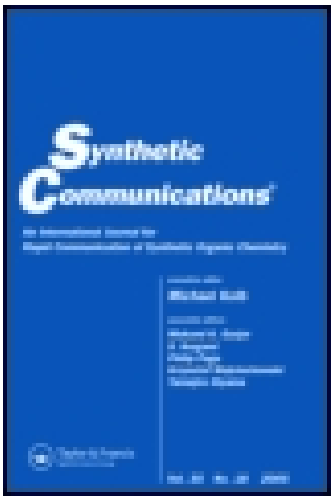

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An Improved Method for the Synthesis of 2-(p-Halobenzyl)-3-aryl-6-methoxybenzofurans as Selective Ligands for the Antiestrogen-Binding Sites

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AN IMPROVED METHOD FOR THE SYNTHESIS OF 2-(p-HALOBENZYL)-3-ARYL-6-METHOXYBENZOFURANS AS SELECTIVE LIGANDS FOR THE ANTIESTROGEN-BINDING SITES

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Abstract: A series of 2-(p-fluorobenzyl)-3-aryl-6-methoxybenzofurans has been prepared in good yields in a two-step sequence from the corresponding benzylidencoumaranones (aurones).

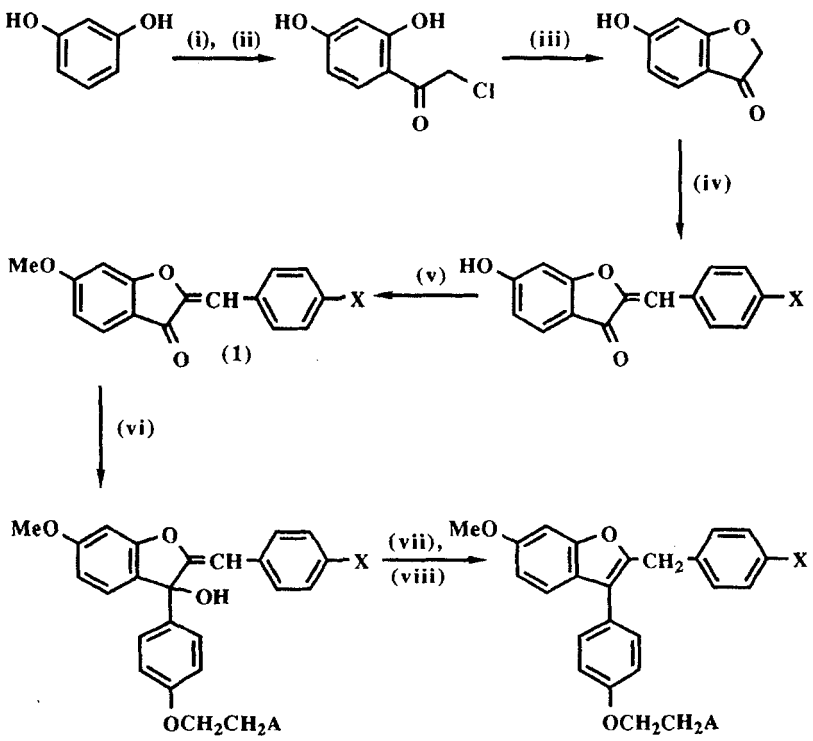
Nonsteroidal antiestrogens such as tamoxifen are established therapeutic agents for estrogen-dependent tumours, especially breast cancer[1, 2]. Antiestrogens bind to two distinct intracellular proteins *viz.* the estrogen receptor (ER) and antiestrogen-binding sites (AEBS). AEBS differ from the estrogen receptor in ligand-binding specificity, physical characteristics, tissue and subcellular

distribution[3,4,5,6]. Whether AEBS have any role in mediating nonreceptor inhibition of cellular proliferation is unresolved. In an attempt to better define the role of AEBS we have undertaken a programme to synthesize compounds having a combination of selectivity and high affinity in order to examine their antiproliferative activity in tumour cell lines. We have recently reported[7] the synthesis of a series of basic ethers of 2-(p-chlorobenzyl)-3-aryl-6-methoxybenzofurans which bind to AEBS with equivalent or greater affinity than tamoxifen and display no significant interaction with ER. These compounds were also more inhibitory than tamoxifen in antiproliferative studies on AEBS containing EL-4 lymphoid cells and MCF breast cancer cells but had no effect on an AEBS-deficient cell line, RTx6. Two of these active compounds also significantly inhibited *de novo* cholesterol biosynthesis in EL4 cells which lack ER. As these interesting compounds were synthesized in only moderate yields, we have been investigating on improving their syntheses. We report herein a 2-step synthetic procedure of these compounds in good yields.

