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Triaryl (*Z*)-olefins suitable for radiolabeling with iodine-124 or fluorine-18 radionuclides for positron emission tomography imaging of estrogen positive breast tumors

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ABSTRACT

A group of (*Z*)-1,2-diphenyl-1-[4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl]but-1-enes were synthesized using methodologies that will allow incorporation of a [^{124}I]iodine substituent at the *para*-position of either the C-1 phenyl ring or the C-2 phenyl ring, or a [^{18}F]OCH_2CH_2F substituent at the *para*-position of the C-2 phenyl ring. These [^{124}I] and [^{18}F] radiotracers are designed as potential radiopharmaceuticals to image estrogen positive breast tumors using positron emission tomography (PET).

Tamoxifen (**1**) is a non-steroidal triphenylbut-1-ene anti-estrogenic drug used extensively to treat hormone-responsive human breast cancer[1,2] that is believed to act[3] primarily by competing with estradiol for its estrogen receptor (ER). The basic aminoalkyloxy moiety present in tamoxifen ($OCH_2CH_2NMe_2$) is a major determinant of receptor binding affinity (RBA) where the relative binding profile with respect to the amino group is 4-methylpiperazin-1-yl > pyrrolidin-1-yl > NEt_2 > NMe_2 > piperidin-1-yl > morpholin-4-yl.[4] Decreasing the basicity of the protonated amino group (cationic site) is believed to diminish the binding interaction with Asp351 (anionic carboxylate site) on the estrogen receptor.[5] Although replacement of the $-CH_2CH_3$ substituent in tamoxifen (**1**) by a $-CH_2CH_2F$ substituent does not change the RBA,[6] there is the possibility for elimination of HF to furnish the respective vinyl ($-CH{=}CH_2$) product.[6,7] The 4-hydroxytamoxifen metabolite **2**, which shows a higher in vitro anti-estrogenic potency than tamoxifen, is less potent than tamoxifen in vivo owing to rapid glucuronidation of the hydroxyl group and subsequent excretion.[8,9] 4-Iodotamoxifen (**3**)[9,10] is a more potent in vitro inhibitor of MCF-7 cancer cell growth than tamoxifen[9] (see structures **1**–**3** in Fig. 1).

The most common positron emitting radionuclides include ^{11}C ($t_{1/2}$ = 20.4 min) and ^{18}F ($t_{1/2}$ = 109.6 min). The radiosynthesis of [^{11}C]tamoxifen having the short half-life ^{11}C label in one of the N–$^{11}CH_3$ substituents has been reported.[11] The observation that replacement of the $-NMe_2$ group in tamoxifen by a 4-methylpiperazin-1-yl ring resulted in a fivefold enhancement in estrogen RBA[4]

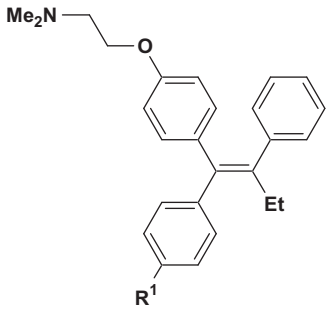

Figure 1. Structures of tamoxifen (**1**, R^1 = H), 4-hydroxytamoxifen (**2**, R^1 = OH) and 4-iodotamoxifen (**3**, R^1 = I).

prompted us to design candidate imaging agents having a 4-methylpiperazin-1-yl moiety (see structures in Fig. 2). It was envisioned that the 4-position on the C-1 phenyl ring would be a suitable location to position a longer half-life ^{124}I ($t_{1/2}$ = 4.18 days) radionuclide since 4-iodotamoxifen (**3**)[9,10] is a more potent in vitro inhibitor of MCF-7 cancer cell growth than tamoxifen.[9] Access to [^{124}I]radiotracers with a longer radionuclide half-life is highly relevant since it provides an extended time period, relative to [^{11}C] and [^{18}F], during which optimal imaging can be carried out based on the biodistribution and elimination properties of the radiotracer being investigated. Furthermore, placement of an iodine radionuclide at this position would result in metabolic halogenic obstruction preventing formation of a putative 4-hydroxy metabolite that was observed in the

