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# Synthesis and Structure−Affinity Relationships of Novel Dibenzylideneacetone Derivatives as Probes for β-Amyloid Plaques

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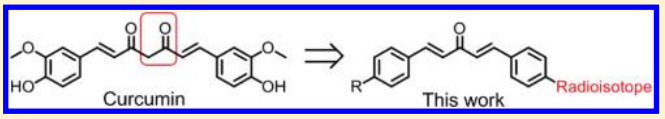
Supporting Information

**ABSTRACT:** A new and extensive set of dibenzylideneacetone derivatives was synthesized and screened for affinity toward $A\beta_{1-42}$ aggregates. Structure−activity relationships revealed the binding of dibenzylideneacetones to be affected by various substituents. The introduction of a substituent group in the ortho position reduced or abolished the binding. However, the para position was highly tolerant of sterically demanding substitutions. Three radioiodinated ligands (**6**, **70**, and **71**) and two $^{18}$F fluoropegylated (FPEG) ligands (**83** and **85**) were prepared, all of which displayed high affinity for $A\beta_{1-42}$ aggregates ($K_i$ ranging from 0.9 to 7.0 nM). In biodistribution experiments, they exhibited good initial penetration (1.59, 4.68, 4.56, 4.13, and 5.15% ID/g, respectively, at 2 min) of and fast clearance from the brain. Autoradiography with sections of postmortem AD brain and transgenic mouse brain confirmed the high affinity of these tracers. These preliminary results strongly suggest the dibenzylideneacetone structure to be a potential new scaffold for β-amyloid imaging probes.




## INTRODUCTION

Alzheimer's disease (AD) is an irreversible, progressive brain disorder that accounts for the majority of dementia cases. Histopathologically, AD is characterized by β-amyloid (Aβ) plaques composed mainly of mis-folded Aβ peptides and neurofibrillary tangles (NFTs) containing hyperphosphorylated τ protein.[1,2] However, the precise molecular mechanisms leading to AD remain unknown. Several theories have arisen, with the amyloid cascade hypothesis perhaps the most prominent.[3,4] Moreover, a refined version of the amyloid cascade hypothesis proposes that soluble Aβ peptides (soluble oligomers or protofibrils), not mature Aβ plaques, exert toxic effects on neuronal cells.[5,6] The clinical diagnosis of AD is primarily based on neurological observations and patient history and is often difficult and unreliable. Although there is a lack of correlation between cognitive decline and elevated levels of Aβ plaques in the brain,[7,8] several reports indicate that overaccumulation of Aβ peptides initiates a sequence of events that lead to neurodegeneration.[9,10] Therefore, Aβ plaques could be considered a biomarker for the early diagnosis of AD.

With the assistance of nuclear imaging techniques such as positron emission tomography (PET) and single photon emission computed tomography (SPECT), radionuclide-labeled agents targeting Aβ plaques in the brain may greatly facilitate the diagnosis of AD.[11,12] Over the past 10 years, several agents for imaging Aβ plaques have been tested in humans (Figure 1). Pittsburgh compound B, 2-(4′-[$^{11}$C]methylaminophenyl)-6-hydroxybenzothiazole ([$^{11}$C]PIB), is, to date, the most widely used PET radioligand for amyloid imaging[13,14] and clearly distinguishes between AD and control cases. However, the short half-life of carbon-11 (20.4 min) limits the potential clinical use of this agent. Great efforts have been made to develop imaging agents labeled with a longer half-life isotope, fluorine-18 (109.4 min). An analogue of PIB, [$^{18}$F]-2-(3-fluoro-4-(methylamino)phenyl) benzo[*d*]thiazol-6-ol ([$^{18}$F]GE-067),[15] and the stilbene derivatives [$^{18}$F]-4-(*N*-methylamino)-4′-(2-(2-(2-fluoroethoxy)ethoxy) ethoxy)-stilbene ([$^{18}$F]BAY94-9172)[16] and [$^{18}$F]-(*E*)-4-(2-(6-(2-(2-(2-fluoroethoxy)ethoxy)ethoxy)pyridin-3-yl)vinyl)-*N*-methylaniline ([$^{18}$F]AV-45)[17,18] are under commercial development for the mapping of Aβ plaque burden in living brain tissue. In addition, [$^{123}$I]-6-iodo-2-(4′-dimethylamino-)phenyl-imidazo [1,2]pyridine ([$^{123}$I]IMPY)[19−21] is the first SPECT probe to be evaluated in humans. The preliminary clinical data showed a poor signal-to-noise ratio, making it difficult to distinguish AD patients. Currently, some research groups have continued to develop more useful probes for the SPECT imaging of cerebral Aβ plaques.[22−24]

Almost all of the agents evaluated in humans have been developed based on thioflavin T (ThT) and Congo Red (CR), dyes used for Aβ plaques in sections of AD brain. Aβ plaques are known to have various binding sites for ligands,[25] and numerous Aβ-binding compounds besides ThT and CR derivatives have been reported. The application of these new compounds to PET/SPECT imaging should contribute to the development of new probes with improved properties including higher affinity for Aβ plaques and less nonspecific binding in the white matter of the brain. Indeed, we have found that flavonoids such as

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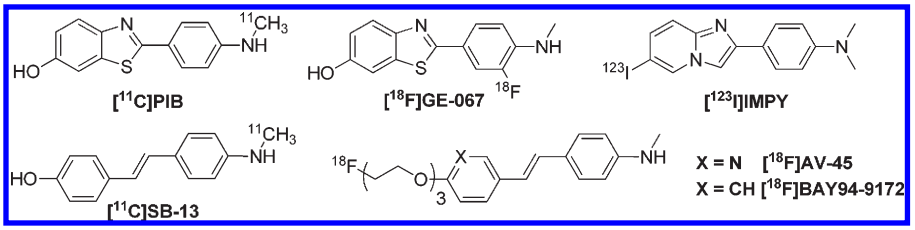
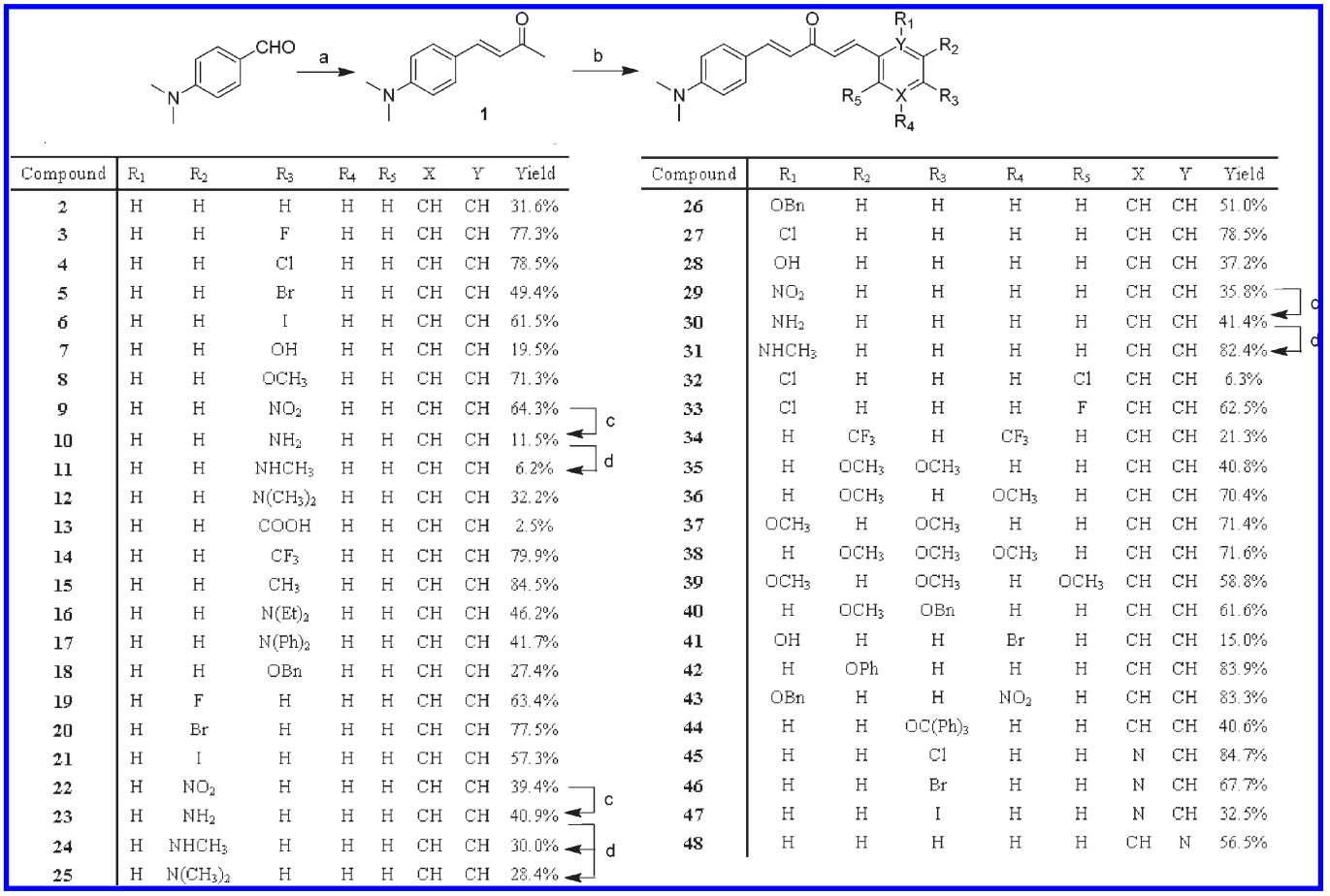



**Figure 1.** Chemical structure of A$\beta$ imaging probes used in clinical trials.

**Scheme 1**[a]



| Compound | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | X | Y | Yield |
|---|---|---|---|---|---|---|---|---|
| 2 | H | H | H | H | H | CH | CH | 31.6% |
| 3 | H | H | F | H | H | CH | CH | 77.3% |
| 4 | H | H | Cl | H | H | CH | CH | 78.5% |
| 5 | H | H | Br | H | H | CH | CH | 49.4% |
| 6 | H | H | I | H | H | CH | CH | 61.5% |
| 7 | H | H | OH | H | H | CH | CH | 19.5% |
| 8 | H | H | $OCH_3$ | H | H | CH | CH | 71.3% |
| 9 | H | H | $NO_2$ | H | H | CH | CH | 64.3% |
| 10 | H | H | $NH_2$ | H | H | CH | CH | 11.5% |
| 11 | H | H | $NHCH_3$ | H | H | CH | CH | 6.2% |
| 12 | H | H | $N(CH_3)_2$ | H | H | CH | CH | 32.2% |
| 13 | H | H | COOH | H | H | CH | CH | 2.5% |
| 14 | H | H | $CF_3$ | H | H | CH | CH | 79.9% |
| 15 | H | H | $CH_3$ | H | H | CH | CH | 84.5% |
| 16 | H | H | $N(Et)_2$ | H | H | CH | CH | 46.2% |
| 17 | H | H | $N(Ph)_2$ | H | H | CH | CH | 41.7% |
| 18 | H | H | OBn | H | H | CH | CH | 27.4% |
| 19 | H | F | H | H | H | CH | CH | 63.4% |
| 20 | H | Br | H | H | H | CH | CH | 77.5% |
| 21 | H | I | H | H | H | CH | CH | 57.3% |
| 22 | H | $NO_2$ | H | H | H | CH | CH | 39.4% |
| 23 | H | $NH_2$ | H | H | H | CH | CH | 40.9% |
| 24 | H | $NHCH_3$ | H | H | H | CH | CH | 30.0% |
| 25 | H | $N(CH_3)_2$ | H | H | H | CH | CH | 28.4% |

| Compound | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | X | Y | Yield |
|---|---|---|---|---|---|---|---|---|
| 26 | OBn | H | H | H | H | CH | CH | 51.0% |
| 27 | Cl | H | H | H | H | CH | CH | 78.5% |
| 28 | OH | H | H | H | H | CH | CH | 37.2% |
| 29 | $NO_2$ | H | H | H | H | CH | CH | 35.8% |
| 30 | $NH_2$ | H | H | H | H | CH | CH | 41.4% |
| 31 | $NHCH_3$ | H | H | H | H | CH | CH | 82.4% |
| 32 | Cl | H | H | H | Cl | CH | CH | 6.3% |
| 33 | Cl | H | H | H | F | CH | CH | 62.5% |
| 34 | H | $CF_3$ | H | $CF_3$ | H | CH | CH | 21.3% |
| 35 | H | $OCH_3$ | $OCH_3$ | H | H | CH | CH | 40.8% |
| 36 | H | $OCH_3$ | H | $OCH_3$ | H | CH | CH | 70.4% |
| 37 | $OCH_3$ | H | $OCH_3$ | H | H | CH | CH | 71.4% |
| 38 | H | $OCH_3$ | $OCH_3$ | $OCH_3$ | H | CH | CH | 71.6% |
| 39 | $OCH_3$ | H | $OCH_3$ | H | $OCH_3$ | CH | CH | 58.8% |
| 40 | H | $OCH_3$ | OBn | H | H | CH | CH | 61.6% |
| 41 | OH | H | H | Br | H | CH | CH | 15.0% |
| 42 | H | OPh | H | H | H | CH | CH | 83.9% |
| 43 | OBn | H | H | $NO_2$ | H | CH | CH | 83.3% |
| 44 | H | H | $OC(Ph)_3$ | H | H | CH | CH | 40.6% |
| 45 | H | H | Cl | H | H | N | CH | 84.7% |
| 46 | H | H | Br | H | H | N | CH | 67.7% |
| 47 | H | H | I | H | H | N | CH | 32.5% |
| 48 | H | H | H | H | H | CH | N | 56.5% |

[a] Reagents and conditions: (a) NaOH (1 M), acetone, room temperature. (b) NaOMe (28% in MeOH), EtOH, substituted benzaldehyde, room temperature. (c) $SnCl_2$, EtOH, HCl, reflux. (d) $K_2CO_3$, $CH_3I$, room temperature.

flavone,[26,27] chalcone,[28,29] and aurone[30,31] strongly bind to A$\beta$ plaques and applied them as new PET/SPECT probes (Figure 2). However, there is still a need for novel molecular scaffolds to serve in smart A$\beta$ probes. Furthermore, many basic scientific questions regarding how these small organic molecular probes attach to amyloid fibrils remain to be answered. Elucidation of the mode of binding between A$\beta$ aggregates and small ligands may enable the rational molecular design of more useful imaging probes in the future.

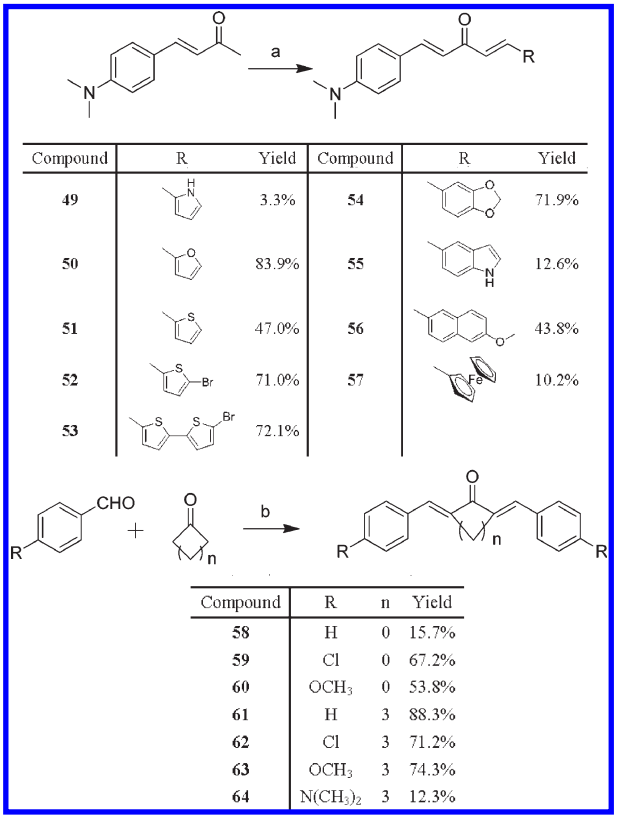
In 2006, Ryu et al. reported a [$^{18}$F]-fluoropropyl-substituted curcumin derivative, 1-[4-(3-[$^{18}$F]fluoropropoxy)-3-methoxyphenyl]-5-hydroxy-7-(4-hydroxy-3-methoxyphenyl)-1,4,6-heptatrien-3-one, as a specific A$\beta$ probe with high affinity (0.07 nM using [$^{125}$I]-1-iodo-2,5-bis(3-hydroxycarbonyl-4-methoxy)styrylbenzene ([$^{125}$I]IMSB) as the radiolabeled standard). However, its poor penetration of the brain together with instability in vivo hampered its potential clinical use (0.52% ID/g at 2 min and 0.11% ID/g at 30 min). Studies indicated that this derivative was quickly converted to an unidentified polar product, which cannot cross the blood−brain barrier (BBB).[32] Several papers demonstrated that the $\beta$-diketone moiety (methylene moiety) in the middle of curcumin's structure is responsible for the instability and poor pharmacokinetic profile under physiological conditions.[33] In addition, the decomposition of curcumin can occur as a result of exposure to light, a process also mediated by the active methylene moiety.[34,35]

To improve the pharmacokinetic profile of curcumin, modifications to the middle of the compound that lead to a dibenzylideneacetone structure lacking an active methylene

moiety and one carbonyl moiety but maintaining the two aromatic rings responsible for the binding of A$\beta$ plaques were explored. Such dibenzylideneacetone derivatives can be simply obtained by a one-pot reaction.

In the present study, a series of dibenzylideneacetones with various substitutents were synthesized and screened for A$\beta$ binding. We examined the possible structure−activity relationship (SAR) of these analogues using substitutions on the aryl rings, believing the SAR results would allow for a more rational design of ligands. Three radioiodinated and two $^{18}$F FPEG (fluoro-pegylated) derivatives with high affinity for A$\beta$ aggregates were evaluated in vitro and in vivo as potential probes for PET or SPECT.

**Scheme 2**[a]




| Compound | R | Yield | Compound | R | Yield |
|---|---|---|---|---|---|
| 49 | | 3.3% | 54 | | 71.9% |
| 50 | | 83.9% | 55 | | 12.6% |
| 51 | | 47.0% | 56 | | 43.8% |
| 52 | | 71.0% | 57 | | 10.2% |
| 53 | | 72.1% | | | |

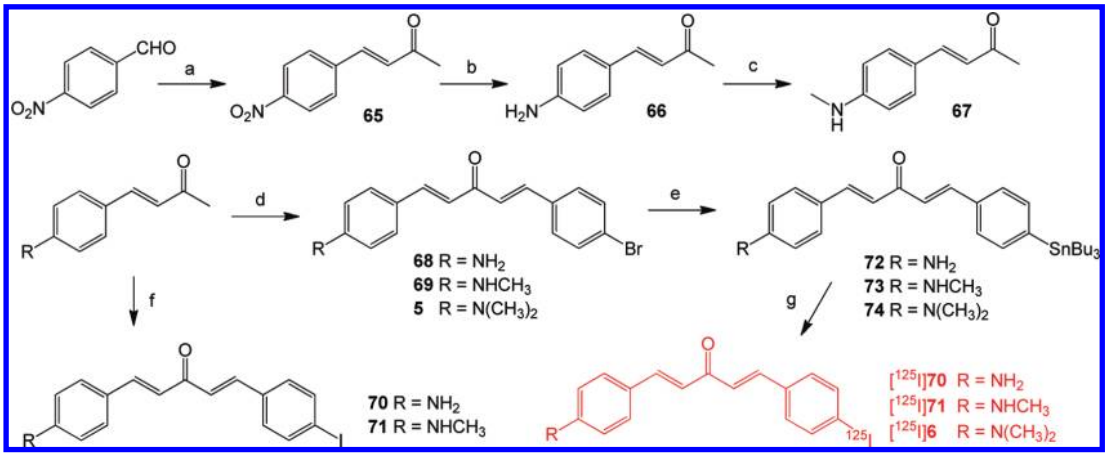
| Compound | R | n | Yield |
|---|---|---|---|
| 58 | H | 0 | 15.7% |
| 59 | Cl | 0 | 67.2% |
| 60 | $OCH_3$ | 0 | 53.8% |
| 61 | H | 3 | 88.3% |
| 62 | Cl | 3 | 71.2% |
| 63 | $OCH_3$ | 3 | 74.3% |
| 64 | $N(CH_3)_2$ | 3 | 12.3% |

[a] Reagents and conditions: (a) NaOMe (28% in MeOH), EtOH, substituted aromatic aldehyde, room temperature. (b) NaOMe (28% in MeOH), EtOH, room temperature.

