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A Concise Synthesis and the Antibacterial Activity of 5,6-Dimethoxynaphthalene-2-carboxylic Acid

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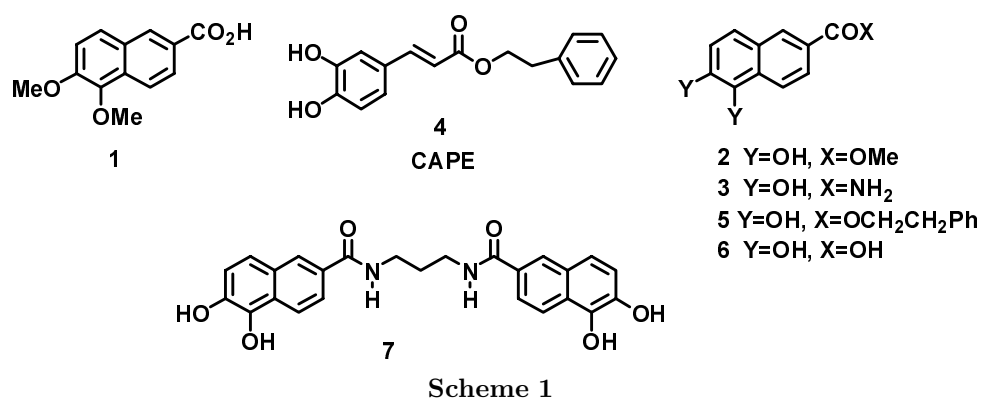
5,6-Dimethoxynaphthalene-2-carboxylic acid was synthesized in 7 steps and with an overall yield of 46%. Bromination of 2-naphthol, and methylation with dimethyl sulfate followed by Friedel-Crafts acylation with AcCl gave 2-acetyl-5-bromo-6-methoxynaphthalene. 2-Acetyl-5-bromo-6-methoxynaphthalene was converted to 5-bromo-6-methoxynaphthalene-2-carboxylic acid by a haloform reaction. The esterification of the acid with methanol, methoxylation with NaOCH₃ in the presence of CuI and subsequent de-esterification with NaOH afforded 5,6-dimethoxynaphthalene-2-carboxylic acid. The 5-bromo-6-methoxynaphthalene-2-carboxylic acid and 5,6-dimethoxynaphthalene-2-carboxylic acid were found to have in vitro antibacterial activity against some pathogenic bacteria.

Key Words: Naphthalene-2-carboxylic acids, 2-naphthol, bromination, haloform, antibacterial activity.

Introduction

5,6-Dimethoxynaphthalene-2-carboxylic acid (**1**), demethylated ester (**2**) and amide (**3**) analogues have moderate inhibitory activity for protein-tyrosine kinases (PTKs)¹. Caffeic acid phenylethyl ester (CAPE) (**4**) has been reported to have HIV-1 integrase inhibitory activity². Demethylated phenylethyl ester analogue (**5**), having constrained CAPE moiety, also shows HIV-1 integrase inhibitory activity and it is somewhat similar in potency to CAPE. 5,6-Dihydroxynaphthalene-2-carboxylic acid methyl ester (**2**) is equipotent to CAPE. Even though its demethylated acid analogue (**6**) is less potent, its demethylated dimeric amide form (**7**) is the most potent for HIV-1 integrase inhibitory activity³.

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To our knowledge, the synthesis of 5,6-dimethoxynaphthalene-2-carboxylic acid has only been performed by Burke et al.¹ from 6-bromo-2-naphthol. In the literature synthesis, oxidation of 6-bromo-2-naphthol with potassium nitrosodisulfonate gives 6-bromo-1,2-naphthalenedione⁴. The reduction of 6-bromo-1,2-naphthalenedione with $\text{Na}_2\text{S}_2\text{O}_4$ gives 6-bromo-1,2-naphthalenediol, from which 6-bromo-1,2-dimethoxynaphthalene is prepared by methylation with dimethyl sulfate⁵. Metalation of 6-bromo-1,2-dimethoxynaphthalene with *n*-BuLi and then treatment with CO_2 gives 5,6-dimethoxynaphthalene-2-carboxylic acid¹. The overall yield of this reaction sequence is 34%.

