SYNTHESIS OF SOME NOVEL TETRAHYDRONAPHTHALENE BENZIMIDAZOLE DERIVATIVES

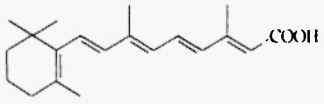
Zeynep Ates-Alagoz and Erdem Buyukbingol*

Department of Pharmaceutical Chemistry, University of Ankara, Faculty of Pharmacy, Ankara, Turkey

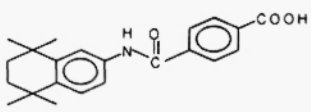
Abstract : Retinoids, synthetic and natural analogues of *all-trans*-retinoic acid (RA), exert their biological effects with responsive elements of DNA to promote on cell differentiation and proliferation and behave as potent adipogenic hormones. Herein, we describe the synthesis of a number of novel tetrahydrotetramethylnaphthalene benzimidazole derivatives as retinoids. Analogs were prepared as depicted in Scheme 1 and 2. As is evident from both shemes, a variety of tetrahydrotetramethylnaphthalene benzimidazole derivatives have been synthesized by using an appropiate $NaHSO_3$ addiction product

Introduction

Retinoids, natural and synthetic analogs of vitamin A (retinol) have a wide spectrum of biological activities. Retinoic acid (RA) and retinoids play essential roles in many diverse biological events including cell diffrentiation/poliferation[1,2] and lipid peroxidase inhibition[3]. These properties confer a high potential for the treatment of hyperproliferative disorders[4]. Clinically retinoids are used in the treatment of proliferative dermatological diseases and leukemia, and in the prevention of some tumors[5]. Retinoids have been shown to inhibit the growth of different tumour cell lines[6-8] and to supress the induction of growth-related properties[9]. Therefore, retinoids have recently received considerable attention as agents that may have utility for both cancer prevention and treatment due to their cell differentiation/proliferation[10]. Additionally, retinoids have been shown to inhibit microsomal lipid peroxidation as effective antioxidants[11,12]. Recently there has been a great deal of interest in the study on the free radicals such as superoxide anion, hydroxyl anion and hydrogen peroxide which are related with atherosclerosis, nephrititis and carcinogenesis[13,14]. To investigate the antioxidant activity and consequently a cell differentiation and poliferation activity, some benzimidazole derivatives, related to the structure of RA and well known compound Am 580[15] have been synthesized. As part of our ongoing retinoid program, we had observed that a benzimidazole-type of retinoid compound inhibits hepatic CYP1A1/2 and CYP 2B1 enzymes, since these enzymes activate polycyclic hydrocarbons to their ultimate mutagenic and carcinogenic forms, and are effective in producing reactive oxygen species such as superoxide and hydroxyl radicals[16]. The actions of arylbenzimidazoles on the hepatic cytochrome P450 enzymes have been also reported, previously[17].