## RESULTS AND DISCUSSION

**Chemistry and Radiochemistry.** The core structure of the dibenzylideneacetones was produced as shown in Schemes 1−3. The key step was the base-catalyzed Claisen condensation reaction starting from suitably substituted aromatic aldehydes and aliphatic ketones. The unsymmetrical dibenzylideneacetones (**2**−**9**, **12**−**22**, **26**−**29**, **32**−**57**, and **68**−**71**) were obtained in 3−85% yields, and the symmetric compounds (**58**−**64**) were obtained in 12−88% yields. The amino-substituted compounds **10**, **23**, **30**, and **66** were produced by reducing the nitro group using $SnCl_2$. Subsequent methylation of the amino group using methyl iodide afforded mono- or dimethylated derivatives (**11**, **24**, **25**, **31**, and **67**). The tributyltin precursors (**72**−**74**) were prepared from the corresponding bromo compounds (**5**, **68**, and **69**) in a bromo to tributyltin exchange reaction catalyzed by $(Ph_3P)_4Pd$ (yield, 22.9−30.2%). The FPEG dibenzylideneacetones **81**−**83** and **85** were prepared by the procedures shown in Schemes 4 and 5. To prepare compounds with different numbers of ethoxy units as the linkage, the dimethylated derivative **1** or monomethylated derivative **67** was coupled with the polyethyleneglycol-modified benzaldhyde to obtain **75**−**77** and **86**, respectively. For the dimethylated dibenzylideneacetone, tosylation of the free hydroxyl groups present in **75**−**77** afforded the precursor **78**−**80**, which readily reacted with anhydrous tetra-*n*-butylammonium fluoride (TBAF) at reflux to give the "cold" FPEG dibenzylideneacetones, **81**−**83** (Scheme 4). For the monomethylated dibenzylideneacetone, the hydroxy group in **86** was subsequently protected with *tert*-butyldimethylsilyl chloride (TBDMSCl) to give the TBS-protected compound **87**. Compound **88** was obtained by protecting the methylamino group of **87** with

**Scheme 3**[a]




[a] Reagents and conditions: (a) (1) $K_2CO_3$, acetone, room temperature; (2) HCl, room temperature. (b) $SnCl_2$, EtOH, HCl, reflux. (c) $K_2CO_3$, $CH_3I$, room temperature. (d) NaOMe (28% in MeOH), EtOH, 4-bromobenzaldehyde, room temperature. (e) $(Bu_3Sn)_2$, $(Ph_3P)_4Pd$, toluene, reflux. (f) NaOMe (28% in MeOH), EtOH, 4-iodobenzaldehyde, room temperature. (g) [$^{125}$I]NaI, HCl (1 M), $H_2O_2$ (3%).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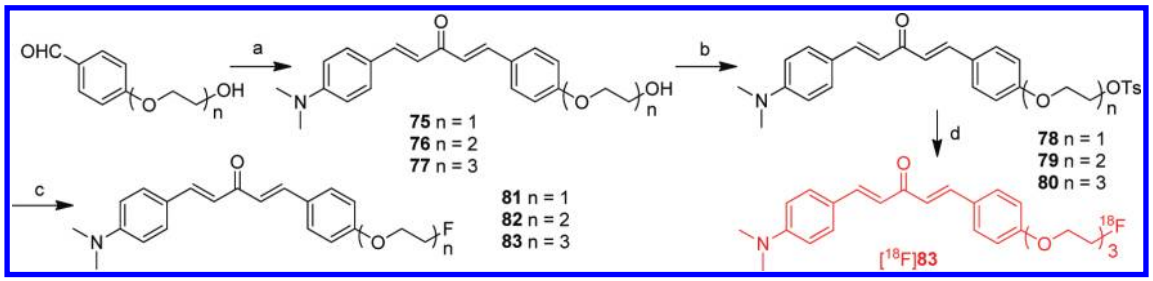
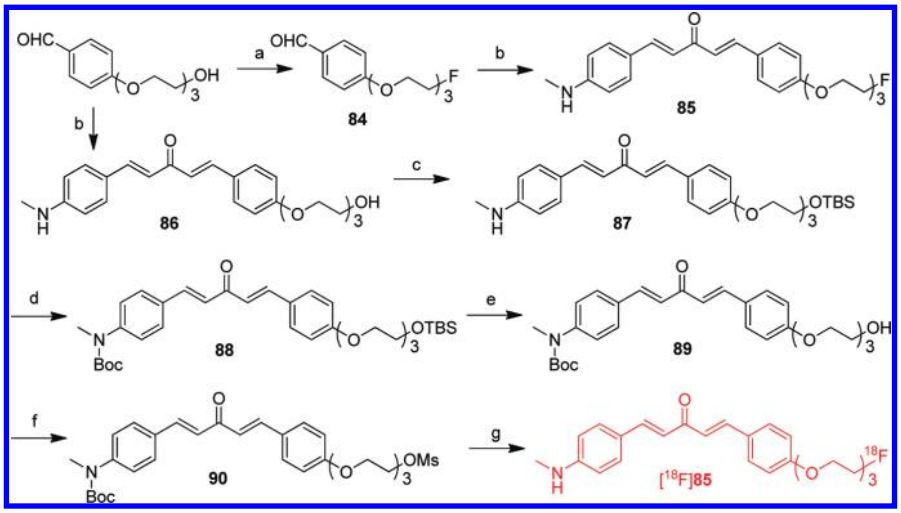
Scheme 4[a]




[a] Reagents and conditions: (a) NaOMe (28% in MeOH), EtOH, **1**, room temperature. (b) TsCl, pyridine, room temperature. (c) THF, TBAF (1 M), reflux. (d) $K_{222}$, $[^{18}F]^-$, DMSO, 120 °C.

Scheme 5[a]




[a] Reagents and conditions: (a) DAST, $CHCl_3$, −78 °C. (b) NaOMe (28% in MeOH), EtOH, **67**, room temperature. (c) TBDMSCl, imidazole, DCM, room temperature. (d) $(BOC)_2O$, THF, reflux. (e) THF, TBAF (1 M), reflux. (f) MsCl, $Et_3N$, DCM, room temperature. (g) (1) $K_{222}$, $[^{18}F]^-$, DMSO, 120 °C; (2) HCl (1 M), 120 °C.

butyloxycarbonyl (BOC). After removal of the TBS-protecting group of **88** with TBAF, the free hydroxyl group was converted into mesylates by reacting with methanesulfonyl chloride in the presence of triethylamine to give **89**. The "cold" fluorinated compound **85** was successfully obtained by stirring **67** and the FPEG benzaldhyde **84** in ethanol (Scheme 5).

The radioiodinated ligands $[^{125}I]$**6**, **70**, and **71** were prepared from the corresponding tributyltin precursors through an iodo-destannylation reaction using hydrogen peroxide as an oxidant with radiochemical yield of 27.6, 15.3, and 24.1%, respectively (Scheme 3). After purification by high-performance liquid chromatography (HPLC), the radiochemical purity of these radiotracers was greater than 98%. The specific activity of the no carrier-added preparation was comparable to that of $Na^{125}I$, 2200 Ci/mmol. Finally, the radiochemical identities of $[^{125}I]$**6**, **70**, and **71** were verified using HPLC by coinjection with the nonradioactive compounds. To make the desired $^{18}F$-labeled dibenzylideneacetone $[^{18}F]$**83**, the tosylate precursor **80** was mixed with $[^{18}F]$fluoride/potassium carbonate and Kryptofix 222 in dimethyl sulfoxide (DMSO) under heating at 120 °C for 5 min. The mixture was loaded on a Sep-Pak Plus-C18 cartridge (Waters), and the elution was purified by HPLC (radiochemical purity >98%, radiochemical yield 49%, decay corrected). For $[^{18}F]$**85**, the *N*-BOC-protected mesylate **90** was employed as the precursor. After 5 min at 120 °C, the mixture was treated with aqueous HCl to remove the *N*-BOC-protecting group. The crude product was purified by HPLC (radiochemical purity >98%, radiochemical yield 13%, decay corrected).

**SAR Analysis.** The affinity of these dibenzylideneacetone derivatives (**2**−**64**, **70**, **71**, **81**−**83**, and **85**) for $A\beta_{1-42}$ aggregates was examined with competition binding assays using $[^{125}I]$IMPY as the competing radioligand. IMPY and curcumin were also screened using the same system for comparison. The results are listed in Table 1. Dibenzylideneacetone (**58**) without any substituents showed moderate affinity ($K_i$ = 242.5 ± 42.8 nM). Introducing Cl or methoxy groups at the para position on both phenyl rings to form symmetrical ligands increased the binding (e.g., **59**, $K_i$ = 9.0 ± 1.2 nM; **60**, $K_i$ = 6.5 ± 1.2 nM), especially for **12** with two *N*,*N*-dimethylamino groups ($K_i$ = 2.7 ± 0.6 nM), whose affinity increased about 90-fold. As compared with **58**, **61** with a cyclohexanone spacer in the middle showed a decrease in affinity ($K_i$ = 704.3 ± 90.3 nM). A comparable increase in binding was also observed on introducing Cl (**62**, $K_i$ = 11.4 ± 0.8 nM), methoxy (**63**, $K_i$ = 24.8 ± 2.5 nM), or *N*,*N*-dimethylamino (**64**, $K_i$ = 1.0 ± 0.3 nM) groups for these symmetrical dibenzylidenecyclohexanones. These observations demonstrated again that the *N*,*N*-dimethylamino moiety plays a critical role in maintaining affinity for $A\beta$ aggregates.

**Table 1. Inhibition Constants ($K_i$, nM) for Binding to Aggregates of A$\beta_{1-42}$ versus [$^{125}$I]IMPY**

| compound | $K_i$ (nM)[a] | compound | $K_i$ (nM)[a] | compound | $K_i$ (nM)[a] |
|---|---|---|---|---|---|
| **2** | 1.2 ± 0.2 | **26** | 18.6 ± 8.1 | **50** | 8.5 ± 0.8 |
| **3** | 3.7 ± 0.9 | **27** | 0.9 ± 0.1 | **51** | 5.3 ± 0.5 |
| **4** | 1.1 ± 0.2 | **28** | 28.2 ± 5.1 | **52** | 3.8 ± 0.4 |
| **5** | 2.8 ± 0.5 | **29** | 18.8 ± 3.0 | **53** | 11.7 ± 1.1 |
| **6** | 0.9 ± 0.2 | **30** | 8.4 ± 3.0 | **54** | 1.8 ± 0.2 |
| **7** | 6.8 ± 1.6 | **31** | 2636.5 ± 140.8 | **55** | 4.2 ± 0.4 |
| **8** | 0.7 ± 0.1 | **32** | 18.5 ± 0.9 | **56** | 2.5 ± 0.2 |
| **9** | 5.2 ± 1.1 | **33** | 9.2 ± 1.0 | **57** | 21.1 ± 1.2 |
| **10** | 3.7 ± 0.4 | **34** | 4.0 ± 0.5 | **58** | 242.5 ± 42.8 |
| **11** | 2.9 ± 0.5 | **35** | 5.4 ± 0.9 | **59** | 9.0 ± 1.2 |
| **12** | 2.7 ± 0.6 | **36** | 4.7 ± 2.1 | **60** | 6.5 ± 1.2 |
| **13** | 78.1 ± 8.5 | **37** | 2.8 ± 0.8 | **61** | 704.3 ± 90.3 |
| **14** | 0.8 ± 0.2 | **38** | 5.2 ± 0.6 | **62** | 11.4 ± 0.8 |
| **15** | 1.3 ± 0.2 | **39** | 39.1 ± 4.8 | **63** | 24.8 ± 2.5 |
| **16** | 15.7 ± 3.9 | **40** | 4.1 ± 0.4 | **64** | 1.0 ± 0.3 |
| **17** | 131.2 ± 20.3 | **41** | 16.2 ± 5.1 | **70** | 7.0 ± 2.2 |
| **18** | 2.0 ± 0.2 | **42** | 3.8 ± 1.1 | **71** | 2.8 ± 0.5 |
| **19** | 1.2 ± 0.1 | **43** | 33.3 ± 3.8 | **81** | 5.6 ± 2.5 |
| **20** | 1.9 ± 0.3 | **44** | 2.8 ± 0.4 | **82** | 4.4 ± 1.3 |
| **21** | 5.5 ± 1.7 | **45** | 2.2 ± 0.3 | **83** | 6.9 ± 1.4 |
| **22** | 4.0 ± 1.4 | **46** | 2.3 ± 0.1 | **85** | 8.6 ± 1.3 |
| **23** | 13.7 ± 3.4 | **47** | 4.8 ± 1.3 | IMPY | 10.5 ± 1.0 |
| **24** | 8.1 ± 1.4 | **48** | 23.0 ± 1.6 | curcumin | 49.8 ± 8.0 |
| **25** | 8.0 ± 0.6 | **49** | 5.8 ± 1.2 | | 0.20 ± 0.06[b] |

[a] Measured in triplicate with results given as the mean ± SD. [b] Data from ref 32.

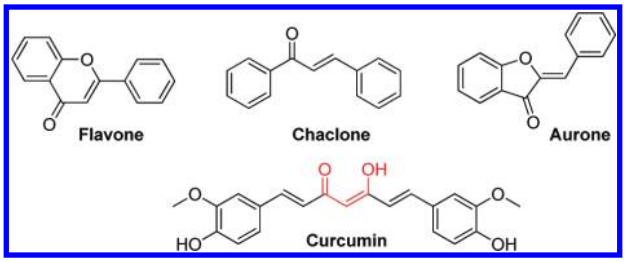



**Figure 2.** New backbone structures as A$\beta$ imaging probes.

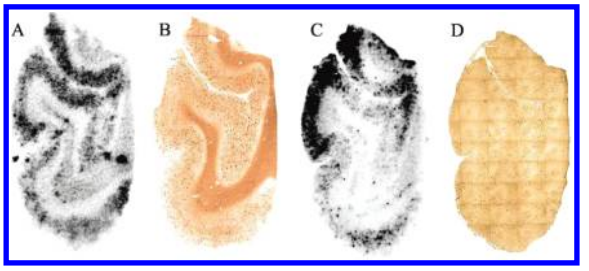



**Figure 3.** Autoradiography of [$^{125}$I]**6** and [$^{125}$I]**70** in vitro in AD brain sections (temporal lobe) (A and C). The presence and distribution of plaques in the sections were confirmed with immunohistochemical staining using a monoclonal A$\beta$ antibody (B and D).

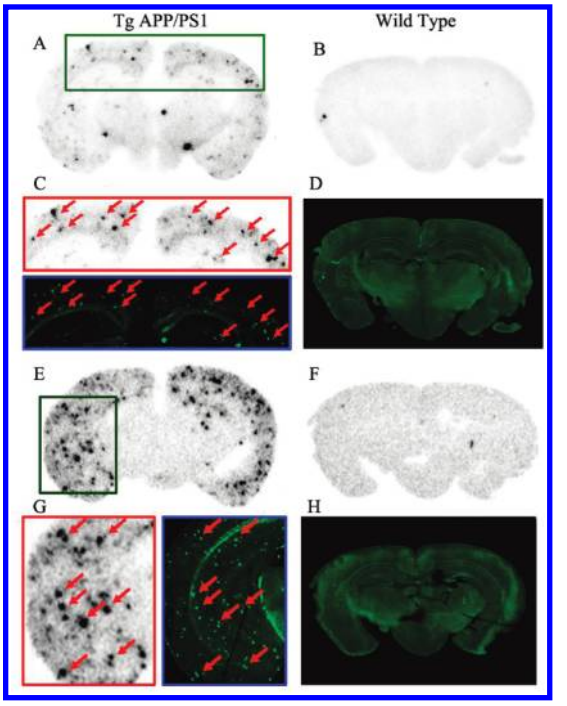



**Figure 4.** Autoradiography of [$^{18}$F]**83** and [$^{18}$F]**85** in vitro in Tg model mouse (C57BL6-APP/PS1, 12 months old, male) brain sections (A and E) and control sections (B and F). The presence and distribution of plaques in the sections were confirmed with thioflavin-S (C and G). Arrows show the correspondence to A$\beta$ plaques.

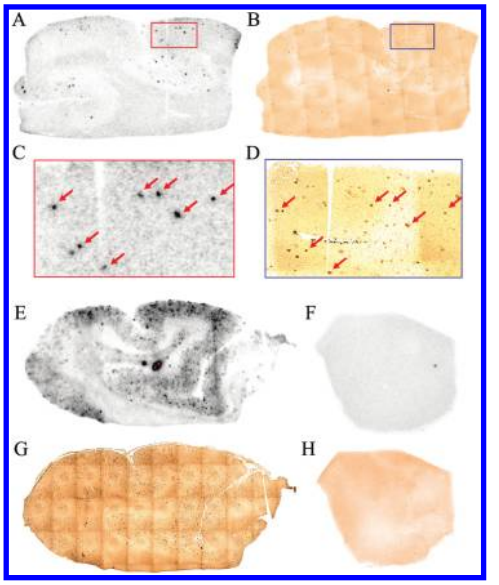



**Figure 5.** Autoradiography of [$^{18}$F]**83** and [$^{18}$F]**85** in vitro in AD brain sections and control sections (temporal lobe) (A, C, E, and F). The presence and distribution of plaques in the sections were confirmed with immunohistochemical staining using a monoclonal A$\beta$ antibody (B, D, and G).