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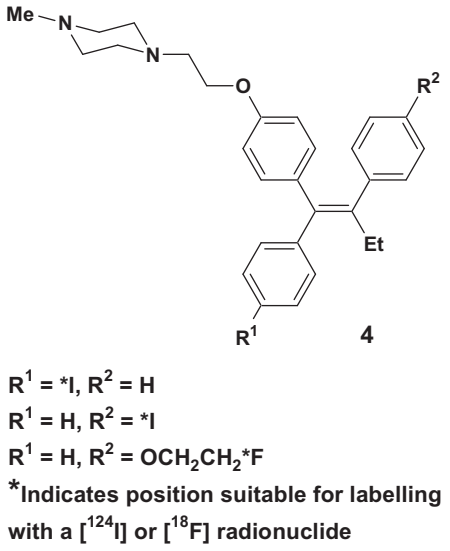


Figure 2. Putative positions (*) where a [^{124}I]- or [^{18}F]-radionuclide may be incorporated for assessment as PET radiopharmaceuticals to image estrogen-responsive breast tumors.

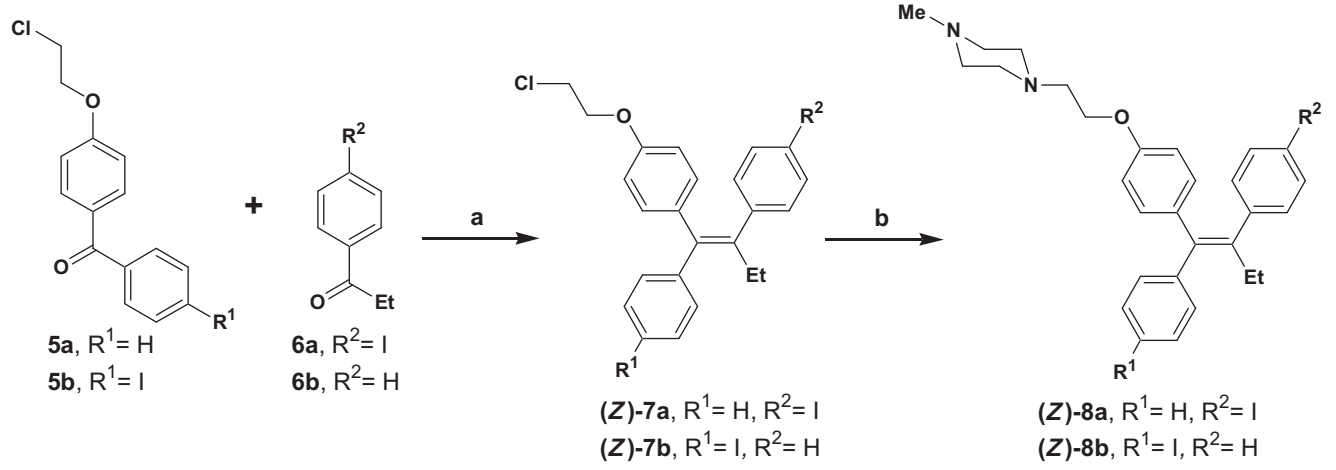
case of tamoxifen.[8,9] Alternatively, a [^{124}I], or [^{18}F]OCH_2CH_2F, substituent could be placed at the *para*-position of the C-2 phenyl ring. We now describe non-radioactive synthetic methodologies that will be applicable to the future radiochemical synthesis of the three putative radiopharmaceuticals illustrated in Figure 2 employing reaction conditions and reagents that employ the corresponding [^{124}I]- or [^{18}F]-reagents. These putative radiopharmaceuticals will warrant future assessment as PET imaging agents targeted to the detection of estrogen positive breast tumors.

The (*Z*)-1-[4-(2-chloroethoxy)phenyl]-2-(4-iodophenyl)-1-phenylbut-1-ene [**(*Z*)-7a**] was synthesized using a McMurry olefination reaction by Zn–$TiCl_4$ catalyzed reductive cross-coupling of 4-(2-chloroethoxy)benzophenone (**5a**) with 4-iodopropiophenone (**6a**) in 35% yield as illustrated in Scheme 1. The **(*Z*)-7a** product was the sole stereoisomer obtained after silica gel column chromatography and recrystallization from EtOH. A similar cross-coupling reaction of the iodobenzophenone analog **5b** with propiophenone (**6b**) afforded the (*Z*)-1-[4-(2-chloroethoxy)phenyl]-1-(4-iodophenyl)-2-phenylbut-1-ene [**(*Z*)-7b**] regioisomer (20%). Subsequent reaction of the chloroethoxy **(*Z*)-7a** and **(*Z*)-7b** regioisomers with *N*-methylpiperazine in EtOH at reflux furnished the respective *N*-methylpiperazinyl product **(*Z*)-8a** (54%) and **(*Z*)-8b** (59%). Stereoisomer assignments were made based on ^{1}H NMR chemical shifts from published information.[4,6,8,12,13]