The synthetic route used to obtain the chlorobenzylbenzofuran (**5f**) and the new fluoro-analogues (**5b-e**) is depicted in FIG 1. We had previously obtained the target compounds by the reaction of 2-benzyl-3(2H)-benzofuranones, prepared from catalytic hydrogenation of the corresponding benzylidenecoumaranones (**1**), with arylorganomagnesium or arylorganolithium reagent followed by acid-catalysed dehydration of the tertiary alcohol obtained[7]. The moderate yields in the step involving the organometallic reagents, which could be attributed to the enolisation of the keto group and subsequent preferential deprotonation of the enol hydroxy moiety, prompted us to explore an alternative approach. We found that reaction of the benzylidenecoumaranones (**1**) directly with the

FIG 1

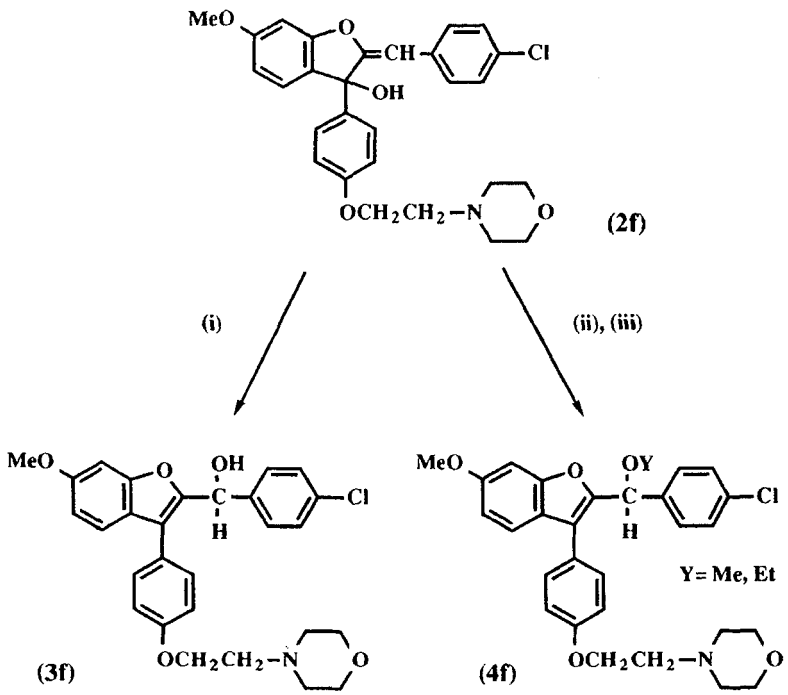
Synthesis of 2-Benzyl-3-arylbenzo[b]furans



2a : NMe_2, X = F
2b : NEt_2, X = F
2c : $N(CH_2CH_2)_2$, X = F
2d : $N(CH_2CH_2)_2CH_2$, X = F
2e : $N(CH_2CH_2)_2O$, X = F
2f : $N(CH_2CH_2)_2O$, X = Cl

5b : A = NEt_2, X = F
5c : A = $N(CH_2CH_2)_2$, X = F
5d : A = $N(CH_2CH_2)_2CH_2$, X = F
5e : A = $N(CH_2CH_2)_2O$, X = F
5f : A = $N(CH_2CH_2)_2O$, X = Cl

Reagents and conditions: (i) $ClCH_2CN$/anhyd. $ZnCl_2$/HCl/Et_2O; (ii) H_2O/reflux (iii) NaOAc /EtOH /reflux; (iv) p-XC_6H_6CHO /HCl/ EtOH/reflux; (v) Me_2SO_4/ K_2CO_3/acetone /reflux; (vi) p-$BrC_6H_6OCH_2CH_2A$ / n-BuLi/ THF / -78°C, then sat. NH_4Cl; (vii) $MgBr_2.OEt_2/Et_2O$/RT; (viii) $LiAlH_4$



Reagents and conditions: (i) H_2SO_4/THF/0°C; (ii) $MgBr_2.OEt_2/Et_2O$/RT; (iii) MeOH or EtOH