An extensive set of unsymmetrical dibenzylideneacetones with a *N*,*N*-dimethylamino group were synthesized. In general, the methylation of a primary amino group to form a secondary amino or tertiary amino group increased the affinity [e.g., **6** > **71** > **70** (para position); **12** > **11** > **10** (para position); **25** > **24** > **23**

Table 2. Biodistribution of in ddY Normal Mice after iv Injections of [$^{125}$I]Tracers (% ID/g, Mean ± SD, $n$ = 4)

| organ | 2 min | 15 min | 30 min | 60 min | 120 min |
|---|---|---|---|---|---|
| | | [$^{125}$I]**6** (Log $D$ = 3.66 ± 0.09) | | | |
| blood | 11.62 ± 1.22 | 6.58 ± 2.15 | 3.98 ± 0.28 | 2.16 ± 0.55 | 2.29 ± 0.65 |
| brain | 1.59 ± 0.04 | 1.11 ± 0.28 | 0.63 ± 0.03 | 0.28 ± 0.03 | 0.26 ± 0.07 |
| heart | 6.42 ± 0.80 | 2.69 ± 0.85 | 1.62 ± 0.20 | 1.03 ± 0.24 | 1.19 ± 0.17 |
| liver | 44.64 ± 6.19 | 32.80 ± 5.01 | 24.64 ± 2.85 | 11.54 ± 0.60 | 16.47 ± 1.38 |
| spleen | 11.59 ± 1.10 | 9.94 ± 2.07 | 12.26 ± 3.95 | 6.28 ± 2.87 | 7.34 ± 0.67 |
| lung | 24.45 ± 1.67 | 12.97 ± 3.05 | 6.91 ± 1.32 | 3.64 ± 0.47 | 3.35 ± 0.12 |
| kidney | 15.86 ± 1.37 | 22.23 ± 5.52 | 15.63 ± 1.71 | 7.00 ± 2.62 | 8.55 ± 1.98 |
| stomach[a] | 1.16 ± 0.15 | 1.75 ± 0.15 | 1.85 ± 0.27 | 0.61 ± 0.24 | 0.77 ± 0.29 |
| intestine | 1.38 ± 0.38 | 7.38 ± 2.75 | 11.62 ± 3.42 | 7.68 ± 2.53 | 17.65 ± 2.91 |
| thyroid | 11.56 ± 2.61 | 14.93 ± 1.09 | 26.77 ± 1.41 | 23.53 ± 6.25 | 32.22 ± 1.13 |
| | | [$^{125}$I]**71** (Log $D$ = 3.55 ± 0.02) | | | |
| blood | 7.48 ± 0.81 | 6.02 ± 1.80 | 4.84 ± 1.40 | 3.35 ± 0.90 | 4.46 ± 0.92 |
| brain | 4.68 ± 0.25 | 2.62 ± 0.22 | 1.38 ± 0.23 | 0.71 ± 0.06 | 0.54 ± 0.09 |
| heart | 8.11 ± 1.74 | 4.14 ± 1.36 | 3.29 ± 1.42 | 1.74 ± 0.73 | 1.91 ± 0.60 |
| liver | 39.22 ± 4.48 | 40.83 ± 4.21 | 23.88 ± 4.99 | 22.63 ± 3.73 | 27.83 ± 2.15 |
| spleen | 4.57 ± 0.55 | 3.36 ± 0.14 | 2.22 ± 0.94 | 1.52 ± 0.38 | 1.23 ± 0.23 |
| lung | 9.67 ± 1.12 | 7.42 ± 2.95 | 6.18 ± 2.58 | 3.50 ± 0.70 | 3.90 ± 0.73 |
| kidney | 14.73 ± 2.23 | 16.49 ± 3.52 | 15.54 ± 5.56 | 10.46 ± 2.92 | 13.43 ± 4.53 |
| stomach[a] | 3.26 ± 1.37 | 3.82 ± 0.67 | 3.17 ± 0.97 | 3.34 ± 0.93 | 4.49 ± 0.82 |
| intestine | 3.53 ± 1.19 | 10.33 ± 4.30 | 13.19 ± 5.85 | 23.62 ± 3.87 | 41.29 ± 9.04 |
| thyroid | 18.20 ± 2.65 | 28.09 ± 4.45 | 27.78 ± 10.74 | 23.96 ± 3.78 | 72.93 ± 10.03 |
| | | [$^{125}$I]**70** (Log $D$ = 3.26 ± 0.05) | | | |
| blood | 3.89 ± 0.34 | 4.93 ± 1.91 | 4.12 ± 0.33 | 1.72 ± 0.58 | 2.52 ± 0.19 |
| brain | 4.56 ± 0.42 | 2.37 ± 0.32 | 1.36 ± 0.19 | 0.54 ± 0.12 | 0.40 ± 0.07 |
| heart | 7.06 ± 1.37 | 3.45 ± 0.59 | 2.01 ± 0.30 | 0.83 ± 0.17 | 1.11 ± 0.09 |
| liver | 16.98 ± 2.29 | 29.08 ± 4.93 | 24.17 ± 4.15 | 16.43 ± 2.32 | 17.57 ± 1.63 |
| spleen | 2.80 ± 0.15 | 2.02 ± 0.41 | 1.79 ± 0.17 | 0.80 ± 0.14 | 1.13 ± 0.39 |
| lung | 9.25 ± 1.09 | 6.06 ± 1.18 | 4.81 ± 0.43 | 2.43 ± 0.76 | 2.82 ± 0.16 |
| kidney | 11.20 ± 0.10 | 22.81 ± 3.42 | 16.31 ± 1.81 | 9.00 ± 1.67 | 9.52 ± 0.79 |
| stomach[a] | 1.37 ± 0.37 | 3.10 ± 2.24 | 3.12 ± 0.92 | 2.12 ± 0.62 | 3.07 ± 0.58 |
| intestine | 2.27 ± 0.17 | 6.90 ± 2.44 | 10.85 ± 3.68 | 25.97 ± 4.93 | 25.70 ± 1.48 |
| thyroid | 8.64 ± 2.19 | 8.39 ± 0.51 | 11.49 ± 3.53 | 14.14 ± 4.83 | 21.98 ± 3.75 |

[a] Expressed as % injected dose per organ.

(meta position)], which is consistent with previous data on primary, secondary, and tertiary amino ligands.[12,36] In contrast, methylation of the amino group at the ortho position reduced the binding affinity dramatically [e.g., **31** ($K_i$ = 2636.5 ± 140.8 nM) ≫ **30** ($K_i$ = 8.4 ± 3.0 nM)], which we will discuss later.

Increasing the size of the substituent at the para position does not affect the affinity for A$\beta$ aggregates. The ligands **18** and **40** with a benzyloxy group showed $K_i$ values of 2.0 ± 0.2 and 4.1 ± 0.4 nM, respectively, and **44** with a bulky trityloxy group also showed high affinity ($K_i$ = 2.8 ± 0.4 nM). These results show high tolerance for steric bulk at this position. For the purpose of developing PET or SPECT agents targeting A$\beta$ plaques, this finding regarding the dibenzylideneacetone scaffold is important. For example, a large chelating structure is necessary for technetium-99 m, and a long polyethylene glycol chain is adapted in the design of fluorine-18.[18,37,38] Indeed, the FPEG ligands **81**−**83** and **85** with different numbers of polyethylene glycol units ($n$ = 1−3) all show excellent affinity ($K_i$ < 10 nM), and the length of the linkage did not bring about an appreciable change in the binding properties. Interestingly, increasing the size of the substutient at the aromatic amino group decreased the binding affinity, as reflected in **16** with a *N*,*N*-diethylamino group ($K_i$ = 15.7 ± 3.9 nM) and **17** with a *N*,*N*-diphenylamino group ($K_i$ = 131.2 ± 20.3 nM).

The ligands with both electron-withdrawing substituents [e.g., F (**3** and **19**), $NO_2$ (**9** and **22**), and $CF_3$ (**14**)] and electron-donating substituents [e.g., $OCH_3$ (**8**) and $N(CH_3)_2$ (**12** and **25**)] at the para or meta position showed high affinity for A$\beta$ aggregates, except for **13** with a carboxyl group ($K_i$ = 78.1 ± 8.5 nM). Tolerance for steric bulk at the meta position was also observed, as the binding was not affected when different substituents were introduced [e.g., 3,5-$(CF_3)_2$ (**34**), 3,5-$(OCH_3)_2$ (**36**), and 3-phenoxy (**42**)]. In comparison, ligands with substituents at the ortho position showed less affinity for A$\beta$ aggregates ($K_i$ > 8 nM, e.g., **26**, **28**−**33**, **39**, **41**, and **43**) except for **27**. This may be due to the steric effects that arise between the ortho subsituents and the hydrogen atom on the carbon−carbon double bond, and the coplanar geometry of the conjugation $\pi$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system may be disrupted. As compared with **30**, the analogue with a *N*-methylamino group at the ortho position (**31**) exhibited greater steric effects, resulting in a loss of affinity.

When a phenyl ring in the dibenzylideneacetone structure is changed to a heterocyclic ring, such as a thiophene, furan, pyridine, or pyrrole ring, the ligands also show high affinity, as reflected in **44**−**55**. Use of a naphthalenyl group instead of the phenyl group (**56**) had little effect on binding affinity, consistent with the proposed $\pi-\pi$ interaction between ligands and A$\beta$ fibers. There are distinct binding sites for CR and ThT on A$\beta$ aggregates, which were clearly differentiated by Kung et al.[39] These two ligands did not inhibit each other, indicating that the two sites on A$\beta$ aggregates are nonoverlapping.

A previous study using [$^{125}$I]IMSB as the radioligand showed that curcumin derivatives bound to A$\beta$ aggregates at the CR site (curcumin, $K_i = 0.20 \pm 0.06$ nM; fluoropropyl-curcumin, $K_i = 0.07 \pm 0.01$).[32] However, in the present study, most of the dibenzylideneacetone ligands inhibited the binding of [$^{125}$I]IMPY to A$\beta_{1-42}$ aggregates, indicating that they attach at the ThT-binding site. We consider the distance between the two phenyl rings important to the selection of the binding site. After removal of the active methylene moiety and one carbonyl moiety in the middle of curcumin, the distance between the two phenyl rings decreases, resulting in a change of the binding site.

**Biological Evaluation.** As compared with the binding of IMPY to A$\beta_{1-42}$ aggregates ($K_i$ = 10.5 nM), the affinity of iodinated compounds (**71**, **70**, and **6**) with primary, secondary, and tertiary amine groups and FPEG compounds (**83** and **85**, $n = 3$) was superior, and these compounds were evaluated further. The binding of these radiolabeled tracers to A$\beta$ plaques in sections of brain tissue from AD patients or transgenic (Tg) model mice (APP/PS1) was evaluated by in vitro autoradiography. As shown in Figure 3A,C, two of the radioiodinated probes (**6** and **71**) exhibited intensive labeling of plaques showing a strong signal in the cortex region and a low background level in white matter in the AD brain sections. The hot spots of radioactivity were consistent with the results of immunohistochemical staining in vitro in the same sections using the A$\beta$ antibody BC05 (Figure 3B,D). Autoradiographic studies of the two $^{18}$F FPEG probes (**83** and **85**) were first performed with sections from Tg mice. Both ligands showed effective labeling of plaques and minimal background labeling (Figure 4A,E). The control cases were clearly void of any notable A$\beta$ labeling (Figure 4B,F). The same sections were also stained with thioflavin-S, and the distribution of A$\beta$ plaques perfectly accorded with the results of autoradiography (Figure 4C,G, red arrows). Autoradiographic studies of [$^{18}$F]**83** and [$^{18}$F]**85** were then performed with AD brain sections. As shown in Figure 5A,E, specific labeling of plaques was observed. Immunohistochemical staining confirmed the prescence of plaques in the sections (Figure 5B,D,G).

The lipophilicity (log *D*) of the radiolabeled tracers ([$^{125}$I]**6**, [$^{125}$I]**70**, [$^{125}$I]**71**, [$^{18}$F]**83**, and [$^{18}$F]**85**) measured under experimental conditions showed relatively high partition coefficients (log $D = 2.97-3.66$), a reflection of the lipophilic properties of these probes. Biodistribution experiments were performed in normal mice with these radiolabeled tracers. As shown in Tables 2 and 3, [$^{125}$I]**70** [$^{125}$I]**71**, [$^{18}$F]**83**, and [$^{18}$F]**85**, but not [$^{125}$I]**6**, exhibited good initial penetration of the BBB with excellent initial uptake in the brain (4.56, 4.68, 4.13, and 5.15% ID/g at 2 min, respectively). As compared with a previously reported radiofluorinated curcumin (0.52% ID/g at 2 min), these dibenzylideneacetones showed greatly improved uptake into the brain, suggesting them to have more suitable pharmacokinetic properties for imaging A$\beta$ in AD brains. Because there are no plaques to cause the retention of A$\beta$-specific probes, the high uptake was subsequently followed by a fast washout (0.54, 0.71, 0.90, and 1.27% ID/g at 60 min). The tracer [$^{125}$I]**6** with a *N*, *N*-dimethylamino group showed a lower uptake at 2 min (1.59% ID/g), indicating low penetration of the intact BBB. Relatively high lipophilicity was observed for [$^{125}$I]**6** (log $D = 3.66 \pm 0.09$), and this disparity may account for the lower brain uptake and high blood uptake. The ratio brain$_{2\ min}$/brain$_{60\ min}$ is considered an important index with which to select tracers with appropriate kinetics in vivo. The five radiolabeled dibenzylideneacetone probes showed brain$_{2\ min}$/brain$_{60\ min}$ ratios of 5.68, 8.44, 6.59, 4.59, and 4.06 for [$^{125}$I]**6**, [$^{125}$I]**70**, [$^{125}$I]**71**, [$^{18}$F]**83**, and [$^{18}$F]**85**, respectively. As compared with [$^{18}$F]AV-45 (3.90), the two $^{18}$F FPEG probes [$^{18}$F]**83** and [$^{18}$F]**85** had superior brain$_{2\ min}$/brain$_{60\ min}$ ratios. Accordingly, they may have better signal-to-noise ratios and therefore may be better for detecting A$\beta$ plaques. Additionally, the thyroid uptake of the three radioiodinated probes ([$^{125}$I]**6**, [$^{125}$I]**70**, and [$^{125}$I]**71**) reached 14−24% ID/g at 1 h postinjection, which indicated deiodination in vivo. The defluorination, as reflected by bone uptake, for the two radiofluorinated probes ([$^{18}$F]**83** and [$^{18}$F]**85**) was low (2.33 and 2.54% ID/g at 1 h). As can be expected from the relatively high log *D* values, these radiolabeled tracers were cleared from plasma predominantly by the hepatobiliary system (ranging from 14.1 to 24.6% ID/g in liver and at 30 min pi). The hepatobiliar excretion to the intestines was also rather fast, and radioactivity was observed to accumulate within the intestine at later time points (ranging from 17.6 to 26.3% ID/g at 60 min pi). Also, a moderate uptake of these tracers was observed in the

**Table 3. Biodistribution of [$^{18}$F]83 and [$^{18}$F]85 in ddY Normal Mice (% ID/g, Mean ± SD, $n = 4$)**

| organ | 2 min | 15 min | 30 min | 60 min |
|---|---|---|---|---|
| | [$^{18}$F]**83** (Log $D = 2.97 \pm 0.12$) | | | |
| brain | 4.13 ± 0.41 | 1.51 ± 0.17 | 1.04 ± 0.23 | 0.90 ± 0.14 |
| blood | 5.38 ± 0.32 | 3.89 ± 0.36 | 2.46 ± 0.54 | 1.60 ± 0.17 |
| bone | 2.88 ± 0.37 | 2.42 ± 0.14 | 2.08 ± 0.54 | 2.33 ± 0.30 |
| liver | 22.32 ± 3.12 | 24.41 ± 3.34 | 14.07 ± 1.94 | 6.88 ± 1.51 |
| kidney | 12.95 ± 0.79 | 12.77 ± 2.42 | 7.13 ± 2.64 | 3.67 ± 0.85 |
| spleen | 4.26 ± 1.05 | 6.19 ± 1.06 | 4.46 ± 0.80 | 1.93 ± 0.67 |
| stomach[a] | 6.28 ± 5.75 | 7.39 ± 1.87 | 6.00 ± 1.14 | 3.98 ± 1.52 |
| intestine | 4.12 ± 0.48 | 10.53 ± 2.11 | 17.50 ± 4.47 | 21.57 ± 7.37 |
| lung | 12.30 ± 1.99 | 6.34 ± 0.88 | 3.38 ± 0.43 | 1.86 ± 0.25 |
| heart | 7.60 ± 1.32 | 3.33 ± 0.35 | 1.90 ± 0.26 | 1.47 ± 0.13 |
| | [$^{18}$F]**85** (Log $D = 3.08 \pm 0.05$) | | | |
| brain | 5.15 ± 0.17 | 1.89 ± 0.17 | 1.35 ± 0.19 | 1.27 ± 0.12 |
| blood | 7.44 ± 1.22 | 7.99 ± 0.34 | 4.68 ± 0.59 | 3.59 ± 0.93 |
| bone | 2.97 ± 0.35 | 2.93 ± 0.37 | 2.94 ± 0.91 | 2.54 ± 0.84 |
| liver | 24.15 ± 5.77 | 30.09 ± 4.43 | 19.24 ± 3.64 | 14.07 ± 1.87 |
| kidney | 16.48 ± 2.51 | 14.15 ± 0.98 | 11.51 ± 1.76 | 9.43 ± 1.50 |
| spleen | 5.39 ± 1.79 | 6.62 ± 0.42 | 5.44 ± 1.24 | 5.35 ± 2.06 |
| stomach[a] | 3.26 ± 0.63 | 2.61 ± 0.18 | 1.93 ± 0.33 | 1.28 ± 0.49 |
| intestine | 6.58 ± 0.89 | 12.82 ± 3.23 | 24.34 ± 3.83 | 26.26 ± 3.57 |
| lung | 12.19 ± 2.31 | 11.77 ± 1.94 | 7.43 ± 1.03 | 5.44 ± 1.45 |
| heart | 10.55 ± 1.10 | 7.64 ± 1.23 | 5.67 ± 0.72 | 5.14 ± 0.88 |

[a] Expressed as % injected dose per organ.

kidneys, indicating that they too were excreted via the renal system.

## CONCLUSIONS

In conclusion, a new series of novel dibenzylideneacetone derivatives, containing various substituents, were successfully prepared as a new backbone structure for A$\beta$ imaging agents. Most of them displayed excellent affinity for A$\beta$ aggregates ($K_i$ in the nM range). The SAR study described above indicated that the introduction of a substituted group at the ortho position reduced or abolished the binding. However, the para position was highly tolerant of steric bulk substitutions, which opens up the possibility of developing new, easily labeled radioligands for imaging A$\beta$ plaques in vivo. Furthermore, the radiolabeled probes showed good penetration and fast washout in the mouse brain. A specific plaque-labeling signal was clearly demonstrated for these probes in Tg mouse brain sections as well as postmortem AD brain sections. Taken together, the present results suggest that these novel dibenzylideneacetones may be useful probes for the diagnosis of AD. Additional chemical modifications of the dibenzylideneacetone structure may lead to more useful A$\beta$ imaging agents for both PET and SPECT.

## EXPERIMENTAL SECTION

All of the chemicals used were commercial products employed without further purification. The $^1$H NMR spectra were obtained at 400 MHz on Jeol JNM-AL400 NMR spectrometers in $CDCl_3$ solutions at room temperature with TMS as an internal standard. Chemical shifts are reported as $\delta$ values relative to the internal TMS. Coupling constants are reported in Hertz. Multiplicity is defined by s (singlet), d (doublet), t (triplet), and m (multiplet). Mass spectra were acquired with a Shimadzu GC-MS-QP2010 Plus (ESI). HPLC was performed with a Shimadzu system (a LC-20AT pump with a SPD-20A UV detector, $\lambda$ = 254 nm) using a column of Cosmosil C18 (Nakalai Tesque, 5$C_{18}$-AR-II, 4.6 mm × 150 mm or 10 mm × 150 mm) and acetonitrile/water as the mobile phase. Fluorescence was observed with a Nikon Eclipse 80i microscope equipped with a BV-2A filter set (excitation, 400−440 nm; diachronic mirror, 455 nm; and long pass filter, 470 nm). The purity of the synthesized compounds was determined using analytical HPLC and was found to be more than 95%.

**Chemistry.** *General Procedure A: Preparation of Compounds* ***2*****−****9***, ***12*****−****22***, ***26*****−****29***, *and* ***32*****−****48***. To a solution of **1** (1−2 mmol) and substitued aromatic aldehydes (1−2 mmol) in 20 mL of ethanol was added 0.2 mL of NaOMe (28% in methanol). The reaction mixture was stirred for 12 h at room temperature. The precipitate was collected by filtration, washed with water and hexane, and recrystallized from ethanol or purified by silica gel chromatography to afford the final products.

