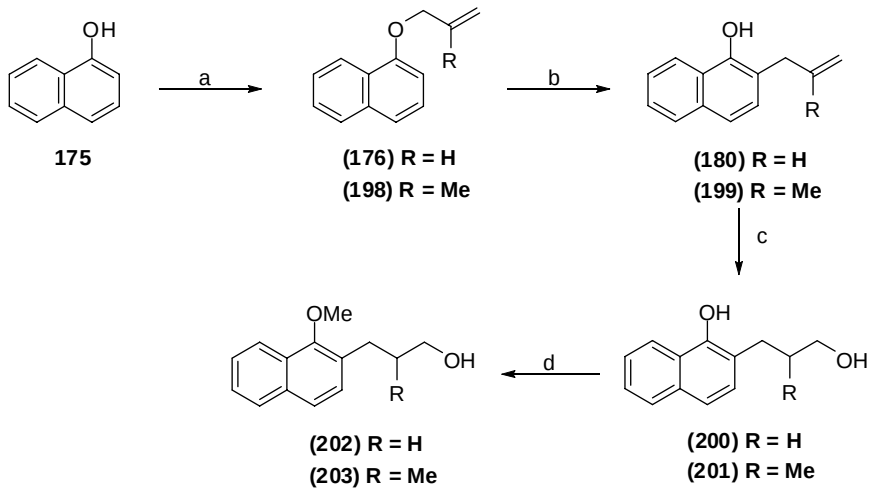
The conditions applied throughout the docking simulations were those, which reproduced the co-crystals of flurbiprofen and SC-558 bound to COX-1 and COX-2 enzymes with root mean square deviation (RMSD) value of 0.7 Å for both cases using flurbiprofen and SC-558 at the binding sites in 1eqh and 1cx2 as references. The estimated free energy of binding using these docking conditions for SC-558 binding to COX-2 was -11.65 kcal/mol, which was slightly different from the value from the literature (-11.35 kcal/mol). Therefore, the AutoDock method and the parameter set could be extended to search the enzyme binding conformations for other inhibitors accordingly.

Finally, the docked complexes of inhibitor-enzyme were selected according to the criteria of interacting energy combined with geometrical matching quality. All amino acid residues within a 5.0 Å radius of the inhibitor atom were considered and analyzed for their activity contributions.

RESULTS

1. Synthesis of naphthol derivatives

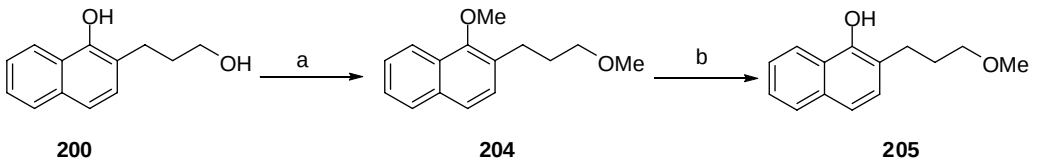
The 2-substituted-1-naphthol derivatives **200** and **205** were synthesized in several steps with high yields as shown in **Schemes 34** and **35**, respectively. In the same manner, the 2-substituted-1-naphthol derivative **201** was also synthesized from 1-naphthol (**175**) in three steps with 75% overall yield. While the synthesis of their methyl naphthyl ether derivatives (**202** and **203**) were also obtained in good yield as shown in **Schemes 34** and **35**.



Scheme 34

Reagents and conditions:

a) (i) Allyl bromide, K_2CO_3, reflux, 3h; (ii) 2-chloro-3-methyl-1-propene, K_2CO_3, reflux, 2h, **176** (86%), **198** (84%).
b) 180 °C, DMF, 6h, **180** (82%), **199** (93%).
c) BH_3·THF and then H_2O_2-NaOH, 8h, **200** (71%), **201** (96%).
d) MeI, K_2CO_3, acetone, reflux, 4h, **202** (quant.), **203** (quant.).

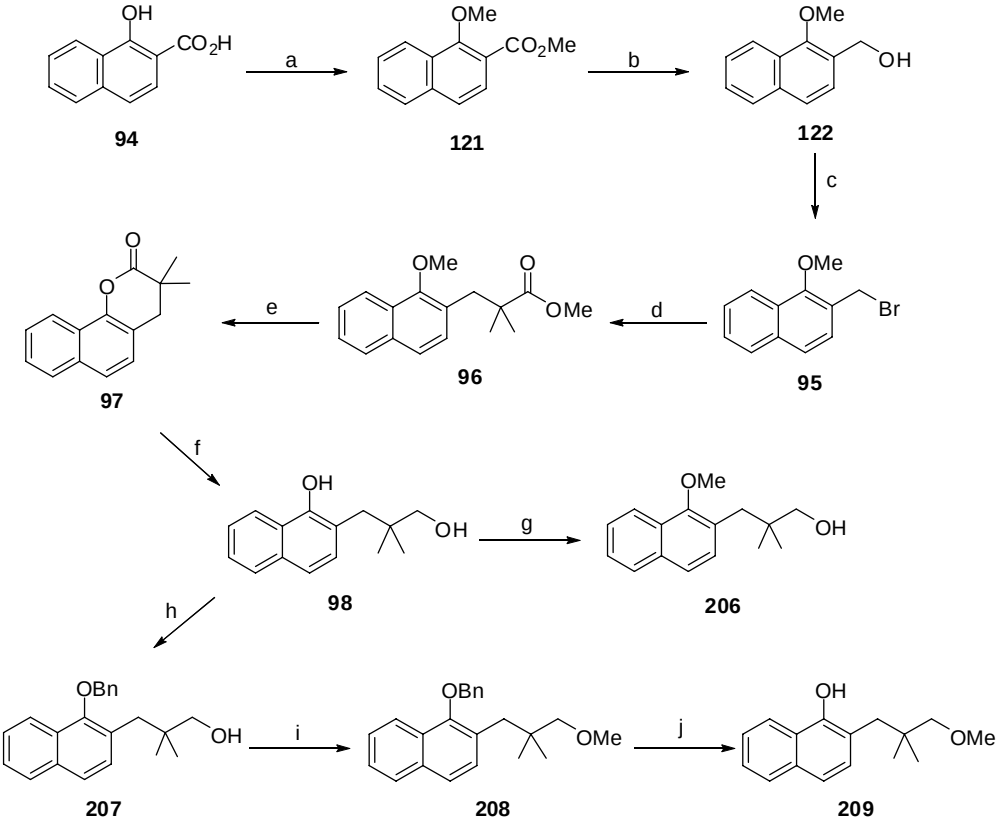


Scheme 35

Reagents and conditions:

a) NaH, MeI, dry THF, reflux, 3h, 93%.
b) BBr_3, dry CH_2Cl_2, 0 °C, 1h, 45%.

