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Synthesis Of 2'-Amino-3'-Methoxyflavone (Pd 98059)

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SYNTHETIC COMMUNICATIONS, 29(10), 1645-1652 (1999)

SYNTHESIS OF 2′-AMINO-3′-METHOXYFLAVONE (PD 98059)

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Summary
2′-Amino-3′-methoxyflavone selectively blocks the activity of MAP kinase kinase (MEK) by inhibiting the activation of MAP kinase. This paper reports a straightforward synthesis of PD 98059 and 2-*tert*-butyl-8-methoxy-1,4-dihydro-quinolin-4-one.

2′-Amino-3′-methoxyflavone (PD 98059, 5 mg ~ 200 $ [1]) (**6**) selectively blocks the activity of MAP kinase kinase (MEK) by inhibiting the activation of MAP kinase and the subsequent phosphorylation both *in vitro* and in intact cells. The title compound inhibits cell growth and reverses the phenotype of ras-transformed BALB 3T3 mouse fibroblasts and rat kidney cells [2,3]. Furthermore, PD 98059 remarkably attenuates low-density lipoprotein (LDL), and it is also known to be a mitogenic factor for vascular smooth muscle cells and fibroblasts [2,3].

With endothelial cells, PD 98059 activates MSAP kinases and DNA synthesis [4-9]

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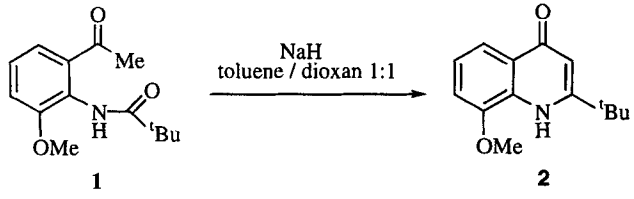
Although PD 98059 is commercially available, no synthesis of this compound has yet been published. Because we required this molecule in substantial quantities for various tests, we have developed a synthesis, which takes advantage of procedures well known for the the preparation of flavones.

Tsutomu et al. have synthesized flavones by condensation of *O*-protected salicylates (THP-ethers) and acetophenone derivates with followed by cyclisation with hydrochloric acid [10,11]

The reaction of an *O*-silylated salicylate with the acetophenone **1** did not afford the flavone **5** but yielded the quinolinone **2** by intramolecular cyclisation of acetophenone, whilst the salicylate was recovered (FIG. 1).



1 **2**

FIG. 1

On the other side, Nagarathman and Cushman [12] synthesized hydroxyflavones according to FIG. 2:

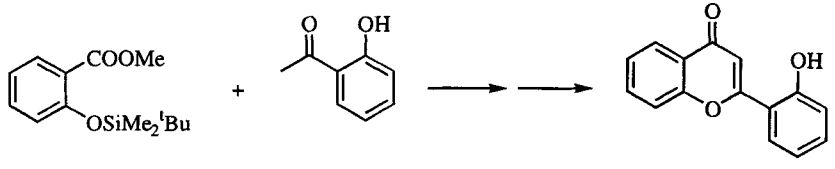


FIG. 2

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We have used this procedure for the synthesis of PD 98059 (FIG. 3) by condensing 2-pivaloylamino-3-methoxyacetophenone (**1**) with methyl 2-[(*tert*-butyl-dimethylsily)oxy]-benzoate (**3**).