*General Procedure B: Preparation of Compounds* ***10***, ***23***, *and* ***30***. A mixture of nitro compounds (1−2 mmol) and $SnCl_2$ (2−4 mmol) dissolved in 20 mL of ethanol containing 4 mL of concentrated hydrochloric acid was stirred under reflux for 2 h. After the mixture had cooled to room temperature, 2 M NaOH (50 mL) was added and extracted with ethyl acetate (100 mL). The organic layer was dried over $Na_2SO_4$. The solvent was removed, and the residue was purified by silica gel chromatography to afford the final products.

*General Procedure C: Preparation of Compounds* ***11***, ***24***, ***25***, *and* ***31***. To a solution of amino compounds (1−2 mmol) and $K_2CO_3$ (1−2 mmol) in 20 mL of acetone was added $CH_3I$ (2−4 mmol) dropwise, and the reaction mixture was stirred for 8 h at room temperature. After evaporation, the solvent was removed, and the residue was purified by silica gel chromatography to afford the final products.

*(E)-4-(4-(Dimethylamino)phenyl)but-3-en-2-one (**1**).* To a solution of 4-(dimethylamino)benzaldehyde (14.92 g, 100 mmol) in 300 mL of acetone was added 10 mL of NaOH (1 M), and the reaction mixture was stirred for 12 h at room temperature. The solvent was concentrated to 100 mL, 300 mL of water was added, and the yellow crystal that formed was collected by filtration, washed with water and cold hexane, and then dried under vacuum to obtain 13.70 g of **1** (72.5%). $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 7.46 (d, $J$ = 16.1 Hz, 1H), 7.44 (d, $J$ = 9.0 Hz, 2H), 6.68 (d, $J$ = 8.9 Hz, 2H), 6.55 (d, $J$ = 16.1 Hz, 1H), 3.03 (s, 6H), 2.34 (s, 3H). MS (ESI): $m/z$ calcd for $C_{12}H_{15}NO$, 189.12; found, 190.10 ($M + H^+$).

*(1E,4E)-1-(4-(Dimethylamino)phenyl)-5-phenylpenta-1,4-dien-3-one (**2**).* Compound **2** was prepared following general procedure A. Yield, 31.6%. $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 7.73 (d, $J$ = 15.8 Hz, 1H), 7.71 (d, $J$ = 15.9 Hz, 1H), 7.62 (dd, $J$ = 7.5, 2.0 Hz, 2H), 7.53 (d, $J$ = 8.9 Hz, 2H), 7.45−7.33 (m, 3H), 7.10 (d, $J$ = 15.9 Hz, 1H), 6.89 (d, $J$ = 15.8 Hz, 1H), 6.70 (d, $J$ = 8.9 Hz, 2H), 3.05 (s, 6H). MS (ESI): $m/z$ calcd for $C_{19}H_{19}NO$ 277.15; found 278.15 ($M + H^+$).

*(1E,4E)-1-(4-(Dimethylamino)phenyl)-5-(4-fluorophenyl)penta-1,4-dien-3-one (**3**).* Compound **3** was prepared following general procedure A. Yield, 77.3%. $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 7.74 (d, $J$ = 15.8 Hz, 1H), 7.69 (d, $J$ = 15.9 Hz, 1H), 7.62 (dd, $J$ = 8.7, 5.4 Hz, 2H), 7.54 (d, $J$ = 8.9 Hz, 2H), 7.11 (t, $J$ = 8.6 Hz, 2H), 7.04 (d, $J$ = 15.9 Hz, 1H), 6.88 (d, $J$ = 15.7 Hz, 1H), 6.72 (d, $J$ = 8.9 Hz, 2H), 3.06 (s, 6H). MS (ESI): $m/z$ calcd for $C_{19}H_{18}FNO$ 295.14; found 296.15 ($M + H^+$).

*(1E,4E)-1-(4-Chlorophenyl)-5-(4-(dimethylamino)phenyl)penta-1, 4-dien-3-one (**4**).* Compound **4** was prepared following general procedure A. Yield, 78.5%. $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 7.72 (d, $J$ = 15.7 Hz, 1H), 7.65 (d, $J$ = 15.9 Hz, 1H), 7.54 (d, $J$ = 8.2 Hz, 2H), 7.52 (d, $J$ = 8.6 Hz, 2H), 7.37 (d, $J$ = 8.5 Hz, 2H), 7.06 (d, $J$ = 15.9 Hz, 1H), 6.85 (d, $J$ = 15.8 Hz, 1H), 6.69 (d, $J$ = 8.9 Hz, 2H), 3.05 (s, 6H). MS (ESI): $m/z$ calcd for $C_{19}H_{18}ClNO$, 311.11; found, 312.10 ($M + H^+$).

*(1E,4E)-1-(4-Bromophenyl)-5-(4-(dimethylamino)phenyl)penta-1, 4-dien-3-one (**5**).* Compound **5** was prepared following general procedure A. Yield, 49.4%. $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 7.72 (d, $J$ = 15.7 Hz, 1H), 7.63 (d, $J$ = 15.9 Hz, 1H), 7.55−7.50 (m, 4H), 7.47 (d, $J$ = 8.5 Hz, 2H), 7.08 (d, $J$ = 15.8 Hz, 1H), 6.86 (d, $J$ = 15.7 Hz, 1H), 6.70 (d, $J$ = 8.8 Hz, 2H), 3.05 (s, 6H). MS (ESI): $m/z$ calcd for $C_{19}H_{18}BrNO$, 355.06; found, 356.05 ($M + H^+$).

*(1E,4E)-1-(4-(Dimethylamino)phenyl)-5-(4-iodophenyl)penta-1, 4-dien-3-one (**6**).* Compound **6** was prepared following general procedure A. Yield, 61.5%. $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 7.76 (d, $J$ = 8.4 Hz, 2H), 7.74 (d, $J$ = 15.8 Hz, 1H), 7.63 (d, $J$ = 15.8 Hz, 1H), 7.54 (d, $J$ = 8.9 Hz, 2H), 7.35 (d, $J$ = 8.5 Hz, 2H), 7.11 (d, $J$ = 15.9 Hz, 1H), 6.88 (d, $J$ = 15.7 Hz, 1H), 6.72 (d, $J$ = 8.9 Hz, 2H), 3.07 (s, 6H). HRMS (EI): $m/z$ ($EI^+$): calcd for $C_{19}H_{18}INO$, 403.0433; found, 403.0426 ($M + H^+$).

*(1E,4E)-1-(4-(Dimethylamino)phenyl)-5-(4-hydroxyphenyl)penta-1, 4-dien-3-one (**7**).* Compound **7** was prepared following general procedure A. Yield, 19.5%. $^1$H NMR (400 MHz, $CD_3OD$): $\delta$ 7.72 (d, $J$ = 16.3 Hz, 1H), 7.67 (d, $J$ = 16.4 Hz, 1H), 7.56 (d, $J$ = 8.8 Hz, 4H), 7.05 (d, $J$ = 15.8 Hz, 1H), 6.97 (d, $J$ = 15.7 Hz, 1H), 6.83 (d, $J$ = 8.6 Hz, 2H), 6.76 (d, $J$ = 9.0 Hz, 2H), 3.03 (s, 6H). MS (ESI): $m/z$ calcd for $C_{19}H_{19}NO_2$, 293.14; found, 294.20 ($M + H^+$).

*(1E,4E)-1-(4-(Dimethylamino)phenyl)-5-(4-methoxyphenyl)penta-1,4-dien-3-one (**8**).* Compound **8** was prepared following general procedure A. Yield, 71.3%. $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 7.73 (d, $J$ = 15.8 Hz, 1H), 7.70 (d, $J$ = 15.8 Hz, 1H), 7.59 (d, $J$ = 8.8 Hz, 2H), 7.53 (d, $J$ = 8.9 Hz, 2H), 6.99 (d, $J$ = 15.8 Hz, 1H), 6.95 (d, $J$ = 8.8 Hz, 2H), 6.89 (d, $J$ = 15.7 Hz, 1H), 6.71 (d, $J$ = 8.9 Hz, 2H), 3.87 (s, 3H), 3.05 (s, 6H). MS (ESI): $m/z$ calcd for $C_{20}H_{21}NO_2$, 307.16; found, 308.15 ($M + H^+$).

*(1E,4E)-1-(4-(Dimethylamino)phenyl)-5-(4-nitrophenyl)penta-1,4-dien-3-one (**9**).* Compound **9** was prepared following general procedure A. Yield, 64.3%. $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 8.28 (d, $J$ = 8.8 Hz, 2H), 7.77 (d, $J$ = 14.9 Hz, 1H), 7.77 (d, $J$ = 9.0 Hz, 2H), 7.73 (d, $J$ = 15.2 Hz,

1H), 7.55 (d, $J$ = 8.9 Hz, 2H), 7.22 (d, $J$ = 15.8 Hz, 1H), 6.88 (d, $J$ = 15.8 Hz, 1H), 6.72 (d, $J$ = 8.9 Hz, 2H), 3.08 (s, 6H). MS (ESI): $m/z$ calcd for $C_{19}H_{18}N_2O_3$, 322.13; found, 323.10 ($M + H^+$).

*(1E,4E)-1-(4-Aminophenyl)-5-(4-(dimethylamino)phenyl)penta-1,4-dien-3-one (**10**).* Compound **10** was prepared following general procedure B. Yield, 11.5%. $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 7.71 (d, $J$ = 15.1 Hz, 1H), 7.67 (d, $J$ = 15.1 Hz, 1H), 7.53 (d, $J$ = 8.8 Hz, 2H), 7.47 (d, $J$ = 8.4 Hz, 2H), 6.93 (d, $J$ = 15.8 Hz, 1H), 6.89 (d, $J$ = 15.7 Hz, 1H), 6.72 (d, $J$ = 8.5 Hz, 2H), 6.69 (d, $J$ = 8.2 Hz, 2H), 3.98 (s, 2H), 3.06 (s, 6H). MS (ESI): $m/z$ calcd for $C_{19}H_{20}N_2O$, 292.16; found, 293.15 ($M + H^+$).

*(1E,4E)-1-(4-(Dimethylamino)phenyl)-5-(4-(methylamino)phenyl)penta-1,4-dien-3-one (**11**).* Compound **11** was prepared following general procedure C. Yield, 6.2%. $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 7.68 (d, $J$ = 16.3 Hz, 1H), 7.67 (d, $J$ = 15.7 Hz, 1H), 7.51 (d, $J$ = 8.9 Hz, 2H), 7.48 (d, $J$ = 8.6 Hz, 2H), 6.88 (d, $J$ = 15.7 Hz, 1H), 6.88 (d, $J$ = 15.7 Hz, 1H), 6.69 (d, $J$ = 8.9 Hz, 2H), 6.59 (d, $J$ = 8.6 Hz, 2H), 3.04 (s, 6H), 2.89 (s, 3H). MS (ESI): $m/z$ calcd for $C_{20}H_{22}N_2O$, 306.176; found, 307.20 ($M + H^+$).

*(1E,4E)-1,5-Bis(4-(dimethylamino)phenyl)penta-1,4-dien-3-one (**12**).* Compound **12** was prepared following general procedure A. Yield, 32.2%. $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 7.71 (d, $J$ = 15.7 Hz, 2H), 7.54 (d, $J$ = 8.9 Hz, 4H), 6.91 (d, $J$ = 15.7 Hz, 2H), 6.72 (d, $J$ = 8.9 Hz, 4H), 3.06 (s, 12H). MS (ESI): $m/z$ calcd for $C_{21}H_{24}N_2O$, 320.19; found, 321.20 ($M + H^+$).

*4-((1E,4E)-5-(4-(Dimethylamino)phenyl)-3-oxopenta-1,4-dien-1-yl)-benzoic Acid (**13**).* Compound **13** was prepared following general procedure A. Yield, 2.5%. $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 8.14 (d, $J$ = 8.3 Hz, 2H), 7.75 (d, $J$ = 15.8 Hz, 1H), 7.73 (d, $J$ = 15.6 Hz, 1H), 7.71 (d, $J$ = 8.1 Hz, 2H), 7.54 (d, $J$ = 8.8 Hz, 2H), 7.20 (d, $J$ = 15.9 Hz, 1H), 6.88 (d, $J$ = 15.7 Hz, 1H), 6.71 (d, $J$ = 8.8 Hz, 2H), 3.06 (s, 6H). MS (ESI): $m/z$ calcd for $C_{20}H_{19}NO_3$, 321.14; found, 322.10 ($M + H^+$).

*(1E,4E)-1-(4-(Dimethylamino)phenyl)-5-(4-(trifluoromethyl)phenyl)penta-1,4-dien-3-one (**14**).* Compound **14** was prepared following general procedure A. Yield, 79.9%. $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 7.76 (d, $J$ = 15.9 Hz, 1H), 7.75−7.66 (m, 5H), 7.55 (d, $J$ = 8.8 Hz, 2H), 7.17 (d, $J$ = 15.9 Hz, 1H), 6.89 (d, $J$ = 15.7 Hz, 1H), 6.72 (d, $J$ = 8.9 Hz, 2H), 3.08 (s, 6H). MS (ESI): $m/z$ calcd for $C_{20}H_{18}F_3NO$, 345.13; found, 346.15 ($M + H^+$).

*(1E,4E)-1-(4-(Dimethylamino)phenyl)-5-(p-tolyl)penta-1,4-dien-3-one (**15**).* Compound **15** was prepared following general procedure A. Yield, 84.5%. $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 7.74 (d, $J$ = 15.8 Hz, 1H), 7.72 (d, $J$ = 15.9 Hz, 1H), 7.55 (d, $J$ = 8.9 Hz, 2H), 7.54 (d, $J$ = 8.0 Hz, 2H), 7.24 (d, $J$ = 8.0 Hz, 2H), 7.08 (d, $J$ = 15.9 Hz, 1H), 6.91 (d, $J$ = 15.7 Hz, 1H), 6.72 (d, $J$ = 8.9 Hz, 2H), 3.07 (s, 6H), 2.41 (s, 3H). MS (ESI): $m/z$ calcd for $C_{21}H_{20}NO$, 291.16; found, 292.00 ($M + H^+$).

*(1E,4E)-1-(4-(Diethylamino)phenyl)-5-(4-(dimethylamino)phenyl)penta-1,4-dien-3-one (**16**).* Compound **16** was prepared following general procedure A. Yield, 46.2%. $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 7.47 (d, $J$ = 15.9 Hz, 2H), 7.44 (d, $J$ = 8.9 Hz, 4H), 6.68 (d, $J$ = 8.8 Hz, 4H), 6.55 (d, $J$ = 16.1 Hz, 2H), 3.03 (s, 12H), 2.34 (s, 6H). MS (ESI): $m/z$ calcd for $C_{23}H_{28}N_2O$, 348.22; found, 349.20 ($M + H^+$).

*(1E,4E)-1-(4-(Dimethylamino)phenyl)-5-(4-(diphenylamino)phenyl)penta-1,4-dien-3-one (**17**).* Compound **17** was prepared following general procedure A. Yield, 41.7%. $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 7.70 (d, $J$ = 15.4 Hz, 1H), 7.66 (d, $J$ = 15.5 Hz, 1H), 7.52 (d, $J$ = 8.8 Hz, 2H), 7.46 (d, $J$ = 8.7 Hz, 2H), 7.30 (t, $J$ = 7.9 Hz, 4H), 7.14 (dd, $J$ = 7.7, 0.9 Hz, 4H), 7.09 (td, $J$ = 7.5, 1.0 Hz, 2H), 7.02 (d, $J$ = 8.6 Hz, 2H), 6.95 (d, $J$ = 15.8 Hz, 1H), 6.87 (d, $J$ = 15.7 Hz, 1H), 6.69 (d, $J$ = 8.8 Hz, 2H), 3.04 (s, 6H). MS (ESI): $m/z$ calcd for $C_{31}H_{28}N_2O$, 444.22; found, 445.15 ($M + H^+$).

*(1E,4E)-1-(4-(Benzyloxy)phenyl)-5-(4-(dimethylamino)phenyl)penta-1,4-dien-3-one (**18**).* Compound **18** was prepared following general procedure A. Yield, 27.4%. $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 7.70 (d, $J$ = 15.8 Hz, 1H), 7.68 (d, $J$ = 15.7 Hz, 1H), 7.57 (d, $J$ = 8.7 Hz, 2H), 7.52 (d, $J$ = 8.9 Hz, 2H), 7.47−7.31 (m, 5H), 7.00 (d, $J$ = 8.8 Hz, 2H), 6.97 (d, $J$ = 15.7 Hz, 1H), 6.87 (d, $J$ = 15.8 Hz, 1H), 6.70 (d, $J$ = 8.9 Hz, 2H), 5.11 (s, 2H), 3.04 (s, 6H). MS (ESI): $m/z$ calcd for $C_{26}H_{25}NO_2$, 383.19; found, 384.25 ($M + H^+$).

*(1E,4E)-1-(4-(Dimethylamino)phenyl)-5-(3-fluorophenyl)penta-1,4-dien-3-one (**19**).* Compound **19** was prepared following general procedure A. Yield, 63.4%. $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 7.87 (d, $J$ = 15.8 Hz, 1H), 7.79 (d, $J$ = 15.8 Hz, 1H), 7.67 (d, $J$ = 8.9 Hz, 2H), 7.51 (ddd, $J$ = 5.4, 3.7, 1.7 Hz, 2H), 7.45 (dd, $J$ = 10.2, 3.0 Hz, 1H), 7.22 (d, $J$ = 15.8 Hz, 1H), 7.00 (d, $J$ = 15.7 Hz, 1H), 6.84 (d, $J$ = 8.9 Hz, 2H), 3.19 (s, 6H). MS (ESI): $m/z$ calcd for $C_{19}H_{18}FNO$, 295.14; found, 296.10 ($M + H^+$).

*(1E,4E)-1-(3-Bromophenyl)-5-(4-(dimethylamino)phenyl)penta-1,4-dien-3-one (**20**).* Compound **20** was prepared following general procedure A. Yield, 77.5%. $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 7.79 (t, $J$ = 1.7 Hz, 1H), 7.75 (d, $J$ = 15.8 Hz, 1H), 7.64 (d, $J$ = 15.8 Hz, 1H), 7.58−7.50 (m, 4H), 7.30 (t, $J$ = 7.9 Hz, 1H), 7.11 (d, $J$ = 15.8 Hz, 1H), 6.88 (d, $J$ = 15.7 Hz, 1H), 6.72 (d, $J$ = 8.9 Hz, 2H), 3.08 (s, 6H). MS (ESI): $m/z$ calcd for $C_{19}H_{18}BrNO$, 355.06; found, 356.05 ($M + H^+$).

*(1E,4E)-1-(4-(Dimethylamino)phenyl)-5-(3-iodophenyl)penta-1,4-dien-3-one (**21**).* Compound **21** was prepared following general procedure A. Yield, 57.3%. $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 7.98(s, 1H), 7.73 (d, $J$ = 15.6 Hz, 1H), 7.71 (d, $J$ = 7.6 Hz, 1H), 7.61−7.52 (m, 4H), 7.15 (t, $J$ = 7.6 Hz, 1H), 7.08 (d, $J$ = 16.0 Hz, 1H), 6.86 (d, $J$ = 15.6 Hz, 1H), 6.71 (d, $J$ = 9.2 Hz, 2H), 3.06 (s, 6H). MS (ESI): $m/z$ calcd for $C_{19}H_{18}INO$, 403.04; found, 404.05 ($M + H^+$).

