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Kuo-Long Yu [a], Jacek Ostrowski [b], Simon Chen [b], Peter R. Reczek [b], Muzammil M. Mansuri [a] & John E. Starrett Jr [a]

[a] Bristol-Myers Squibb Company, Pharmaceutical Research Institute, 5 Research Parkway, Wallingford, Connecticut, 06492

[b] Westwood-Squibb Pharmaceuticals, 100 Forest Avenue, Buffalo, New York, 14213

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SYNTHESIS OF NITRONE ANALOGUES OF RAR α SELECTIVE RETINOID AM580

Kuo-Long Yu,* Jacek Ostrowski,+ Simon Chen,+
Peter R. Reczek,+ Muzammil M. Mansuri and John E. Starrett Jr.

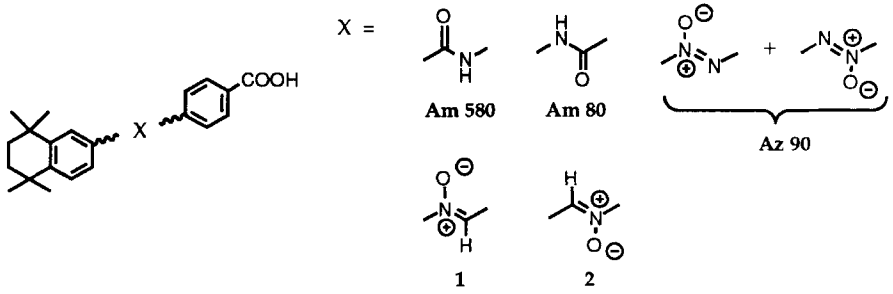
Bristol-Myers Squibb Company, Pharmaceutical Research Institute
5 Research Parkway, Wallingford, Connecticut 06492
+ Westwood-Squibb Pharmaceuticals, 100 Forest Avenue,
Buffalo, New York 14213

ABSTRACT Synthesis of nitrone analogues of RAR α-selective retinoid **Am 580** in which the amide linker is replaced with a nitrone moiety is discribed. The nitrone segment was constructed by oxidizing the corresponding amine using MCPBA or dimethyldioxirane. The resulting nitrone derivatives were found unstable in acidic and basic conditions. The stability limitations of using this nitrone moiety as an amide surrogate are briefed.

Retinoic acid (RA) and its derivatives (retinoids) have been used in the treatment of cancers and several dermatological diseases such as acne and psoriasis.[1] Although the retinoids have shown significant beneficial effects in treating these diseases, concern of their side effects such as teratogenecity, hypervitaminosis-A and skin irritation has prevented their broad use in patients. Recent evidence has indicated that retinoic acid may exert its functions by regulating gene expression mediated by two classes of nuclear receptors: RARs

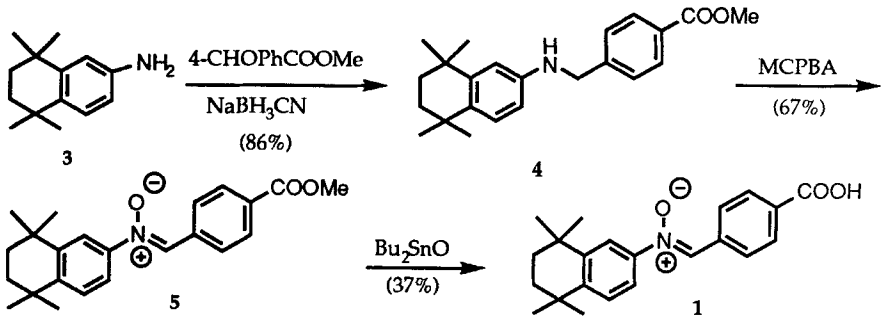
* To whom correspondence should be addressed.

