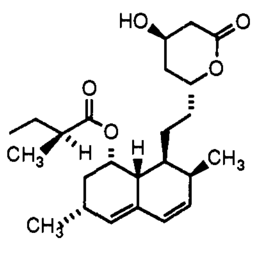
3-Hydroxy-3-methylglutaryl-coenzyme A Reductase Inhibitors. 8.[1] Side Chain Ether Analogues of Lovastatin

T.-J. Lee,*,† W. J. Holtz,† R. L. Smith,† A. W. Alberts,‡ and J. L. Gilfillan‡

Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania 19486, and Merck Sharp & Dohme Research Laboratories, Rahway, New Jersey 07065. *Received January 7, 1991*

A general route for preparing side chain ether analogues of lovastatin is presented. These analogues proved to be weaker inhibitors of HMG-CoA reductase than the corresponding side chain ester analogues. Interestingly, inhibitory potency was enhanced markedly when the 4-fluoro group was incorporated in the aromatic moiety of the side chain benzyl group of **2d**.

The discovery of lovastatin (**1**), a novel fungal metabolite isolated independently from broths of *Aspergillus terreus*[2] and *Monascus ruber*,[3] has been hailed as an important medicinal breakthrough in the on-going quest to develop better therapeutic agents for controlling plasma cholesterol levels. This natural product has proved to be both a potent inhibitor of HMG-CoA reductase, a rate-limiting enzyme in cholesterol biosynthesis, and an effective hypocholesterolemic agent in man.[4] As part of our continuing effort to delineate the SAR of this important natural product, we wish to report here the synthesis of a series of side chain ether analogues **2** and their inhibitory activities against HMG-CoA reductase.



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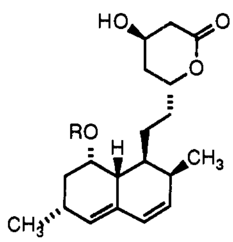


2

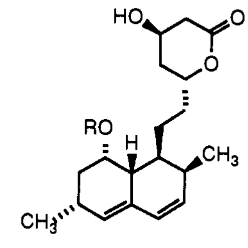
Chemistry

The synthetic route to the side chain ether analogues reported in this study is outlined in Scheme I. The previously described procedure[5] for synthesing **2a**, **2b**, and **2d** also was employed in the preparation of **2c** and **2e**. However, as discussed below, the synthesis of **2f** has followed a modified course which is amenable to the preparation of multigram quantities. The synthesis of **2f** began with alcohol **3**, the common intermediate which is used in the preparation of all of the ether analogues and is readily available from lovastatin in four steps.[5] Heating a mixture of **3**, 4-fluorobenzyl chloride, and sodium hydride in THF–DMF (10:1)[6] under a nitrogen atmosphere at reflux for an extended period of time consistently gave an excellent yield of **4f**. Hydrolysis of **4f** in THF–HOAc–H_2O (3:1:1) in the presence of pyridinium tosylate (PPTS) provided mainly **5f** in addition to a small amount of desilylated **5f**. Oxidation of **5f** to **6f** can be effected with either Fetizon's reagent (Ag_2CO_3/Celite)[7] or Collins' reagent ($CrO_3 \cdot 2PY$)[8] generated in situ. The latter method is the method of choice for large-scale reactions. Finally, desilylation of **6f** with tetra-*n*-butylammonium fluoride in THF–HOAc afforded **2f**.