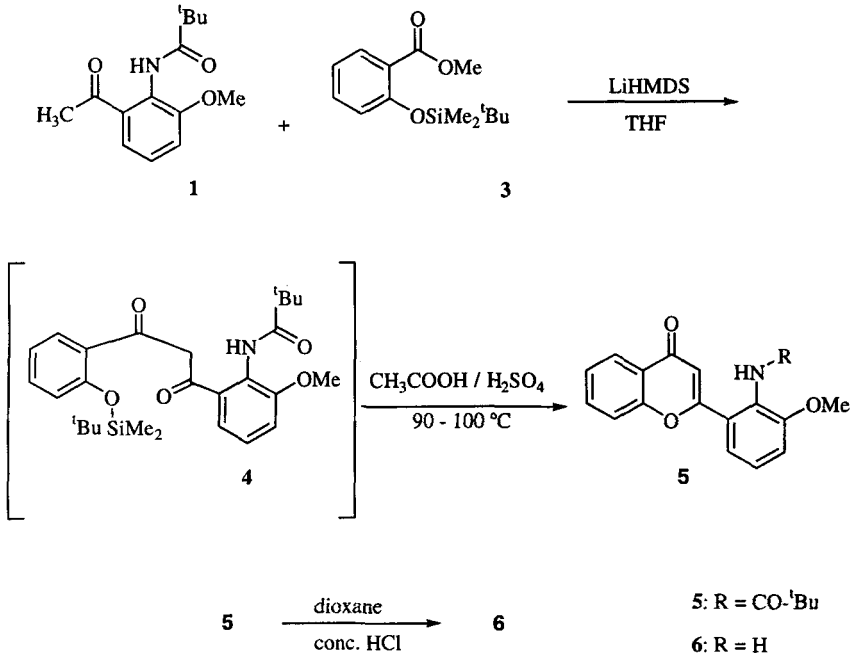

FIG. 3

EXPERIMENTAL

General: Melting points were recorded on a Reichert Thermovar 300419 microscope heating apparatus and are uncorrected. Proton nuclear magnetic resonance spectra were recorded on a Bruker AC250 (250 MHz) spectrometer. All chemical shifts are reported with the δ-scale. The following abbreviations were used to explain multiplicities: s, singlet; d, doublet; m, multiplet. Mass spectra

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were recorded on a Varian MAT 311 A, 70 eV, by using electron impact ionisation (EI). FT-IR-spectroscopy was performed on a Nicolet 510 FT-IR-spectrometer. Microanalyses were performed by the Analytical Laboratory at the University of Regensburg. Thin layer chromatography (t.l.c.) was carried out on Al-sheets coated with $60F_{245}$ silica. Column chromatography was carried out using Merck 60 (70 - 230 mesh ASTM) silica. Solvents and commercially available reagents were dried and purified before use according to standard procedures. All reactions were carried out under dry N_2 in flame- or oven-dried vessels.

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2-Pivaloylamino-3-methoxyacetophenone (**1**):

2-Nitro-3-methoxyacetophenone and *2-Amino-3-methoxyacetophenone*: cf. ref. [13,14]

This synthesis is a modification of reference 10 [10]: 34.0 g (0.21 mole) of 2-amino-3-methoxyacetophenone were dissolved in 80 ml of pyridine. After cooling to 0 °C, 30.0 ml (0.24 mole) of pivaloyl chloride were added within 15 min at this temp. under stirring. Then the mixture was poured onto 250 ml of water, extracted with ethyl acetate, and the org. layer was washed with 5 % NaOH and with water. After drying (Na_2SO_4), the solvent was removed *in vacuo* and the residue was purified by column chromatography (SiO_2 / ethyl acetate): 41.90 g (80%), colorless wax, m.p. 61-62 °C. - IR (KBr): $\tilde{\nu}$ = 3434, 3361 (N-H), 3085, 2967, 2873, 2840 (C-H), 1694 (C=O) cm^{-1}. - ^1H NMR (DMSO-d6): δ = 8.85 (s, 1H, NH), 7.35-7.05 (m, 3H, aromatic), 3.80 (s, 3H, OCH_3), 2.85 (s, 3H, $CO\text{-}CH_3$), 1.18 [s, 9H, $C(CH_3)_3$]. - MS (70 eV); *m/z* (%): 249 (88) [M^+], 234 (19) [M^+ -

CH_3], 218 (17) [M^+ - OCH_3], 206 (41) [M^+ - $COCH_3$], 192 (100) [M^+ - C_4H_9]. - $C_{14}H_{19}NO_3$ (249.31): calcd. C 67.45 H 7.68 N 5.62; found C 67.16 H 7.54 N 5.63.

2-tert-Butyl-8-methoxy-1,4-dihydroquinolin-4-one (**2**): 1.68 g (56.2 mmole) NaH (80% in paraffin oil) were suspended in 40 ml of toluene / dioxan 1:1 and refluxed. While refluxing, a solution of 6.36 g (25.5. mmole) of **1** in 80 ml of toluene / dioxan 1:1 was added slowly. Refluxing was continued for 30 min, then the mixture was cooled in the ice bath, mixed with 200 ml of water and extracted with ethyl acetate. The organic phase was dried with Na_2SO_4,nd evaporation *in vacuo* afforded an oil, which crystallized after addidtion of ether: 3.54 g (60%) colorless crystalls, m.p. 157-159 °C. - IR (KBr): $\tilde{\nu}$ = 3224, 3156, 3121 (N-H), 3008, 2967, 2950, 2838 (C-H), 1630 (C=O) cm^{-1}. - ^1H NMR (DMSO-d6): δ = 9.25 (br s, 1H, NH), 7.63-7.52 (m, 1H, aromatic), 7.26-7.18 (m, 2H, aromatic), 6.06 (d, J = 3.2 Hz, 1H, CH), 3.99 (s, 3H, OCH_3), 1.36 [s, 9H, $C(CH_3)_3$]. - MS (70 eV); m/z (%): 231 (100) [M^+], 216 (45) [M^+ - CH_3], 200 (6), 189 (10). - $C_{14}H_{17}NO_2$ (231.30): calcd. C 72.70, H 7.41, N 6.06; found C 72.52, H 7.19, N 6.00.