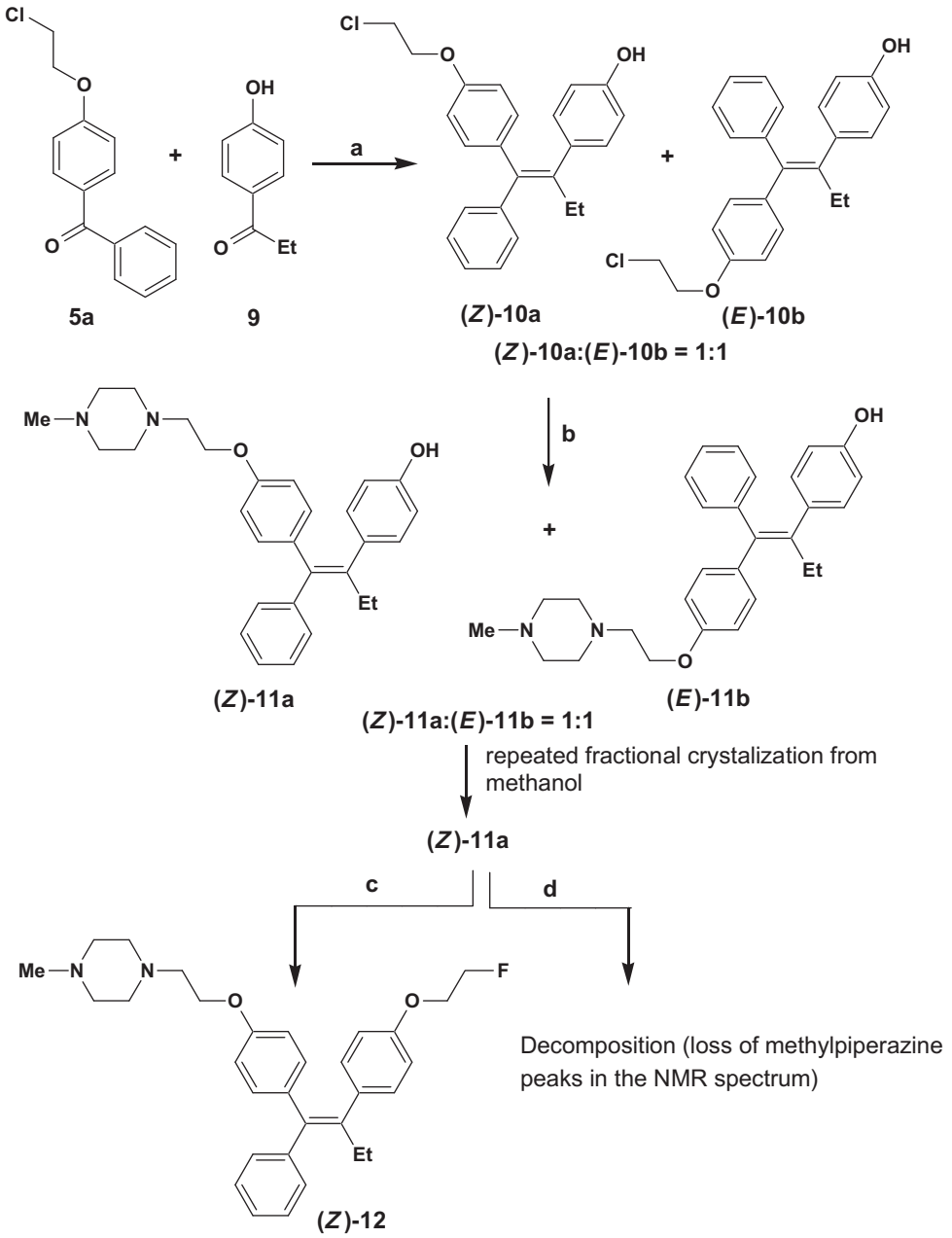
A McMurry olefination reaction employing the Zn–$TiCl_4$ catalyzed reductive cross-coupling of 4-(2-chloroethoxy)benzophenone (**5a**) with 4-hydroxypropiophenone (**9**) yielded a 1:1 mixture (^{1}H NMR integrals) of the 1-(4-chloroethoxyphenyl)-2-(4-hydroxyphenyl)-1-phenylbut-1-ene **(*Z*)-10a** and **(*E*)-10b** stereoisomers in 44% yield as illustrated in Scheme 2. Attempts to separate these **(*Z*)-10a** and **(*E*)-10b** stereoisomers by fractional crystallization from solvents of varied polarity (diethyl ether, ethyl acetate, isopropanol and ethanol) were unsuccessful. Therefore, the mixture of **(*Z*)-10a** and **(*E*)-10b**, without separation, was reacted with *N*-methylpiperazine to give a 1:1 mixture of the **(*Z*)-11a** and **(*E*)-11b** stereoisomers in 90% yield (1.05 g). Repeated fractional crystallization of this mixture from methanol furnished 170 mg of **(*Z*)-11a**. Condensation of the *para*-hydroxyphenyl **(*Z*)-11a** stereoisomer with 2-fluoroethyl *p*-toluenesulfonate in the presence of K_2CO_3 and Kryptofix 222 with CH_3CN as solvent yielded the target fluoroethoxy **(*Z*)-12** product (35% yield). In contrast, an attempted methylation of the *para*-hydroxyphenyl **(*Z*)-11a** stereoisomer with CH_3I in DMF using NaH or 5 N NaOH as base resulted in loss of the *N*-methylpiperazine moiety.