In our ongoing synthesis of biologically active naphthalene compounds⁶, in the present study we performed an easy alternative synthesis of 5,6-dimethoxynaphthalene-2-carboxylic acid (**1**) starting from 2-naphthol (**8**) in 7 steps with a 46% total yield. As there has been no detailed study regarding the antibacterial properties of 5,6-dimethoxynaphthalene-2-carboxylic acid (**1**) and 5-bromo-6-methoxynaphthalene-2-carboxylic acid (**12**), in this study we investigated the *in vitro* antibacterial activities of these compounds against 17 pathogenic bacteria

Experimental

The ^1H and ^{13}C -NMR spectra were recorded on 200 (50) MHz Varian spectrometers. Column chromatography experiments were performed on silica gel 60 (70-230 mesh ASTM). TLC was carried out on Merck 2.0 mm silica gel and 60 F₂₅₄ analytical aluminum plates. Melting points were determined on a Buchi 530 apparatus, and are uncorrected.

1-Bromo-naphthalene-2-ol (9). To a stirred solution of 2-naphthol (**8**) (30.00 g, 208.3 mmol) in acetic acid (100 mL) was added dropwise a solution of bromine (36.70 g, 229.4 mmol) in acetic acid (20 mL) over 30 min at 18 °C. The reaction mixture was stirred at room temperature for 2 h and poured into 1000 mL of water. The precipitated product was isolated with suction and washed with 100 mL of water. Drying of the crude product at 30 °C and recrystallization from ethanol gave bromonaphthol **9** (37.20 g, 80%). White crystals. M.p. 81-83 °C (from EtOH). Lit.⁷ M.p. 83 °C. ^1H -NMR (200 MHz, CDCl_3) δ 8.05 (dm, 1H, H₅ or H₈, J=8.5 Hz), 7.80 (dm, 1H, H₅ or H₈, J=7.4 Hz), 7.76 (bd, 1H, H₄, J_{3,4}=8.9 Hz), 7.59 (ddd, 1H, H₆ or H₇, J=8.3, 6.9, 1.3 Hz), 7.41 (ddd, 1H, H₆ or H₇, J=8.1, 6.9, 1.1 Hz), 7.28 (bd, 1H, H₃, J_{3,4}=8.9 Hz), 5.95 (bs, 1H, OH). ^{13}C -NMR (50 MHz, CDCl_3): δ 150.6, 129.7, 129.3, 128.2, 127.8, 125.3, 124.2, 117.2, 106.2.

1-Bromo-2-methoxy-naphthalene (10). A 500 mL, 3-necked flask fitted with a condenser and a 50 mL dropping funnel was charged with anhydrous K_2CO_3 (17.30 g, 125.4 mmol), 200 mL of acetone and bromonaphthol **9** (20.00 g, 89.7 mmol). Me_2SO_4 (14.70 g, 11.3 mL, 116.7 mmol) was added under stirring from the dropping funnel to the mixture over 2 min. The stirred mixture was heated gently under reflux for 12 h. The precipitate was filtered off and the acetone was evaporated. The residue was dissolved in $CHCl_3$ (150 mL) and the solution was washed with water (2 x 60 mL) and dried (Na_2SO_4). Removal of the solvent gave **10** (20.20 g, 95%). White solid. M.p. 81-83 °C (from CH_2Cl_2 /hexane). Lit.⁸ M.p. 82-83 °C. 1H and ^{13}C -NMR are in agreement with the data given in the literature⁸.