Biological Results and Discussion

The side chain ethers listed in Table I were converted to the corresponding ring-opened dihydroxy acid sodium salts and evaluated for intrinsic inhibitory activity against HMG-CoA reductase. The enzyme preparation and the

Table I. In Vitro HMG-CoA Reductase Inhibitory Activity[a]



2

no.	R	IC_{50}, nM	rel potency
a	CH_3	2810	0.2
b	$CH_2{=}CHCH_2$	370	1.5
c	$CH_2{=}C(CH_3)CH_2$	360	1.5
d	$PhCH_2$	27	20
e	$4\text{-}ClC_6H_4CH_2$	170	8.5
f	$4\text{-}FC_6H_4CH_2$	4.7	119
g	CH_3CO	269	2.1
h	$CH_2{=}CHCH_2CO$	2.9	187
i	$PhCH_2CO$	19	29

[a] All compounds in this table were tested after being converted to the sodium salts of the corresponding dihydroxy acids. The relative potency of each test compound was determined by comparing its IC_{50} with that of mevastatin (i.e., compactin), which was tested simultaneously and arbitrarily assigned a relative potency value of 100. The biological data of **2g**, **2h**, and **2i** were taken from ref 10.

† West Point, PA.
‡ Rahway, NJ.

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(4) For a recent review on HMG-CoA reductase inhibitors and their use as hypocholesterolemic agents, please see: Lee, T.-J. Synthesis, SARs and Therapeutic Potential of HMG-CoA Reductase Inhibitors. *Trends Pharm. Sci.* **1987**, *8*, 442–446.
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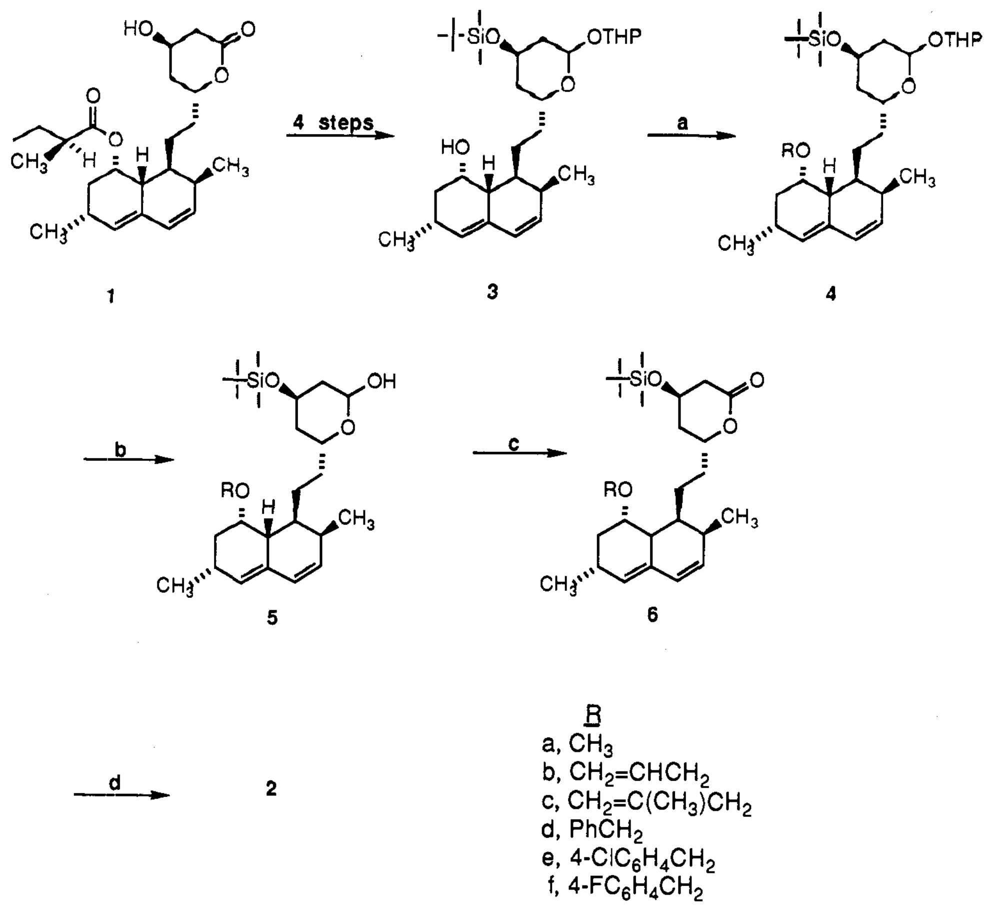
0022-2623/91/1834-2474$02.50/0