Retinoic acid



Am580

Figure 1: Structures of *all-trans*-retinoic acid (RA) and Am 580

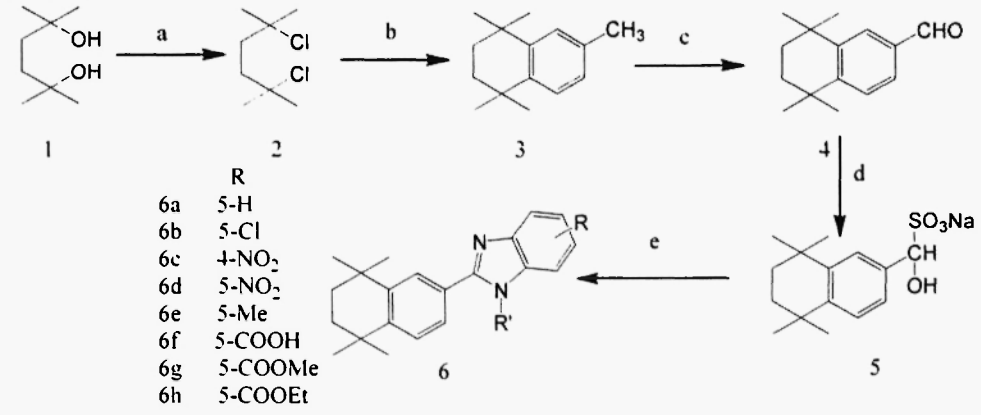
Experimental

Although a number of improved synthetic routes to retinoids have been revealed in the literature, we have synthesized benzimidazole-linked tetrahydronaphthalene type compounds. The synthesis of the compounds can be divided into two parts. The first part of our synthesis, (**6a-h**) were carried out as shown in Scheme 1. The starting material was the 2,5-dichloro-2,5-dimethyl hexane, **2**, was prepared in 56 % yield by passing dry hydrogen chloride gas over 2,5-dimethyl-2,5-hexandiole, **1**, as described by Boehm et all, 1994[18]. Toluene was alkylated by 2,5-dichloro-2,5-dimethyl hexane in dichloromethane catalyzed with aluminum chloride to produce 1,2,3,4-tetrahydro-1,1,4,4,6-pentamethylnaphthalene, **3**, in 91 % yield[18] followed by synthesizing of 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalene-carboxaldehyde, **4**, was achieved by ammonium cerium nitrate ($(NH_4)_2Ce(NO_3)_6$) as described[19]. An intermediate addiction product, **5**, has been obtained by the procedure that aldehyde compound, **4**, in etanol was added to the solution $NaHSO_3$ in water (m.p. decomp. >300°C)[20]. To obtain the desired compounds, Weidenhagen procedure was used[20]. Thus, the treatment of the intermediate, **5**, with substituted o-phenylenediamine afforded the expected 2-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalene)]-4-or-5-substituted benzimidazole compounds[21], **6a-h**, in several yields. The general synthesis of the compounds is seen in Scheme 1.

The second part of synthesis (Scheme 2) consists of to obtain alkyl derivatives of tetrahydro-tetramethylnaphthalene-benzimidazoles at imidazole ring nitrogen. The starting material was 4-chloro-3-nitro-benzoic acid, **7**, which was refluxed in methanol (or ethanol) followed by passing through the HCl gas to obtain 4-chloro-3-nitro-methyl benzoic acid methyl/ethyl esters, **8a-b**. The exchange of chloride by substituted amine, **9a-c**, moiety was done according to the procedure of Goker et al[22]. The next step was a reduction of the nitro group. The use of $Zn/NiCl_2.6H_2O$ in methanol gave compounds, **10a-c** in excellent yields. The condensing of these compounds with the $NaHSO_3$ addiction product, **5**, in DMF for 70 hrs afforded tetrahydronaphthalene-benzimidazole derivatives, **11a-b**. The hydrolysis of the latter products gave final compounds, **12a-b**. The physical data of the compounds are summarized in Table 1.