(α, β, γ) and RXRs (α, β, γ)[1] which are unevenly distributed in tissues. It is believed that development of retinoids which selectively interact with a specific receptor might have the advantage of exerting their desired pharmacological actions without the adverse effects.[2] Among the receptor selective retinoids reported, **Am 580** and **Am 80** have demonstrated RAR α selective activity in the RAR transactivation assays.[3] In addition, the inseparable mixture of azoxy derivatives **Az 90** in which the amide linker of **Am 580** was replaced with a azoxy group has shown extemely potent activity in the differentiation assay in HL60 cell.[4] The results prompted us to propose nitrone derivatives **1** and **2** in an attempt to study the structure-activity relationship by using a nitrone moiety to replace the amide linker of **Am580** and **Am80** . Although the nitrone moiety was first proposed as a "reversed amide surrogate" by Grunke et al.,[5] to our knowledge, no biologically active compounds using this segment as an amide bond surrogate has been reported.



The synthesis of nitrone retinoid **1** is shown in scheme 1. Reductive amination of methyl 4-formylbenzoate and 2-amino-5,5,8,8-tertamethyl-5,6,7,8-tetrahydronaphthaleneusing $NaBH_3CN$[6] followed by oxidation of the amine with

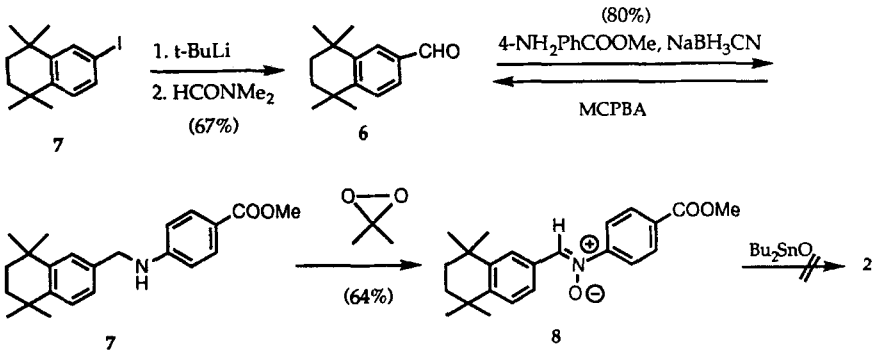
Scheme 1



MCPBA[7] yielded nitrone ester **5** in 67% yield. Saponification of the ester using NaOH failed to to produce the desired nitrone acid **1**. Analysis of the mixture of the products using ^{1}H NMR indicated that the nitrone linkage was cleaved. Milder reaction conditions by refluxing the ester with dibutyltin oxide[8] in toluene followed by hydrolysis of the tin ester with dilute HCl solution provided nitrone acid **1** in 37 % yield.

To prepare the nitrone derivative **2**, amine **7** was first synthesized from aryl aldehyde **6** and methyl 4-aminobenzoate using reaction conditions described above (scheme 2). Unlike the previous oxidation reaction, treatment of amine **7** with MCPBA in methylene chloride gave the recovered aldehyde **6** and the amine. This is due to the deactivation effect of the electron-withdrawing benzoate group and the hydrolysis of the imine intermediate. The more powerful oxidation agent, dimethyldioxirane,[10] however, successfully converted amine **7** to nitrone ester **8** in 64 % yield. Unfortunately, the nitrone was found unstable in basic and acidic conditions (NaOH and TFA) due to the activation of the nitrone

Scheme 2



by the benzoic acid. Hydrolysis of **8** using Bu_2SnO also gave a mixture of the products. Because of the instabilility of nitrone **2** and weak retinoidic activity and no receptor selectivity of nitrone **1** in the RAR transactivation assays,[11] nitrone acid **2** was not further pursued.

In conclusion, although only one of the two proposed nitrone derivatives of **Am 580** was prepared, our study has demonstrated the stability limitations of using nitrone moiety as an amide bond surrogate. In adition, we have showed that dimethyldioxirane is superior to MCPBA in the oxidation of an amine to a nitrone.

Experimental:

Methyl 4-[(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-aminomethyl]-benzoate (4).