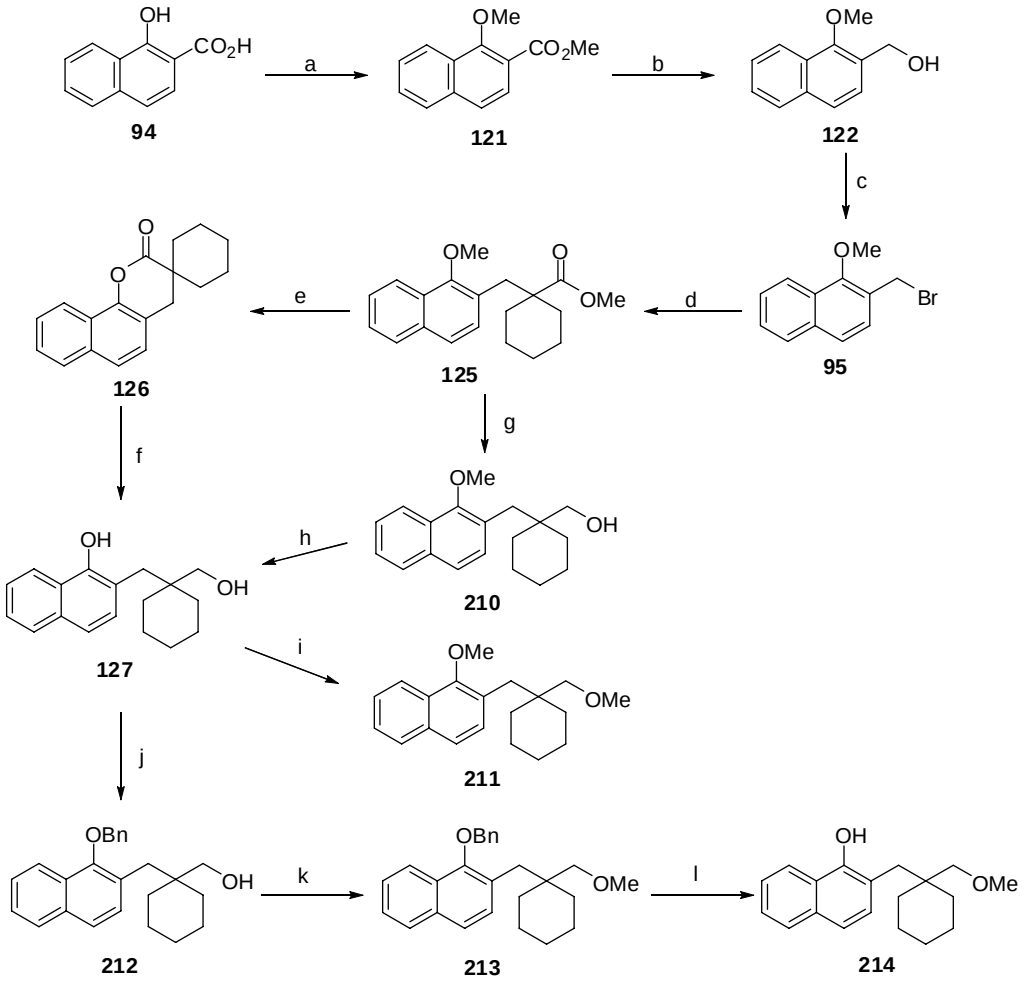
The syntheses of 2',2'-dimethylpropyl (**98**, **206** and **209**) and 2',2'-cyclohexylpropyl-1-naphthol (**127**, **210**, **211** and **214**) derivatives were achieved by the same method and are shown in **Schemes 36** and **37**, respectively.



Scheme 36

Reagents and conditions:

a) MeI, K_2CO_3, acetone, reflux, 12h, 96%.
b) $LiAlH_4$, dry ether, rt., 2h, 88%.
c) PBr_3, dry CH_2Cl_2, rt., 6h, quant.
d) LDA, methyl isobutylate, HMPA, dry THF, -78 °C, 2h, 89%.
e) $AlCl_3$, chlorobenzene, reflux, 4h, 83%.
f) $LiAlH_4$, dry ether, rt., 2h, 71%.
g) MeI, K_2CO_3, acetone, reflux, 4h, 98%.
h) BnCl, K_2CO_3, acetone, reflux, 24h, 95%.
i) MeI, NaH, dry THF, reflux, 5h, 94%.
j) TMSCl, KI, CH_3CN, rt., 1h, 87%.



Scheme 37

Reagents and conditions:

a) MeI, K_2CO_3, acetone, reflux, 12h, 96%.
b) $LiAlH_4$, dry ether, rt., 2h, 88%.
c) PBr_3, dry CH_2Cl_2, rt., 6h, quant.
d) LDA, methyl cyclohexylcarboxylate, HMPA, dry THF, -78 °C, 2h, 87%.
e) $AlCl_3$, chlorobenzene, reflux, 4h, 81%.
f) $LiAlH_4$, dry THF, rt., 2h, 89%.
g) $LiAlH_4$, dry THF, rt., 2h, 76%.
h) BBr_3, CH_2Cl_2, 0 °C, 1h, 89%.
i) MeI, NaH, dry THF, rt., 6h, 82%.
j) BnCl, K_2CO_3, acetone, reflux, 24h, 91%.
k) NaH, MeI, dry THF, reflux, 5h, 68%.
l) H_2, Pd-C, EtOH, rt., 24h, 80%.

Biological Activities

Anti-inflammatory activity of all naphthol derivatives was tested at the BIOTEC as shown in **Table 7**.

Table 7. The experimental activity (IC_{50} values) of naphthol derivatives tested as inhibitors of COX-1 and COX-2.

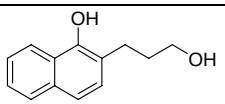
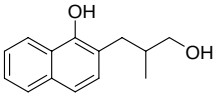
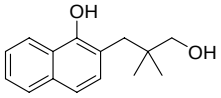
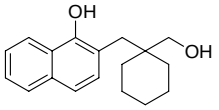
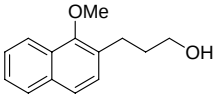
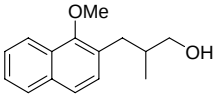
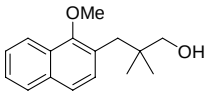
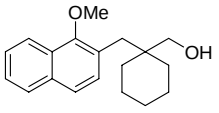
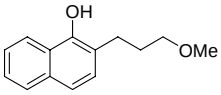
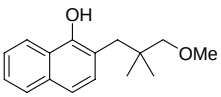
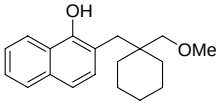
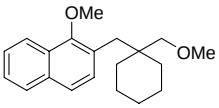
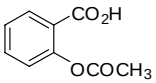
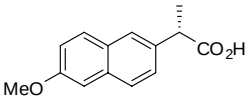
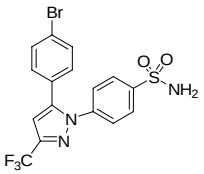
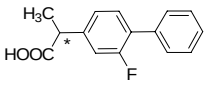
Compound	Structure	IC_{50} of COX-1 (μM)	IC_{50} of COX-2 (μM)
200		93.9	4.20
201		87.8	4.60
98		3.40	1.70
127		5.55	7.77
202		inactive	inactive
203		inactive	inactive
206		inactive	inactive
210		inactive	inactive
205		15.7	0.25
209		>40.90	4.10
214		inactive	inactive

Table 7. Continued

Compound	Structure	IC_{50} of COX-1 (μM)	IC_{50} of COX-2 (μM)
211		inactive	inactive
Aspirin (**165**)*		77.7	321.9
Naproxen (**168**)*		27.8	43.4
SC-558[1]		17.7	0.0093
Flurbiprofen[1]		2.56	0.29