The stereochemical integrity of electron-rich tetra-substituted olefinic bonds is frequently compromised under both alkaline and acidic conditions.[14] It was recently reported[14] that (*Z*)-4-hydroxy-*N*-desmethyltamoxifen (endoxifen) could be readily separated from the corresponding (*E*)-stereoisomer by preparative RP-HPLC with isocratic elution using a buffer containing 50% of 20 mM triethylammonium bicarbonate in MeCN at pH 8.8. Accordingly, it is possible that the (*Z*)- and (*E*)-stereoisomer mixtures (**10a** and **10b**; **11a** and **11b**) could also be separated using this RP-HPLC methodology. Separation of (*Z*)- and (*E*)-4-hydroxy-*N*-desmethyltamoxifen stereoisomers worked well even at significant column overload since the retention times of the two stereochemical isomers differed by 28 min.

Access to [^{124}I] ($t_{1/2}$ = 4.18 days) and [^{18}F] ($t_{1/2}$ = 109.6 min) radiotracers with a longer radionuclide half-life is highly relevant since it provides an extended time period, compared to [^{11}C] with a $t_{1/2}$ = 20.4 min, during which optimal imaging can be carried out based on the biodistribution and elimination (background washout) properties of the radiotracer being investigated. In this regard, [^{124}I] analogs of the iodophenyl **(*Z*)-8a** and **(*Z*)-8b** regioisomers will be accessible using a $CuSO_4$ catalyzed iodine isotope exchange reaction using [^{124}I]NaI.[15] Alternatively, elaboration of the unlabeled iodophenyl **(*Z*)-8a** and **(*Z*)-8b** regioisomers to the respective



Scheme 1. Reagents and conditions: (a) Zn, $TiCl_4$, THF, reflux 3.5 h; (b) *N*-methylpiperazine, EtOH, reflux 24 h.