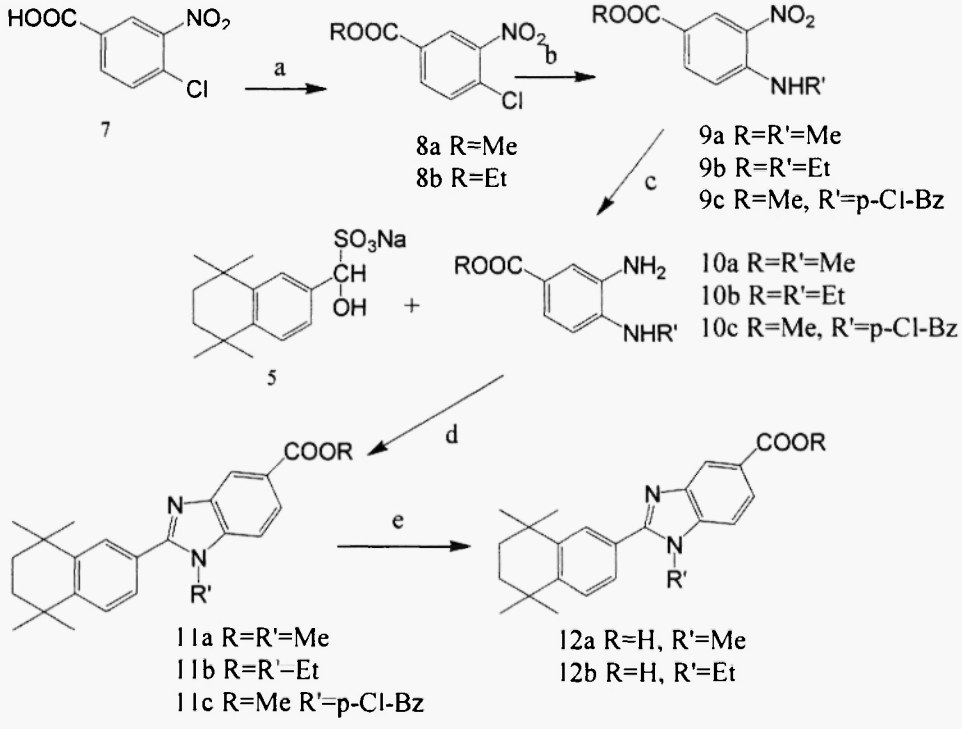
Melting points were determined with a Buchi SMP-20 and Buchi 9100 melting point apparatus and are uncorrected. The ^1H NMR spectra were recorded with a Bruker GmbH DPX-400 (400 MHz) spectrophotometer, in DMSO-d_6 or $CDCl_3$ unless otherwise stated, δ scale (ppm) from internal standart TMS. The IR spectra were recorded on a Jasco FT/IR-420 spectrophotometer as potassium bromide pellets. The Mass spectra (in EI mode at 70 eV) were recorded with a Nicromass UK. Platform II LC-MS and elemental analysis were performed on LECO 932 CHNSO.

Scheme 1



a) HCl/H_2SO_4, EtOH
b) Toluene, $AlCl_3$, CH_2Cl_2, reflux
c) $(NH_4)_2Ce(NO_3)_6$, AcOH, reflux
d) $NaHSO_3$
e) Substituted o-phenelediamine, DMF, reflux

Scheme 2



a) MeOH/Et, HCl, reflux; b) $R'NH_2$, THF, reflux; c) $Zn/NiCl_2$, MeOH, reflux;
d) DMF, reflux; e) NaOH, EtOH, reflux

Synthesis of 1,2,3,4-tetrahydro-1,1,4,4,6-pentamethylnaphthalene (3).
To a 250 ml round bottomed flask fitted with a magnetic stirring bar and reflux condenser were added 10.0 g (54.5 mmol) of 2,5-Dichloro-2,5-dimethyl hexane, 10.0 g (110 mmol) of toluene and 50 ml of dichloromethane. To this vigorously stirred solution was slowly added 100 mg (0.75 mmol) of aluminum chloride which resulted in rapid evolution of gaseous hydrochloric acid. The reaction mixture was stirred at room temperature for 30 min followed

by reflux for an additional 15 min to give a red solution containing 1,2,3,4-tetrahydro-1,1,4,4,6-pentamethylnaphthalene. After cooling 10ml of 20% aqueous hydrochloric acid was added to the stirred solution and the reaction mixture turned clear/white . The organics were extracted with 2x100 ml of hexanes, washed with water and brine, dried over magnesium sulfate, filtered, concentrated and distilled to give 10.0 g (49.5 mmol) of 1,2,3,4-tetrahydro-1,1,4,4,6-pentamethylnaphthalene compound (91% yield, m.p. 31-32°C)[18].