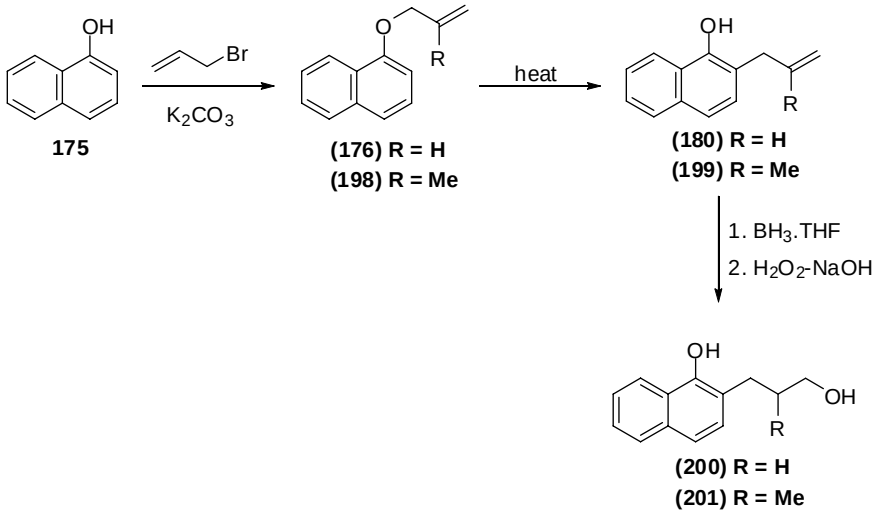
*Used as reference.

[1]Reference no. 11 (Kurumbail *et al.*, 1996)

DISCUSSION

Naphthol derivatives are the intermediates in the process of the syntheses of naphthoquinone ester derivatives and some naphthols such as naproxen have been reported to possess anti-inflammatory activity. So, our synthesized naphthols were also tested for anti-inflammatory activity. It was found that they inhibited cyclooxygenase enzymes (COX) in the inflammation process. So it is very interesting to synthesize derivatives of these molecules for evaluation of their anti-inflammatory activity. Methyl substitution of each hydroxyl group and alkyl substituents at the 2'-position of the propyl side chain were focused for this study. Docking experiment was also done for the structure-activity relationships.

2-Substituted-1-naphthol derivatives (**200** and **201**) were prepared in three steps with high yield. Naphthols **200** without 2'-methyl and **201** with 2'-methyl on the propyl side chain were prepared starting from the same compound, 1-naphthol (**175**), in three steps involving *O*-allylation, Claisen rearrangement and then hydroboration-oxidation as shown in **Scheme 38**.



175

(176) R = H
(198) R = Me

(180) R = H
(199) R = Me

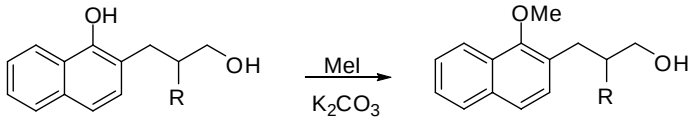
(200) R = H
(201) R = Me

Scheme 38

O-Allylated naphthalene **176** and **198** were obtained from *O*-allylation of 1-naphthol. The hydroxyl group was disappeared which confirmed by the IR spectrum.

Claisen rearrangement of **176**, followed by hydroboration-oxidation gave naphthol **200** which was identified by spectroscopic data. The ^{1}H NMR (400 MHz) spectrum of 2-(3-hydroxy-propyl)-1-naphthalen-1-ol (**200**) in $CDCl_3$ showed two triplet signals at δ 2.95 and 3.65 ppm which were characteristics of the methylene proton adjacent to the naphthalene ring and methylene proton connecting to hydroxyl group, respectively. Another methylene proton showed multiplet at 1.95 ppm. The IR spectrum of this compound showed the absorption band at 3481 cm^{-1} which was a characteristic of the O-H stretching. The EI mass spectrum showed by the molecular ion peak at *m/z* 202 confirmed this molecule. The ^{1}H NMR (400 MHz) spectrum of 2-(3-hydroxy-2-methyl-propyl)-naphthalen-1-ol (**201**) in $CDCl_3$ showed a singlet signal at δ 1.08 ppm which is characteristic of the methyl proton. The methylene proton next to the naphthalene ring showed multiplet at δ 2.90 ppm and the methylene proton connecting to the hydroxyl group showed two doublet of doublet signals at δ 3.38 and 3.60 ppm. Moreover, the methine proton showed the characteristic at δ 2.10 ppm as multiplet. The IR spectrum of this compound showed the absorption band at 3376 cm^{-1} which is a characteristic of O-H stretching. The EI mass spectrum showed the molecular ion peak at *m/z* 216 to confirm the structure of this molecule.

Treatment of these two naphthol derivatives (**200** and **201**) with methyl iodide (MeI) in the presence of potassium carbonate (K_2CO_3) in acetone provided methyl ether derivatives of naphthol **202** and **203** in quantitative yield as shown in **Scheme 39**.



(200) R = H
(201) R = Me

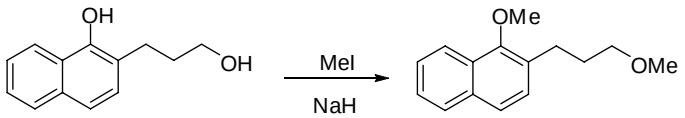
(202) R = H
(203) R = Me

Scheme 39

The ^{1}H NMR (400 MHz) spectrum of 3-(1-methoxy-naphthalen-2-yl)-propan-1-ol (**202**) in $CDCl_3$ showed the methoxy proton signal at δ 3.89 ppm. The IR

spectrum of this compound showed the absorption band at 3380 cm^{-1} which was a characteristic of O-H stretching. The EI mass spectrum showed the molecular ion peak at *m/z* 216 as the base peak to confirm this molecule. The ^1H NMR (400 MHz) spectrum of 3-(1-methoxy-naphthalen-2-yl)-2-methyl-propan-1-ol (**203**) in $CDCl_3$ also showed the methoxy proton signal at δ 3.85 ppm. The IR spectrum of this compound showed the absorption band at 3400 cm^{-1} which was a characteristic of O-H stretching. The molecular ion peak at *m/z* 230 revealed in the EI mass spectrum of this compound, further confirmed the structure of this molecule.

The naphthol **200**, was methylated on both naphthol and hydroxyl groups using MeI in the presence of sodium hydride (NaH) under reflux in dry THF to give dimethyl ether (**204**) in 93% yield (**Scheme 40**).



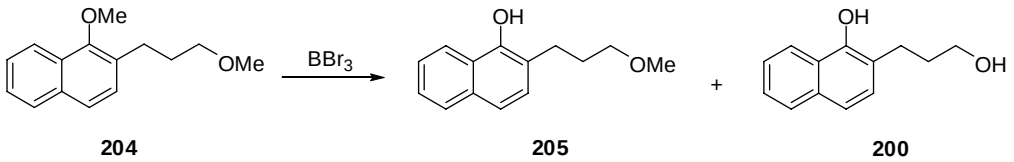
200 **204**

Scheme 40

The ^1H NMR (400 MHz) spectrum of this compound in $CDCl_3$ showed two singlet signals at δ 3.40 and 3.97 ppm which were characteristics of the methoxy protons on the side chain and naphthalene ring, respectively. In the EI mass spectrum the molecular ion peak at *m/z* 230, further confirmed the structure of this molecule.

