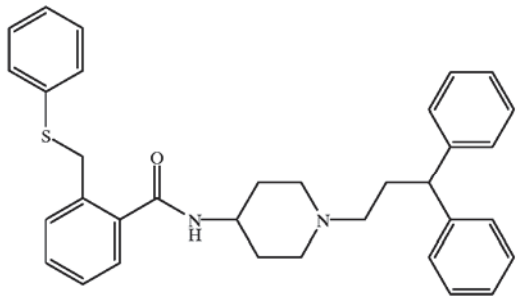
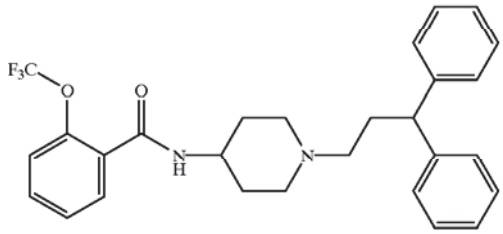
252.



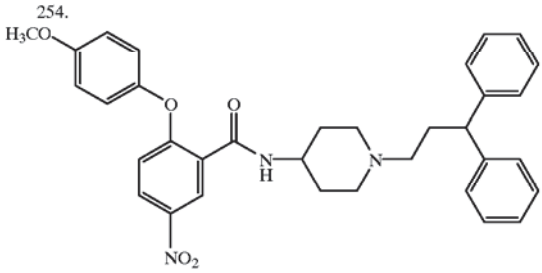
M.S. (elecrospray, pos. ions) 521 (M + H).

253.



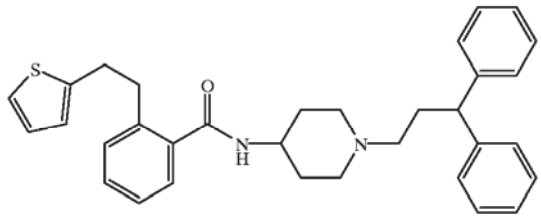
M.S. (elecrospray, pos. ions) 483 (M + H).

254.



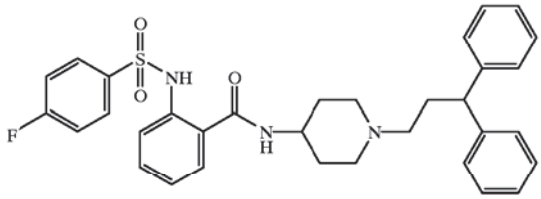
M.S. (elecrospray, pos. ions) 566 (M + H).

255.



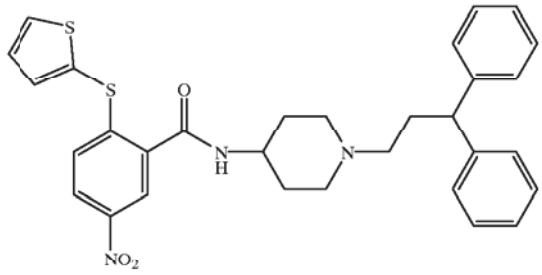
M.S. (elecrospray, pos. ions) 509 (M + H).

256.



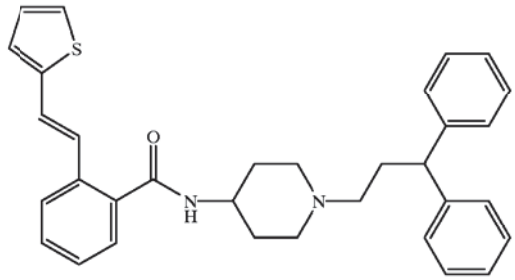
M.S. (elecrospray, pos. ions) 572 (M + H).

257.