FIG 2

Rearrangement Studies on Allylic Alcohol (2f)

organomagnesium or organolithium reagents gave good yields of the allylic alcohols (**2a-f**) which could be transformed into the target compounds (**5a-f**) by treatment with magnesium bromide-etherate followed by lithium aluminium hydride. We have also examined the detailed mechanism of this interesting transformation. We find that the alcoholic group in (FIG 2, **2f**) can undergo an allylic rearrangement, presumably via the intermediacy of carbocations to

the alcohol (**3f**) on treatment with sulphuric acid. This rearranged allylic alcohol (**3f**) can also be obtained by treatment of the allylic alcohol (**2f**) with magnesium bromide-etherate followed by quenching with water of the highly coloured magnesium complex. Treatment of the magnesium complex with methanol or ethanol yielded the corresponding colourless methyl and ethyl ethers (**4f**).

Preliminary biological screening of the synthetic 2-(p-fluorobenzyl)-3-aryl-6-methoxybenzofurans **5(b-e)** indicated that they possess similar interesting biological properties as the chloro-analogues and the results will be reported elsewhere.

EXPERIMENTAL SECTION

All melting points are uncorrected and were determined with a Thomas Hoover apparatus. IR spectra were recorded with a Perkin-Elmer 1310 Infrared spectrophotometer. ^{1}H and ^{13}C spectra were obtained at 300 MHz with a Bruker ACF 300 NMR spectrometer (internal standard $SiMe_4$ and $CDCl_3$ as solvent unless indicated). Mass Spectra were performed on a VG7035 Micromass mass spectrometer at a source temperature of 200 °C and an ion current of 70 ev. Elemental analysis were performed on a Perkin-Elmer Model 240C elemental analyzer and were within ±0.4% of calculated values. Analytical thin-layer chromatography (TLC) was performed on polygram precoated plastic sheets of silica gel 60 and inspected under ultraviolet radiation (254 nm). Flash chromatography was performed according to the method of Still[8] using 0.040 - 0.063 mm silica gel.

Preparation of the compounds 2(a - f); Typical Procedure: ^{n}BuLi (2.87 ml of a 1.28 M solution, 3.675 mmol) was added dropwise to a solution of 4-[2-morpholinoethoxy]phenyl bromide (1.05 g, 3.675 mmol) in THF (10 ml) at -78 °C under oxygen free nitrogen atmosphere. After stirring for one hour at -78 °C, 2-[p-chlorobenzylidene]-6-methoxybenzofuranone [1 g, 3.50 mmol] in THF (5 ml) was added dropwise to the mixture at -78 °C. The reaction mixture was left overnight at ambient temperature (30 °C). After stirring overnight, it was quenched with satd. ammonium chloride. THF was evaporated off to yield an oil which was extracted with ethyl acetate (2x20 ml). The ethyl acetate extract was washed with water followed by Brine (2x20ml), dried (anhydrous $MgSO_4$) and the solvent was evaporated to give an oil which was chromatographed on silica gel. Elution with $CHCl_3$:hexane:Et_3N (5:5:1) yielded a solid of the free base.

2f, Yield 56%, m.p. 69-70 °C; ^{1}H NMR: δ 1.55 [bs, 1H, OH], 2.54-2.58 [t, 4H, $N(C\underline{H}_2CH_2)_2O$], 2.79 [t, 2H, $OCH_2C\underline{H}_2N$], 3.7-3.74 [t, 4H, $N(CH_2C\underline{H}_2)_2O$], 3.84 [3H, CH_3O], 4.09 [2H, $OC\underline{H}_2CH_2N$], 5.64 [s, 1H, =CH-], 6.72-7.60 [11H, ArHs]; ^{13}C NMR δ 54.1[CH_3O], 81.0 [C-3], 104.4 [=$\underline{C}$H-], 133.1[C-2]; IR(KBr): ν 1680 [C=C], 3400cm^{-1} [OH]; m/z(%): 495 (M^+, 10) 493 (10), 100 (100). Found: C, 68.14; H, 5.89; N, 2.75; Cl, 7.30. $C_{28}H_{28}O_5NCl$ requires: C, 68.15; H, 5.68; N, 2.84; Cl, 7.10.