2-Amino-5,5,8,8-tertamethyl-5,6,7,8-tetrahydronaphthalene (100 mg, 0.49 mmol) and methyl 4-formylbenzoate (80 mg, 0.49 mmol) in 3 mL of MeOH was

added 0.2 mL of acetic acid. After stirring for 5 min, $NaBH_3CN$ (34 mg, 0.54 mmol) was added. The mixture was stirred for addditional 5 min. The solvent was evaporated, and the residue was diluted with saturated $NaHCO_3$ solution (15 mL) and extracted EtOAc (20 mL X 3). The combined extracts were dried over $MgSO_4$ and evaporated. The residue was purified by flash chromatography (EtOAc:hexane = 1:20 to 1:7) to give 148 mg (86%) of the title compound as a white solid. ^1H NMR ($CDCl_3$) δ 1.22 (s, 6 H), 1.24 (s, 6 H), 1.65 (s, 4 H), 3.92 (s, 3 H), 4.38 (s, 2 H), 6.47 (dd, J = 2.6, 8.5 Hz, 1 H), 6.56 (d, J = 2.6 Hz, 1 H), 7.13 (d, J = 8.5 Hz, 1 H), 7.47 (d, J = 8.5 Hz, 2 H), 8. 02 (d, J = 8.5 Hz, 2 H). MS *m/e* 352 (MH^+). Anal. Cald for $C_{23}H_{27}NO_3$: C, 78.60; H, 8.32; N, 3.98. Found: C, 78.67; H, 8.57; N, 4.10.

Methyl 4-[[(5,5,8,8-tetramethyl-5,6,7,8-terahydro-naphthalene)-2-imino]methylene]-benzoate, N-oxide (5).

To a solution of amine **4** in 4 mL of acetone was slowly added MCPBA in 3 mL of acetone at 0 °C in 1 h. After stirring for 30 min, the mixture was diluted with saturated K_2CO_3 solution (20 mL), extracted with CH_2Cl_2 (30 mL x 3). The combined extracts were washed with water, dried over $MgSO_4$, and evaporated. The residue was purified by chromatography (EtOAc: hexane = 1:20 to 1:5) to give a solid which crystallized from EtOAc-hexane to give 195 mg (67%) of nitrone ester **5**. ^1H NMR ($CDCl_3$) δ 1.31 (s, 6 H), 1.34 (s, 6 H), 1.73 (s, 4 H), 3.95 (s, 3 H), 7.40 (d, J = 8.6 Hz, 1 H), 7.47 (d, J = 2.3, 8.6 Hz, 1 H), 7.73 (d, J = 2.3 Hz, 1 H), 7.95 (s, 1 H), 8.13 (d, J = 8.5 Hz, 2 H), 8.45 (d, J = 8.5 Hz, 2 H). MS *m/e* 366 (MH^+). Anal. Cald for $C_{23}H_{27}NO_3$: C, 75.59; H, 7.45; N, 3.83. Found: C, 75.67; H, 7.38; N, 3.94.

4-[[(5,5,8,8-Tetramethyl-5,6,7,8-terahydro-naphthalene)-2-imino]methylene]-benzoic acid (1).

Ester **5** (204 mg, 0.56 mmol) and dibutyltin oxide (416 mg, 1.68 mmol) in 5 mL of anhydrous toluene were stirred at reflux for 18 h. The solvent was evaporated under reduced pressure. The residue was diluted with 15 mL of 1 N HCl, extracted with a mixture of THF-EtOAc (1:3, 20 mL X 3). The combined extracts were washed with water, dried over $MgSO_4$, and evaporated. The residue was triturated with ether to give 72 mg (37% yield) of acid **1** as yellow solids. ^{1}H NMR (DMSO-d_6) δ 1.26 (s, 6 H), 1.29 (s, 6 H), 1.66 (s, 4 H), 7.49 (d, J = 8.6 Hz, 1 H), 7.62 (dd, J = 2.4, 8.6 Hz, 1 H), 7.81 (d, J = 2.4 Hz, 1 H), 8.02 (d, J = 8.6 Hz, 2 H), 8.53 (s, 1 H), 8.54 (d, J = 8.6 Hz, 2 H), 13.10 (s, 1 H). MS *m/e* 352 (MH^+). Anal. Cald for $C_{22}H_{25}NO_3$. 0.125 H_2O: C, 77.7; H, 7.20; N, 3.96. Found: C, 74.62; H, 6.99; N, 3.82.