Scheme I[a]



[a] (a) NaH, RX, DMF (and THF), (b) TsOH·PY, HOAC, H_2O, (c) Ag_2CO_3/Celite, benzene, Δ or CrO_3·2PY, CH_2Cl_2. (d) n-Bu_4NF, THF, HOAc.

assay procedure used in the current study were the same as those described in an earlier report from our laboratories.[9] The data in Table I clearly indicate that **2a**, **2b**, and **2d** are weaker inhibitors than the corresponding side chain ester analogues,[10] i.e., **2g**, **2h**, and **2i**, respectively. These results reveal that the deletion of the carbonyl moiety in the side chain ester group has a detrimental effect on intrinsic inhibitory activity. Interestingly, when a suitable substitution is made on the aromatic ring of the side chain benzyl moiety in **2d**, the potency of inhibition can be enhanced as reflected by the high level of activity displayed by 4-fluorobenzyl ether analogue **2f**. Hence, as described in earlier reports on the benzyl ether[11] and biphenyl[12] series of synthetic analogues, the 4-fluoro substitution once again proved to be potency enhancing.

In summary, the side chain ether analogues of lovastatin generally are weaker inhibitors of HMG-CoA reductase than the corresponding side chain ester analogues. This result indicates that the carbonyl group plays an important role in determining intrinsic inhibitory potency. In addition, as observed in two earlier series of inhibitors, intrinsic inhibitory potency was improved markedly by introduction of the 4-fluoro group on an aromatic moiety.

Experimental Section

General Methods. Proton NMR spectra were recorded in $CDCl_3$ on a Varian EM390 spectrometer; chemical shifts are reported in δ units with Me_4Si as the internal standard. Mass spectra were taken on a VG Micromass MM7035 mass spec-

(6) It should be noted that this reaction would not work when THF was used as the sole solvent. Also, if the reaction was run in DMF, it gave lower yields of the product and the extent of the conversion varied from time-to-time, even when a large excess of 4-fluorobenzyl chloride was used.

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trometer. Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected.

4(*R*)-(*tert*-Butyldimethysiloxy)-6(*R*)-[2-[8(*S*)-(2-methylalloxy)-1,2,6,7,8,8a(*S*)-hexahydro-2(*S*),6(*R*)-dimethyl-1(*S*)-naphthyl]ethyl]-2-[(tetrahydropyran-2-yl)-oxy]-3,4,5,6-tetrahydro-2*H*-pyran (4c). To a stirred suspension of sodium hydride (50% oil dispersion, 100 mg, 2.08 mmol, washed with hexane prior to use) in DMF (3 mL) was added a solution of 3[5] (210 mg, 0.4 mmol) in DMF (3 mL) at room temperature under a nitrogen atmosphere. The resulting mixture was heated on a steam bath for 1 min. After cooling, it was treated with methallyl chloride (195 mg, 2.2 mmol) and the resulting mixture was heated on a steam bath for 20 min. After cooling, the reaction mixture was poured into cold water and extracted with ether. The ethereal extract was washed with diluted hydrochloric acid, aqueous sodium bicarbonate, and brine, dried over $MgSO_4$, and filtered. The filtrate was evaporated to yield a residue which was purified, by preparative TLC on an Analtech silica gel plate. Elution of the plate with methylene chloride–acetone (50:1, v:v) afforded 4c (160 mg, 0.28 mmol, 70%) as a colorless, glassy oil: NMR ($CDCl_3$) δ 0.07 (6 H, s), 0.9 (9 H, s), 1.14 (3 H, d, J = 7 Hz), 1.73 (3 H, br s), 3.65 (H, d, J = 12 Hz), 4.12 (H, d, J = 12 Hz), 4.7~5.3 (4 H, m), 5.50 (H, m), 5.76 (H, d of d, J = 10, 6 Hz), 6.01 (H, d, J = 10 Hz).