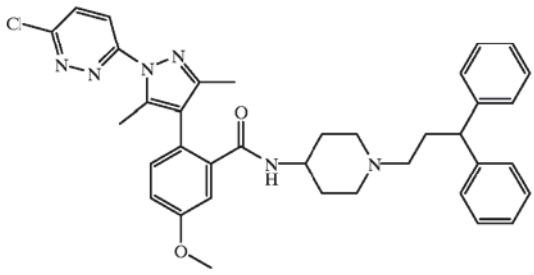
M.S. (elecrospray, pos. ions) 558 (M + H).

258.



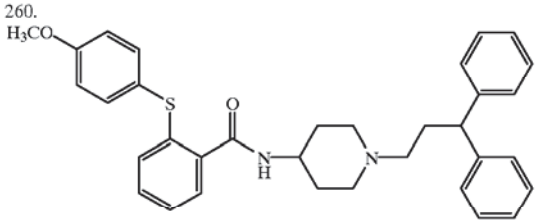
M.S. (elecrospray, pos. ions) 507 (M + H).

259.



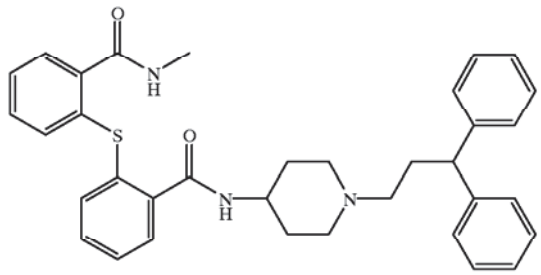
M.S. (electrospray, pos. ions) 635 (M + H).

260.



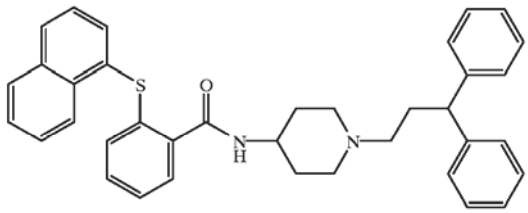
M.S. (electrospray, pos. ions) 537 (M + H).

261.



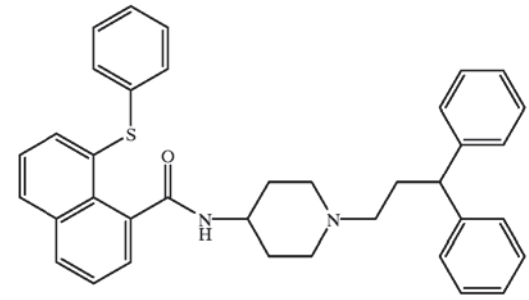
M.S. (electrospray, pos. ions) 564 (M + H).

262.



M.S. (electrospray, pos. ions) 557 (M + H).

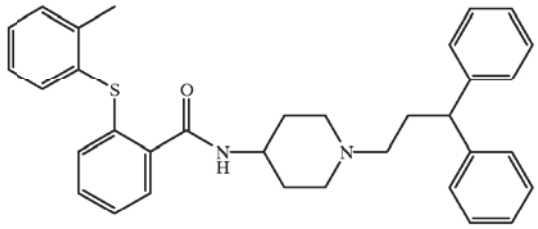
263.



-continued

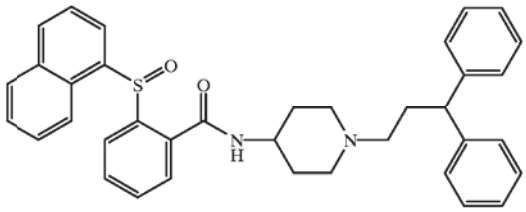
M.S. (electrospray, pos. ions) 557 (M + H).

264.



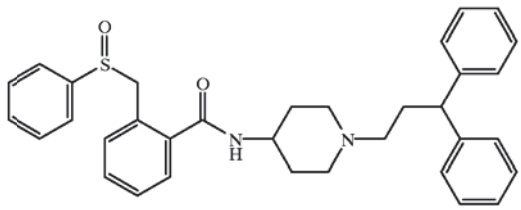
M.S. (electrospray, pos. ions) 521 (M + H).