Synthesis of 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalene-carboxaldehyde (4).
This compound was synthesized as described by Dawson et all[19]. To a vigorously stirred 100 °C mixture of 10.0 g (0.0494 mol) of 1,2,3,4-tetrahydro-1,1,4,4,6-pentamethylnaphthalene and 20 ml of glacial acetic acid was added a solution of 150.0 g (0.274 mol) of $(NH_4)_2Ce(NO_3)_6$ in 500 ml of 50% aqueous acetic acid over 3h period. The mixture was stirred 1h, cooled, poured onto ice and extracted with petroleum ether (3x300 ml). The extract were washed 2 times with water, dried on magnesium sulphate and concentrated to give 8.5 g (78%) of compound column chromatography (silicagel, 10% Et_2O/hexane) was used to obtain colourless crystals (m.p: 52-54°C).

Synthesis of sulfide addiction product (5).
A procedure by Weidehagen was used[20]. To a solution of 6.6 g (30 mmol) of 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalene-carboxaldehyde in 20 ml ethanol was added to the solution of 3.12 g (30 mmol) $NaHSO_3$ in 20 ml H_2O, stirred in ice-bath to give 7.2 g white precipitate which was filtered and dried. (74% yield, m.p. decom.>300°C).

General synthesis of 2-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalene)]-5- benzimidazole derivatives (6a-h).
The $NaHSO_3$ addiction product, **5** (10 mmol), and 1-substituted-3,4-diamino-benzoic acid (10 mmol) were refluxed in DMF for 72 hours, poured onto ice-cold water with stirring. The precipitate was filtered off and extracted with ethyl acetate (3x30 ml) washed with excess amount of water followed by column chromatography for purification [21].

Synthesis of 4-chloride,3-nitro benzoic acid methyl/ethyl ester (8a-b).
4-chloride, 3-nitro-benzoic acid (25 mmol) was refluxed in 50 ml methanol/ethanol presence of HCl gas. The solvent was evaporated and 50 ml water was added. Then neutralized with $NaHCO_3$ to give white precipitate which was filtered and dried (m.p. and yield, respectively, **8a**: 63°C, 97%; **8b**:59.5°C, 95%) [22].

Synthesis of 4-alkylamino, 3-nitro, benzoic acid methyl/ethyl ester (9a-c).
4-chloride-3-nitro-methyl/ethyl benzoat (4.6 mmol) was refluxed in 40 ml alkylamine (methyl amine, ethyl amine or p-Cl-Benzyl amine) and 10 ml tetrahydrofuran for 2 hour at 40 °C. Then solvents were evaporated, water was added to give yellow precipitate which was filtered and dried (m.p. and yield, respectively, **9a**:211°C, 78%; **9b**:104°C, 84%; **9c**:142 °C, 89%) [22].

Synthesis of 3-amino, 4-alkylamino, benzoic acid methyl/ethyl ester (10a-c).
4-Alkylamino-3-nitro-benzoic acid methyl/ethyl ester (4.7 mmol) was solved with 15 mL methanol and reduction with 1.3 g $NiCl_2.6H_2O$ and 1.5 g Zn. The mixture was filtered while boiling. The precipitate washed with boiled methanol and concentrated to give3-amino-4-alkyl amino-benzoic acid methyl/ethyl ester (m.p. and yield, respectively, **10a**:144°C, 46%; **10b**:73°C, 34%; **10c**:223 °C, 96%)[22].

General synthesis of 1-alkyl-2-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalene)]-5- benzimidazole derivatives (11a-c) and (12a-b)
The addiction product **(5)** (2mmol), and 1-substituted-3-amino, 4-alkylamino-benzoic acid (2 mmol) were refluxed in DMF for 72 hours, poured onto ice-cold water with stirring. The precipitate was filtered off and extracted with ethyl acetate (3x30 ml) washed with excess amount of water followed by column chromatography for purification. Final products **(12a-b)**, were obtained hydrolysis procedure from **(11a-b)**. Compounds **11a** (0.7 mmol) or 11b (0.7 mmol) was solved in 1.5 ml ethanol and were refluxed in 5 ml %5 NaOH for 6 hours. Reaction mixture was acidified with glasial asetic acid. The precipitate was filtered and washed with water, then crystalized from ethanol for purification to give desired compounds.