4(*R*)-(*tert*-Butyldimethylsiloxy)-6(*R*)-[2-[8(*S*)-(2-methylalloxy)-1,2,6,7,8,8a(*S*)-hexahydro-2(*S*),6(*R*)-dimethyl-1(*S*)-naphthyl]ethyl]-2-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran (5c). Powdered PPTS (73 mg) was added in one portion to a stirred mixture of 4c (300 mg, 0.52 mmol) in THF (7.3 mL), acetic acid (2.9 mL), and water (2.2 mL); the resulting mixture was stirred at room temperature for 50 h, poured into cold water, and extracted with ether. The ethereal extract was washed with aqueous sodium bicarbonate, dried over $MgSO_4$, and filtered. The filtrate was evaporated to afford a residue which was purified by preparative TLC on an Analtech silica gel plate. Elution of the plate with methylene chloride–acetone (25:1, v:v) provided 5c (120 mg, 0.24 mmol, 47%) as a colorless, glassy oil: NMR ($CDCl_3$) δ 0.06 and 0.12 (combined 6 H, 2 s), 0.90 and 0.93 (combined 9 H, 2 s), 1.14 (3 H, d, J = 7 Hz), 1.73 (3 H, br s), 3.66 (H, d, J = 12 Hz), 4.16 (H, d, J = 12 Hz), 4.85 (H, br s), 5.00 (H, br s), 5.50 (H, m), 5.75 (H, d of d, J = 10, 6 Hz), 6.00 (H, d, J = 10 Hz).

4(*R*)-(*tert*-Butyldimethylsiloxy)-6(*R*)-[2-[8(*S*)-(2-methylalloxy)-1,2,6,7,8,8a(*S*)-hexahydro-2(*S*),6(*R*)-dimethyl-1(*S*)-naphthyl]ethyl]-3,4,5,6-tetrahydro-2*H*-pyran-2-one (6c). A mixture of 5c (120 mg, 0.24 mmol) and freshly prepared Ag_2CO_3/Celite[7] (2.5 g) in benzene (8 mL) was heated at reflux for 20 min, then an additional amount of Ag_2CO_3/Celite (1 g) was added followed by 0.5 h of heating. After this process being repeated three times, the solid was filtered off and the filtrate was concentrated by evaporation to leave a residue. Purification of the residue by preparative TLC on an Analtech silica gel plate with methylene chloride–acetone (25:1, v:v) as the eluant provided 6c (90 mg, 0.18 mmol, 75%) as a colorless gum: NMR ($CDCl_3$) δ 0.08 (6 H, s), 0.92 (9 H, s), 1.11 (3 H, d, J = 7 Hz), 1.70 (3 H, br s), 2.57 (2 H, d, J = 5 Hz), 3.61 (H, d, J = 12 Hz), 3.83 (H, m), 4.10 (H, d, J = 12 Hz), 4.30 (H, m), 4.64 (H, m), 4.81 (H, br s), 4.94 (H, br s), 5.50 (H, m), 5.73 (H, d of d, J = 10, 5 Hz), 6.01 (H, d, J = 10 Hz).