Selective demethylation at the hydroxyl group on the naphthalene ring was achieved by treatment of the methyl ether **204** with BBr_3 in dry CH_2Cl_2. But the desired product (**205**) was obtained in low yield (45%) because the methyl ether of the propyl side chain was also removed to provide compound **200** in 25% yield (**Scheme 41**). The ^1H NMR (400 MHz) spectrum of **205** in $CDCl_3$ showed only one singlet at δ 3.49 ppm which is characteristic of the methoxy proton on the propyl side chain. The IR spectrum showed absorption band at 3290 cm^{-1}, confirming O-H stretching of the

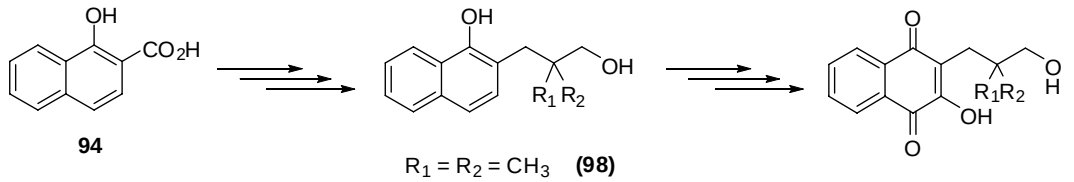
naphthol. In the EI mass spectrum the molecular ion peak at *m/z* 216, further confirmed the structure of this molecule.



204 **205** **200**

Scheme 41

The naphthol derivatives bearing 2'-dimethyl (**98**) and 2'-cyclohexyl substituent (**127**) are intermediates in the synthesis of the naphthoquinones alcohols **102** and **158**, respectively (**Scheme 42**).



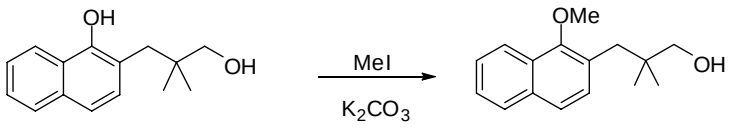
94

$R_1 = R_2 = CH_3$ **(98)**
$R_1, R_2 = (CH_2)_5$ **(127)**

$R_1 = R_2 = CH_3$ **(102)**
$R_1, R_2 = (CH_2)_5$ **(158)**

Scheme 42

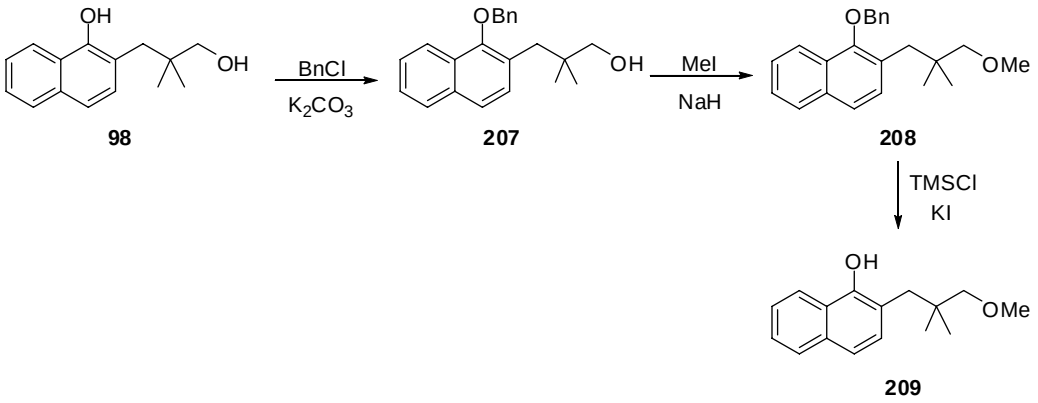
Naphthol **98** was converted to the monomethyl ether **206** by treatment with methyl iodide (MeI) and K_2CO_3 (**Scheme 43**). The ^{1}H NMR (400 MHz) spectrum of 3-(1-methoxy-naphthalen-2-yl)-2,2-dimethyl-propan-1-ol (**206**) in $CDCl_3$ showed singlet signal at δ 3.91 ppm which was characteristic of the methoxy proton on the naphthalene ring. A broad singlet at δ 1.87 ppm was assigned to the hydroxyl proton. The IR spectrum of this compound showed the absorption band at 3437 cm^{-1} which is a characteristic of O-H stretching. In the EI mass spectrum the molecular ion peak at *m/z* 244, further confirmed the structure of this molecule.



98 **206**

Scheme 43

Since demethylation of methyl naphthyl ether **204** occurred in low yield as previously described, so, 2-(3-methoxy-2,2-dimethyl-propyl)-naphthalen-1-ol (**209**) was derived by a three-step sequence involving selective benzylation of the hydroxyl group of naphthol, methylation of hydroxyl side chain and then debenzylation of benzyl naphthyl ether to solve this problem (**Scheme 44**).

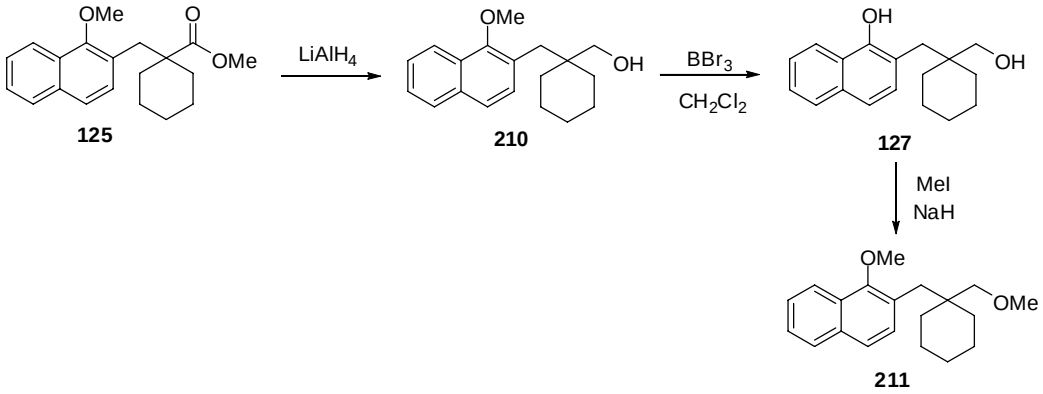


Scheme 44

Benzylation was achieved in 95% yield by reaction of naphthol **97** with benzyl chloride in the presence of K_2CO_3. The ^{1}H NMR (400 MHz) spectrum of compound **207** in $CDCl_3$ showed singlet signal at δ 5.08 ppm which is a characteristic of the methylene proton of the benzyl group. The IR spectrum of this compound showed the absorption band at 3447 cm^{-1} which is a characteristic of O-H stretching. In the EI mass spectrum the molecular ion peak at *m/z* 320, confirmed this molecule. The resulting product (**207**) was treated with MeI and NaH in dry THF under reflux to provide methyl ether side chain product (**208**) in 94% yield. The ^{1}H NMR (400 MHz) spectrum of compound **208** in $CDCl_3$ showed singlet signal at δ 3.41 ppm which is characteristic of the methoxy proton on the propyl side chain. Another singlet at δ 5.05 ppm was assigned to the methylene proton of the benzyl group. The IR spectrum did not show the characteristic absorption band of the O-H stretching. In the EI mass spectrum the molecular ion peak at *m/z* 334, confirmed this molecule. Then treatment of compound **208** with trimethylsilyl chloride (TMSCl) and potassium iodide (KI) in acetonitrile afforded the desired naphthol (**209**) with methyl ether side chain in 87% yield. The ^{1}H NMR (400 MHz) spectrum of this compound in $CDCl_3$