Scheme 2. Reagents and conditions: (a) Zn, $TiCl_4$, THF, reflux 3.5 h; (b) 1-methylpiperazine, EtOH, reflux 24 h; (c) (i) K_2CO_3, Kryptofix 222, CH_3CN, 50 °C, 15 min; (ii) $TsOCH_2CH_2F$, reflux 10 min; (d) 5 N NaOH, CH_3I, DMF, 60 °C, 3 min, or NaH, CH_3I, DMF, 60 °C, 5 min.

tributylstannyl derivative and then treatment with [^{124}I]ICl will provide high specific activity [^{124}I)-labeled **(*Z*)-8a** and **(*Z*)-8b** (-I→-$SnBu_3$ + [^{124}I]ICl→-[^{124}I]).[16] Reaction of the *para*-hydroxyphenyl **(*Z*)-11a** stereoisomer with [^{18}F]$TsOCH_2CH_2F$ in the presence of K_2CO_3 and Kryptofix 222 with CH_3CN as solvent at reflux with a reaction time of 10 min will provide a suitable method to synthesize [^{18}F] labeled **(*Z*)-8**.

In conclusion, (i) synthetic methodologies[17] suitable for the synthesis of the putative [^{124}I] and [^{18}F]labeled radiotracers illustrated in Figure 2 have been developed, and (ii) these potential radiopharmaceuticals warrant investigation as PET imaging agents to detect estrogen positive breast tumors.