6(*R*)-[2-[8(*S*)-(2-Methylalloxy)-1,2,6,7,8,8a(*S*)-hexahydro-2(*S*),6(*R*)-dimethyl-1(*S*)-naphthyl]ethyl]-4(*R*)-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran-2-one (2c). A solution of 6c (90 mg, 0.18 mmol) in THF (11 mL) was successively treated with acetic acid (90 μL, 1.58 mmol) and tetra-*n*-butylammonium fluoride solution (0.313 M in THF, 2.8 mL, 0.87 mmol). The resulting mixture was stirred at room temperature for 36 h. It was poured into water and extracted with ether. The ethereal extract was washed with aqueous sodium bicarbonate and brine, dried over $MgSO_4$, and filtered. The filtrate was evaporated to give a residue which was purified by flash chromatography on a silica gel column. Elution of the column with methylene chloride–acetone (10:1, v:v) provided 2c (50 mg, 0.13 mmol, 74%) as a solid. An analytical sample was obtained after recrystallization from ether–hexane: mp 98–99 °C; NMR ($CDCl_3$) δ 0.93 (3 H, d, J = 7 Hz), 1.13 (3 H, d, J = 7 Hz), 1.72 (3 H, br s), 3.73 (H, d, J = 12 Hz), 3.84 (H, m), 4.12 (H, d, J = 12 Hz), 4.35 (H, m), 4.66 (H, m), 4.82 (H, br s), 4.98 (H, br s), 5.50 (H, m), 5.74 (H, d of d, J = 10, 5 Hz), 6.00 (H, d, J = 10 Hz). Anal. ($C_{23}H_{34}O_4$) C, H.

4(*R*)-(*tert*-Butyldimethylsiloxy)-6(*R*)-[2-[8(*S*)-[(4-chlorobenzyl)oxy]-1,2,6,7,8,8a(*S*)-hexahydro-2(*S*),6(*R*)-dimethyl-1(*S*)-naphthyl]ethyl]-2-[(tetrahydropyran-2-yl)-oxy]-3,4,5,6-tetrahydro-2*H*-pyran (4e). Compound 4e was prepared from 3 by the same procedure described for the preparation of 4c but with 4-chlorobenzyl chloride instead of methallyl chloride: NMR ($CDCl_3$) δ 0.06 (6 H, s), 0.88 (9 H, s), 1.18 (3 H, d, J = 7 Hz), 4.35 (H, d, J = 12 Hz), 4.75 (H, d, J = 12 Hz), 5.50 (H, m), 5.77 (H, d of d, J = 10, 5 Hz), 6.00 (H, d, J = 10 Hz), 7.28 (4 H, m).

4(*R*)-(*tert*-Butyldimethylsiloxy)-6(*R*)-[2-[8(*S*)-[(4-chlorobenzyl)oxy]-1,2,6,7,8,8a(*S*)-hexahydro-2(*S*),6(*R*)-dimethyl-1(*S*)-naphthyl]ethyl]-2-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran (5e). Compound 5e was prepared from 4e by using a procedure similar to that described in the preparation of 5c: NMR ($CDCl_3$) δ 0.88 (9 H, s), 1.11 (3 H, d, J = 7 Hz), 4.25 (H, d, J = 12 Hz), 4.68 (H, d, J = 12 Hz), 5.48 (H, m), 5.73 (H, d of d, J = 10, 5 Hz), 5.97 (H, d, J = 10 Hz), 7.24 (4 H, s).

4(*R*)-(*tert*-Butyldimethylsiloxy)-6(*R*)-[2-[8(*S*)-[(4-chlorobenzyl)oxy]-1,2,6,7,8,8a(*S*)-hexahydro-2(*S*),6(*R*)-dimethyl-1(*S*)-naphthyl]ethyl]-3,4,5,6-tetrahydro-2*H*-pyran-2-one (6e). Compound 6e was prepared from 5e by using a procedure similar to that described in the preparation of 6c: NMR ($CDCl_3$) δ 0.04 (3 H, s), 0.05 (3 H, s), 0.85 (9 H, s), 1.14 (3 H, d, J = 7 Hz), 2.52 (2 H, d, J = 4 Hz), 3.92 (H, m), 4.25 (H, d, J = 12 Hz), 4.72 (H, d, J = 12 Hz), 5.52 (H, m), 5.75 (H, d of d, J = 10, 5 Hz), 6.00 (H, d, J = 10 Hz), 7.30 (4 H, s).