2a, Yield 48%; m.p. 113-114 °C; ^{1}H NMR: δ 2.29 [s, 6H, $N(CH_3)_2$], 2.55 [bs, 1H, OH], 2.69 [t, 2H, $OCH_2C\underline{H}_2N$], 3.83 [s, 3H, OCH_3], 4.03 [t, 2H, $OC\underline{H}_2CH_2N$], 5.65 [s, 1H, =CH-], 6.57-7.65 [11H, ArHs]. ^{13}C NMR: δ 130.34 [C-2], 104.4 [=CH-], 80.97 [C-3], 55.71 [CH_3O]. IR(KBr): ν 1680 [C=C], 3400 cm^{-1} [broad, OH]; m/z(%): 435 (M^+,5), 58 100). Found: C, 71.61; H, 5.89; N, 3.15; F, 4.25. $C_{26}H_{26}O_4NF$ requires: C, 71.72; H, 5.98; N, 3.22; F, 4.37.

2b, Yield 48%; m.p. 108-109 °C; ^{1}H NMR: δ 1.04 [t, 6H, N($CH_2C\underline{H}_3$)$_2$], 2.51 [bs, 1H, OH], 2.59 [q, 4H, N($C\underline{H}_2CH_3$)$_2$], 2.84 [t, 2H, $OCH_2C\underline{H}_2N$], 3.83 [s, 3H, OCH3], 4.02 [t, 2H, $OC\underline{H}_2CH_2N$], 5.65 [s, 1H, =CH-], 6.57-7.65 [11H, ArHs]. ^{13}C NMR: δ 130.75 [C-2], 104.4 [=CH-], 80.98 [C-3], 55.69 [CH3O]. IR(KBr): ν 1680 [C=C], 3400cm^{-1} [OH], m/z(%) 463 (M^+,10), 86 (100). Found: C, 72.43; H, 6.39; N, 2.89; F, 3.93. $C_{28}H_{30}O_4NF$ requires: C, 72.57; H, 6.48; N, 3.02; F, 4.10.

2c, Yield 51%; m.p. 99-101 °C; ^{1}H NMR: δ 1.75 [bs, 1H, OH], 1.77 [m, 4H, N($C\underline{H}_2CH_2$)$_2$], 2.58 [m, 4H, N($C\underline{H}_2CH_2$)$_2$], 2.86 [t, 2H, $OCH_2C\underline{H}_2N$], 3.83 [s, 3H, CH_3O], 4.07 [t, 2H, $OC\underline{H}_2CH_2N$], 5.65 [s, 1H, =CH-], 6.58-7.66 [11H, ArHs]. ^{13}C NMR: δ 130.77 [C-2], 104.41 [=CH-], 66.98 [C-3], 54.64 [CH_3O]. IR(KBr): ν 1680 [C=C], 3400cm^{-1} [broad, OH]; m/z(%): 461 (M+, 10), 84 (100). Found: C, 72.77; H, 5.98; N, 2.97; F, 3.99. $C_{28}H_{28}O_4NF$ requires: C, 72.89; H, 6.07; N, 3.04; F, 4.12.

2d, Yield 54%; m.p. 90-92 °C; ^{1}H NMR: δ 1.41-2.46 [m, 10H, N(CH_2CH_2)$_2CH_2$, 2.72 [t, 2H, $OCH_2C\underline{H}_2N$], 3.83 [s, 3H, OCH_3], 4.06 [t, 2H, $OC\underline{H}_2CH_2N$], 5.65 [s, 1H, =CH-], 6.58-7.63 [11H, ArHs]. ^{13}C NMR: δ 130.76 [C-2], 104.39 [=CH-], 80.84 [C-3], 54.97 [CH_3O]. IR(KBr): ν 1680 [C=C], 3400cm^{-1} [OH]; m/z(%): 475(M+, 10), 98 (100). Found: C, 73.17; H, 6.27; N, 2.88; F, 3.91. $C_{29}H_{30}O_4NF$ requires: C, 73.26; H, 6.32; N, 2.95; F, 4.00.

2e, Yield 56%; m.p. 78-79 °C; ^{1}H NMR: δ 1.55 [bs, 1H, OH], 2.53-2.57 [m, 4H, N($C\underline{H}_2CH_2$)$_2$O], 2.78 [2H, $OCH_2C\underline{H}_2N$], 3.7-3.74 [m, 4H, N($CH_2C\underline{H}_2$)$_2$O]. 3.85 [3H, OCH_3], 4.09 [2H, $OC\underline{H}_2CH_2N$], 5.65 [s, 1H, =CH-], 6.58-7.63 [11H, ArHs]. ^{13}C NMR: δ 130.80 [C-2], 104.41 [=CH-], 80.90 [C-3], 54.05 [CH_3O].