265.



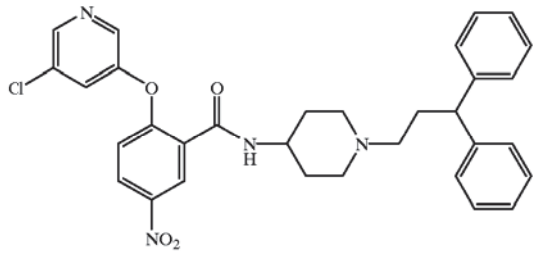
M.S. (electrospray, pos. ions) 573 (M + H).

266.



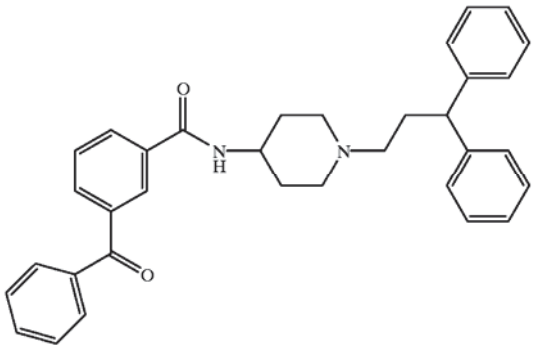
M.S. (electrospray, pos. ions) 537 (M + H).

267.



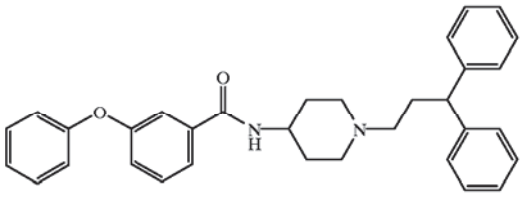
M.S. (electrospray, pos. ions) 571 (M + H).

268.



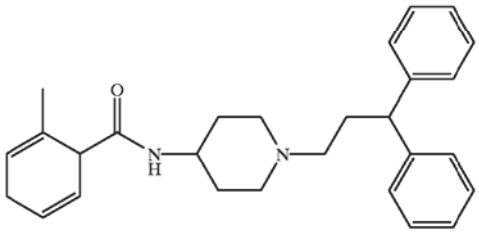
M.S. (electrospray, pos. ions) 503 (M + H).

269.



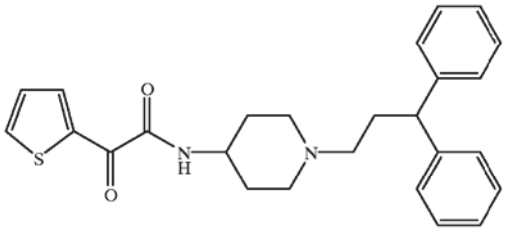
M.S. (electrospray, pos. ions) 491 (M + H).

270.



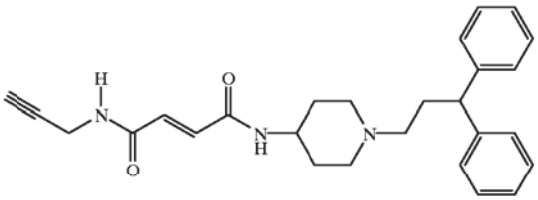
M.S. (electrospray, pos. ions) 415 (M + H).

271.



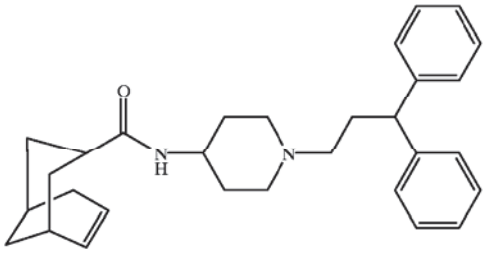
M.S. (electrospray, pos. ions) 433 (M + H).

272.