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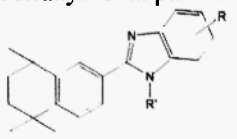
Table 1. Structural and Physical Data for Tetrahydronahpthalene-benzimidazole compounds.



Comp.	R	R'	M.P (°C)	Yield (%)	NMR	MASS m/z	IR (KBr cm^{-1})
6a	H	H	249	19	δ (d_6-DMSO) 1.28, d, $4CH_3$; 1.66, s, $(CH_3)_2$; 7.12-8.09, m, aromatic	304 (M^+), 305 (M+1), 290 ((M+1)-CH_3), 289 (M-CH_3), 275 ((M+1)-$2CH_3$), 274 (M-$2CH_3$), 260 ((M+1)-$3CH_3$), 259 (M-$3CH_3$), 245 ((M+1)-$4CH_3$)	3050- CH_3, CH_2 2750- =CH
6b	5-Cl	H	218	16	δ (d_6-DMSO) 1.31, d, $4CH_3$; 1.68, s, $(CH_3)_2$; 7.19-8.13, m, aromatic	338 (M^+), 340 (M+2), 341 (M+3),342 (M+4), 323 (M-CH_3), 325 ((M+2)-CH_3), 308 (M-$2CH_3$), 293 (M-$3CH_3$)	2959-2859 CH_3-CH_2
6c	4-NO_2	H	198	30	δ ($CDCl_3$) 1.37, s, $2CH_3$; 1.43, s, $2CH_3$; 1.78, s, $(CH_3)_2$; 7.6-8.3, m, aromatic)	350 (M+1), 335 ((M+1)-CH_3), 319 ((M-$2CH_3$), 305 (M-$3CH_3$), 289 (M-$4CH_3$), 289 (335-NO_2)	1541, 1362 (NO_2)
6d	5-NO_2	H	290	31	δ ($CDCl_3$) 1.31, s, $2CH_3$; 1.33, s, $2CH_3$; 1.72, s, $(CH_3)_2$; 7.43-8.51, m, aromatic	350 (M+1), 335 ((M+1)-CH_3), 289 (M-$4CH_3$),289 (335-NO_2), 259 (289-$2CH_3$), 244 (259-CH_3)	1537, 1344 (NO_2)
6e	5-Me	H	222	37.5	δ ($CDCl_3$) 1.04, s, $2CH_3$; 1.24, s, $2CH_3$; 1.62, dd, $(CH_3)_2$; 2.41, s, -CH_3; 7.04-8.3, m, aromatic	319 (M+1), 318 (M^+), 303 (M-CH_3), 289 ((M+1)-$2CH_3$), 288 (M-$2CH_3$), 273 (M-$3CH_3$), 259 ((M+1)-4CH3)	3050-2850- CH_3 CH_2,=CH
6f	5-COOH	H	215	34	δ (d_6-DMSO) 1.33, d, $4CH_3$; 1.70, s, $(CH_3)_2$; 7.5-8.3, m, aromatic, 13.00, broad s, -OH	348 (M^+), 349 (M+1), 303 (M-COOH), 333 (M-CH_3), 318 (M-$2(CH_3)$, 303 (M-(CH_3)	1684 COOH
6g	5-COOMe	H	223	30.2	δ ($CDCl_3$) 0.96, s, $2CH_3$; 1.22, s, $2CH_3$; 1.59, dd, J 8 Hz, $(CH_2)_2$; 3.88, s, -OCH_3; 7.31-8.34, m, aromatic	362 (M^+), 363 (M+1), 347 (M-CH_3), 332 (M-$2CH_3$),331 (M-OCH_3), 317 (M-$3CH_3$), 304 ((M+1)-$COOCH_3$), 303 (M-$COOCH_3$), 303 ((M+1)-$4CH_3$)	1693 COOMe