*(1E,4E)-1-(4-(Dimethylamino)phenyl)-5-(3-nitrophenyl)penta-1,4-dien-3-one (**22**).* Compound **22** was prepared following general procedure A. Yield, 39.4%. $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 8.49 (s, 1H), 8.23 (dd, $J$ = 8.2, 2.2 Hz, 1H), 7.88 (d, $J$ = 7.8 Hz, 1H), 7.76 (d, $J$ = 15.2 Hz, 1H), 7.72 (d, $J$ = 14.8 Hz, 1H), 7.59 (t, $J$ = 8.0 Hz, 1H), 7.54 (d, $J$ = 8.6 Hz, 2H), 7.22 (d, $J$ = 15.9 Hz, 1H), 6.87 (d, $J$ = 15.8 Hz, 1H), 6.71 (d, $J$ = 8.8 Hz, 2H), 3.06 (s, 6H). MS (ESI): $m/z$ calcd for $C_{19}H_{18}N_2O_3$, 322.13; found, 323.15 ($M + H^+$).

*(1E,4E)-1-(3-Aminophenyl)-5-(4-(dimethylamino)phenyl)penta-1,4-dien-3-one (**23**).* Compound **23** was prepared following general procedure B. Yield, 40.9%. $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 7.71 (d, $J$ = 15.7 Hz, 1H), 7.62 (d, $J$ = 15.9 Hz, 1H), 7.52 (d, $J$ = 8.9 Hz, 2H), 7.19 (t, $J$ = 7.8 Hz, 1H), 7.04 (d, $J$ = 2.3 Hz, 1H), 7.03 (d, $J$ = 15.9 Hz, 1H), 6.92 (d, $J$ = 1.8 Hz, 1H), 6.87 (d, $J$ = 15.7 Hz, 1H), 6.71 (dd, $J$ = 9.9, 2.3 Hz, 1H), 6.70 (d, $J$ = 8.9 Hz, 2H), 3.74 (s, 2H), 3.05 (s, 6H). MS (ESI): $m/z$ calcd for $C_{19}H_{20}N_2O$, 292.16; found, 293.10 ($M + H^+$).

*(1E,4E)-1-(4-(Dimethylamino)phenyl)-5-(3-(methylamino)phenyl)penta-1,4-dien-3-one (**24**).* Compound **24** was prepared following general procedure C. Yield, 30.0%. $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 7.73 (d, $J$ = 15.7 Hz, 1H), 7.67 (d, $J$ = 15.8 Hz, 1H), 7.54 (d, $J$ = 8.9 Hz, 2H), 7.24 (t, $J$ = 7.8 Hz, 1H), 7.06 (d, $J$ = 15.9 Hz, 1H), 7.01 (d, $J$ = 7.6 Hz, 1H), 6.92 (d, $J$ = 15.8 Hz, 1H), 6.84 (s, 1H), 6.72 (d, $J$ = 8.9 Hz, 2H), 6.67 (d, $J$ = 8.0 Hz, 1H), 3.07 (s, 6H), 2.90 (s, 3H). MS (ESI): $m/z$ calcd for $C_{20}H_{22}N_2O$, 306.17; found, 307.15 ($M + H^+$).

*(1E,4E)-1-(3-(Dimethylamino)phenyl)-5-(4-(dimethylamino)phenyl)penta-1,4-dien-3-one (**25**).* Compound **25** was prepared following general procedure C. Yield, 28.4%. $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 7.72 (d, $J$ = 15.7 Hz, 1H), 7.68 (d, $J$ = 15.8 Hz, 1H), 7.53 (d, $J$ = 8.7 Hz, 2H), 7.27 (t, $J$ = 7.7 Hz, 1H), 7.05 (dd, $J$ = 15.9, 0.7 Hz, 1H), 7.01 (d, $J$ = 7.3 Hz, 1H), 6.93 (s, 1H), 6.91 (dd, $J$ = 15.7, 0.8 Hz, 1H), 6.78 (dd, $J$ = 8.1, 2.4 Hz, 1H), 6.70 (d, $J$ = 8.6 Hz, 2H), 3.04 (s, 6H), 2.99 (s, 6H). MS (ESI): $m/z$ calcd for $C_{21}H_{24}N_2O$, 320.19; found, 321.10 ($M + H^+$).

*(1E,4E)-1-(2-(Benzyloxy)phenyl)-5-(4-(dimethylamino)phenyl)penta-1,4-dien-3-one (**26**).* Compound **26** was prepared following general procedure A. Yield, 51.0%. $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 8.06 (d, $J$ = 16.1 Hz, 1H), 7.62 (d, $J$ = 7.4 Hz, 1H), 7.61 (d, $J$ = 15.8 Hz, 2H), 7.53−7.28 (m, 10H), 7.23 (d, $J$ = 16.1 Hz, 1H), 7.00 (t, $J$ = 8.1 Hz, 2H), 6.85 (d, $J$ = 15.8 Hz, 1H), 6.68 (d, $J$ = 8.8 Hz, 2H), 5.19 (s, 2H), 3.04 (s, 8H). MS (ESI): $m/z$ calcd for $C_{26}H_{25}NO_2$, 383.19; found, 384.15 ($M + H^+$).

*(1E,4E)-1-(2-Chlorophenyl)-5-(4-(dimethylamino)phenyl)penta-1,4-dien-3-one (**27**).* Compound **27** was prepared following general procedure A. Yield, 78.5%. $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 7.72 (d, $J$ = 15.7 Hz, 1H), 7.62 (d, $J$ = 16.0 Hz, 2H), 7.60 (s, 1H), 7.52 (d, $J$ = 8.9 Hz, 2H), 7.48−7.45 (m, 1H), 7.39−7.32 (m, 2H), 7.09 (d, $J$ = 15.8 Hz, 1H), 6.85 (d, $J$ = 15.8 Hz, 1H), 6.70 (d, $J$ = 8.9 Hz, 2H), 3.05 (s, 6H). MS (ESI): $m/z$ calcd for $C_{19}H_{18}ClNO$, 311.11; found, 312.15 ($M + H^+$).

*(1E,4E)-1-(4-(Dimethylamino)phenyl)-5-(2-hydroxyphenyl)penta-1,4-dien-3-one (**28**).* Compound **28** was prepared following general procedure A. Yield, 37.2%. $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 8.09 (d, $J$ = 16.1 Hz, 1H), 7.76 (d, $J$ = 15.7 Hz, 1H), 7.59 (d, $J$ = 7.6 Hz, 1H), 7.55 (d, $J$ = 8.8 Hz, 2H), 7.33−7.21 (m, 2H), 7.00−6.90 (m, 3H), 6.71 (d, $J$ = 8.8 Hz, 2H), 3.06 (s, 6H). MS (ESI): $m/z$ calcd for $C_{19}H_{19}NO_2$, 293.14; found, 294.00 ($M + H^+$).

*(1E,4E)-1-(4-(Dimethylamino)phenyl)-5-(2-nitrophenyl)penta-1,4-dien-3-one (**29**).* Compound **29** was prepared following general procedure A. Yield, 35.8%. $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 8.07 (d, $J$ = 15.9 Hz, 1H), 8.05 (dd, $J$ = 8.1, 1.2 Hz, 1H), 7.75 (d, $J$ = 15.8 Hz, 1H), 7.73 (dd, $J$ = 7.7, 1.5 Hz, 1H), 7.66 (td, $J$ = 7.8, 1.3 Hz, 1H), 7.55 (d, $J$ = 7.7 Hz, 1H), 7.53 (d, $J$ = 8.9 Hz, 2H), 6.93 (d, $J$ = 15.9 Hz, 1H), 6.92 (d, $J$ = 15.7 Hz, 1H), 6.70 (d, $J$ = 8.9 Hz, 2H), 3.05 (s, 6H). MS (ESI): $m/z$ calcd for $C_{19}H_{18}N_2O_3$, 322.13; found, 323.15 ($M + H^+$).

*(1E,4E)-1-(2-Aminophenyl)-5-(4-(dimethylamino)phenyl)penta-1,4-dien-3-one (**30**).* Compound **30** was prepared following general procedure B. Yield, 41.4%. $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 8.09 (d, $J$ = 15.4 Hz, 1H), 8.07 (d, $J$ = 15.6 Hz, 1H), 7.78 (d, $J$ = 8.1 Hz, 1H), 7.70 (ddd, $J$ = 8.4, 6.9, 1.5 Hz, 1H), 7.67 (d, $J$ = 8.6 Hz, 1H), 7.64 (d, $J$ = 16.3 Hz, 1H), 7.57 (d, $J$ = 8.9 Hz, 2H), 7.48 (ddd, $J$ = 8.0, 6.9, 1.1 Hz, 1H), 7.25 (d, $J$ = 16.3 Hz, 1H), 6.76 (d, $J$ = 8.9 Hz, 2H), 3.04 (s, 6H). MS (ESI): $m/z$ calcd for $C_{19}H_{20}N_2O$, 292.16; found, 293.00 ($M + H^+$).

*(1E,4E)-1-(4-(Dimethylamino)phenyl)-5-(2-(methylamino)phenyl)penta-1,4-dien-3-one (**31**).* Compound **31** was prepared following general procedure C. Yield, 82.4%. $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 8.35 (d, $J$ = 8.8 Hz, 1H), 8.03 (d, $J$ = 8.4 Hz, 1H), 8.00−7.92 (m, 6H), 7.84 (d, $J$ = 16.2 Hz, 1H), 7.78 (t, $J$ = 7.2 Hz, 1H), 7.59 (d, $J$ = 16.2 Hz, 1H), 7.56 (d, $J$ = 16.4 Hz, 1H), 3.72 (s, 9H). MS (ESI): $m/z$ calcd for $C_{20}H_{22}N_2O$, 306.17; found, 307.10 ($M + H^+$).

*(1E,4E)-1-(2,6-Dichlorophenyl)-5-(4-(dimethylamino)phenyl)penta-1,4-dien-3-one (**32**).* Compound **32** was prepared following general procedure A. Yield, 6.3%. $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 7.77 (d, $J$ = 16.2 Hz, 1H), 7.74 (d, $J$ = 15.8 Hz, 1H), 7.54 (d, $J$ = 8.9 Hz, 2H), 7.40 (d, $J$ = 8.1 Hz, 2H), 7.25 (d, $J$ = 16.2 Hz, 1H), 7.21 (t, $J$ = 8.0 Hz, 1H), 6.88 (d, $J$ = 15.8 Hz, 1H), 6.72 (d, $J$ = 8.9 Hz, 2H), 3.07 (s, 6H). MS (ESI): $m/z$ calcd for $C_{19}H_{17}Cl_2NO$, 345.07; found, 346.95 ($M + H^+$).

*(1E,4E)-1-(2-Chloro-6-fluorophenyl)-5-(4-(dimethylamino)phenyl)penta-1,4-dien-3-one (**33**).* Compound **33** was prepared following general procedure A. Yield, 62.5%. $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 7.91 (d, $J$ = 16.2 Hz, 1H), 7.75 (d, $J$ = 15.8 Hz, 1H), 7.55 (d, $J$ = 8.9 Hz, 2H), 7.39 (d, $J$ = 16.2 Hz, 1H), 7.35−7.22 (m, 2H), 7.16−7.02 (m, 1H), 6.88 (d, $J$ = 15.8 Hz, 1H), 6.72 (d, $J$ = 8.9 Hz, 2H), 3.07 (s, 6H). MS (ESI): $m/z$ calcd for $C_{19}H_{17}ClFNO$, 329.10; found, 330.15 ($M + H^+$).

*(1E,4E)-1-(3,5-Bis(trifluoromethyl)phenyl)-5-(4-(dimethylamino)phenyl)penta-1,4-dien-3-one (**34**).* Compound **34** was prepared following general procedure A. Yield, 21.3%. $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 8.01 (s, 1H), 7.87 (s, 1H), 7.76 (d, $J$ = 15.8 Hz, 1H), 7.72 (d, $J$ = 15.9 Hz, 1H), 7.54 (d, $J$ = 8.9 Hz, 1H), 7.21 (d, $J$ = 15.8 Hz, 1H), 6.86 (d, $J$ = 15.7 Hz, 1H), 6.70 (d, $J$ = 8.9 Hz, 1H), 3.06 (s, 6H). MS (ESI): $m/z$ calcd for $C_{21}H_{17}F_6NO$, 413.12; found, 413.85 ($M + H^+$).

*(1E,4E)-1-(3,4-Dimethoxyphenyl)-5-(4-(dimethylamino)phenyl)penta-1,4-dien-3-one (**35**).* Compound **35** was prepared following general procedure A. Yield, 40.8%. $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 7.74 (d, $J$ = 15.7 Hz, 1H), 7.69 (d, $J$ = 15.8 Hz, 1H), 7.55 (d, $J$ = 8.9 Hz, 2H), 7.22 (dd, $J$ = 8.3, 1.9 Hz, 1H), 7.17 (d, $J$ = 1.9 Hz, 1H), 6.97 (d, $J$ = 15.8 Hz, 1H), 6.92 (d, $J$ = 15.8 Hz, 1H), 6.91 (d, $J$ = 8.4 Hz, 1H), 6.72 (d, $J$ = 8.9 Hz, 2H), 3.97 (s, 3H), 3.95 (s, 3H), 3.06 (s, 6H). MS (ESI): $m/z$ calcd for $C_{21}H_{23}NO_3$, 337.17; found, 338.15 ($M + H^+$).

*(1E,4E)-1-(3,5-Dimethoxyphenyl)-5-(4-(dimethylamino)phenyl)penta-1,4-dien-3-one (**36**).* Compound **36** was prepared following general procedure A. Yield, 70.4%. $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 7.72 (d, $J$ = 15.7 Hz, 1H), 7.62 (d, $J$ = 15.8 Hz, 1H), 7.53 (d, $J$ = 8.9 Hz, 2H), 7.05 (d, $J$ = 15.8 Hz, 1H), 6.89 (d, $J$ = 15.8 Hz, 1H), 6.76 (s, 2H), 6.70 (d, $J$ = 8.9 Hz, 2H), 6.51 (s, 1H), 3.84 (s, 6H), 3.05 (s, 6H). MS (ESI): $m/z$ calcd for $C_{21}H_{23}NO_3$, 337.17; found, 338.15 ($M + H^+$).

*(1E,4E)-1-(2,4-Dimethoxyphenyl)-5-(4-(dimethylamino)phenyl)penta-1,4-dien-3-one (**37**).* Compound **37** was prepared following general procedure A. Yield, 71.4%. $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 7.97 (d, $J$ = 16.1 Hz, 1H), 7.69 (d, $J$ = 15.7 Hz, 1H), 7.55 (d, $J$ = 8.6 Hz, 1H), 7.52 (d, $J$ = 8.9 Hz, 2H), 7.05 (d, $J$ = 16.0 Hz, 1H), 6.92 (d, $J$ = 15.7 Hz, 1H), 6.69 (d, $J$ = 8.9 Hz, 2H), 6.53 (dd, $J$ = 8.6, 2.4 Hz, 1H), 6.47 (d, $J$ = 2.3 Hz, 1H), 3.90 (s, 3H), 3.85 (s, 3H), 3.03 (s, 6H). MS (ESI): $m/z$ calcd for $C_{21}H_{23}NO_3$, 337.17; found, 338.10 ($M + H^+$).

*(1E,4E)-1-(4-(Dimethylamino)phenyl)-5-(3,4,5-trimethoxyphenyl)penta-1,4-dien-3-one (**38**).* Compound **38** was prepared following general procedure A. Yield, 71.6%. $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 7.73 (d, $J$ = 15.7 Hz, 1H), 7.63 (d, $J$ = 15.8 Hz, 1H), 7.53 (d, $J$ = 8.7 Hz, 2H), 6.97 (d, $J$ = 15.8 Hz, 1H), 6.90 (d, $J$ = 15.7 Hz, 1H), 6.84 (s, 2H), 6.69 (d, $J$ = 8.7 Hz, 2H), 3.92 (s, 6H), 3.90 (s, 3H), 3.05 (s, 6H). MS (ESI): $m/z$ calcd for $C_{22}H_{25}NO_4$, 367.18; found, 368.05 ($M + H^+$).

*(1E,4E)-1-(4-(Dimethylamino)phenyl)-5-(2,4,6-trimethoxyphenyl)-penta-1,4-dien-3-one (**39**).* Compound **39** was prepared following general procedure A. Yield, 58.8%. $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 8.14 (d, $J$ = 16.1 Hz, 1H), 7.67 (d, $J$ = 15.7 Hz, 1H), 7.52 (d, $J$ = 8.9 Hz, 2H), 7.41 (d, $J$ = 16.1 Hz, 1H), 6.93 (d, $J$ = 15.7 Hz, 1H), 6.69 (d, $J$ = 8.9 Hz, 2H), 6.14 (s, 2H), 3.90 (s, 6H), 3.86 (s, 3H), 3.03 (s, 6H). MS (ESI): $m/z$ calcd for $C_{22}H_{25}NO_4$, 367.18; found, 368.05 ($M + H^+$).

*(1E,4E)-1-(4-(Benzyloxy)-3-methoxyphenyl)-5-(4-(dimethylamino)phenyl)penta-1,4-dien-3-one (**40**).* Compound **40** was prepared following general procedure A. Yield, 61.6%. $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 7.71 (d, $J$ = 15.7 Hz, 1H), 7.65 (d, $J$ = 15.8 Hz, 1H), 7.52 (d, $J$ = 8.9 Hz, 2H), 7.45 (d, $J$ = 8.4 Hz, 2H), 7.42−7.35 (m, 2H), 7.32 (d, $J$ = 7.1 Hz, 1H), 7.16 (d, $J$ = 1.9 Hz, 1H), 7.13 (dd, $J$ = 8.3, 2.0 Hz, 1H), 6.94 (d, $J$ = 15.8 Hz, 1H), 6.90 (d, $J$ = 8.7 Hz, 1H), 6.89 (d, $J$ = 15.6 Hz, 1H), 6.69 (d, $J$ = 8.9 Hz, 2H), 5.21 (s, 2H), 3.95 (s, 3H), 3.04 (s, 6H). MS (ESI): $m/z$ calcd for $C_{27}H_{27}NO_3$, 413.20; found, 414.20 ($M + H^+$).

*(1E,4E)-1-(4-Bromo-2-hydroxyphenyl)-5-(4-(dimethylamino)phenyl)penta-1,4-dien-3-one (**41**).* Compound **41** was prepared following general procedure A. Yield, 15.0%. $^1$H NMR (400 MHz, $CD_3OD$): $\delta$ 7.93 (d, $J$ = 16.0 Hz, 1H), 7.89 (s, 1H), 7.76 (d, $J$ = 2.7 Hz, 1H), 7.74 (d, $J$ = 16.4 Hz, 1H), 7.56 (d, $J$ = 8.9 Hz, 2H), 7.32 (dd, $J$ = 9.2, 3.0 Hz, 1H), 7.29 (d, $J$ = 16.0 Hz, 1H), 6.94 (d, $J$ = 15.7 Hz, 1H), 6.80 (d, $J$ = 8.7 Hz, 1H), 6.75 (d, $J$ = 9.0 Hz, 2H), 3.04 (s, 6H). MS (ESI): $m/z$ calcd for $C_{19}H_{18}BrNO_2$, 371.05; found, 372.00 ($M + H^+$).

*(1E,4E)-1-(4-(Dimethylamino)phenyl)-5-(3-phenoxyphenyl)penta-1,4-dien-3-one (**42**).* Compound **42** was prepared following general procedure A. Yield, 83.9%. $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 7.70 (d, $J$ = 15.7 Hz, 1H), 7.64 (d, $J$ = 15.9 Hz, 1H), 7.51 (d, $J$ = 8.8 Hz, 2H), 7.42−7.31 (m, 4H), 7.25 (s, 1H), 7.15 (t, $J$ = 7.4 Hz, 1H), 7.08−6.99 (m, 4H), 6.85 (d, $J$ = 15.7 Hz, 1H), 6.69 (d, $J$ = 8.8 Hz, 2H), 3.04 (s, 6H). MS (ESI): $m/z$ calcd for $C_{25}H_{23}NO_2$, 369.17; found, 370.15 ($M + H^+$).