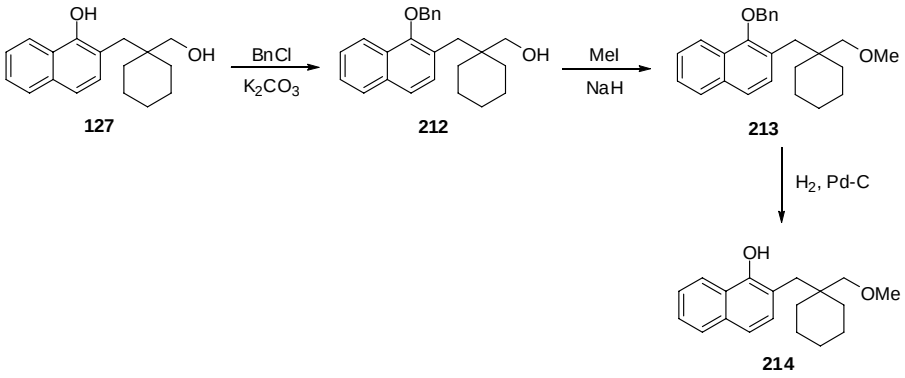
showed singlet signal at δ 3.50 ppm which is characteristic of methoxy proton on the propyl side chain and loss of the methylene proton signal of benzyl group at δ 5.05 ppm. The IR spectrum showed a characteristic absorption band of O-H stretching at 3229 cm^{-1}. In the EI mass spectrum the molecular ion peak at *m/z* 244 confirmed the structure of this molecule.

Naphthol derivatives bearing 2'-cyclohexyl substituent, (1-((1-methoxynaphthalen-2-yl)methyl)cyclohexyl)methanol (**210**) were synthesized by reduction of methyl 1-((1-methoxynaphthalen-2-yl)methyl)cyclohexanecarboxylate (**125**) using lithium aluminium hydride ($LiAlH_4$) in dry THF to yield 76%. Dimethoxy ether **211** was obtained in good yield (82%) by dimethylation of naphthol **127** using methyl iodide in a suspension of sodium hydride in dry THF. (**Scheme 45**)



Scheme 45

In the same manner, 2-((1-(methoxymethyl)cyclohexyl)methyl)naphthalen-1-ol (**214**) was synthesized starting from naphthol **127** by sequential steps of benzylation, methylation and debenzylation. (**Scheme 46**) The desired product (**214**) was obtained in 52% yield in 3 steps from compound **127**. The ^1H NMR (400 MHz) spectrum of this compound in $CDCl_3$ showed singlet signal at δ 3.48 ppm which is characteristic of methoxy proton on the propyl side chain. The IR spectrum showed the characteristic absorption band of O-H stretching at 3268 cm^{-1}. In the EI mass spectrum the molecular ion peak at *m/z* 284, further confirmed the structure of this molecule.



Scheme 46

Herein, three types of naphthol derivatives were synthesized. Type I is comprised of 2-substituted-1-naphthols containing hydroxyl group at the 3′-position of the propyl side chain (**98**, **127**, **200** and **201**)(**Figure 2**). Type II comprises 2-substituted-1-naphthols having methoxy group at the 3′-position of the propyl side chain (**205**, **209** and **214**). Type III is composed of 2-substituted-methyl naphthyl ethers with hydroxyl group at the 3′-position of the propyl side chain (**202**, **203**, **206** and **210**). There are some reports of naphthol derivatives such as naproxen exerting anti-inflammatory activity (Kolasa *et al*., 1997; Cryer *et al*., 1998). So, our naphthol derivatives were evaluated for anti-inflammatory activity.

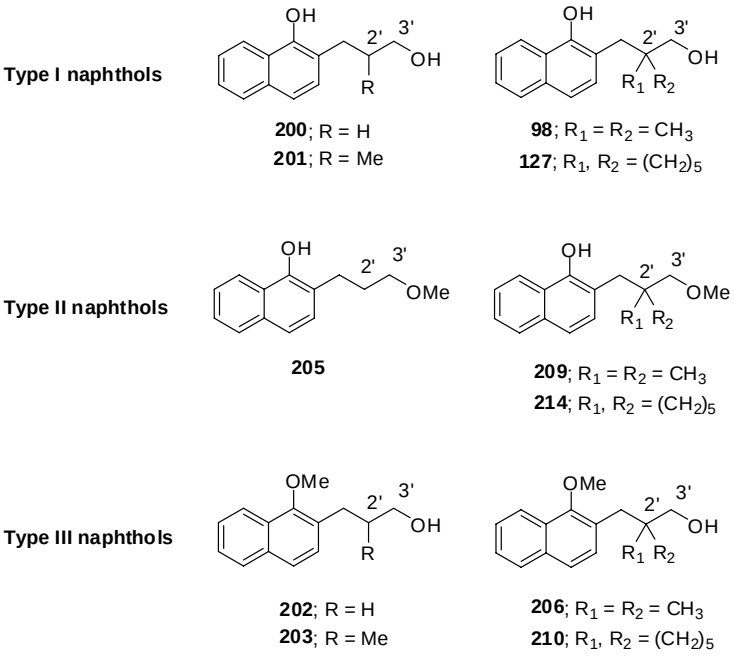


Figure 2. Three types of synthesized naphthol derivatives

These naphthol derivatives were tested for anti-inflammatory activity and aspirin was used as positive control. The results are shown in **Table 7 (**page 158**)**. Type I naphthols (**98**, **127**, **200** and **201**) exhibited potent inhibition of COX-2. Naphthols without methyl and with monomethyl substituent at the 2′-position of the propyl side chain (**200** and **201**) showed similar potency against COX-2 with IC_{50} values of 4.20 and 4.60 μM, respectively. Naphthols with C-2' dimethyl substituents (**98**) showed more potency against COX-2 (IC_{50} = 1.70 μM) than that with 2'-cyclohexyl substituent (**127**) (IC_{50} = 7.77 μM). Naphthols **198** and **199** showed slightly inhibition of COX-1 with IC_{50} values of 93.9 and 87.8 μM, respectively while the other two naphthols **98** and **127** showed potent inhibition of COX-1 with IC_{50} values of 3.40 and 5.50 μM, respectively. This means these compounds, with the exception of compound **127**, have selective inhibition of COX-2 over COX-1 because their inhibition of COX-1 are lower than COX-2. C-2' substituents affect cyclooxygenase inhibition. Methyl group is more effective than the cyclohexyl group because the latter imparts rigidity or strain to the molecule. Naphthol type II (**203** and **209**) also exhibited potent inhibition of both COX enzymes while 2′-cyclohexyl substituent naphthol (**214**) showed no inhibition. Compounds **205** and **209** also showed strong activity on COX-2 over COX-1. This indicates that the substituent on C-2' effectively inhibits COX enzymes. The structure has more rigidity or strain caused less inhibition of COX isozymes. Naphthol type III (**202**, **203**, **206** and **210**) showed no inhibition of both COX enzymes. Also, 1-methoxy-2-((1-(methoxymethyl)cyclohexyl)methyl)naphthalene (**211**) exhibited no activity on both COXs. Therefore, the hydroxyl group at 1-position of naphthol plays an important role for the anti-inflammatory activity.