6h	5-COOEt	H	129	84	δ (d_6-DMSO) 1.33, d, $4CH_3$; 1..36, t, -CH_2CH_3; 1.7, s, $(CH_2)_2$; 4.35, q, -OCH_2-CH_3; 7.5 –8.2, m, aromatic	377 (M+1), 362 ((M+1)-CH_3), 348 ((M+1)-CH_2CH_3), 332 ((M+1)-$3CH_3$), 332 ((M+1)-OCH_2CH_3), 320 (348-C0), 304 ((M+1)-$COOCH_2CH_3$)	1715 COOEt
11a	5-COOMe	Me	250	51.5	δ ($CDCl_3$) 1.36, d, $4CH_3$; 1.76, s, $(CH_2)_2$; 3.00, d, N-CH_3; 3.89, s, -OCH_3; 6.42–8.22, m, aromatic	377 (M+1), 376 (M^+), 362 ((M+1)-CH_3), 361 (M-CH_3), 347 ((M+1)-$2CH_3$), 346 (M-$2CH_3$), 346((M+1)-OCH_3), 345 (M-OCH_3), 332 ((M+1)-$3CH_3$), 331 (M-$3CH_3$), 317 (M-$COOCH_3$), 317 ((M+1)-$4CH_3$)	1628 COOMe
11b	5-COOEt	Et	178	16.8	δ ($CDCl_3$) 1.36, d, $4CH_3$; 1.45, t, N-CH_2CH_3; 1.54, t, O-CH_2CH_3; 1.7, s, $(CH_2)_2$; 4.3, q, N-CH_2CH_3; 4.4, q, O-CH_2CH_3; 7.28-8.57, m, aromatic	405 (M+1), 404 (M^+), 390 ((M+1)-CH_3), 389 (M-CH_3), 374 (M-$2CH_3$), 360 ((M+1)-$3CH_3$), 360 (M-OCH_2CH_3), 359 (M-$3CH_3$), 344(M-$4CH_3$), 333 ((M+1)-$COOCH_2CH_3$)	1710 COOEt
11c	5-COOMe	p-Cl-Bz	209	16.8	δ ($CDCl_3$) 1.08, s, $2CH_3$; 1.23, s, $2CH_3$; 1.62, d, $(CH_2)_2$; 3.88, s, -OCH_3; 5.37, s, N-CH_2; 7.11-8.51, m, aromatic	488 (M+2), 486 (M^+), 471 (M-CH_3), 455 ((M+1)-$2CH_3$), 455 (M-OCH_3), 429 ((M+2)-$COOCH_3$)	1708 COOMe
12a	5-COOH	Me	282	41.5	δ (d_6-DMSO) 1.33, d, $4CH_3$; 1.72, s, $(CH_2)_2$; 3.9, s, N-CH_3; 7.5–8.3, m, aromatic	363 (M+1), 348 ((M+1)-CH_3), 346 ((M+1)-OH), 332 (M)-$2CH_3$), 318 (346-CO), 318 ((M+1)-$3CH_3$), 318 ((M+1)-COOH), 303 ((M+1)-$4CH_3$)	1664 COOH
12b	5-COOH	Et	286	41.5	δ ($CDCl_3$) 1.27, d, $4CH_3$; 1.46, t, (CH_2CH_3);, 1.67, s, $(CH_2)_2$; 4.24, q, (CH_2CH_3); 7.39-8.56, m, aromatic	377 (M+1), 376 (M^+), 361 (M)-CH_3), 346 (M)-$2CH_3$), 331(M)-$4CH_3$), 317 (M-$COOCH_3$)	1671 COOH

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