2-Acetyl-5-bromo-6-methoxy-naphthalene (11). To a stirred solution of **10** (20.00 g, 84.4 mmol) in 300 mL of dry 1,2-dichloroethane were added freshly distilled $AcCl$ (8.00 g, 101.9 mmol) in 1 portion and $AlCl_3$ (33.80 g, 253.2 mmol) in small portions over 1 h at 0 °C. The mixture was stirred at 0 °C for 12 h and monitored by TLC. After the completion of the reaction, the mixture was poured into 250 g of ice and 100 mL of conc. HCl . The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 120 mL). The organic phases were combined and washed with 100 mL of dilute Na_2CO_3 and 100 mL of H_2O . Drying of the organic phase (Na_2SO_4), evaporation of the solvent and then chromatography of the residue through a short silica-gel column (15 g, CH_2Cl_2) afforded **11** (20.20 g, 86%). Yellowish crystals. M.p. 125-127 °C (from CH_2Cl_2 /hexane). Lit.⁹ M.p. 128 °C (from $EtOH$). 1H -NMR (200 MHz, $CDCl_3$): δ 8.32 (d, 1H, H_1 , $J_{1,3}=1.6$ Hz), 8.18 (A part of AB system, d, 1H, H_4 , $J_{3,4}=9.0$ Hz), 8.03 (B part of AB system, dd, 1H, H_3 , $J_{3,4}=9.0$ Hz, $J_{1,3}=1.6$ Hz), 7.88 (A part of AB system, d, 1H, H_8 , $J_{7,8}=9.0$ Hz), 7.53 (B part of AB system, d, 1H, H_7 , $J_{7,8}=9.0$ Hz), 4.03 (s, 3H, OCH_3), 2.68 (s, 3H, $C(O)CH_3$). ^{13}C -NMR (50 MHz, $CDCl_3$): δ 197.3, 155.6, 135.2, 132.8, 130.6, 130.1, 128.5, 126.4, 125.6, 113.8, 108.4, 55.8, 26.5.

5-Bromo-6-methoxy-naphthalene-2-carboxylic acid (12). To a stirred solution of $NaOH$ (21.60 g, 539.4 mmol) in 75 mL of H_2O was added dropwise Br_2 (28.40 g, 177.5 mmol) over 25-30 min at 0 °C. A solution of **11** (15.00 g, 53.8 mmol) in 100 mL of THF was added to the reaction mixture in 1 portion at 0-5 °C. The mixture was stirred at room temp. for 12 h and the organic phase was dispatched from the separatory funnel. To the aqueous solution were added ice (100 g) and a 20% aqueous solution of $NaHSO_3$ (100 mL). After acidification with 37% HCl ($pH \leq 2$) the solidified acid was filtered with suction and dried at 50 °C (13.30 g, 88%). White crystals. Solidified. M.p. 284 \geq decomposition. Lit.¹⁰ M.p. 290-291 °C. 1H -NMR (200 MHz, $DMSO-d_6$): δ 8.60 (bs, 1H, H_1), 8.19 (A part of AB system, d, 1H, H_8 , $J_{7,8}=9.2$ Hz), 8.09 (A part of AB system, d, 1H, H_3 or H_4 , $J_{3,4}=8.5$ Hz), 8.06 (B part of AB system, d, 1H, H_3 or H_4 , $J_{3,4}=8.5$ Hz), 7.59 (B part of AB system, d, 1H, H_7 , $J_{7,8}=9.2$ Hz), 4.03 (s, 3H, OCH_3). ^{13}C -NMR (50 MHz, $DMSO-d_6$): δ 168.9, 157.2, 136.1, 132.9, 132.8, 130.1, 129.0, 128.2, 127.3, 116.6, 108.5, 58.7.