IR(KBr): ν 1680 [C=C], 3400cm^{-1} [OH]; m/z(%): 477 (M+, 10), 100 (100). Found: C, 70.38; H, 5.77; N, 2.83; F, 3.89; $C_{28}H_{28}O_5NF$ requires: C, 70.44; H, 5.87; N, 2.94; F, 3.98.

Preparation of the compound 3f: The compound **2f** (1.00 g, 2.03 mmol) was dissolved in freshly distilled THF (10ml). The reaction mixture was stirred at 0 °C for 10 minutes and 2-3 drops of conc. H_2SO_4 were added. After 30 min., 0.5 ml of water was added and the reaction mixture was allowed to warm to RT. After stirring for 3 hrs, THF was evaporated off to yield an oil which was extracted with ether (2x20ml). Satd. $NaHCO_3$ was added to the ether extract till the effervesence ceased. The ether extract was washed with water followed by brine (2x20ml), dried (anhyd. $MgSO_4$) and then evaporated to give an oil which under vacuum afforded a solid, yield (0.96 g, 96%); m.p. 59-60 °C; ^{1}H NMR: δ 2.59-2.62 [m, 4H, $N(C\underline{H}_2CH_2)_2O$], 2.84 [t, 2H, $OCH_2C\underline{H}_2N$], 3.73-3.77 [m, 4H, $N(CH_2C\underline{H}_2)_2O$], 3.84 [s, 3H, CH_3O], 4.20 [t, 4H, $OC\underline{H}_2CH_2N$], 5.95 [1H, -C<u>H</u>(OH)-] 6.86-7.44 [ArHs], 1.60 [1H, -CH(O<u>H</u>)-]. ^{13}C NMR: δ 150.39 [C-3], 139.46 [C-2], 67.73 [-CH_2-], 54.1 [CH_3O]. IR(KBr): ν 3400 [OH]; m/z(%): 495 (10), 493 (10), 100 (100). Found: C, 68.09; H, 5.79; N, 2.79; Cl, 7.24. $C_{28}H_{28}O_5NCl$ requires: C, 68.15; H, 5.68; N, 2.84; Cl, 7.10.

Preparation of the compounds 5[b-f]; Typical procedure: 2- (4-chlorophenylmethylene)- 3-(2- morpholinoethoxy)phenyl- 6- methoxy- 2,3-dihydrobenzo[b]furan- 3-ol (**2f**) (0.487 g, 0.5 mmol) in ether (10 ml) was added dropwise to a solution of magnesium bromide etherate (0.194 g, 0.75 mmol) in ether (20 ml) under nitrogen atmosphere at RT. After stirring for 4 hours, $LiAlH_4$ (0.076 g, 2.0 mmol) was added and the reaction mixture was left stirring overnight at RT. Ethyl acetate was added dropwise till H_2 evolution ceased. The

mixture was washed with water followed by brine (2x20 ml), dried (anhyd. $MgSO_4$) and the solvent evaporated off to give an oil which was chromatographed on silica. Elution with $CHCl_3$: hexane : Et_3N (5:5:1) yielded a white solid of the free base which was converted to the hydrochloride salt as follows: The free base was dissolved in ether and cooled to 0 °C whence a saturated solution of dry hydrogen chloride in ether was added. After 30 minutes, the hydrochloride salt which precipitated out was filtered off at the pump, rinsed with ether and recrystallized from isopropanol / methanol mixtures.

4f, (procedure as above except that MeOH was added in place of $LiAlH_4$). Yield 92%; m.p. 148-149 °C; ^1H NMR: δ 2.6-2.63 [t, 4H, $N(C\underline{H}_2CH_2)_2O$], 2.86 [t, 2H, $OCH_2C\underline{H}_2N$], 3.74-3.78 [t, 4H, $N(C\underline{H}_2CH_2)_2O$], 3.33, 3.84 [s, 6H, 2 OMe], 4.18 [t, 2H, $OC\underline{H}_2CH_2N$], 5.42 [s, 2H, $-CH_2-$], 6.85-7.43 [11H, ArHs]. ^{13}C NMR: δ 148.83 [C-3], 124.07 [C-2], 76.24 [-CH at C-2], 57.68, 54.14 [MeO at C-2, C-6]; m/z(%): 509 (M^+, 10), 507 (20), 100 (100). Found: C, 68.90; H, 5.90; N, 2.62; Cl, 7.03; $C_{29}H_{30}O_5NCl$ requires: C, 68.64; H, 5.92; N, 2.76; Cl, 6.90.