6(*R*)-[2-[8(*S*)-[(4-Chlorobenzyl)oxy]-1,2,6,7,8,8a(*S*)-hexahydro-2(*S*),6(*R*)-dimethyl-1(*S*)-naphthyl]ethyl]-4(*R*)-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran-2-one (2e). Compound 2e was prepared from 6e by using a procedure similar to that described in the preparation of 2c: mp 75–77 °C; NMR ($CDCl_3$) δ 0.86 (3 H, d, J = 7 Hz), 1.15 (3 H, d, J = 7 Hz), 3.91 (H, m), 4.1~5.6 (3 H, containing a doublet at 4.28), 4.71 (H, d, J = 12 Hz), 5.52 (H, m), 5.77 (H, d of d, J = 10, 5 Hz), 6.00 (H, d, J = 10 Hz), 7.32 (4H, s); MS m/e 444 (M).

4(*R*)-(*tert*-Butyldimethylsiloxy)-6(*R*)-[2-[8(*S*)-[(4-fluorobenzyl)oxy]-1,2,6,7,8,8a(*S*)-hexahydro-2(*S*),6(*R*)-dimethyl-1(*S*)-naphthyl]ethyl]-2-[(tetrahydropyran-2-yl)-oxy]-3,4,5,6-tetrahydro-2*H*-pyran (4f). To a stirred suspension of sodium hydride (50% oil dispersion, 0.72 g, 15 mmol, washed with hexane prior to use) in THF (25 mL, freshly distilled over benzophenone ketyl prior to use) was added at room temperature under a nitrogen atmosphere a solution of 3 (5.80 g, 11.1 mmol) and 4-fluorobenzyl chloride (2.02 g, 14 mmol) in THF (25 mL), the resulting mixture was treated with DMF (5 mL), then heated at reflux for 18 h. After cooling, the reaction mixture was poured into cold water and extracted with ether. The ethereal extract was washed with brine, dried over $MgSO_4$, and filtered. The filtrate was evaporated to give a residue which was purified by flash chromatography on a silica gel column. Elution of the column with methylene chloride, then methylene chloride–acetone (200:1, v:v), afforded 4f (5.84 g, 9.28 mmol, 84%) as a colorless oil: NMR ($CDCl_3$) δ 0.02 (3 H, s), 0.03 (3 H, s), 0.88 (9 H, s), 1.15 (3 H, d, J = 7 Hz), 4.27 (H, d, J = 12 Hz), 4.70 (H, d, J = 12 Hz), 5.50 (H, m), 5.73 (H, d of d, J = 10, 5 Hz), 6.00 (H, d, J = 10 Hz), 6.98 (2 H, m), 7.28 (2, H, m).

4(*R*)-(*tert*-Butyldimethylsiloxy)-6(*R*)-[2-[8(*S*)-[(4-fluorobenzyl)oxy]-1,2,6,7,8,8a(*S*)-hexahydro-2(*S*),6(*R*)-dimethyl-1(*S*)-naphthyl]ethyl]-2-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran (5f). Powdered PPTS (2.0 g) was added in one portion to a stirred mixture of 5f (8.2 g, 13.0 mmol) in THF (180 mL), acetic acid (60 mL), and water (60 mL). The resulting mixture was stirred at room temperature for 65 h, then poured into cold water, and extracted with ether. The ethereal extract was washed with water (3 × 500 mL), and 5% sodium bicarbonate (2 × 150 mL), dried over $MgSO_4$, and filtered. The filtrate was evaporated to yield a residue which was purified by flash chromatography on a silica gel column. Elution of the column with methylene chloride gave a mixture of starting 4f and 5f (2.65 g). Further elution with methylene chloride–acetone (50:1, v:v) provided the pure desired 5f (2.27 g, 4.17 mmol, 32%): NMR ($CDCl_3$) δ 0.08 and 0.10 (combined 6 H, 2 s), 0.9 (9 H, s), 1.15 (3 H, d, J = 7 Hz), 4.30 (H, d, J = 12 Hz), 4.75 (H, d, J = 12 Hz), 5.50 (H, m), 5.80 (H, d of d, J = 10, 5 Hz), 6.00 (H, d, J = 10 Hz), 7.0 (2 H, m), 7.32 (2 H, m). Continued elution with methylene chloride–acetone (10:1, v:v) yielded the desilylated **5f** (0.72 g, 1.67 mmol, 13%).