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17. *Experimental procedures and spectral data for compounds* **(*Z*)-7a–b**, **(*Z*)-8a–b**, **(*Z*)-11a**, **(*Z*)-12**. *General*: Melting points were determined on a Thomas–Hoover capillary apparatus and are uncorrected. Infrared (IR) spectra were recorded as films on NaCl plates using a Nicolet 550 Series II Magna FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were measured on a Bruker AM-300 spectrometer in $CDCl_3$, CD_3OD, or $CDCl_3$ + CD_3OD with TMS as the internal standard, where *J* (coupling constant) values are estimated in Hertz (Hz). Mass spectra (MS) were recorded on a Water's Micromass ZQ 4000 mass spectrometer using the electrospray (ES) ionization mode. Microanalyses were performed for C, H, N by the Microanalytical Service Laboratory, Department of Chemistry, University of Alberta. Silica gel column chromatography was performed using Merck silica gel 60 ASTM (70–230 mesh). All other reagents, purchased from the Aldrich Chemical Company (Milwaukee, WI), were used without further purification. The 4-(2-chloroethoxy)benzophenone (**5a**),[18] 1-[4-(2-chloroethoxy)phenyl](4-iodophenyl)methanone (**5b**)[19] and *p*-iodopropiophenone (**6a**)[20] were prepared according to the literature procedures. The chemical name for K222 (Kryptofix 222) is 1,10-diaza-4,7,13,16,21,24-hexaoxabicyclo[8.8.8]hexacosane.
(Z)-1-[4-(2-Chloroethoxy)phenyl]-2-(4-iodophenyl)-1-phenylbut-1-ene [**(*Z*)-7a**]: Titanium tetrachloride (0.99 mL, 9 mmol) was added drop wise to a stirred suspension of Zn powder (1.18 g, 18 mmol) in dry THF (15 mL) under an argon atmosphere at −10 °C, and this mixture was heated at reflux for 1.5 h to produce the titanium reagent. A cooled suspension of this titanium reagent was added to a solution of 4-(2-chloroethoxy)benzophenone (**5a**, 0.78 g, 3.0 mmol) and *p*-iodopropiophenone (**6a**, 0.78 g, 3.0 mmol) in THF (20 mL) at 0 °C, and the reaction was allowed to proceed at reflux for 2 h. After cooling to 25 °C, the reaction mixture was poured into a 10% aqueous K_2CO_3 solution (45 mL), this mixture was stirred vigorously for 5 min, and the dispersed insoluble material was removed by vacuum filtration. The organic fraction was separated, the aqueous layer was extracted with EtOAc (3 × 25 mL), and the combined organic fractions were dried (Na_2SO_4). Removal of the solvent in vacuo afforded a residue which was purified by silica gel column chromatography using EtOAc–hexane (1:4, v/v) as eluent followed by recrystallization of the product from ethanol to give **(*Z*)-7a** as a white solid (0.5 g, 35%); mp 117–118 °C; IR (film): 2966 (C–H aromatic), 2931 (C–H aliphatic) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.92 (t, *J* = 7.4 Hz, 3H, CH_2CH_3), 2.43 (q, *J* = 7.4 Hz, 2H, CH_2CH_3), 3.73 (t, *J* = 5.5 Hz, 2H, OCH_2CH_2Cl), 4.13 (t, *J* = 5.5 Hz, 2H, OCH_2CH_2Cl), 6.59 (dd, *J* = 6.7, 1.8 Hz, 2H, chloroethoxyphenyl H-3, H-5), 6.78 (dd, *J* = 6.7, 1.8 Hz, 2H, chloroethoxyphenyl H-2, H-6), 6.88 (d, *J* = 8.3 Hz, 2H, iodophenyl H-2, H-6), 7.20–7.37 (m, 5H, phenyl hydrogens), 7.50 (d, *J* = 8.3 Hz, 2H, iodophenyl H-3, H-5); ^{13}C NMR ($CDCl_3$): δ 13.5, 28.8, 41.8, 67.8, 91.5, 113.8, 126.7, 128.2, 129.3, 131.7, 131.9, 135.8, 137.0, 138.9, 140.4, 142.0, 143.4, 156.3; MS *m*/*z* (ES$^+$) 489.0, $C_{24}H_{23}ClIO$ (M+H) requires 489.79.
(Z)-1-[4-(2-Chloroethoxy)phenyl]-1-(4-iodophenyl)-2-phenylbut-1-ene (**7b**): The title compound **7b** was synthesized using the same procedure described for the preparation of **7a**, by reaction of (4-chloroethoxyphenyl)(4-iodophenyl)-methanone (**5b**) with the propiophenone (**6b**). The product obtained after column chromatography is a 1:1 mixture (NMR) of the (*Z*)- and (*E*)-stereoisomers from which the target **(*Z*)-7b** stereoisomer could be recrystallized from ethanol as white crystals in 20% yield; mp 94–96 °C (Lit.[13] mp 96–97 °C). The ^{1}H NMR spectral data for **(*Z*)-7b** was the same as previously reported data.[13]