5f, Yield 60%; m.p. 126-128 °C; ^1H NMR: δ 2.6-2.63 [t, 4H, $N(C\underline{H}_2CH_2)_2O$], 2.85 [t, 2H, $OCH_2C\underline{H}_2N$], 3.74-3.77 [m, 4H, $N(CH_2C\underline{H}_2)_2O$], 3.84 [s, 3H, CH_3O], 4.11 [s, 2H, $-CH_2-$], 4.17[t, 2H, $OC\underline{H}_2CH_2N$], 6.84-7.44 [11H, ArHs]. ^{13}C NMR: δ 150.41 [C-3], 132.35 [C-2], 65.96 [$-CH_2-$], 54.13 [CH_3O]; m/z(%): 479 (10), 477 (35), 100 (100). Found: C, 70.37; H, 5.79; N, 2.85; Cl, 7.20; $C_{28}H_{28}O_4NCl$ requires: C, 70.44; H, 5.87; N, 2.94; Cl, 7.34.

5b, Yield 52%; m.p. 146-147 °C; ^1H NMR: δ 1.49 [t, 6H, $N(CH_2C\underline{H}_3)_2$], 3.30 [q, 4H, $N(C\underline{H}_2CH_3)_2$], 3.49 [t, 2H, $OCH_2C\underline{H}_2N$], 3.85 [s, 3H, OCH_3], 4.11 [s, 2H, $-CH_2-$], 4.62 [t, 2H, $OC\underline{H}_2CH_2N$], 6.85-7.42 [11H, ArHs]; m/z(%): 447

(M^+,10), 86 (100). Found: C, 67.05; H, 6.36; N, 2.77; F, 3.79. $C_{28}H_{30}O_3NF.HCl.H_2O$ requires: C, 67.07; H, 6.59; N, 2.79; F, 3.79.

5c, Yield 54%; m.p. 178-179 °C; ^1H NMR: δ 1.85 [m, 4H, $N(CH_2\underline{CH_2})_2$], 3.52 [m, 4H, $N(\underline{CH_2}CH_2)_2$], 3.75 [t, 2H, $OCH_2\underline{CH_2}N$], 3.85 [s, 3H, CH_3O], 4.11 [s, 2H, $-CH_2-$], 4.61 [t, 2H, $O\underline{CH_2}CH_2N$], 6.85-7.42 [11H, ArHs]; m/z(%): 445 (M^+, 10), 84 (100). Found: C, 68.61; H, 6.06; N, 3.24; F, 4.07; $C_{28}H_{28}O_3NF.HCl.5H_2O$ requires: C, 68.57; H, 6.12; N, 2.86; F, 3.86.

5d, Yield 59%; m.p. 154-156 °C; ^1H NMR: δ 1.88-2.89 [m, 10H, $N(\underline{CH_2}\underline{CH_2})_2\underline{CH_2}$], 3.44 [t, 2H, $OCH_2\underline{CH_2}N$], 3.85 [s, 3H, OCH_3], 4.11 [s, 2H, $-CH_2-$], 4.64 [t, 2H, $O\underline{CH_2}CH_2N$], 6.85-7.41 [11H, ArHs]; m/z(%): 459 (10), 98 (100). Found: C, 68.48; H, 6.39; N, 2.88; F, 4.00; $C_{29}H_{30}O_3NF.HCl.H_2O$ requires: C, 67.84; H, 6.43; N, 2.73; F, 3.70.

5e, Yield 60%; m.p. 105-106 °C; ^1H NMR: δ 2.59-2.63 [m, 4H, $N(\underline{CH_2}CH_2)_2O$], 2.85 [t, 2H, $OCH_2\underline{CH_2}N$], 3.74-3.77 [m, 4H, $N(CH_2\underline{CH_2})_2O$] 3.84 [s, 3H, CH_3O], 4.12 [s, 2H, $-CH_2-$], 4.17 [t, 2H, $O\underline{CH_2}CH_2N$], 6.85-7.42 [11H, ArHs]; m/z(%): 461 (M^+, 45), 100(100). Found: C, 72.94; H, 6.10; N, 2.99; F, 3.76. $C_{28}H_{28}O_4NF$ requires: C, 72.89; H, 6.07; N, 3.04; F, 4.12.

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