4(*R*)-(*tert*-Butyldimethylsiloxy)-6(*R*)-[2-[8(*S*)-[(4-fluorobenzyl)oxy]-1,2,6,7,8,8a(*S*)-hexahydro-2(*S*),6(*R*)-dimethyl-1(*S*)-naphthyl]ethyl]-3,4,5,6-tetrahydro-2*H*-pyran-2-one (6f). Solid chromium trioxide (2.22 g, 22.2 mmol) was added at room temperature under a nitrogen atmosphere to a mechanically stirred solution of pyridine (3.51 g, 44.4 mmol) in methylene chloride (130 mL). The resulting mixture was stirred for 0.5 h, then added via a dropping funnel a solution of **5f** (1.87 g, 3.45 mmol) in methylene chloride (20 mL). The resulting mixture was stirred at room temperature for 0.5 h, then quickly filtered through a pad of silica gel on a Buchner filter, washed, and rinsed with portions of methylene chloride–ether. The combined washings and filtrate were washed successively with diluted hydrochloric acid and 5% sodium bicarbonate, dried over $MgSO_4$, and filtered. The filtrate was evaporated to leave a residue which was purified by flash chromatography on a silica gel column. Elution of the column with methylene chloride followed by methylene chloride–acetone (50:1, v:v) provided **6f** (1.16 g, 2.14 mmol; 62%) as a solid: NMR ($CDCl_3$) δ 1.16 (3 H, d, J = 7 Hz), 2.52 (2 H, d, J = 4 Hz), 3.97 (H, m), 4.30 (H, d, J = 12 Hz), 4.72 (H, d, J = 12 Hz), 5.52 (H, m), 5.75 (H, d of d, J = 10, 5 Hz), 6.00 (H, d, J = 10 Hz), 7.0 (2 H, m), 7.3 (2 H, m).

6(*R*)-[2-[8(*S*)-[(4-Fluorobenzyl)oxy]-1,2,6,7,8,8a(*S*)-hexahydro-2(*S*),6(*R*)-dimethyl-1(*S*)-naphthyl]ethyl]-4(*R*)-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran-2-one (2f). Acetic acid (3.20 mL, 55 mmol) was added to a stirred solution of **6f** (6.8 g, 12.5 mmol) in THF (20 ml) followed by the addition of a solution of tetra-*n*-butylammonium fluoride (1 M in THF, 42 mL, 42 mmol). The resulting mixture was stirred at room temperature for 18 h, poured into cold water, and extracted with ether. The ethereal extract was washed successively with water and 5% sodium bicarbonate, dried, filtered, and evaporated to afford a residue. Purification of the residue on a silica gel column eluted with methylene chloride–acetone (10:1, v:v) provided **2f** (5.3 g, 12.4 mmol, 99%) as a solid. Analytical sample was obtained via recrystallization from ether–hexane: mp 100–103 °C; NMR ($CDCl_3$) δ 0.86 (3 H, d, J = 7 Hz), 1.17 (3 H, d, J = 7 Hz), 2.59 (2 H, m), 3.90 (H, m), 4.30 (H, d, J = 12 Hz), 4.71 (H, d, J = 12 Hz), 5.53 (H, m), 5.76 (H, d of d, J = 10, 5 Hz), 6.01 (H, d, J = 10 Hz), 7.03 (2 H, t), 7.33 (2 H, m). Anal. ($C_{26}H_{33}FO_4$) C, H.