*(1E,4E)-1-(2-(Benzyloxy)-4-nitrophenyl)-5-(4-(dimethylamino)phenyl)penta-1,4-dien-3-one (**43**).* Compound **43** was prepared following general procedure A. Yield, 83.3%. $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 8.54 (d, $J$ = 2.8 Hz, 1H), 8.20 (dd, $J$ = 9.1, 2.8 Hz, 1H), 8.02 (d, $J$ = 16.0 Hz, 1H), 7.67 (d, $J$ = 15.8 Hz, 1H), 7.56−7.36 (m, 7H), 7.30 (d, $J$ = 15.9 Hz, 1H), 7.05 (d, $J$ = 9.2 Hz, 1H), 6.82 (d, $J$ = 15.7 Hz, 1H), 6.70 (d, $J$ = 8.9 Hz, 2H), 5.30 (s, 2H), 3.06 (s, 6H). MS (ESI): $m/z$ calcd for $C_{26}H_{24}N_2O_4$, 428.17; found, 429.15 ($M + H^+$).

*(1E,4E)-1-(4-(Dimethylamino)phenyl)-5-(4-(trityloxy)phenyl)penta-1,4-dien-3-one (**44**).* Compound **44** was prepared following general procedure A. Yield, 40.6%. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.65 (d, $J$ = 15.8 Hz, 1H), 7.53 (d, $J$ = 15.8 Hz, 1H), 7.50−7.41 (m, 8H), 7.33−7.23 (m, 11H), 6.85 (d, $J$ = 15.8 Hz, 1H), 6.81 (d, $J$ = 15.7 Hz, 1H), 6.71 (d, $J$ = 8.6 Hz, 2H), 6.68 (d, $J$ = 8.8 Hz, 2H), 3.03 (s, 6H). MS (ESI): $m/z$ calcd for $C_{38}H_{33}NO_2$, 535.25; found, 536.75 ($M + H^+$).

*(1E,4E)-1-(6-Chloropyridin-3-yl)-5-(4-(dimethylamino)phenyl)penta-1,4-dien-3-one (**45**).* Compound **45** was prepared following general procedure A. Yield, 84.7%. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.59 (d, $J$ = 2.3 Hz, 1H), 7.87 (dd, $J$ = 8.3, 2.5 Hz, 1H), 7.73 (d, $J$ = 15.7 Hz, 1H), 7.63 (d, $J$ = 15.9 Hz, 1H), 7.52 (d, $J$ = 8.9 Hz, 2H), 7.37 (d, $J$ = 8.3 Hz, 1H), 7.12 (d, $J$ = 15.9 Hz, 1H), 6.85 (d, $J$ = 15.7 Hz, 1H), 6.69 (d, $J$ = 8.9 Hz, 2H), 3.05 (s, 6H). MS (ESI): $m/z$ calcd for $C_{18}H_{17}ClN_2O$, 312.10; found, 313.05 ($M + H^+$).

*(1E,4E)-1-(6-Bromopyridin-3-yl)-5-(4-(dimethylamino)phenyl)penta-1,4-dien-3-one (**46**).* Compound **46** was prepared following general procedure A. Yield, 67.7%. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.57 (d, $J$ = 2.5 Hz, 1H), 7.76 (dd, $J$ = 8.1, 2.5 Hz, 1H), 7.74 (d, $J$ = 15.6 Hz, 1H), 7.61 (d, $J$ = 15.9 Hz, 1H), 7.53 (dd, $J$ = 8.6, 1.9 Hz, 3H), 7.14 (d, $J$ = 16.0 Hz, 1H), 6.85 (d, $J$ = 15.8 Hz, 1H), 6.70 (d, $J$ = 8.7 Hz, 2H), 3.06 (s, 6H). MS (ESI): $m/z$ calcd for $C_{18}H_{17}BrN_2O$, 356.05; found, 357.10 ($M + H^+$).

*(1E,4E)-1-(4-(Dimethylamino)phenyl)-5-(6-iodopyridin-3-yl)penta-1,4-dien-3-one (**47**).* Compound **47** was prepared following general procedure A. Yield, 32.5%. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.50 (d, $J$ = 2.5 Hz, 1H), 7.72 (d, $J$ = 8.3 Hz, 1H), 7.69 (d, $J$ = 15.8 Hz, 1H), 7.54 (d, $J$ = 16.0 Hz, 1H), 7.51−7.46 (m, 3H), 7.09 (d, $J$ = 15.9 Hz, 1H), 6.80 (d, $J$ = 15.7 Hz, 1H), 6.65 (d, $J$ = 8.9 Hz, 2H), 3.01 (s, 6H). MS (ESI): $m/z$ calcd for $C_{18}H_{17}IN_2O$, 404.04; found, 405.10 ($M + H^+$).

*(1E,4E)-1-(4-(Dimethylamino)phenyl)-5-(pyridin-2-yl)penta-1,4-dien-3-one (**48**).* Compound **48** was prepared following general procedure A. Yield, 56.5%. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.68 (ddd, $J$ = 4.7, 1.7, 0.8 Hz, 1H), 7.77 (d, $J$ = 16.1 Hz, 1H), 7.72 (dd, $J$ = 7.6, 1.9 Hz, 1H), 7.67 (d, $J$ = 5.3 Hz, 2H), 7.52 (d, $J$ = 8.9 Hz, 2H), 7.47 (d, $J$ = 7.8 Hz, 1H), 7.28 (dd, $J$ = 4.8, 1.1 Hz, 1H), 6.89 (d, $J$ = 15.8 Hz, 1H), 6.70 (d, $J$ = 9.0 Hz, 2H), 3.05 (s, 6H). MS (ESI): $m/z$ calcd for $C_{18}H_{18}N_2O$, 278.14; found, 279.15 ($M + H^+$).

*(1E,4E)-1-(4-(Dimethylamino)phenyl)-5-(1H-pyrrol-2-yl)penta-1,4-dien-3-one (**49**).* Compound **49** was prepared following general procedure A. Yield, 3.3%. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.72 (d, $J$ = 15.6 Hz, 1H), 7.53 (d, $J$ = 8.9 Hz, 2H), 7.08 (s, 1H), 6.84−6.77 (m, 2H), 6.71 (d, $J$ = 8.9 Hz, 2H), 6.62 (d, $J$ = 1.9 Hz, 1H), 6.36 (dd, $J$ = 6.0, 2.4 Hz, 1H), 6.15 (d, $J$ = 12.2 Hz, 1H), 3.07 (s, 6H). MS (ESI): $m/z$ calcd for $C_{17}H_{18}N_2O$, 266.14; found, 267.15 ($M + H^+$).

*(1E,4E)-1-(4-(Dimethylamino)phenyl)-5-(furan-2-yl)penta-1,4-dien-3-one (**50**).* Compound **50** was prepared following general procedure A. Yield, 83.9%. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.70 (d, $J$ = 15.8 Hz, 1H), 7.51 (d, $J$ = 8.8 Hz, 2H), 7.50 (d, $J$ = 1.9 Hz, 1H), 7.48 (d, $J$ = 15.5 Hz, 1H), 7.02 (d, $J$ = 15.5 Hz, 1H), 6.81 (d, $J$ = 15.8 Hz, 1H), 6.69 (d, $J$ = 8.8 Hz, 2H), 6.66 (d, $J$ = 3.2 Hz, 1H), 6.50 (dd, $J$ = 3.3, 1.7 Hz, 1H), 3.04 (s, 6H). MS (ESI): $m/z$ calcd for $C_{17}H_{17}NO_2$, 267.13; found, 268.25 ($M + H^+$).

*(1E,4E)-1-(4-(Dimethylamino)phenyl)-5-(thiophen-2-yl)penta-1,4-dien-3-one (**51**).* Compound **51** was prepared following general procedure A. Yield, 47.0%. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.98 (d, $J$ = 15.2 Hz, 1H), 7.84 (d, $J$ = 15.8 Hz, 1H), 7.66 (d, $J$ = 8.9 Hz, 2H), 7.52 (d, $J$ = 5.0 Hz, 1H), 7.46 (d, $J$ = 3.2 Hz, 1H), 7.22 (dd, $J$ = 4.8, 3.7 Hz, 1H), 7.04 (d, $J$ = 15.5 Hz, 1H), 6.97 (d, $J$ = 15.7 Hz, 1H), 6.84 (d, $J$ = 8.9 Hz, 2H), 3.19 (s, 6H). MS (ESI): $m/z$ calcd for $C_{17}H_{17}NOS$, 283.10; found, 284.10 ($M + H^+$).

*(1E,4E)-1-(5-Bromothiophen-2-yl)-5-(4-(dimethylamino)phenyl)penta-1,4-dien-3-one (**52**).* Compound **52** was prepared following general procedure A. Yield, 71.0%. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.69 (d, $J$ = 15.4 Hz, 1H), 7.68 (d, $J$ = 15.8 Hz, 1H), 7.51 (d, $J$ = 8.8 Hz, 2H), 7.05−7.02 (m, 2H), 6.79 (d, $J$ = 15.7 Hz, 1H), 6.78 (d, $J$ = 15.5 Hz, 1H), 6.69 (d, $J$ = 8.9 Hz, 2H), 3.05 (s, 6H). MS (ESI): $m/z$ calcd for $C_{17}H_{16}BrNOS$, 361.01; found, 362.10 ($M + H^+$).

*(1E,4E)-1-(5′-Bromo-[2,2′-bithiophen]-5-yl)-5-(4-(dimethylamino)-phenyl)penta-1,4-dien-3-one (**53**).* Compound **53** was prepared following general procedure A. Yield, 72.1%. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.76 (d, $J$ = 15.2 Hz, 1H), 7.69 (d, $J$ = 15.6 Hz, 1H), 7.52 (d, $J$ = 8.8 Hz, 2H), 7.20 (d, $J$ = 3.2 Hz, 1H), 7.06 (d, $J$ = 4.0 Hz, 1H), 7.00 (dd, $J$ = 6.8, 4.0 Hz, 2H), 6.84 (d, $J$ = 15.2 Hz, 1H), 6.81 (d, $J$ = 15.6 Hz, 1H), 6.69 (d, $J$ = 9.2 Hz, 2H), 3.05 (s, 6H). MS (ESI): $m/z$ calcd for $C_{21}H_{18}BrNOS_2$, 443.00; found, 444.25 ($M + H^+$).

*(1E,4E)-1-(Benzo[d][1,3]dioxol-5-yl)-5-(4-(dimethylamino)phenyl) penta-1,4-dien-3-one (**54**).* Compound **54** was prepared following general procedure A. Yield, 71.9%. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.70 (d, $J$ = 15.8 Hz, 1H), 7.63 (d, $J$ = 15.8 Hz, 1H), 7.52 (d, $J$ = 8.9 Hz, 2H), 7.13 (d, $J$ = 1.6 Hz, 1H), 7.09 (dd, $J$ = 8.0, 1.7 Hz, 1H), 6.93 (d, $J$ = 15.8 Hz, 1H), 6.86 (d, $J$ = 11.6 Hz, 1H), 6.83 (d, $J$ = 3.9 Hz, 1H), 6.69 (d, $J$ = 8.9 Hz, 2H), 6.02 (s, 2H), 3.04 (s, 6H). MS (ESI): $m/z$ calcd for $C_{20}H_{19}NO_3$, 321.14; found, 322.15 ($M + H^+$).

*(1E,4E)-1-(4-(Dimethylamino)phenyl)-5-(1H-indol-5-yl)penta-1,4-dien-3-one (**55**).* Compound **55** was prepared following general procedure A. Yield, 12.6%. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.33 (s, 1H), 7.90 (s, 1H), 7.88 (d, $J$ = 15.9 Hz, 1H), 7.73 (d, $J$ = 15.7 Hz, 1H), 7.54 (d, $J$ = 8.9 Hz, 3H), 7.42 (d, $J$ = 8.5 Hz, 1H), 7.25 (t, $J$ = 2.8 Hz, 1H), 7.09 (d, $J$ = 15.8 Hz, 1H), 6.93 (d, $J$ = 15.8 Hz, 1H), 6.71 (d, $J$ = 8.8 Hz, 2H), 6.64−6.59 (m, 1H), 3.05 (s, 6H). MS (ESI): $m/z$ calcd for $C_{21}H_{20}N_2O$, 316.16; found, 316.95 ($M + H^+$).

*(1E,4E)-1-(4-(Dimethylamino)phenyl)-5-(6-methoxynaphthalen-2-yl)penta-1,4-dien-3-one (**56**).* Compound **56** was prepared following general procedure A. Yield, 43.8%. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.96 (s, 1H), 7.88 (d, $J$ = 15.8 Hz, 1H), 7.84−7.73 (m, 4H), 7.56 (d, $J$ = 8.9 Hz, 2H), 7.23−7.14 (m, 3H), 6.94 (d, $J$ = 15.8 Hz, 1H), 6.73 (d, $J$ = 8.9 Hz, 2H), 3.97 (s, 3H), 3.07 (s, 6H). MS (ESI): $m/z$ calcd for $C_{24}H_{23}NO_2$, 357.17; found, 358.05 ($M + H^+$).

*(1E,4E)-1-(4-(Dimethylamino)phenyl)-5-(ferrocenyl)penta-1,4-dien-3-one (**57**).* Compound **57** was prepared following general procedure A. Yield, 10.2%. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.68 (d, $J$ = 15.7 Hz, 1H), 7.63 (d, $J$ = 15.6 Hz, 1H), 7.52 (d, $J$ = 8.9 Hz, 2H), 6.82 (d, $J$ = 15.7 Hz, 1H), 6.70 (d, $J$ = 8.8 Hz, 2H), 6.68 (d, $J$ = 15.6 Hz, 1H), 4.57 (d, $J$ = 1.8 Hz, 2H), 4.45 (d, $J$ = 1.8 Hz, 2H), 4.17 (s, 5H), 3.04 (s, 6H). MS (ESI): $m/z$ calcd for $C_{23}H_{23}FeNO$, 385.13; found, 386.05 ($M + H^+$).

*(1E,4E)-1,5-Diphenylpenta-1,4-dien-3-one (**58**).* To a solution of benzyaldehyde (2.0 mmol) and acetone (1.0 mmol) in 15 mL of ethanol was added 0.2 mL of NaOMe (28% in methanol). The reaction mixture was stirred for 12 h at room temperature. The precipitate was collected by filtration, washed with water and hexane, and recrystallized from ethanol. Yield, 15.7%. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.83 (d, $J$ = 15.9 Hz, 2H), 7.71 (dd, $J$ = 6.6, 2.9 Hz, 4H), 7.50 (dd, $J$ = 4.9, 1.8 Hz, 4H), 7.17 (d, $J$ = 15.9 Hz, 2H). MS (ESI): $m/z$ calcd for $C_{17}H_{14}O$, 234.10; found, 235.10 ($M + H^+$).

*(1E,4E)-1,5-Bis(4-chlorophenyl)penta-1,4-dien-3-one (**59**).* The same reaction described above to prepare **58** was used. Compound **59** was obtained in a yield of 67.2%. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.68 (d, $J$ = 15.9 Hz, 2H), 7.54 (d, $J$ = 8.4 Hz, 4H), 7.39 (d, $J$ = 8.5 Hz, 4H), 7.03 (d, $J$ = 16.0 Hz, 2H). MS (ESI): $m/z$ calcd for $C_{17}H_{12}Cl_2O$, 302.03; found, 303.05 ($M + H^+$).

*(1E,4E)-1,5-Bis(4-methoxyphenyl)penta-1,4-dien-3-one (**60**).* The reaction described above to prepare **58** was used. Compound **60** was obtained in a yield of 53.8%. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.71 (d, $J$ = 15.9 Hz, 2H), 7.58 (d, $J$ = 8.8 Hz, 4H), 6.96 (d, $J$ = 15.8 Hz, 2H), 6.94 (d, $J$ = 8.8 Hz, 4H), 3.86 (s, 6H). MS (ESI): $m/z$ calcd for $C_{19}H_{18}O_3$, 294.13; found, 295.15 ($M + H^+$).

*(2E,6E)-2,6-Dibenzylidenecyclohexanone (**61**).* To a solution of benzyaldehyde (2.0 mmol) and cyclohexanone (1.0 mmol) in 15 mL

of ethanol was added 0.2 mL of NaOMe (28% in methanol). The reaction mixture was stirred for 12 h at room temperature. The precipitate was collected by filtration, washed with water and hexane, and recrystallized from ethanol. Yield, 88.3%. $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 7.81 (s, 2H), 7.51−7.31 (m, 12H), 2.94 (dd, $J$ = 8.3, 3.9 Hz, 4H), 1.80 (dt, $J$ = 12.3, 6.3 Hz, 2H). MS (ESI): $m/z$ calcd for $C_{20}H_{18}O$, 274.14; found, 275.10 ($M + H^+$).

*(2E,6E)-2,6-Bis(4-chlorobenzylidene)cyclohexanone (**62**).* The same reaction described above to prepare **61** was used. Compound **62** was obtained in a yield of 71.2%. $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 7.73 (s, 2H), 7.38 (s, 8H), 2.89 (dd, $J$ = 8.3, 3.9 Hz, 4H), 1.81 (dd, $J$ = 12.0, 6.0 Hz, 2H). MS (ESI): $m/z$ calcd for $C_{20}H_{16}Cl_2O$, 342.06; found, 343.10 ($M + H^+$).

*(2E,6E)-2,6-Bis(4-methoxybenzylidene)cyclohexanone (**63**).* The same reaction described above to prepare **61** was used, and **63** was obtained in a yield of 74.3%. $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 7.76 (s, 2H), 7.45 (d, $J$ = 8.8 Hz, 4H), 6.94 (d, $J$ = 8.8 Hz, 4H), 3.84 (s, 6H), 3.05−2.84 (m, 4H), 1.81 (dd, $J$ = 11.9, 5.8 Hz, 2H). MS (ESI): $m/z$ calcd for $C_{22}H_{22}O_3$, 334.16; found, 335.05 ($M + H^+$).

*(2E,6E)-2,6-Bis(4-(dimethylamino)benzylidene)cyclohexanone (**64**).* The same reaction described above to prepare **61** was used, and **64** was obtained in a yield of 12.3%. $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 7.75 (s, 2H), 7.44 (d, $J$ = 8.9 Hz, 4H), 6.71 (d, $J$ = 8.9 Hz, 4H), 3.01 (s, 12H), 2.96−2.90 (m, 4H), 1.82 (dd, $J$ = 11.8, 5.7 Hz, 2H). MS (ESI): $m/z$ calcd for $C_{24}H_{28}N_2O$, 360.22; found, 361.15 ($M + H^+$).

*(E)-4-(4-Nitrophenyl)but-3-en-2-one (**65**).* To a solution of 4-nitrobenzaldehyde (6.04 g, 50 mmol) in 150 mL of acetone were added 1.38 g of $K_2CO_3$ and 10 mL of water, and the reaction mixture was stirred for 12 h at room temperature. Then, 20 mL of concentrated HCl was added, and the mixture was stirred for an additional 6 h at room temperature. After 300 mL of water was added, the white precipitate formed was collected by filtration, washed with water, and dried under vacuum to obtain 8.34 g of **65** (87.2%). $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 8.26 (d, $J$ = 8.9 Hz, 2H), 7.70 (d, $J$ = 8.8 Hz, 2H), 7.54 (d, $J$ = 16.3 Hz, 1H), 6.82 (d, $J$ = 16.3 Hz, 1H), 2.42 (s, 3H). MS (ESI): $m/z$ calcd for $C_{10}H_9NO_3$, 191.06; found, 192.10 ($M + H^+$).