From the results of the inhibitory testing, it was found that the presence of the hydroxyl group at 1-position of naphthalene ring (Type I and II naphthols) shows an important role for the activity whereas the presence of methoxy group has no inhibitory effect. Moreover, the substituent at C-2' of the propyl side chain has some inhibitory effect.

There are some reports described about the benchmark descriptions of the cyclooxygenase binding site. This binding domain in both isozymes is a long, narrow hydrophobic channel reaching out from the point of enzyme attachment on the endoplasmic reticulum. At the mount of the channel entrance leading to the active site, the COOH of arachidonic acid interacts with the guanidinium group of Arg120, and the carboxylate group of traditional NSAIDs competes with this linkage, preventing access of arachidonic acid to the channel. (**Figure 3**) At the upper right-hand of the channel amino acid no. 523 is isoleucine (Ile523) in COX-1 and valine (Val523) in COX-2, creating a side pocket which imparts COX-2 selectivity. However, like arachidonic acid or NSAIDs, naphthol derivatives can occupy the remainder of the channel leading to the active site and might block access of arachidonic acid.

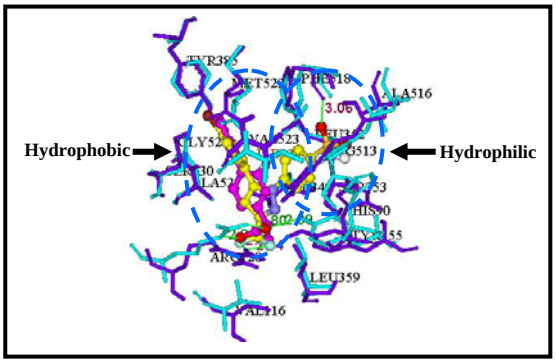


Figure 3. The COX-1 and COX-2 active sites are shown superimposed. Two inhibitors are seen: flurbiprofen (magenta), a nonselective inhibitor, and SC-558 (yellow), a COX-2 selective inhibitor. Note how the COX-2 selective inhibitor projects rightward into a side pocket that is not exploited by the nonselective inhibitor.

Our docking on COX-2, the highly selective inhibitor SC-558 was chosen for comparison with these naphthol derivatives. The presence of hydroxyl group at 1-position of the naphthalene ring (Type I naphthols: **98**, **127**, **200** and **201**) showed H-bonding with Val523 whereas the hydroxyl group at 3'-position of the propyl side

chain revealed H-bond formation with Arg120 and Tyr355 in the COX-2 binding site (**Figure 4**)

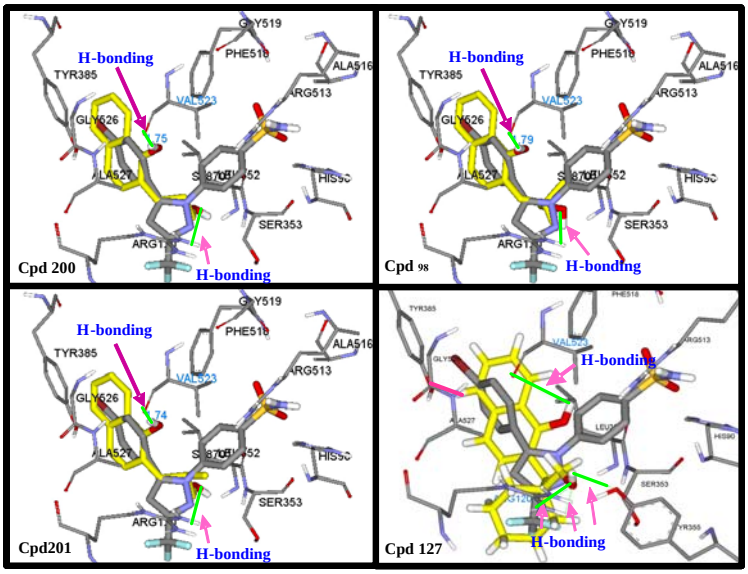


Figure 4. AutoDock binding on COX-2 of naphthol inhibitors **98**, **127**, **200** and **201** (yellow), superimposed on SC-558 (grey). The H-bonding interactions are shown in green lines. The interaction between the phenolic group of Tyr385 with C-5 hydrogen of naphthalene nucleus (**127**) is shown in pink line.

Furthermore, all active naphthols (**98, 127, 200** and **201**) also showed the orientation of the hydrogen at the C-5 position of naphthalene nucleus to be close to the phenolic group of Tyr385 which interacts by van der Waals interaction. On the other hand, the C-5 hydrogen of the inactive naphthols (**202, 203, 206** and **210**) were very far from the phenolic group of Tyr385. (**Figure 4**)

When the substituent at 1-position of naphthalene ring is methoxy group (Type III naphthols: **202**, **203**, **206** and **210**), the methyl naphthyl ether moiety is oriented downward which is far from the Val523. (**Figure 5**)

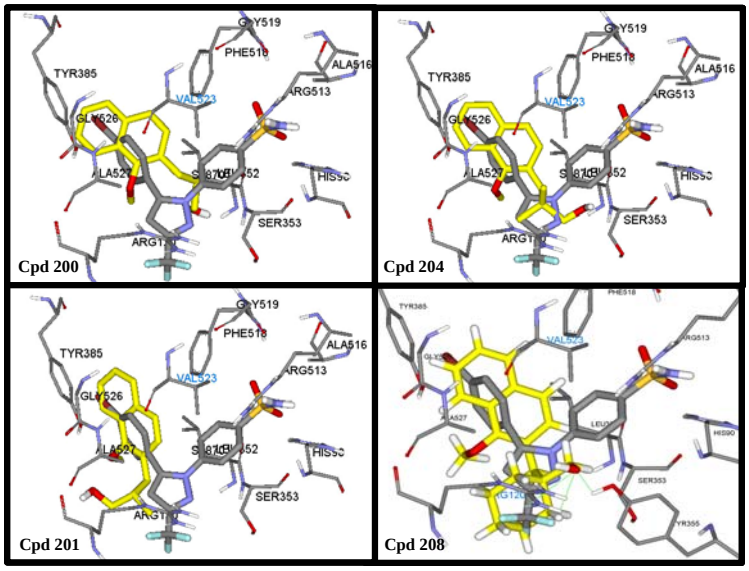


Figure 5. Orientation of inactive naphthols (**202, 203, 206** and **210**) (yellow) on COX-2, superimposed on SC-558 (grey).