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Naphthosultam Derivatives: A New Class of Potent and Selective 5-HT$_2$ Antagonists

Jean-Luc Malleron,*,† Marie-Thérèse Comte,† Claude Gueremy,† Jean François Peyronel,† Alain Truchon,† Jean Charles Blanchard,‡ Adam Doble,‡ Odile Piot,‡ Jean-Luc Zundel,‡ Christian Huon,† Brigitte Martin,† Pierre Mouton,† Alain Viroulaud,† Djamel Allam,‡ and Josette Betschart‡

Départements de Chimie Pharmaceutique et de Biologie, Centre de Recherches de Vitry Alfortville Rhône-Poulenc Rorer, 13 Quai Jules Guesde B.P. 14, F-94403 Vitry-sur-Seine Cédex, France. *Received December 21, 1990*

A series of 2-(aminoalkyl)naphth[1,8-*cd*]isothiazole 1,1-dioxides was synthesized and examined in various receptor binding tests. Most compounds demonstrated high affinity for the 5-HT$_2$ receptor with moderate to high selectivity. A member of this series, compound **24** (RP 62203), displays high 5-HT$_2$ receptor affinity (K_i = 0.26 nM), which is respectively more than 100 and 1000 times higher than its affinity for α_1 (K_i = 38 nM) and D$_2$ (K_i > 1000 nM) receptors. This compound is a potent orally effective and long lasting 5-HT$_2$ antagonist in the mescaline-induced head-twitches test in mice and rats.

Serotonin (5-HT) may be involved in thermoregulation, appetite, pain, sleep, sexual behavior, and behavioral disorders such as depression and anxiety.[1]

Recent progress in 5-HT research was stimulated by the discovery of multiple 5-HT receptors. The 5-HT$_2$ subtype has been the most completely characterized due to the availability of more and more selective antagonists.[2]

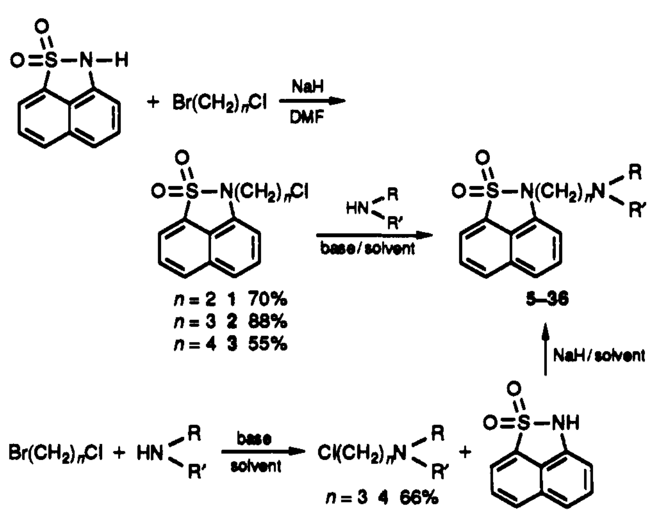
Ritanserin[3] was the first compound identified with a reasonable separation of 5-HT$_2$ and non 5-HT effects. Clinical studies with ritanserin indicate that this 5-HT$_2$ antagonist may be effective in anxiety or disthymic disorders.[4]

We describe here a series of naphtho[1,8-*cd*]isothiazole 1,1-dioxide (naphthosultam) derivatives, incidentally discovered and structurally unrelated to ritanserin. These compounds were evaluated in vitro for their binding affinity to rat 5-HT$_2$, α^1, and D$_2$ receptors. We describe the structure–activity relationships within this series that led to the discovery of RP 62203 (compound **24**). Its pharmacological profile is compared with that of ritanserin.

Chemistry

The synthetic pathway for the preparation of naphthosultam derivatives[5] listed in Tables I–IV is shown in Scheme I. Two methods were used. Naphthosultam was condensed with a ω-bromochloroalkane in the presence

Scheme I



† Département de Chimie.
‡ Département de Biologie.

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