Methyl 5-bromo-6-methoxy-naphthalene-2-carboxylate (13). To a stirred solution of **12** (10.00 g, 35.6 mmol) in 100 mL of $MeOH$ was added $TsOH$ (100 mg) followed by refluxing for 12 h. $MeOH$ was evaporated and the residue was dissolved in 100 mL of $EtOAc$ and washed with a solution of Na_2CO_3 (2 x 50 mL). Drying of the solution (Na_2SO_4) and evaporation of the solvent gave **13** (10.30 g, 98%). White solid. M.p. 164-166 °C (from $MeOH$). Lit.¹⁰ M.p. 162-163 °C, lit.¹¹ 164 °C (from acetone/ H_2O). 1H -NMR (200 MHz, $CDCl_3$): δ 8.40 (bs, 1H, H_1), 8.12 (A part of AB system, d, 1H, H_3 or H_4 , $J_{3,4}=9.0$ Hz), 8.03 (B part of AB system, d, 1H, H_3 or H_4 , $J_{3,4}=9.0$ Hz), 7.78 (A part of AB system, d, 1H, H_8 , $J_{7,8}=9.2$ Hz), 7.18 (B part of AB system, d, 1H, H_7 , $J_{7,8}=9.2$ Hz), 3.98 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3). ^{13}C -NMR

(50 MHz, CDCl₃): δ 166.8, 155.4, 135.1, 131.1, 130.4, 128.4, 126.8, 126.2, 125.6, 113.7, 108.2, 56.6, 52.1.

5,6-Dimethoxy-naphthalene-2-carboxylic acid (1). To refluxing MeOH (60 mL) was added Na (1.20 g, 52.2 mmol) in small pieces over 1 h under N₂. To this solution was added a solution of **13** (5.00 g, 16.9 mmol) in freshly distilled DMF (25-30 mL). While the reaction mixture was being refluxed, CuI (approximately 100-150 mg) was added. After refluxing for 12 h, the reaction mixture was cooled to room temp. and MeOH was evaporated. Then 100 mL of CH₂Cl₂ and 50 mL of H₂O were added and the organic phase was separated. The organic phase was washed with H₂O (4 x 50 mL). After evaporation of the solvent, the residue was hydrolyzed with 2 M NaOH in MeOH/H₂O at room temp. over 12 h. Then MeOH was evaporated. To the residue were added H₂O (50 mL) and CH₂Cl₂ (70 mL). The organic phase was dispatched and the aqueous phase was acidified with 37% HCl (pH \leq 2). The solidified acid **1** was filtered with suction (or workups with EtOAc) and dried at 40 °C (3.20 g, 82%). White crystals. M.p. 213-215 °C (from MeOH). Lit.¹ M.p. 209-211 °C. ¹H-NMR is in agreement with the data given in the literature¹. ¹³C-NMR (50 MHz, DMSO-d₆): δ 169.2, 151.8, 143.6, 132.5, 132.1, 129.8, 128.0, 127.7, 127.2, 122.8, 118.0, 62.4, 58.3.

Measurement of in vitro antibacterial activity. The antibacterial activity of naphthalene carboxylic acid **1** and **12** was determined by the disk diffusion method of Bauer-Kirby using Mueller-Hinton agar medium with a slight modification¹² and compared with well known antibacterial substances such as tetracycline and netilmicin.