From these reasons for active naphthols, the hydroxyl group at 1-position shows an important role for the inhibitory effect. So, type I (**98**, **127**, **200** and **201**) and type II naphthols (**205** and **209**) contain 1-hydroxyl group which inhibited on COX-2 according to the molecular docking experiment. Exception of naphthol **214** bearing 2'-cyclohexyl ring showed no inhibition on COX-2 because the 1-hydroxyl group oriented downward and very far from Val523. (**Figure 6**)

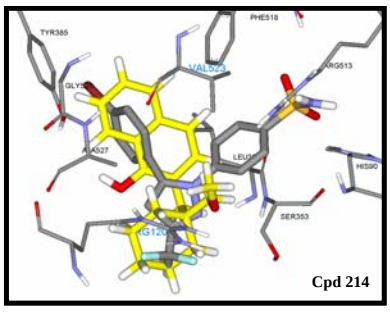


Figure 6. Orientation of inactive naphthols (**214**) (yellow) on COX-2, superimposed on SC-558 (grey).

In COX-1 docking experiments, our synthesized naphthols were also superimposed on flurbiprofen which is one order of magnitude more selective to

COX-2 than to COX-1. In the binding site of COX-1, the C-1 hydroxyl group of compounds **127** and **200** formed H-bonding with Ile523, and the C-3′ hydroxyl with Arg120 and Tyr355 whereas compound **210** possesses C-1 methoxy group and C-3′ hydroxyl group, showed H-bonds of C-3′ hydroxyl group with Arg120 and Tyr355 but no H-bond with Ile523. Also the C-1 hydroxyl group of compound **214** formed H-bonding with Ile523 but no H-bond formation with Arg120 and Tyr355 (because they have methoxy group instead of hydroxyl group at C-3′) in the docking and it has no inhibition on COX-1. (**Figure 7**)

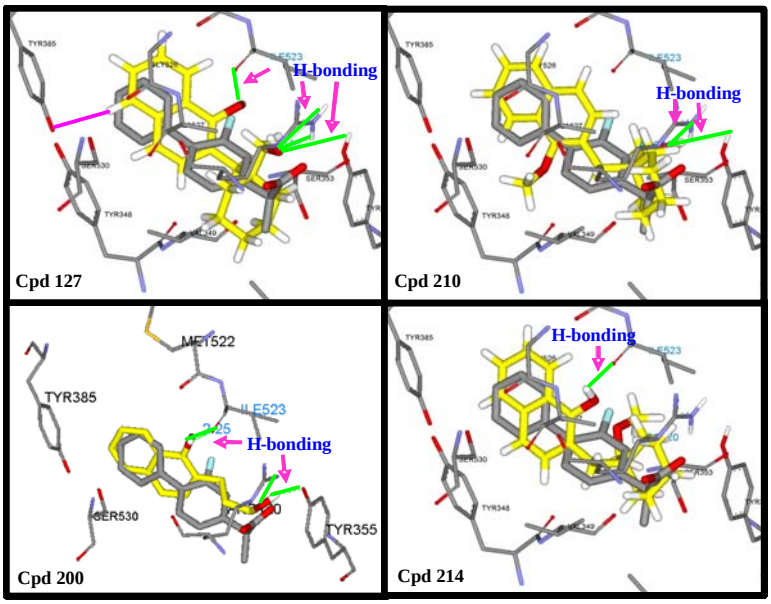


Figure 7. AutoDock binding on COX-1 of active naphthols (**127** and **200**) on the left and inactive naphthols (**210** and **214**) on the right (yellow), superimposed on flurbiprofen (grey). The H-bonding interactions are shown in green lines. The interaction between the phenolic group of Tyr385 with C-5 hydrogen of naphthalene nucleus (**127**) is shown in pink line.

Additionally, the C-5 hydrogen of the naphthalene nucleus of naphthols **127** and **200** are close to the phenolic group of Tyr385, whereas other naphthols **210**, **211** and **214** were far from Tyr385. (**Figures 4** and **7**) So, the interaction between the C-5 hydrogen and the phenolic group of Tyr385 affected or enhanced the activity.

Another naphthol **211** contain methoxy groups at C-1 and C-3′ showed no H-bond with Ile523, Arg120 and Tyr355, which corresponded to the IC_{50} testing result that no inhibition of COX-1 was observed. (**Figure 8**)

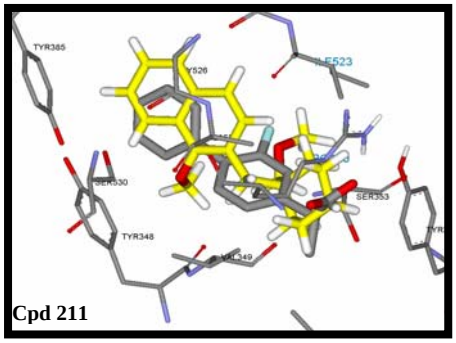


Figure 8. AutoDock binding on COX-1 of inactive naphthol **211** (yellow), superimposed on flurbiprofen (grey).

CONCLUSION

Synthesis of 2-substituted-1-naphthol derivatives without 2'-methyl group (**200**) and with 2'-methyl group on the propyl side chain (**201**) were accomplished in three steps involving *O*-allylation, Claisen rearrangement and hydroboration. Their methyl ether derivatives, **202** and **203**, were achieved in quantitative yield by methylation of naphthols **200** and **201**, respectively. Additionally, methyl ether on the propyl side chain (**205**) was synthesized in two steps from naphthol **200** with an overall yield of 42%.

2-Substituted-1-naphthol derivative with C-2' dimethyl groups of the propyl chain (**98**) was synthesized from 1-hydroxy-2-naphthoic acid with an overall yield of 44% in six sequential steps involving methylation, reduction of methyl ester, bromination, alkylation, demethylation and reduction of lactone. Methyl naphthyl ether (**206**) was obtained in 98% yield by methylation and the methyl ether of naphthol **98** (**209**) was synthesized from naphthol **98** in a three-step sequence involving benzylation, methylation and debenzylation.

Synthesis of 2-substituted-1-naphthol derivative bearing cyclohexyl ring at the 2'-position of the propyl chain (**127**) was achieved in six steps with 53% overall yield. Methyl naphthyl ether (**210**) was obtained in 76% yield by reduction of the ester **125** while naphthyl ether (**211**) was synthesized by dimethylation of naphthol **127**. The generation of methyl ether of the naphthol **127** (**214**) from naphthol **127** was accomplished in three-step sequence involving benzylation, methylation and debenzylation.

These synthesized naphthols were evaluated for anti-inflammatory activity. Naphthols type I, 2-substituted-1-naphthols containing hydroxyl group at the 3′-position of the propyl side chain (**98**, **127**, **200** and **201**), exhibited potent inhibition of both COX enzymes and showed selective inhibition of COX-2 over COX-1 except naphthol **127** which has no selectivity. Naphthols type II, 2-substituted-1-naphthol

with methoxy group at 3′-position of the propyl side chain (**205** and **209**), inhibited both COX enzymes while that containing 2'-cyclohexyl ring on the side chain has no inhibition. The results showed that more rigidity or strain in the molecule exerts less selectivity. Naphthols type III, 2-substituted-methyl naphthyl ethers with hydroxyl group at the 3′-position of the propyl side chain (**202**, **203**, **205** and **208**) and the methyl ether derivative (**209**) exhibited no activity on both COXs. Therefore, the hydroxyl group at 1-position of naphthols and rigidity or strain in the molecule play important roles for the anti-inflammatory activity.