*(E)-4-(4-Aminophenyl)but-3-en-2-one (**66**).* A mixture of **65** (1.92 g, 10 mmol) and $SnCl_2$ (3.79 g, 20 mmol) dissolved in 80 mL of ethanol containing 5 mL of concentrated hydrochloric acid was stirred under reflux for 2 h. After the mixture was cooled to room temperature, 2 M NaOH (100 mL) was added and extracted with ethyl acetate (100 mL). The organic layer was dried over $Na_2SO_4$. The solvent was removed, and the residue was purified by silica gel chromatography to give 1.16 g of **66** (72.1%). $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 7.44 (d, $J$ = 16.2 Hz, 1H), 7.37 (d, $J$ = 8.7 Hz, 2H), 6.66 (d, $J$ = 8.6 Hz, 2H), 6.55 (d, $J$ = 16.1 Hz, 1H), 4.00 (s, 2H), 2.34 (s, 3H). MS (ESI): $m/z$ calcd for $C_{10}H_{11}NO$, 161.08; found, 162.10 ($M + H^+$).

*(E)-4-(4-(Methylamino)phenyl)but-3-en-2-one (**67**).* To a solution of **66** (483 mg, 3 mmol) and 414 mg of $K_2CO_3$ in 50 mL of acetone was added $CH_3I$ (852 mg, 6 mmol) dropwise, and the reaction mixture was stirred for 8 h at room temperature. After filtration, the solvent was removed, and the residue was purified by silica gel chromatography to give 183.5 mg of **67** (34.9%). $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 7.45 (d, $J$ = 16.1 Hz, 1H), 7.40 (d, $J$ = 8.7 Hz, 2H), 6.58 (d, $J$ = 8.7 Hz, 2H), 6.54 (d, $J$ = 16.1 Hz, 1H), 4.13 (s, 1H), 2.88 (s, 3H), 2.33 (s, 3H). MS (ESI): $m/z$ calcd for $C_{11}H_{13}NO$, 175.10; found, 176.15 ($M + H^+$).

*(1E,4E)-1-(4-Aminophenyl)-5-(4-bromophenyl)penta-1,4-dien-3-one (**68**).* Compound **68** was prepared following general procedure A. Yield, 55.7%. $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 7.68 (d, $J$ = 15.8 Hz, 1H), 7.63 (d, $J$ = 15.9 Hz, 1H), 7.54 (d, $J$ = 8.5 Hz, 2H), 7.46 (d, $J$ = 8.5 Hz, 2H), 7.45 (d, $J$ = 8.5 Hz, 2H), 7.05 (d, $J$ = 15.9 Hz, 1H), 6.87 (d, $J$ = 15.8 Hz, 1H), 6.68 (d, $J$ = 8.6 Hz, 2H), 4.01 (s, 1H). MS (ESI): $m/z$ calcd for $C_{17}H_{14}BrNO$, 327.03; found, 328.05 ($M + H^+$).

*(1E,4E)-1-(4-Bromophenyl)-5-(4-(methylamino)phenyl)penta-1,4-dien-3-one (**69**).* Compound **69** was prepared following general procedure A. Yield, 63.1%. $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 7.70 (d, $J$ = 15.8 Hz, 1H), 7.62 (d, $J$ = 15.9 Hz, 1H), 7.53 (d, $J$ = 8.5 Hz, 2H), 7.48 (d, $J$ = 8.3 Hz, 2H), 7.46 (d, $J$ = 8.5 Hz, 2H), 7.06 (d, $J$ = 15.9 Hz, 1H), 6.85 (d, $J$ = 15.7 Hz, 1H), 6.59 (d, $J$ = 8.6 Hz, 2H), 2.90 (s, 3H). MS (ESI): $m/z$ calcd for $C_{18}H_{16}BrNO$, 341.04; found, 342.10 ($M + H^+$).

*(1E,4E)-1-(4-Aminophenyl)-5-(4-iodophenyl)penta-1,4-dien-3-one (**70**).* Compound **70** was prepared following general procedure A. Yield, 46.1%. $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 7.74 (d, $J$ = 8.4 Hz, 2H), 7.68 (d, $J$ = 15.8 Hz, 1H), 7.61 (d, $J$ = 15.9 Hz, 1H), 7.45 (d, $J$ = 8.5 Hz, 2H), 7.33 (d, $J$ = 8.4 Hz, 2H), 7.06 (d, $J$ = 15.9 Hz, 1H), 6.87 (d, $J$ = 15.8 Hz, 1H), 6.68 (d, $J$ = 8.5 Hz, 2H), 4.01 (s, 2H). HRMS (EI): $m/z$ ($EI^+$): calcd for $C_{17}H_{14}INO$, 375.0120; found, 375.0116.

*(1E,4E)-1-(4-Iodophenyl)-5-(4-(methylamino)phenyl)penta-1,4-dien-3-one (**71**).* Compound **71** was prepared following general procedure A. Yield, 53.2%. $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 7.74 (d, $J$ = 8.4 Hz, 2H), 7.70 (d, $J$ = 15.8 Hz, 1H), 7.61 (d, $J$ = 15.8 Hz, 1H), 7.48 (d, $J$ = 8.7 Hz, 2H), 7.33 (d, $J$ = 8.5 Hz, 2H), 7.07 (d, $J$ = 15.9 Hz, 1H), 6.85 (d, $J$ = 15.8 Hz, 1H), 6.60 (d, $J$ = 8.7 Hz, 2H), 4.18 (s, 1H), 2.90 (s, 3H). HRMS (EI): $m/z$ ($EI^+$): calcd for $C_{18}H_{16}INO$, 389.0277; found, 389.0281.

*(1E,4E)-1-(4-Aminophenyl)-5-(4-(tributylstannyl)phenyl)penta-1,4-dien-3-one (**72**).* A mixture of **68** (125 mg, 0.38 mmol), $(Bu_3Sn)_2$ (440.9 mg, 0.76 mmol), and $(Ph_3P)_4Pd$ (47 mg, 0.04 mmol) in toluene (10 mL) was stirred under reflux for 10 h. The solvent was removed, and the residue was purified by silica gel chromatography to give 46.8 mg of **72** (22.9%). $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 7.69 (d, $J$ = 15.9 Hz, 1H), 7.68 (d, $J$ = 15.8 Hz, 1H), 7.54 (d, $J$ = 8.4 Hz, 2H), 7.51 (d, $J$ = 8.1 Hz, 2H), 7.45 (d, $J$ = 8.5 Hz, 2H), 7.08 (d, $J$ = 15.9 Hz, 1H), 6.90 (d, $J$ = 15.8 Hz, 1H), 6.67 (d, $J$ = 8.5 Hz, 2H), 4.00 (s, 1H), 1.71−0.71 (m, 27H). MS (ESI): $m/z$ calcd for $C_{29}H_{41}NOSn$, 539.22; found, 540.30 ($M + H^+$).

*(1E,4E)-1-(4-(Methylamino)phenyl)-5-(4-(tributylstannyl)phenyl) penta-1,4-dien-3-one (**73**).* The same reaction described above to prepare **72** was used. Compound **73** was obtained in a yield of 30.2%. $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 7.69 (d, $J$ = 15.8 Hz, 1H), 7.69 (d, $J$ = 15.9 Hz, 1H), 7.54 (d, $J$ = 8.0 Hz, 2H), 7.53 (d, $J$ = 8.0 Hz, 2H), 7.48 (d, $J$ = 8.6 Hz, 2H), 7.09 (d, $J$ = 15.9 Hz, 1H), 6.88 (d, $J$ = 15.7 Hz, 1H), 6.60 (d, $J$ = 8.4 Hz, 2H), 4.12 (s, 1H), 2.90 (s, 3H), 1.82−0.58 (m, 27H). MS (ESI): $m/z$ calcd for $C_{30}H_{43}NOSn$, 552.24; found, 553.25 ($M + H^+$).

*(1E,4E)-1-(4-(Dimethylamino)phenyl)-5-(4-(tributylstannyl)phenyl) penta-1,4-dien-3-one (**74**).* The reaction described above to prepare **72** was used, and **74** was obtained in a yield of 26.9%. $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 7.71 (d, $J$ = 15.7 Hz, 1H), 7.69 (d, $J$ = 15.9 Hz, 1H), 7.60−7.44 (m, 6H), 7.10 (d, $J$ = 15.9 Hz, 1H), 6.88 (d, $J$ = 15.8 Hz, 1H), 6.69 (d, $J$ = 8.9 Hz, 2H), 3.03 (s, 6H), 1.82−0.77 (m, 27H). MS (ESI): $m/z$ calcd for $C_{31}H_{45}$, 567.25; found, 568.25 ($M + H^+$).

*(1E,4E)-1-(4-(Dimethylamino)phenyl)-5-(4-(2-hydroxyethoxy)phenyl) penta-1,4-dien-3-one (**75**).* Compound **75** was prepared following general procedure A. Yield, 89.8%. $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 7.71 (d, $J$ = 15.5 Hz, 1H), 7.68 (d, $J$ = 15.8 Hz, 1H), 7.57 (d, $J$ = 8.1 Hz, 2H), 7.52 (d, $J$ = 8.2 Hz, 2H), 6.98 (d, $J$ = 16.0 Hz, 1H), 6.95 (d, $J$ = 8.0 Hz, 2H), 6.88 (d, $J$ = 15.8 Hz, 1H), 6.70 (d, $J$ = 8.2 Hz, 2H), 4.14 (t, $J$ = 4.0 Hz, 2H), 4.05−3.92 (m, 2H), 3.05 (s, 6H). MS (ESI): $m/z$ calcd for $C_{21}H_{23}NO_3$, 337.17; found, 338.10 ($M + H^+$).

*(1E,4E)-1-(4-(Dimethylamino)phenyl)-5-(4-(2-(2-hydroxyethoxy)-ethoxy)phenyl)penta-1,4-dien-3-one (**76**).* Compound **76** was prepared following general procedure A. Yield, 84.3%. $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 7.70 (d, $J$ = 15.8 Hz, 1H), 7.67 (d, $J$ = 15.8 Hz, 1H), 7.56 (d, $J$ = 8.8 Hz, 2H), 7.52 (d, $J$ = 8.9 Hz, 2H), 6.97 (d, $J$ = 15.2 Hz, 1H), 6.94 (d, $J$ = 8.6 Hz, 2H), 6.87 (d, $J$ = 15.8 Hz, 1H), 6.70 (d, $J$ = 8.8 Hz, 2H), 4.29−4.11 (m, 2H), 3.96−3.84 (m, 2H), 3.80−3.75 (m, 2H), 3.72−3.65 (m, 2H), 3.04 (s, 6H). MS (ESI): $m/z$ calcd for $C_{23}H_{27}NO_4$, 381.19; found, 382.10 ($M + H^+$).

*(1E,4E)-1-(4-(Dimethylamino)phenyl)-5-(4-(2-(2-(2-hydroxyethoxy)ethoxy)ethoxy)phenyl)penta-1,4-dien-3-one (**77**).* Compound 77 was prepared following general procedure A. Yield, 79.2%. $^1$H NMR

(400 MHz, $CDCL_3$): $\delta$ 7.70 (d, $J$ = 12.0 Hz, 1H), 7.67 (d, $J$ = 12.1 Hz, 1H), 7.55 (d, $J$ = 8.8 Hz, 2H), 7.52 (d, $J$ = 8.9 Hz, 2H), 6.97 (d, $J$ = 13.9 Hz, 2H), 6.94 (d, $J$ = 6.8 Hz, 1H), 6.87 (d, $J$ = 15.7 Hz, 1H), 6.69 (d, $J$ = 8.9 Hz, 2H), 4.19−4.16 (m, 2H), 3.91−3.85 (m, 2H), 3.77−3.68 (m, 6H), 3.66−3.59 (m, 2H), 3.04 (s, 6H). MS (ESI): $m/z$ calcd for $C_{25}H_{31}NO_5$, 425.22; found, 426.25 ($M + H^+$).

*2-(4-((1E,4E)-5-(4-(Dimethylamino)phenyl)-3-oxopenta-1,4-dien-1-yl)-phenoxy)ethyl 4-methylbenzenesulfonate (**78**).* To a solution of **75** (101 mg, 0.3 mmol) in pyridine (8 mL) was added tosyl chloride (69 mg, 0.36 mmol). The reaction mixture was stirred for 3 h at room temperature, 50 mL of water was added, and the mixture was extracted with $CHCl_3$. The organic layer was dried over $Na_2SO_4$, and evaporation of the solvent afforded a residue, which was purified by silica gel chromatography to give 69.2 mg of **78** (46.9%). $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 7.82 (d, $J$ = 8.3 Hz, 2H), 7.70 (d, $J$ = 15.8 Hz, 1H), 7.65 (d, $J$ = 15.9 Hz, 1H), 7.52 (d, $J$ = 8.8 Hz, 2H), 7.52 (d, $J$ = 9.0 Hz, 2H), 6.97 (d, $J$ = 15.8 Hz, 1H), 6.86 (d, $J$ = 15.7 Hz, 1H), 6.80 (d, $J$ = 8.8 Hz, 2H), 6.70 (d, $J$ = 8.9 Hz, 2H), 4.50−4.32 (m, 2H), 4.19 (dd, $J$ = 5.5, 3.9 Hz, 2H), 3.04 (s, 6H), 2.45 (s, 3H). MS (ESI): $m/z$ calcd for $C_{28}H_{29}NO_5S$, 491.18; found, 492.34 ($M + H^+$).

*2-(2-(4-((1E,4E)-5-(4-(Dimethylamino)phenyl)-3-oxopenta-1,4-dien-1-yl)phenoxy)ethoxy)ethyl 4-Methylbenzenesulfonate (**79**).* The same reaction described above to prepare **78** was used. Compound **79** was obtained in a yield of 37.5%. $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 7.80 (d, $J$ = 8.3 Hz, 2H), 7.70 (d, $J$ = 15.7 Hz, 1H), 7.67 (d, $J$ = 15.7 Hz, 1H), 7.55 (d, $J$ = 8.7 Hz, 2H), 7.52 (d, $J$ = 8.9 Hz, 2H), 7.30 (d, $J$ = 8.4 Hz, 2H), 6.98 (d, $J$ = 15.8 Hz, 1H), 6.91 (d, $J$ = 8.8 Hz, 2H), 6.87 (d, $J$ = 15.8 Hz, 1H), 6.70 (d, $J$ = 8.9 Hz, 2H), 4.23−4.16 (m, 2H), 4.14−4.02 (m, 2H), 3.90−3.66 (m, 4H), 3.04 (s, 6H), 2.41 (s, 3H). MS (ESI): $m/z$ calcd for $C_{30}H_{33}NO_6S$, 535.20; found, 536.17 ($M + H^+$).

*2-(2-(2-(4-((1E,4E)-5-(4-(Dimethylamino)phenyl)-3-oxopenta-1,4-dien-1-yl)phenoxy)ethoxy)ethoxy)ethyl 4-Methylbenzenesulfonate (**80**).* The reaction described above to prepare **78** was used, and **80** was obtained in a yield of 58.8%. $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 7.80 (d, $J$ = 8.2 Hz, 2H), 7.70 (d, $J$ = 15.7 Hz, 1H), 7.67 (d, $J$ = 15.8 Hz, 1H), 7.55 (d, $J$ = 8.7 Hz, 2H), 7.52 (d, $J$ = 8.8 Hz, 2H), 7.33 (d, $J$ = 8.1 Hz, 2H), 6.97 (d, $J$ = 15.9 Hz, 1H), 6.93 (d, $J$ = 8.7 Hz, 2H), 6.87 (d, $J$ = 15.7 Hz, 1H), 6.70 (d, $J$ = 8.8 Hz, 2H), 4.16 (dd, $J$ = 8.9, 4.0 Hz, 2H), 3.90−3.80 (m, 2H), 3.73−3.68 (m, 2H), 3.64 (ddd, $J$ = 9.0, 5.6, 3.5 Hz, 4H), 3.04 (s, 6H), 2.43 (s, 3H). MS (ESI): $m/z$ calcd for $C_{32}H_{37}NO_7S$, 579.23; found, 580.39 ($M + H^+$).

*(1E,4E)-1-(4-(Dimethylamino)phenyl)-5-(4-(2-fluoroethoxy)phenyl)-penta-1,4-dien-3-one (**81**).* To a solution of **78** (100 mg, 0.2 mmol) in 15 mL of dry tetrahydrofuran (THF) was added anhydrous TBAF (400 $\mu$L, 1 M in THF). The reaction mixture was refluxed for 3 h. After removal of the THF, the residue was purified by silica gel chromatography to give 33.9 mg of **81** (50.0%). $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 7.71 (d, $J$ = 15.7 Hz, 1H), 7.68 (d, $J$ = 15.7 Hz, 1H), 7.57 (d, $J$ = 8.8 Hz, 2H), 7.52 (d, $J$ = 8.9 Hz, 2H), 6.98 (d, $J$ = 15.1 Hz, 1H), 6.95 (d, $J$ = 8.6 Hz, 2H), 6.87 (d, $J$ = 15.7 Hz, 1H), 6.70 (d, $J$ = 8.8 Hz, 2H), 5.09−4.58 (m, 2H), 4.27 (dd, $J$ = 27.6, 4.2 Hz, 2H), 3.04 (s, 6H). MS (ESI): $m/z$ calcd for $C_{21}H_{22}FNO_2$, 339.16; found, 340.17 ($M + H^+$).

*(1E,4E)-1-(4-(Dimethylamino)phenyl)-5-(4-(2-(2-fluoroethoxy)-ethoxy)phenyl)penta-1,4-dien-3-one (**82**).* The same reaction described above to prepare **81** was used. Compound **82** was obtained in a yield of 41.3%. $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 7.70 (d, $J$ = 15.7 Hz, 1H), 7.67 (d, $J$ = 15.8 Hz, 1H), 7.56 (d, $J$ = 8.7 Hz, 2H), 7.52 (d, $J$ = 8.9 Hz, 2H), 6.97 (d, $J$ = 14.9 Hz, 1H), 6.95 (d, $J$ = 8.6 Hz, 2H), 6.87 (d, $J$ = 15.7 Hz, 1H), 6.70 (d, $J$ = 8.9 Hz, 2H), 4.67−4.53 (m, 1H), 4.28−4.11 (m, 2H), 4.02−3.75 (m, 4H), 3.66 (t, $J$ = 5.9 Hz, 1H), 3.04 (s, 6H). MS (ESI): $m/z$ calcd for $C_{23}H_{26}FNO_3$, 383.19; found, 384.21 ($M + H^+$).

*(1E,4E)-1-(4-(Dimethylamino)phenyl)-5-(4-(2-(2-(2-fluoroethoxy)-ethoxy)ethoxy)phenyl)penta-1,4-dien-3-one (**83**).* The reaction described above to prepare **81** was used, and **83** was obtained in a yield of 36.6%. $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 7.70 (d, $J$ = 15.5 Hz, 1H), 7.67 (d, $J$ = 15.5 Hz, 1H), 7.55 (d, $J$ = 7.2 Hz, 2H), 7.51 (d, $J$ = 7.7 Hz, 2H), 6.97 (d, $J$ = 16.0 Hz, 1H), 6.93 (d, $J$ = 8.8 Hz, 2H), 6.86 (d, $J$ = 15.7 Hz, 1H), 6.68 (d, $J$ = 7.7 Hz, 2H), 4.67−4.59 (m, 1H), 4.53−4.45 (m, 1H), 4.17 (t, $J$ = 3.9 Hz, 2H), 3.88 (t, $J$ = 3.9 Hz, 2H), 3.83−3.77 (m, 1H), 3.77−3.67 (m, 5H), 3.03 (s, 6H). HRMS (EI): $m/z$ ($EI^+$): calcd for $C_{25}H_{30}FNO_4$, 427.2159; found, 427.2152.