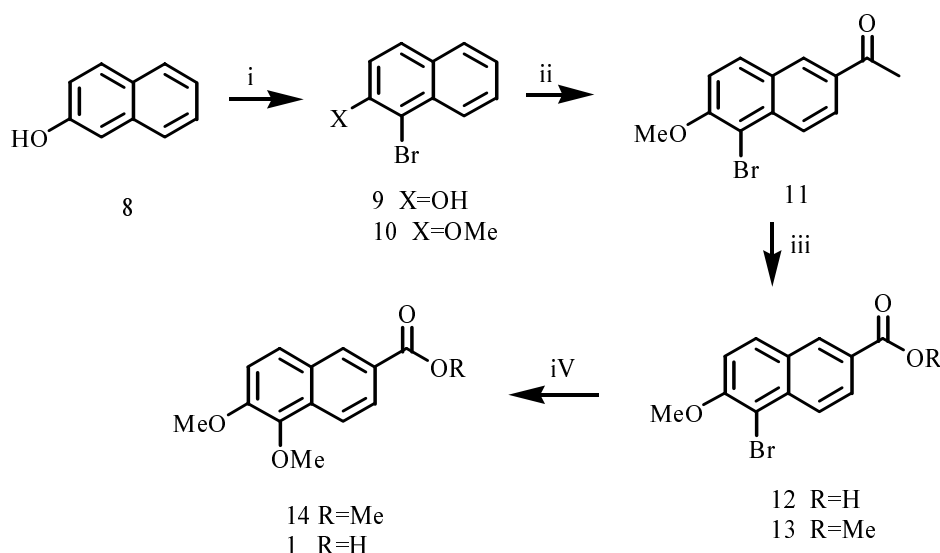
Mueller-Hinton agar medium (prepared in sterile conditions) was cooled to 40-45 °C and each 10 mL portion of it was added to Petri dishes. The organic compounds were dissolved in DMSO (10 mg/2 mL). Then 20 μ L solutions of the compounds (ca. 100 μ g) were applied to the sterile disks. Bacteria suspensions (prepared in McFarland standard 0.5) were applied to the Mueller-Hinton agar medium by the spread plate technique. The prepared sterile disks were placed in bacteria-culture spread Petri dishes using a sterile needle. The Petri dishes were left at +4 °C for 1 h and then incubated in an incubator at 37 °C for 18-24 h.

For the compounds, microorganisms that showed zones of inhibition <10 mm were considered resistant, between 10 and 15 were considered weakly sensitive, and >15 were considered sensitive¹². According to NCCLS (1999), zones of inhibition for tetracycline <14 mm were considered resistant, between 15 and 18 mm were considered weakly sensitive, and >19 were considered sensitive. Zones of inhibition for netilmicin of <12 mm were considered resistant, between 13 and 14 mm were considered weakly sensitive, and >15 were considered sensitive.

Results and Discussion

By a known literature procedure¹³ applied to 2-methoxynaphthalene, the bromination of 2-naphthol (**8**) in acetic acid gave 1-bromo-2-naphthol (**9**). Methylation of 1-bromo-2-naphthol (**9**) with dimethyl sulfate and K₂CO₃ gave 1-bromo-2-methoxynaphthalene (**10**)¹³. Friedel-Crafts acylation with acetyl chloride in the presence of AlCl₃ performed in 1,2-dichloroethane gave 2-acetyl-5-bromo-6-methoxynaphthalene (**11**)⁹. Acetyl compound **11** was converted to carboxylic acid **12**¹⁰ by a haloform reaction (Br₂/NaOH). The acid **12** was converted to ester derivative **13**^{10,11} with the treatment of a catalytic amount of TsOH (p-toluenesulfonic acid) in methanol. The most critical step of our synthesis was the substitution of bromine in compound **13** with NaOMe. Copper-assisted nucleophilic substitutions of aryl halogens are reported in the literature¹⁴.

Considering the applicability of the reaction, we assume that the methoxylation of **13** proceeded with the substitution of methoxide with bromine. Indeed, the reaction of bromoester **13** with NaOMe in the presence of CuI in methanol and DMF afforded methyl 5,6-dimethoxynaphthalene-2-carboxylate (**14**), from which the corresponding carboxylic acid **1** was prepared by NaOH-assisted hydrolysis followed by acidification.



Scheme 2. Reagents and Conditions: (i) a) Br₂, AcOH, 88% b) Me₂SO₄/K₂CO₃, acetone, 95% (ii) AcCl /AlCl₃, 1,2-dichloroethane, 86% (iii) a) Br₂/NaOH, HCl, 88% b) MeOH/TsOH, 98% (iv) a) NaOMe/MeOH, DMF, CuI b) NaOH/MeOH-H₂O, then HCl, 82%.