In the molecular modeling experiments on COX-2, it indicated the hydroxyl group at 1-position enhanced inhibition of COX-2 by H-bond formation with Val523 of COX-2. For inactive naphthols, they have no H-bond interaction with Val523 because methyl naphthyl ether moiety oriented downward which far from the Val523. Moreover, the van der Waals interaction between the C-5 hydrogen of the naphthalene nucleus and the phenolic group of Tyr385 was found in the docking which was established for naphthol inhibitors.

In the COX-1 molecular docking, naphthols possess hydroxyl groups at 1-position showed the H-bond formations between 1-hydroxyl group and Ile523. Naphthols with 1- and 3'-hydroxyl groups revealed the H-bonding with Ile523, Arg120 and Tyr355 whereas inactive naphthols did not show the H-bonding with Ile523.

LITERATURE CITED

Batt, D.G., G.D. Maynard, J.J. Petraitis, J.E. Shaw, W. Galbraith and R.R. Harris. 1990. 2-Substituted-1-naphthols as Potent 5-Lipoxygenase Inhibitors with Topical Antiinflammatory Activity. **J. Med. Chem.** 33: 360-370.

Dannhardt, G. and W. Kiefer. 2001. Cyclooxygenase Inhibitors-Current Status and Future Prospects. **Eur. J. Med. Chem.** 36: 109-126.

Kirtikara, K., S.G. Morham, R. Raghow, S.J.F. Laulederkind, T. Kanekura, S. Goorha and L.R. Ballou. 1998. Compensatory Prostaglandin E_2 Biosynthesis in Cyclooxygenase 1 or 2 Null Cells. **J. Exp. Med.** 187: 517-523.

Kirtikara, K. S. Swangku. And L.R. Ballou. 2001. The Analysis of Nonsteroidal Antiinflammatory Drug Selectivity in Prostaglandin G/H Synthase (PGHS)-Null Cells. **Inflamm. Res.** 50: 327-332.

Kolasa, T., C.D.W. Brooks, K.E. Rodriques, J.B. Summers, J.F. Dellaria, K.I. Hulkower, J. Bouska, R.L. Bell and G.W. Carter. 1997. Nonsteroidal Anti-Inflammatory Drugs as Scaffolds for the Design of 5-Lipoxygenase Inhibitors. **J. Med. Chem.** 40: 819-824.

Kurumbail, R.G., A.M. Stevens, J.K. Gierse, J.J. McDonald, R.A. Stegeman, J.Y. Pak, D. Gildehaus, J.M. Miyashiro, T.D. Penning, K. Seibert, P.C. Isakson and W.C. Stallings. 1996. Structural Basis for Selective Inhibition of Cyclooxygenase-2 by Anti-inflammatory Agents. **Nature** 384: 644-648.

Llorens, O., J.J. Perez, A. Palomer and D. Mauleon. 1999. Structural Basis of the Dynamic Mechanism of Ligand Binding to Cyclooxygenase. **Bioorg. Med. Chem. Lett.** 9: 2779-2784.

Luo, C., M.-L. He and L. Bohlin. 2005. Is COX-2 a Perpetrator or a Protector? Selective COX-2 Inhibitors Remain Controversial. **Acta Pharmacologica Sinica.** 26(8): 926-933.

Morris, G.M., D.S. Goodsell, R.S. Halliday, R. Huey, W.E. Hart, R.K. Belew and A.J. Olison. 1998. Automated Docking Using a Lamarckian Genetic Algorithm and an Empirical Binding Free Energy Function. **J. Comput. Chem.** 19: 1639-1662.

Nakagawa, H., T. Hirabayashi, S. Sakaguchi and Y. Ishii. 2004. Allylation of alcohols and Carboxylic Acids with Allyl Acetate Catalyzed by $[Ir(cod)_2]^+BF_4^-$ Complex. **J. Org. Chem.** 69: 3474-3477.

Picot, D., P.J. Loll and R.M. Garavito. 1994. The X-Ray Crystal Structure of the Membrane Protein Prostaglandin H_2 Synthase-1. **Nature** 367: 243-249.

Plount Price, M.L. and W.L. Jorgensen. 2000. Analysis of Binding Affinities for Celecoxib Analogues with COX-1 and COX-2 from Combined Docking and Monte Carlo Simulations and Insight into the COX-2/COX-1 Selectivity. **J. Am. Chem. Soc.** 122: 9455-9466.

Price, M.L.P. and W.L. Jorgensen. 2000. Analysis of Binding Affinities for Celecoxib Analogues with COX-1 and COX-2 from Combined Docking and Monte Carlo Simulations and Insight into the COX-2/COX-1 Selectivity. **J. Am. Chem. Soc.** 122: 9455-9466.

Purcell, W.P. and J.A. Singer. 1967. A Brief Review and Table of Semiempirical Parameters Used in the Hückel Molecular Orbital Method. **J. Chem. Eng. Data** 12: 235-246.

Reich, S.H., M. Melnick, M.J. Pino, M.A.M. Fuhry, A.J. Trippe, K. Appelt, J.F. Davies II, B.W. Wu and L. Musick. 1996. Structure-based Design and

Synthesis of Substituted 2-Butanols as Nonpeptidic Inhibitors of HIV Protease: Secondary Amide Series. **J. Med. Chem.** 39: 2781-2794.

Satoh, T., M. Ikeda, M. Miura and M. Nomura. 1997. Palladium-Catalyzed Etherification of Allyl Alcohols Using Phenols in the Presence of Titanium(IV) Isopropoxide. **J. Org. Chem.** 62: 4877-4879.

Selinsky, B.S., K. Gupta, C.T. Sharkey and P.J. Loll. 2001. Structural Analysis of NSAID Binding by Prostaglandin H_2 Synthase: Time-Dependet and Time-Independent Inhibitors Elicit Identical Enzyme Conformations. **Biochemistry** 40: 5172-5180.

Sybyl, Version 6.7. Tripos Associates: St. Louis, MO, 2000.

Takahashi, H., S. Sakuraba, H. Takeda and K. Achiwa. 1990. Highly Efficient Asymmetric Hydrogenation of Amino Ketone Derivatives Leading to Practical Syntheses of (*S*)-Propranolol and Related Compounds. **J. Am. Chem. Soc.** 112: 5876-5878.

Talanian, R.V., K.D. Brady and V.L. Cryns. 2000. Caspases as Targets for Anti-Inflammatory and Anti-Apoptotic Drug Discovery. **J. Med. Chem.** 43(18): 3351-3371.

Van, T.N., S. Debenedetti and N.D. Kimpe. 2003. Synthesis of Coumarins by Ring-Closing Metathesis Using Grubbs' Catalyst. **Tetrahedron Lett.** 44: 4199-4201.

Vogel, A.I. 1989. Vogel's Textbook of Practical Organic Chemistry. 5th ed., Longman Group UK Ltd., England. 1600 p.

Weiner, S.J., P.A. Kollman, D.A. Case, U.C. Singh, C. Ghio, G. Alagona, S. Profeta and P. Weiner. 1984. A New Force Field for Molecular Mechanical Simulation of Nucleic Acids and Proteins. **J. Am. Chem. Soc.** 106: 765-784.

Xie, W., J.G. Chipman, D.L. Robertson, R.L. Erikson and D.L. Simmons. 1991. Expression of a Mitogen-Responsive Gene Encoding Prostaglandin Synthase is Regulated by mRNA Splicing. **Proc. Natl. Acad. Sci. USA** 88: 2692-2696.