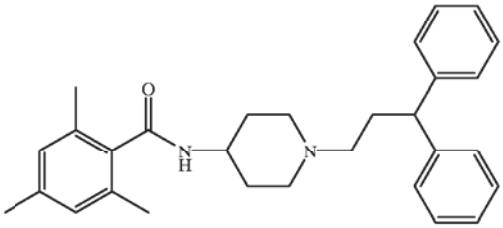
M.S. (electrospray, pos. ions) 430 (M + H).

273.



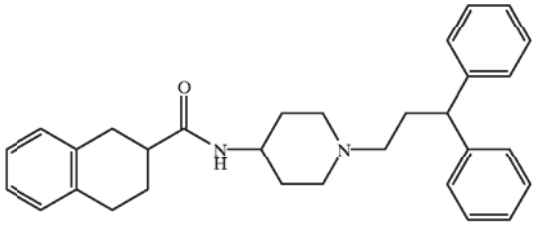
M.S. (electrospray, pos. ions) 443 (M + H).

274.



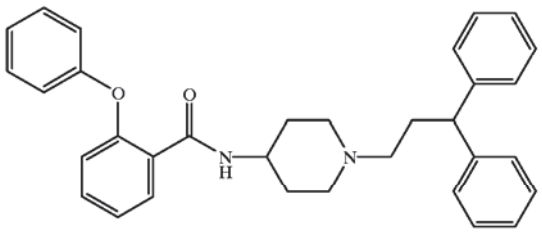
M.S. (Cl, pos. ions) 441 (M+H).

275.



M.S. (electrospray, pos. ions) 453 (M+H).

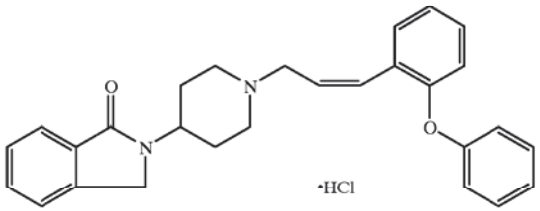
276.



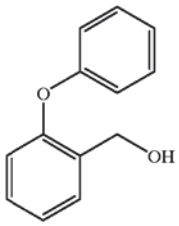
M.S. (electrospray, pos. ions) 491 (M+H).

Example 277

(z)-2, 3-Dihydro-2-[1-[3-(2-phenoxyphenyl)-2-propenyl]-4-piperidin-yl]-1H-isoindol-1-one, monohydrochloride

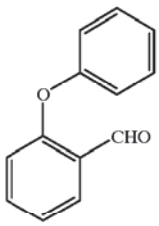


A.



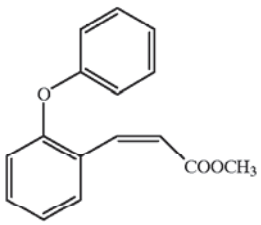
To a solution of 2-phenoxybenzoic acid (Aldrich) (2.5 g, 11.7 mmol) in THF (20 mL) at 0° C. was added dropwise a solution of boranetetrahydrofuran complex in THF (1.0M, 17.5 mL, 17.5 mmol). The reaction was stirred at RT for 3 h. The reaction was quenched with water/THF (1:1, 2 mL) followed by potassium carbonate until solution was basic. Ethyl ether (200 mL) was added and the organic layer was washed with water (2×50 mL), saturated sodium bicarbonate solution (2×50 mL), brine (2×50 mL) and dried over $MgSO_4$. Evaporation gave title compound (2.3 g, 95%) as a crude oil.

B.