As there has been no detailed study regarding the antibacterial properties of carboxylic acids **1** and **12**, in this study we investigated the antibacterial activities of these compounds. As can be seen in the Table, for carboxylic acid **1**, *Aeromonas hydrophila* ATCC 7966, *Micrococcus luteus* LA 2971, *Bacillus subtilis* var. *niger* ATCC 10, *Klebsiella pneumoniae* FMC 5, *Pseudomonas pyocyanea*, *Bacillus megaterium* EU, *Staphylococcus aerogenes*, *Streptococcus faecalis*, *Bacillus megaterium* DSM32 and *Mycobacterium smegmatis* RUT showed inhibition zones >14-26 mm in size and were sensitive. *Bacillus megaterium* NRS, *Bacillus brevis* FMC, *Pseudomonas aeruginosa* ATCC 2785, *Enterococcus faecalis* ATCC 15753 and *Mycobacterium smegmatis* CCM 2067 were weakly sensitive (11-14 mm). *Corynebacterium xerosis* UC 9165 and *Klebsiella oxytoca* showed inhibition zones 0 mm in size and were resistant.

For carboxylic acid **12**, *Pseudomonas pyocyanea*, *Mycobacterium smegmatis* RUT and *Bacillus megaterium* DSM32 showed inhibition zones 16-24 mm in size and were sensitive. *Aeromonas hydrophila* ATCC 7966, *Micrococcus luteus* LA 2971, *Bacillus subtilis* var. *niger* ATCC 10, *Pseudomonas aeruginosa* ATCC 27853, *Enterococcus faecalis* ATCC 15753, *Bacillus brevis* FMC3, *Klebsiella pneumoniae* FMC 5, *Bacillus megaterium* NRS, *Bacillus megaterium* EU, *Staphylococcus aerogenes*, *Streptococcus faecalis* and *Mycobacterium smegmatis* CCM 2067 showed inhibition zones >10-14 mm in size and were weakly sensitive. *Corynebacterium xerosis* UC 9165 and *Klebsiella oxytoca* showed inhibition zones 0 mm in size and were resistant. Tetracycline and netilmicin are well known as antibacterial substances and showed very large inhibition zones (all >17 mm radius) for the same pathogenic bacteria.

Table. Inhibition zones of the naphthalene carboxylic acid **1** and **12** against some bacteria by the disk diffusion method.

Pathogenic bacteria	12 (mm)	1 (mm)	Control DMSO
<i>Corynebacterium xerosis UC 9165</i>	-	-	-
<i>Klebsiella pneumoniae FMC 5</i>	12	16	-
<i>Bacillus megaterium NRS</i>	13	14	-
<i>Bacillus brevis FMC3</i>	10	11	-
<i>Pseudomonas aeruginosa</i>	12	13	-
<i>Bacillus subtilis var. niger</i>	13	17	-
<i>Aeromonas hydrophila ATCC 7966</i>	14	15	-
<i>Enterococcus faecalis ATCC 15753</i>	12	14	-
<i>Pseudomonas pyocyanea</i>	16	17	-
<i>Bacillus megaterium EU</i>	10	18	-
<i>Mycobacterium smegmatis RUT</i>	17	21	-
<i>Bacillus megaterium DSM32</i>	24	26	-
<i>Klebsiella oxytoca</i>	-	-	-
<i>Staphylococcus aerogenes</i>	12	16	-
<i>Streptococcus faecalis</i>	11	15	-
<i>Mycobacterium smegmatis CCM 2067</i>	14	14	-
<i>Micrococcus luteus LA 2971</i>	11	18	-

In summary, with relatively little synthetic effort, we have achieved a concise and alternative synthesis of 5,6-dimethoxynaphthalene-2-carboxylic acid (**1**) in 7 steps starting from 2-naphthol (**8**) (overall yield of 46%) and we have also shown the considerable antibacterial effects of 5,6-dimethoxynaphthalene-2-carboxylic acid (**1**) and 5-bromo-6-methoxynaphthalene-2-carboxylic acid (**12**) against 15 bacteria.

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