5,5,8,8-Tertamethyl-5,6,7,8-tetrahydro-naphthalene-2-carbaldehyde (6).

2-Iodo-5,5,8,8-tertamethyl-5,6,7,8-tetrahydronaphthalene (1.30 g, 4.12 mmol) in 10 mL of anhydrous THF was slowly added t-BuLi (1.7 M in pentane, 5.09 mL, 8.65 mmol) at -78oC. Afterring for 15 min, DMF (0.31 g, 4.12 mmol) was added. The solution was stirred for 30 min, and then slowly warmed to 0oC, and stirred for additional 20 min. The reaction was quenched with saturated NH4Cl solution (20 mL), extracted with EtOAc (20 mL X 3). The combined extracts were dried over MgSO4 and evaporated. The residue was purified by flash chromatography (EtOAc :hexane = 1:30 to 1:20) to give 600 mg (67%) of the product as a white solid. ^{1} H NMR ($CDCl_3$) δ 1.31 (s, 6 H), 1.33 (s, 6 H), 7.47 (d, J = 8.7 Hz, 2 H), 7.63 (dd, J = 1.9; 8.2 Hz, 1 H), 7.83 (d, J = 1.9 Hz, 1 H), 9.95 (s, 1 H).

Methyl 4-[(5,5,8,8-tertamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-methylamino]-benzoate (7).

The same procedure for preparing amine **4** was applied using aldehyde **6** and methyl 4-aminobenzoate to give the title compound in 80% yield. ^{1}H NMR ($CDCl_3$) δ 1.27 (s, 6 H), 1.28 (s, 6 H), 1.69 (s, 4 H), 3.86 (s, 3 H), 4.31 (d, *J* = 5.0 Hz, 2 H), 4.39 (bt, *J* = 5.0 Hz, 1 H), 6.61 (d, *J* = 8.9 Hz, 2 H), 7.12 (dd, *J* = 2.0; 8.2 Hz, 1 H), 7.27 (d, *J* = 2.0 Hz, 1 H), 7.30 (d, J = 8.2 Hz, 1 H), 7.88 (d, J = 8.7 Hz, 2 H). MS *m/e* 352 (MH^+); Anal. Cald for $C_{23}H_{26}O_3$: C, 78.60; H, 8.32; N, 3.98. Found : C, 78.55; H, 8.26; N, 3.94.

Methyl 4-[(5,5,8,8-tetramethyl-5,6,7,8-terahydro-naphthalene)-methyleneimino]-benzoate, N-oxide (8).

Excess dimethyldioxirane in acetone was added to amine **7** (400 mg, 1.14 mmol) in 3 mL of acetone at 0 °C. After stirring for 20 min, the solvent was evaporated. The residue was purified by chromatography (EtOAc-hexane = 1: 10 to 1: 3) to give 265 mg (64%) of nitrone **8** as a white solid. ^{1}H NMR ($CDCl_3$) δ 1.29 (s, 6 H), 1.33 (s, 6 H), 1.70 (s, 4 H), 3.93 (s, 3 H), 7.40 (d, *J* = 8.5 Hz, 1 H), 7.86 (d, *J* = 8.8 Hz, 2 H), 7.95 (s, 1 H), 8.08-8.14 (dd over d, *J* = 1.9, 8.8 Hz and 8.8 Hz, 3 H), 8.46 (d, *J* = 1.9 Hz, 1 H).

MS *m/e* 366 (MH^+). Anal. Cald for $C_{23}H_{27}NO_3$: C, 75.59; H, 7.45; N, 3.83. Found: C, 75.25; H, 7.33; N, 3.84.

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