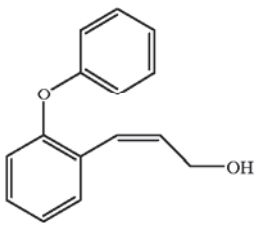
To a solution of oxalyl chloride (2.0M, 4.23 mL, 8.45 mL) in dichloromethane (20 mL) at −74° C. was added dropwise a solution of DMSO (1.2 mL, 16.9 mmol) in dichloromethane (1 mL). The reaction was stirred at −74° C. for 1 h. A solution of Part A compound (1.3 g, 6.50 mmol) in dichloromethane (4 mL) was added dropwise. The reaction was stirred at −74° C. for 1.5 h. Triethylamine (5.4 mL, 39 mmol) was added and the reaction was warmed to RT over 1 h. Ethyl ether (100 mL) was added and the organic layer was washed with 1N HCl solution (2×30 mL), water (2×30 mL), saturated sodium bicarbonate solution (2×30 mL), brine (2×30 mL) and dried over $MgSO_4$. Evaporation gave title compound (1.29 g, 100%) as a crude oil.

C.



To a solution of bis(2,2,2-trifluoroethyl) (methoxycarbonylmethyl)phosphonate (3.04 g, 9.56 mmol), 18-crown-6 (2.53 g, 9.56 mmol) in THF (60 mL) at 0° C. was added a solution of potassium bis(trimethylsilyl)amide in toluene (0.5M, 19.1 mL, 9.56 mmol). The reaction was stirred at 0° C. for 30 min then cooled to −78° C. A solution of Part B compound (1.72 g, 8.79 mmol) in THF (2 mL) was added. The reaction was stirred at −78° C. for 1 h. The reaction was quenched with saturated ammonium chloride solution (5 mL). Ethyl ether (200 mL) was added to the reaction, and the organic layer was washed with water (2×50 mL), brine (2×50 mL) and dried over $MgSO_4$. Purification was performed by flash chromatography on silica gel (200 g), loaded and eluted with 5% ethyl acetate in hexane. Pure fractions were combined and evaporated to give title compound (1.38 g, 58%) as a colorless oil.

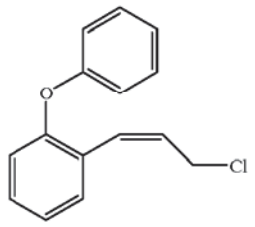
D.



To a solution of Part C compound (1.38 g, 5.15 mmol) in THF (20 mL) at 0° C. was added dropwise a solution of diisobutylaluminum hydride in hexane (1.0M, 11.3 mL, 11.3 mmol). The ice bath was removed and the reaction was stirred at RT for 15 min. The reaction was quenched by methanol (2 mL) followed by potassium sodium tartrate solution (1M, 100 mL). The mixture was stirred at RT overnight. Ethyl ether (200 mL) was added and the organic layer was washed with water (2×50 mL), brine (2×50 mL) and dried over $MgSO_4$. Purification was performed by flash chromatography on silica gel (150 g), loaded and eluted with 20% ethyl acetate in hexane. Pure fractions were combined

and evaporated to give title compound (1.24 g, 100%) as a colorless oil.

E.



To a solution of N-chlorosuccinimide (802 mg, 6.01 mmol) in dichloromethane (15 mL) at −40° C. was added dropwise methyl sulfide (0.56 mL, 7.64 mmol). The reaction was stirred at −40° C. for 10 min then warmed to RT for 30 min. The reaction was recooled to −40° C., and a solution of Part D compound(1.24 g, 5.46 mmol) in dichloromethane (2 mL) was added dropwise. The reaction was stirred at −40° C. for 2 h then warmed to RT for 30 min. Hexane (300 mL) was added to dilute the reaction and the organic layer was washed with water (2×50 mL), brine (2×50 mL) and dried over $MgSO_4$. Evaporation gave title compound (1.12 g, 84%) as a colorless oil.