*4-(2-(2-(2-Fluoroethoxy)ethoxy)ethoxy)benzaldehyde (**84**).* To a solution of 4-(2-(2-(2-hydroxyethoxy)ethoxy)ethoxy)benzaldehyde (508 mg, 2 mmol) in $CHCl_3$ (5 mL) was added DAST (645 mg, 4 mmol) in a dry ice−acetone bath. The reaction mixture was stirred for 2 h at room temperature and then poured into a saturated $NaHSO_3$ solution and extracted with chloroform. The organic phase was separated, dried over $MgSO_4$, and filtered, and the residue was purified by silica gel chromatography to give 299 mg of **84** (58.3%). $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 9.88 (s, 1H), 7.83 (d, $J$ = 8.9 Hz, 2H), 7.02 (d, $J$ = 8.8 Hz, 2H), 4.62 (dd, $J$ = 4.6, 3.7 Hz, 1H), 4.50 (dd, $J$ = 4.7, 3.7 Hz, 1H), 4.22 (dd, $J$ = 5.4, 4.2 Hz, 2H), 3.90 (dd, $J$ = 5.4, 4.2 Hz, 2H), 3.83−3.67 (m, 6H). MS (ESI): $m/z$ calcd for $C_{13}H_{17}FO_4$, 256.11; found, 257.10 ($M + H^+$).

*(1E,4E)-1-(4-(2-(2-(2-Fluoroethoxy)ethoxy)ethoxy)phenyl)-5-(4-(methylamino)phenyl)penta-1,4-dien-3-one (**85**).* Compound **85** was prepared following general procedure A. Yield, 67.2%. $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 7.68 (d, $J$ = 15.8 Hz, 1H), 7.67 (d, $J$ = 15.8 Hz, 1H), 7.54 (d, $J$ = 8.8 Hz, 2H), 7.47 (d, $J$ = 8.7 Hz, 2H), 6.96 (d, $J$ = 15.8 Hz, 1H), 6.93 (d, $J$ = 8.8 Hz, 2H), 6.86 (d, $J$ = 15.8 Hz, 1H), 6.58 (d, $J$ = 8.7 Hz, 2H), 4.62 (dd, $J$ = 4.7, 3.7 Hz, 1H), 4.50 (dd, $J$ = 4.7, 3.7 Hz, 1H), 4.26−4.11 (m, 2H), 3.88 (dd, $J$ = 5.4, 4.2 Hz, 2H), 3.83−3.66 (m, 6H), 2.87 (s, 3H). HRMS (EI): $m/z$ ($EI^+$): calcd for $C_{24}H_{28}FNO_4$, 413.2002; found, 413.2007.

*(1E,4E)-1-(4-(2-(2-(2-Hydroxyethoxy)ethoxy)ethoxy)phenyl)-5-(4-(methylamino)phenyl)penta-1,4-dien-3-one (**86**).* Compound **86** was prepared following general procedure A. Yield, 70.5%. $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 7.68 (d, $J$ = 15.8 Hz, 1H), 7.66 (d, $J$ = 15.8 Hz, 1H), 7.54 (d, $J$ = 8.8 Hz, 2H), 7.47 (d, $J$ = 8.7 Hz, 2H), 6.95 (d, $J$ = 15.8 Hz, 1H), 6.93 (d, $J$ = 8.8 Hz, 2H), 6.85 (d, $J$ = 15.7 Hz, 1H), 6.58 (d, $J$ = 8.7 Hz, 2H), 4.20−4.13 (m, 2H), 3.93−3.83 (m, 2H), 3.72 (ddd, $J$ = 5.8, 4.6, 2.8 Hz, 6H), 3.65−3.58 (m, 2H), 2.88 (s, 3H). MS (ESI): $m/z$ calcd for $C_{24}H_{29}NO_5$, 411.20; found, 412.40 ($M + H^+$).

*(1E,4E)-1-(4-(Methylamino)phenyl)-5-(4-((2,2,3,3-tetramethyl-4,7,10-trioxa-3-siladodecan-12-yl)oxy)phenyl)penta-1,4-dien-3-one (**87**).* Compound **86** (659 mg, 1.60 mmol) and TBDMSCl (386 mg, 2.56 mmol) were dissolved in dichloromethane (15 mL) followed by imidazole (120 mg, 3.20 mmol). The solution was stirred at room temperature for 2 h. A white solid formed and was filtered off. After the filtrate was evaporated, the residue was purified by silica gel column chromatography to afford **87** (502 mg, 59.5%). $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 7.61 (d, $J$ = 15.7 Hz, 1H), 7.59 (d, $J$ = 15.8 Hz, 1H), 7.44 (d, $J$ = 8.7 Hz, 2H), 7.36 (d, $J$ = 8.6 Hz, 2H), 6.88 (d, $J$ = 15.9 Hz, 1H), 6.84 (d, $J$ = 8.7 Hz, 2H), 6.77 (d, $J$ = 15.7 Hz, 1H), 6.48 (d, $J$ = 8.6 Hz, 2H), 4.46 (s, 1H), 4.05 (t, $J$ = 5.3 Hz, 2H), 3.77 (t, $J$ = 5.3 Hz, 2H), 3.70 (t, $J$ = 5.3 Hz, 2H), 3.68−3.57 (m, 4H), 3.49 (t, $J$ = 5.3 Hz, 2H), 2.74 (s, 3H), 0.83 (s, 9H). MS (ESI): $m/z$ calcd for $C_{30}H_{43}NO_5Si$, 525.29; found, 526.29 ($M + H^+$).

*tert-Butylmethyl(4-((1E,4E)-3-oxo-5-(4-((2,2,3,3-tetramethyl-4,7,10-trioxa-3-siladodecan-12-yl)oxy)phenyl)penta-1,4-dien-1-yl)phenyl)-carbamate (**88**).* Under a nitrogen atmosphere, **87** (491 mg, 0.94 mmol) was dissolved in anhydrous THF (20 mL) followed by Boc-anhydride (408 mg, 1.87 mmol). The solution was refluxed for 48 h. After the reaction was complete, the solvent was removed, and the residue was purified by silica gel column chromatography to afford **88** (433 mg, 74.1%). $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 7.64 (d, $J$ = 15.9 Hz, 1H), 7.63 (d, $J$ = 15.9 Hz, 1H), 7.51 (d, $J$ = 3.6 Hz, 2H), 7.49 (d, $J$ = 3.9 Hz, 2H), 7.24 (d, $J$ = 8.6 Hz, 2H), 6.95 (d, $J$ = 15.9 Hz, 1H), 6.89

(d, $J$ = 16.0 Hz, 1H), 6.87 (s, $J$ = 8.5 Hz, 2H), 4.17−4.06 (m, 2H), 3.84−3.80 (m, 2H), 3.71 (t, $J$ = 5.4 Hz, 2H), 3.64 (qdd, $J$ = 4.8, 3.7, 1.8 Hz, 4H), 3.51 (t, $J$ = 5.4 Hz, 2H), 3.23 (s, 3H), 1.41 (s, 9H), 0.83 (s, 9H). MS (ESI): $m/z$ calcd for $C_{35}H_{51}NO_7Si$, 625.34; found, 626.30 ($M + H^+$).

*tert-Butyl(4-((1E,4E)-5-(4-(2-(2-(2-hydroxyethoxy)ethoxy)ethoxy)-phenyl)-3-oxopenta-1,4-dien-1-yl)phenyl)(methyl)carbamate (**89**).* To a solution of **88** (433 mg, 0.69 mmol) in dry THF (15 mL) was added anhydrous TBAF (1.4 mL, 1 M in THF). The solution was stirred at room temperature for 2 h. After removal of the THF, the residue was purified by silica gel chromatography to give 300 mg of **89** (85.0%). $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 7.70 (d, $J$ = 15.9 Hz, 1H), 7.69 (d, $J$ = 15.9 Hz, 1H), 7.57 (d, $J$ = 5.2 Hz, 2H), 7.55 (d, $J$ = 5.3 Hz, 2H), 7.31 (d, $J$ = 8.4 Hz, 2H), 7.02 (d, $J$ = 15.9 Hz, 1H), 6.96 (d, $J$ = 16.3 Hz, 1H), 6.95 (d, $J$ = 8.3 Hz, 2H), 4.21−4.14 (m, 2H), 3.92−3.84 (m, 2H), 3.76−3.66 (m, 6H), 3.65−3.58 (m, 2H), 3.29 (s, 3H), 1.48 (s, 9H). MS (ESI): $m/z$ calcd for $C_{29}H_{37}NO_7$, 511.26; found, 534.35 ($M + Na^+$).

*2-(2-(2-(4-((1E,4E)-5-(4-((tert-Butoxycarbonyl)(methyl)amino)phenyl)-3-oxopenta-1,4-dien-1-yl)phenoxy)ethoxy)ethoxy)ethyl methanesulfonate (**90**).* Compound **89** (290 mg, 0.567 mmol) was dissolved in dichloromethane (15 mL) followed by triethylamine (287.2 mg, 2.84 mmol). Methanesulfonyl chloride (195 mg, 1.70 mmol) was then added via a syringe. The solution was stirred at room temperature for 4 h. Next, 50 mL of water was added and extracted with $CHCl_3$ (3 × 50 mL). The organic layer was dried over $MgSO_4$. After the solvent was removed, the residue was purified by silica gel chromatography to afford **90** (214 mg, 64%). $^1$H NMR (400 MHz, $CDCL_3$): $\delta$ 7.70 (d, $J$ = 15.8 Hz, 1H), 7.69 (d, $J$ = 16.0 Hz, 1H), 7.58 (d, $J$ = 3.1 Hz, 2H), 7.56 (d, $J$ = 3.3 Hz, 2H), 7.31 (d, $J$ = 8.5 Hz, 2H), 7.03 (d, $J$ = 15.9 Hz, 1H), 6.97 (d, $J$ = 15.8 Hz, 1H), 6.94 (d, $J$ = 8.5 Hz, 2H), 4.44−4.29 (m, 2H), 4.23−4.02 (m, 2H), 3.91−3.79 (m, 2H), 3.79−3.75 (m, 2H), 3.74−3.64 (m, 4H), 3.29 (s, 3H), 3.05 (s, 3H), 1.48 (s, 9H). MS (ESI): $m/z$ calcd for $C_{30}H_{39}NO_9S$, 589.23; found, 590.25 ($M + H^+$).

**Radiolabeling.** *Procedure for Labeling of [$^{125}$I]**6**, [$^{125}$I]**70**, and [$^{125}$I]**71**.* The radioiodinated ligands [$^{125}$I]**6**, [$^{125}$I]**70**, and [$^{125}$I]**71** were prepared from the corresponding tributyltin precursors through an iododestannylation reaction using hydrogen peroxide as an oxidant with radiochemical yields of 27.6, 15.3, and 24.1%, respectively. After purification by HPLC, the radiochemical purity of these ligands was greater than 98% [HPLC conditions: Waters 5C18-AR-II column (Analytical 4.6 mm × 150 mm) $CH_3CN/H_2O$ = 6/4, 1 mL/min for **70**, $CH_3CN/H_2O$ = 7/3, 1 mL/min for **71**, and $CH_3CN/H_2O$ = 8/2, 1 mL/min for **6**]. The specific activity of the no carrier-added preparation was comparable to that of Na$^{125}$I, 2200 Ci/mmol. Finally, the radiochemical identity of the radioiodinated ligands was verified by coinjection with nonradioactive compounds using HPLC profiles. The final product was stored at −20 °C for autoradiography and biodistribution experiments.

*Procedure for Labeling of [$^{18}$F]**83** and [$^{18}$F]**85**.* [$^{18}$F]Fluoride was produced by the JSW typeBC3015 cyclotron via an $^{18}$O(p,n)$^{18}$F reaction and passed through a Sep-Pak Light QMA cartridge (Waters) as an aqueous solution in $^{18}$O-enriched water. The cartridge was dried by airflow, and the $^{18}F^-$ activity was eluted with a $K_2CO_3$ solution (33 mM). Kryptofix$_{222}$ (6−8 mg) was dissolved in the solution of [$^{18}$F]fluoride in water. The solvent was removed at 120 °C under a stream of nitrogen gas. The residue was azeotropically dried with 0.3 mL of anhydrous acetonitrile twice at 120 °C under a stream of nitrogen gas. For [$^{18}$F]**83**, a solution of the tosylate precursor **80** (1.0 mg) in DMSO (0.2 mL) was added to the reaction vessel containing the $^{18}F^-$ activity. The mixture was heated at 120 °C for 5 min. Water (3 mL) was added, and the mixture was passed through a preconditioned Sep-Pak Plus-C18 cartridge (Waters). The cartridge was washed with 10 mL of water, and the labeled compound was eluted with 2 mL of acetonitrile. The eluted compound was purified by semipreparative HPLC (Waters, 5C18-AR-II, 10 mm × 150 mm). The retention time of [$^{18}$F]**83** was 13.1 min in this HPLC system ($CH_3CN$/water = 7/3; flow rate = 4 mL/min). The preparation took 40 min, and the radiochemical yield was 49% (decay corrected). For [$^{18}$F]**85**, a solution of the mesylate precursor **90** (1.0 mg) in DMSO (0.2 mL) was added to the reaction vessel containing the $^{18}F^-$ activity. The mixture was heated at 120 °C for 5 min. Water (2 mL) was added, and the solution was cooled down for 1 min. HCl (1 M aqueous solution, 2 mL) was then added, and the mixture was heated at 120 °C again for 5 min. An aqueous solution of $K_2CO_3$ was added to adjust the pH to basic (pH 8−9). The mixture was extracted with ethyl acetate (1 mL × 2), the combined organic layer was dried ($Na_2SO_4$), and the solvent was removed. The residue was dissolved in $CH_3CN$ and subjected to HPLC for purification (Waters, 5C18-AR-II, 10 mm × 150 mm, $CH_3CN$/water = 1/1; flow rate = 4 mL/min). The retention time of [$^{18}$F]**85** was 6.6 min in this HPLC system. The preparation took 80 min, and the radiochemical yield was 13% (decay corrected). The radiochemical purity of both tracers was greater than 98% with an estimated specific activity of 900−1500 Ci/mmol.

**Binding Assay in Vitro Using A$\beta$ Aggregates.** Inhibition experiments were carried out in 12 mm × 75 mm borosilicate glass tubes according to procedures described previously with some modifications.[22] Briefly, 100 $\mu$L of aggregated A$\beta$ fibrils (60 nM in the final assay mixture) was added to a mixture containing 100 $\mu$L of radioligands ([$^{125}$I]IMPY) at an appropriate concentration, 10 $\mu$L of inhibitors ($10^{-5}$−$10^{-10}$ M in ethanol), and 790 $\mu$L of PBS (0.2 M, pH = 7.4) in a final volume of 1 mL. Nonspecific binding was defined in the presence of 1 $\mu$M IMPY. The mixture was incubated for 2 h at 37 °C with constant shaking, and then, the bound and free radioactive fractions were separated by vacuum filtration through borosilicate glass fiber filters (Whatman GF/B) using a M-24 cell harvester (Brandel, Gaithersburg, MD). The radioactivity from filters containing the bound $^{125}$I ligand was measured in a $\gamma$-counter (WALLAC/Wizard 1470, United States) with 70% efficiency. Under the assay conditions, the specifically bound fraction accounted for about 10% of total radioactivity. The half maximal inhibitory concentration ($IC_{50}$) was determined using GraphPad Prism 4.0, and the inhibition constant ($K_i$) was calculated using the Cheng−Prusoff equation: $K_i = IC_{50}/(1 + [L]/K_d)$.[40]

**Autoradiography in Vitro Using Tg Mouse Brains.** Paraffin-embedded mouse brain sections (C57BL6-APP/PS1, 12 months old, male) and wild-type control mouse brain sections (C57BL6, 12 months old, male) were deparaffinized with 2 × 20 min washes in xylene, 2 × 5 min washes in 100% ethanol, a 5 min wash in 90% ethanol/$H_2O$, a 5 min wash in 80% ethanol/$H_2O$, a 5 min wash in 60% ethanol/$H_2O$, and a 10 min wash in running tap water, and then incubated in PBS (0.2 M, pH = 7.4) for 30 min. The sections were incubated with radiolabeled tracers (5 $\mu$Ci/100 $\mu$L) for 1 h at room temperature, then washed with 40% ethanol for 3 min, and rinsed with water for 30 s. After they were dried, the labeled sections were exposed to a Fuji Film imaging plate overnight. The in vitro autoradiographic images were obtained using a BAS5000 scanner system (Fuji Film). The presence and location of plaques in the sections were confirmed with fluorescent staining using thioflavin S.

**Autoradiography in Vitro Using Human AD Brains.** Paraffin-embedded postmortem brain sections (Temporal lobe) of an AD patient (75 year old male) and normal control brain sections (20 year old male) were obtained from BioChain. The same protocol was employed as for the Tg mouse brains. Finally, the presence and location of plaques in the sections were confirmed with immunohistochemical staining using a monoclonal A$\beta_{1-42}$ antibody, BC05 (Wako).

**Biodistribution Experiments in Vivo Using Normal ddY Mice.** The biodistribution experiments were performed in normal female ddY mice (5 weeks, average weight, about 20 g) and approved by the animal care committee of Kyoto University. A saline solution containing the radiolabeled tracers (1 $\mu$Ci/100 $\mu$L for radioiodinated tracers, 10 $\mu$Ci/100 $\mu$L for radiofluorinated tracers) was injected directly into the tail. The mice were sacrificed at various time points

postinjection. The organs of interest were removed and weighed, and the radioactivity was measured with an automatic $\gamma$-counter (WALLAC/Wizard 1470). The percent dose per gram of wet tissue was calculated by a comparison of the tissue counts to suitably diluted aliquots of the injected material.

**Determination of the Partition Coefficient.** The partition coefficients for these radiolabeled compounds were determined as described previously but with some modifications.[41] The radiolabeled compound (10 $\mu$Ci) was added to a premixed suspensions containing 3 g of *n*-octanol and 3 g of PBS (0.05 M, pH = 7.4) in a test tube. The test tube was vortexed for 3 min at room temperature and centrifuged for 5 min at 3000 rpm. Two weighted samples from the *n*-octanol (100 $\mu$L) and buffer (500 $\mu$L) layers were measured. The partition coefficient was expressed as the logarithm of the ratio of the count per gram from *n*-octanol versus PBS. Samples from the *n*-octanol layer were repartitioned until consistent partition coefficient values were obtained. The measurement was done in triplicate and repeated three times.

## ■ ASSOCIATED CONTENT

**Supporting Information.** Purity of key target compounds together with HPLC chromatograms, $^1$H NMR spectra of compounds, and HRMS data of key target compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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## ■ ABBREVIATIONS USED

AD, Alzheimer's disease; A$\beta$, $\beta$-amyloid; NFTs, neurofibrillary tangles; PET, positron emission tomography; SPECT, single photon emission computed tomography; ThT, thioflavin T; CR, Congo Red; BBB, blood−brain barrier; SAR, structure−activity relationship; TBDMSCl, *tert*-butyldimethylsilyl chloride; BOC, butyloxycarbonyl; DMSO, dimethyl sulfoxide; HPLC, high-performance liquid chromatography; THF, tetrahydrofuran; TBAF, tetra-*n*-butylammonium fluoride; FPEG, fluoro-pegylated; Tg, transgenic; IMSB, 1-iodo-2,5-bis(3-hydroxycarbonyl-4-methoxy) styrylbenzene

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