(Z)-2-(4-Iodophenyl)-1-[4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl]-1-phenylbut-1-ene [**(*Z*)-8a**]: (*Z*)-1-[4-(2-Chloroethoxy)phenyl]-2-(4-iodophenyl)-1-phenylbut-1-ene [**(*Z*)-7a**, 245 mg, 0.5 mmol] and *N*-methylpiperazine (5.0 g, 50 mmol) in ethanol (10 mL) was heated under reflux for 24 h. The solvent was evaporated under vacuum and the residue purified by silica gel column chromatography using methanol–chloroform (1:9, v/v) as eluent followed by recrystallization of the product from petroleum ether (35–60 °C) to give **(*Z*)-8a** as a white solid (149 mg, 54%); mp 93–95 °C; IR (film): 2966 (C–H aromatic), 2932 (C–H aliphatic) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.91 (t, *J* = 7.4 Hz, 3H, CH_2CH_3), 2.42 (q, *J* = 7.4 Hz, 2H, CH_2CH_3), 2.44 (s, 3H, NCH_3), 2.55–2.70 (m, 8H, piperazinyl hydrogens), 2.79 (t, *J* = 5.5 Hz, 2H, OCH_2CH_2N), 4.00 (t, *J* = 5.5 Hz, 2H, OCH_2CH_2N), 6.57 (dd, *J* = 6.7, 2.4 Hz, 2H, ethoxyphenyl H-3, H-5), 6.76 (dd, *J* = 6.7, 2.4 Hz, 2H, ethoxyphenyl H-2, H-6), 6.87 (dd, *J* = 6.1, 1.8 Hz, 2H, iodophenyl H-2, H-6), 7.19–7.37 (m, 5H, phenyl hydrogens), 7.49 (dd, *J* = 6.1, 1.8 Hz, 2H, iodophenyl H-3, H-5); ^{13}C NMR ($CDCl_3$): δ 13.6, 28.8, 45.7, 53.1, 54.8, 57.1, 65.7, 91.4, 113.6, 126.7, 128.1, 129.3, 130.7, 131.8 135.2, 137.0, 139.0, 140.1, 142.0, 143.4, 156.8; MS *m*/*z* (ES$^+$) 553.1, $C_{29}H_{34}IN_2O$ (M+H) requires 553.49. Anal. Calcd for $C_{29}H_{33}IN_2O{\cdot}1/2H_2O$: C, 62.04; H, 6.10; N, 4.99. Found: C, 62.12; H, 5.98; N, 5.02.
(Z)-1-(4-Iodophenyl)-1-[4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl]-2-phenylbut-1-ene [**(*Z*)-8b**]: The title compound **(*Z*)-8b** was synthesized from the chloroethoxy compound **(*Z*)-7b** using the same procedure described for the preparation of **(*Z*)-8a** as white crystals in 59% yield; mp 119–120 °C (from ether); IR (film): 2961 (C–H aromatic), 2933 (C–H aliphatic) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.91 (t, *J* = 7.4 Hz, 3H, CH_2CH_3), 2.44 (q, *J* = 7.4 Hz, 2H, CH_2CH_3), 2.47 (s, 3H, NCH_3), 2.65–2.88 (m, 10H, piperazinyl hydrogens and OCH_2CH_2N), 3.98 (t, *J* = 5.5 Hz, 2H, OCH_2CH_2N), 6.58 (d, *J* = 9.2 Hz, 2H, ethoxyphenyl H-3, H-5), 6.80 (d, *J* = 9.2 Hz, 2H, ethoxyphenyl H-2, H-6), 7.02 (dd, *J* = 8.5, 1.8 Hz, 2H, iodophenyl H-2, H-6), 7.06–7.12 (m, 5H, phenyl hydrogens), 7.67 (dd, *J* = 8.5, 1.8 Hz, 2H, iodophenyl H-3, H-5); ^{13}C NMR ($CDCl_3$): δ 13.5, 29.0, 45.7, 53.1, 54.8, 57.0, 65.7, 92.0, 113.6, 126.2, 127.9, 129.4, 129.6, 131.5 131.8, 135.1, 137.1, 137.2, 142.0, 142.1, 156.8; MS *m*/*z* (ES$^+$) 553.1, $C_{29}H_{34}IN_2O$ (M+H) requires 553.49. Anal. Calcd for $C_{29}H_{33}IN_2O$: C, 63.04; H, 6.02; N, 5.07. Found: C, 62.97; H, 5.94; N, 5.07.
(Z)-2-(4-Hydroxylphenyl)-1-[4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl]-1-phenylbut-1-ene [**(*Z*)-11a**]: Titanium tetrachloride (1.97 mL, 18 mmol) was added drop wise to a stirred suspension of Zn powder (2.35 g, 36 mmol) in dry THF (30 mL) under an argon atmosphere at −10 °C, and this mixture was heated at reflux for 1.5 h to produce the titanium reagent. A cooled suspension of this titanium reagent was added to a solution of 4-(2-chloroethoxy)benzophenone (**5a**, 1.56 g, 6.0 mmol) and 4-hydroxypropiophenone (**9**, 0.9 g, 6.0 mmol) in THF (40 mL) at 0 °C, and the reaction was allowed to proceed at reflux for 2 h. After cooling to 25 °C, the reaction mixture was poured into a 10% aqueous K_2CO_3 solution (90 mL), this mixture was stirred vigorously for 5 min, and the dispersed insoluble material was removed by vacuum