F. (Z)-2,3-Dihydro-2-[1-[3-(2-phenoxyphenyl)-2-propenyl]-4-piperidinyl]-1H-isoindol-1-one, monohydrochloride

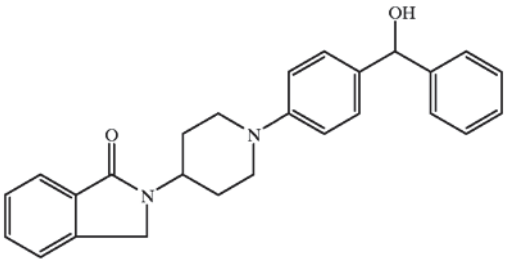
To a solution of Part E compound (600 mg, 2.45 mmol) in DMF (20 mL) was added Example 2 Part A compound (2-(4-piperidinyl)-2,3-dihydro-1H-isoindol-1-one) (530 mg, 2.45 mmol) followed by anhydrous potassium carbonate (372 mg, 2.69 mmol). The reaction was stirred at 55° C. overnight. The reaction was cooled to RT. Ethyl ether (200 mL) was added to dilute the reaction, and the organic layer was washed with water (2×50 mL), brine (2×50 mL) and dried over $MgSO_4$. Evaporation gave a crude oil. Purification was performed by flash chromatography on 100 g of silica gel, loaded and eluted with 2% methanol in dichloromethane. Pure fractions were combined and evaporated to give a colorless oil. The resulting oil was dissolved in methanol (2 mL) and HCl in ethyl ether solution (1.0 M, 3.0 mL, 3.0 mmol) was added. The HCl salt precipitated from the solution. The salt was filtered and dried at 60° C. under vacuum to give title compound (490 mg, 80%) as a white solid.

m.p. 196–198° C.

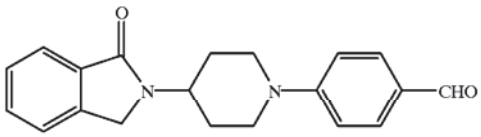
Anal. Calc. for $C_{28}H_{28}N_2O_2$.HCl: C, 72.95; H, 6.34; N, 6.08; Cl, 7.69 Found: C, 72.48; H, 6.42; N, 5.98; Cl, 7.70.

EXAMPLE 278

2,3-Dihydro-2-[1-[4-(hydroxyphenylmethyl)phenyl]-4-piperidinyl]-1H-isoindol-1one



A.



Potassium carbonate (10.6 g, 76.5 mmol) was added to a solution of Example 2 Part A compound (15.0 g, 69.6 mmol) and 4-fluorobenzaldehyde (Aldrich) (8.61 g, 69.6 mmol) in N,N-dimethylacetamide (100 mL) and the reaction was stirred at 125° C. for 24 h, then cooled to RT. The reaction was dissolved in CH_2Cl_2 (500 mL) and washed with water (4×180 mL) and brine (2×200 mL), then dried over $MgSO_4$. Evaporation gave a solid mass. The crude product was triturated with EtOAc (10 mL), then washed with EtOAc (10 mL) and filtered to give title compound (17.8 g, 80%) as a white solid (mp 211–214° C.).

B. 2,3-Dihydro-2-[1-[4-(hydroxyphenylmethyl) phenyl]-4-piperidinyl]-1H-isoindol-1-one

To a solution of Part A compound (2.30 g, 7.19 mmol) in THF (30 mL) at 0° C. was added dropwise phenyl magnesium bromide solution (1.0M, 7.91 mL, 7.91 mmol). The reaction was stirred at RT for 4 h over which time the reaction became clear. Saturated ammonium chloride solution (5 mL) was added to quench the reaction. Ethyl ether (200 mL) was added and the organic layer was washed with water (2×50 mL), brine (2×50 mL) and dried over $MgSO_4$. Purification was performed by flash chromatography on silica gel (200 g), loaded and eluted with 10% acetone in dichloromethane. Pure fractions were combined and evaporated to give title compound (1.5 g, 52%) as a white solid.

m.p. 164–166° C.

Anal. Calc. for $C_{26}H_{26}N_2O_2.0.2H_2O$: C, 77.66; H, 6.62; N, 6.97 Found: C, 77.77; H, 6.44; N, 6.94

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