Methyl-2-[(tert.butyldimethylsilyl)oxy]benzoate (**3**): cf. ref. [5].

2-(2-Pivaloylamino-3-methoxyphenyl)-4H-1-benzopyran-4-one (**5**): 120 ml of a 1-molar solution of Lithiumhexamethyldisilazane (LiHMDS) in THF were cooled to

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-78 °C. Within 30 min, 9.96 g (40 mmol) **6** in 300 ml THF were added dropwise, followed by stirring first for 1 h at -78 °C, then 2 h at -20 °C. After cooling to -78 °C, 9.82 g (40 mmole) **8** in 20 ml of THF were added. After stirring for 1 h at -78 °C, the mixture was warmed to room temperature, stirred for further 40 h and poured onto 800 g of ice and 40 ml of conc. HCl. The organic layer was separated, and the aqueous phase was extracted with ethyl acetate. After drying (Na_2SO_4), the solvents were evaporated *in vacuo*. The remaining oil was further concentrated at the oil pump overnight, then dissolved in 120 ml of glacial acetic acid and 0.8 ml of conc. H_2SO_4 and heated to 100 °C for 3 h. About 80% of the acetic acid were removed *in vacuo* and the residue was mixed with 1.2 l of water. After alkalization of this phase with 10% NaOH, it was extracted with ethyl acetate. After drying with Na_2SO_4 and evaporation under reduced pressure, the residue was purified by column chromatography (SiO_2 / ethyl acetate): 1.56 g (22%) beige crystals, m.p. 60-62 °C. - IR (KBr): $\tilde{\nu}$ = 3315 (N-H), 3071, 2956, 2934, 2869 (C-H), 1669, 1650 (C=O) cm^{-1}. - ^1H NMR (DMSO-d6): δ = 8.90 (s, 1H, NH), 8.10-7.25 (m, 7H, aromatic), 6.45 (s, 1H, CH), 3.85 (s, 3H, OCH_3), 1.10 [s, 9H, $C(CH_3)_3$]. - MS (70 eV); *m/z* (%): 351 (100) [M^+], 321 (44) [M^+ - CH_2O], 267 (68) [M^+ - C_4H_8-CO]. - $C_{21}H_{21}NO_4$ (351.40): calcd. C 71.78 H 6.02 N 3.99; found C 71.33 H 5.86 N 3.62.

2-(2-Amino-3-methoxyphenyl)-4H-1-benzopyran-4-one (**6**): 1.50 g (4.3 mmole) **5** were dissolved in 42 ml of dioxan and 21 ml of conc. HCl and refluxed for 16 h. After cooling and alkalization of the mixture with NaOH, the mixture was

extracted with ethyl acetate. The organic phase was washed with water and dried with Na_2SO_4. After evaporation, the residue was crystallized from acetone / water 2:1. 0.3 g (26%) of yellow crystals, m.p. 154-156 °C. - IR (KBr): $\tilde{\nu}$ = 3440, 3326 (N-H), 3067, 2961, 2849 (C-H), 1650 (C=O) cm^{-1}. – ^1H NMR (DMSO-d6): δ = 8.10 (m, 1H, aromatic), 7.85-7.65 (m, 2H, aromatic), 7.53 -7.45 (m, 1H, aromatic), 7.12-6.97 (m, 2H, aromatic), 6.69 („t", 1H, aromatic), 6.55 (s, 1H, CH), 5.30 (s, 2H, NH_2), 3.85 (s, 3H, OCH_3). - MS (70 eV); *m/z* (%) 267 (78) [M^+], 252 (10) [M^+ - CH_3], 224 (18) [252 - CO], 147 (100) [M^+ - $C_7H_4O_2$] [15].

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