filtration. The organic fraction was separated, the aqueous layer was extracted with EtOAc (3 × 50 mL), and the combined organic fractions were dried (Na_2SO_4). Removal of the solvent in vacuo gave a residue which was purified by silica gel column chromatography using EtOAc–hexane (1:4, v/v) as eluent to furnish a mixture of the **(*Z*)-10a** and **(*E*)-10b** stereoisomers in a ratio of 1:1 (^{1}H NMR integrals) in 44% yield (1.0 g); mp 136–138 °C. All attempts to separate these **(*Z*)-10a** and **(*E*)-10b** stereoisomers by fractional crystallization from solvents of different polarity (diethyl ether, ethyl acetate, isopropanol and ethanol) were unsuccessful. Therefore, this mixture of **(*Z*)-10a** and **(*E*)-10b**, without separation, was added to a solution of *N*-methylpiperazine (26.4 g, 264 mmol) in ethanol (50 mL). The mixture was heated under reflux for 24 h, the solvent was evaporated in vacuo, and the residue obtained was purified by silica gel column chromatography using methanol-chloroform (1:9, v/v) as eluent to give a 1:1 (^{1}H NMR integrals) of the **(*Z*)-11a** and **(*E*)-11b** stereoisomers in 90% yield (1.05 g). Repeated fractional crystallization of this mixture from methanol furnished 170 mg of **(*Z*)-11a** as a white solid; mp 181–183 °C; IR (film): 3505–3097 (O–H), 2967 (C–H aromatic), 2930 (C–H aliphatic) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.95 (t, *J* = 7.4 Hz, 3H, CH_2CH_3), 2.35 (s, 3H, NCH_3), 2.44 (q, *J* = 7.4 Hz, 2H, CH_2CH_3), 2.60–2.77 (m, 8H, piperazinyl hydrogens), 2.75 (t, *J* = 5.5 Hz, 2H, OCH_2CH_2N), 4.01 (t, *J* = 5.5 Hz, 2H, OCH_2CH_2N), 6.53 (d, *J* = 8.6 Hz, 2H, ethoxyphenyl H-3, H-5), 6.63 (d, *J* =8.6 Hz, 2H, hydroxyphenyl H-3, H-5), 6.78 (d, *J* = 8.6 Hz, 2H, ethoxyphenyl H-2, H-6), 7.01 (d, *J* =8.6 Hz, 2H, hydroxyphenyl H-2, H-6), 7.23–7.38 (m, 5H, phenyl hydrogens); MS *m*/*z* (ES$^+$) 443.2, $C_{29}H_{35}N_2O_2$ (M+H) requires 443.59.
(Z)-2-[4-(2-Fluoroethoxy)phenyl]-1-[4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl]-1-phenylbut-1-ene [**(*Z*)-12**]: A mixture of the phenol [**(*Z*)-11a**, 111 mg, 0.25 mmol], Kryptofix 222 (94 mg, 0.25 mmol) and anhydrous potassium carbonate (38 mg, 0.28 mmol) in acetonitrile (3 mL) was heated at 50 °C for 15 min. 2-Fluoroethyl *p*-toluenesulfonate (55 mg, 0.25 mmol) was added and the mixture was heated under reflux for 10 min. After cooling to 25 °C, the solid was separated by filtration, the filtrate was concentrated in vacuo, and the residue was purified by silica gel column chromatography using EtOAc–hexane (9:1, v/v) as eluent to give **(*Z*)-12** as a pale yellow gum (79 mg, 35%); IR (film): 2962 (C–H aromatic), 2933 (C–H aliphatic) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.93 (t, *J* = 7.4 Hz, 3H, CH_2CH_3), 2.31 (s, 3H, NCH_3), 2.44 (q, *J* = 7.4 Hz, 2H, CH_2CH_3), 2.49–2.76 (m, 8H, piperazinyl hydrogens), 2.77 (t, *J* = 5.5 Hz, 2H, OCH_2CH_2N), 4.00 (t, *J* = 5.5 Hz, 2H, OCH_2CH_2N), 4.20 (ddd, *J* = 28.0, *J* = 4.2, 4.2 Hz, 2H, OCH_2CH_2F), 4.74 (ddd, *J* = 48.0, *J* = 4.2, 4.2 Hz, 2H, OCH_2CH_2F), 6.57 (d, *J* = 8.6 Hz, 2H, ethoxyphenyl H-3, H-5), 6.76 (d, *J* = 8.6 Hz, 2H, fluoroethoxyphenyl H-3, H-5), 6.79 (d, *J* = 8.6 Hz, 2H, ethoxyphenyl H-2, H-6), 7.06 (d, *J* = 8.6 Hz, 2H, fluoroethoxyphenyl H-2, H-6), 7.22-7.38 (m, 5H, phenyl hydrogens); ^{13}C NMR ($CDCl_3$): δ 13.6, 28.9, 45.8, 53.2, 54.9, 57.1, 65.6, 66.95 (d, $^2J_{CCF}$ = 19.7 Hz), 81.4 (d, $^1J_{CF}$ = 169.2 Hz), 113.5, 114.1, 127.3, 128.1, 129.4, 130.8, 131.8 135.2, 136.3, 138.0, 140.7, 143.5, 143.9, 156.6; MS *m*/*z* (ES$^+$) 489.2, $C_{31}H_{42}FN_2O_4$ (M+H) requires 489.64. Anal. Calcd for $C_{31}H_{41}FN_2O_4{\cdot}1.7H_2O$: C, 71.46; H, 7.85; N, 5.38. Found: C, 71.22; H, 7.32; N, 5.13.
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