Journal of Medicinal Chemistry

Article

pubs.acs.org/jmc

Novel Carvedilol Analogues That Suppress Store-Overload-Induced Ca^{2+} Release

Chris D. Smith,[†] Aixia Wang,[†] Kannan Vembaiyan,[†] Jingqun Zhang,[§] Cuihong Xie,[§] Qiang Zhou,[§] Guogen Wu,[§] S. R. Wayne Chen,[‡,§] and Thomas G. Back*[,†]

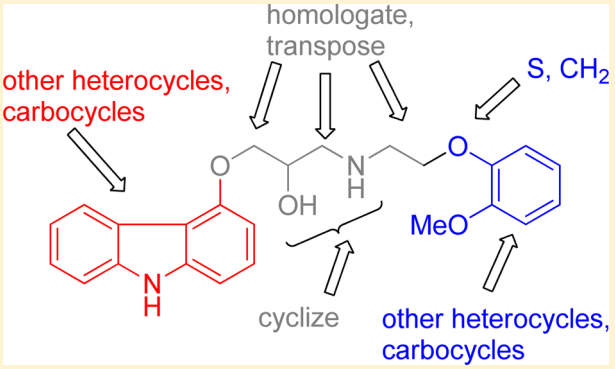
[†]Department of Chemistry, University of Calgary, Calgary, Alberta T2N 1N4, Canada

[‡]Libin Cardiovascular Institute of Alberta, Department of Physiology and Pharmacology, University of Calgary, Calgary, Alberta T2N 4N1, Canada

[§]Department of Molecular Biophysics and Physiology, Rush University Medical Center, Chicago, Illinois 60612, United States

Supporting Information

ABSTRACT: Carvedilol is a uniquely effective drug for the treatment of cardiac arrhythmias in patients with heart failure. This activity is in part because of its ability to inhibit store-overload-induced calcium release (SOICR) through the RyR2 channel. We describe the synthesis, characterization, and bioassay of ca. 100 compounds based on the carvedilol motif to identify features that correlate with and optimize SOICR inhibition. A single-cell bioassay was employed on the basis of the RyR2-R4496C mutant HEK-293 cell line in which calcium release from the endoplasmic reticulum through the defective channel was measured. IC_{50} values for SOICR inhibition were thus obtained. The compounds investigated contained modifications to the three principal subunits of carvedilol, including the carbazole and catechol moieties, as well as the linker chain containing the β-amino alcohol functionality. The SAR results indicate that significant alterations are tolerated in each of the three subunits.



INTRODUCTION

Ventricular arrhythmias are a leading cause of sudden death, particularly in patients with heart failure. Consequently, a variety of antiarrhythmic drug therapies have been evaluated in clinical trials, which revealed only limited survival benefits.[1−3] Antagonists of β-adrenergic receptors (β-blockers) have been of special interest in these studies, as overstimulation of these receptors can trigger fatal ventricular arrhythmias.[4−6] The underlying mechanism of this process involves, in part, an overload of Ca^{2+} in the sarcoplasmic reticulum, which results in spontaneous Ca^{2+} efflux through the RyR2 Ca^{2+}-release channel.[7,8] In turn, this store-overload-induced calcium release (SOICR) through a defective RyR2[7−14] triggers delayed afterdepolarizations (DADs),[15−21] which have been implicated in catecholaminergic polymorphic ventricular tachycardias (CPVTs) as well as in ventricular tachyarrhythmias and sudden death.[4,5,22,23]

The nonselective β-blocker carvedilol (**1**) and certain congeners also inhibit the α-adrenergic receptor[24] and are reported to display antioxidant activity.[25,26] Thus, **1** has proven uniquely effective in suppressing ventricular arrhythmias in patients with failing hearts.[27−30] Unfortunately, the benefits of carvedilol therapy are limited by drug intolerance and excessive β-blockade, with attendant complications of bradycardia and hypotension.[2,31] More recently, we demonstrated that a variety of other α- and β-blockers, as well as antioxidants, failed in the suppression of SOICR.[32] This suggests that the unique efficacy of carvedilol in suppressing SOICR occurs independently of its α- and β-blocking activity and its antioxidant properties, and it is instead principally because of its ability to stabilize Ca^{2+} handling via the RyR2 channel. Indeed, we recently reported three novel carvedilol analogues **2**−**4** (Chart 1) with comparable abilities to inhibit SOICR to that of the parent compound **1** (ca. 10 μM) but with strongly attenuated β-blockade (ca. micromolar compared to nanomolar for **1**). Compounds **2**−**4** proved highly effective in preventing stress-induced ventricular arrhythmias in mice (vide infra) without the undesired effects of excessive β-blockade.[32]

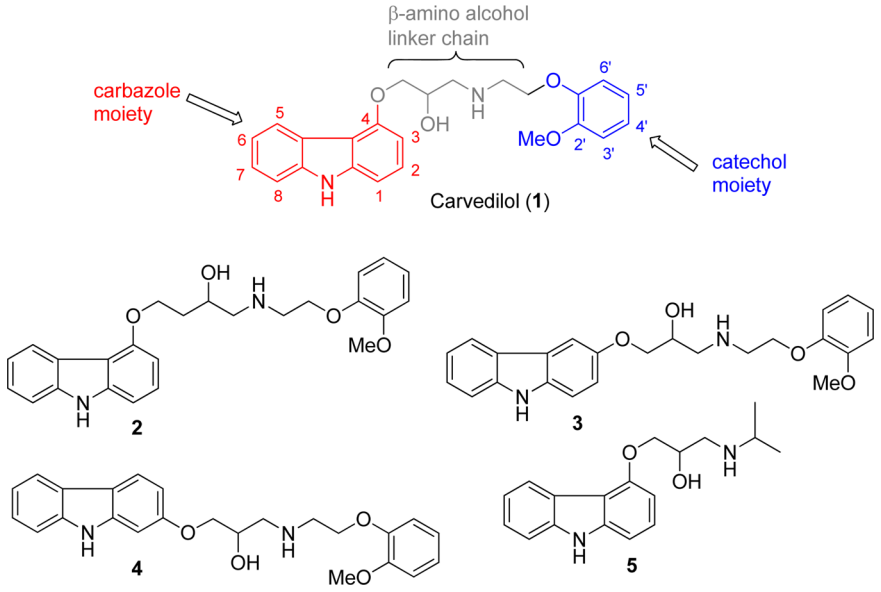
For the purpose of these studies, a convenient single-cell bioassay was developed for measuring SOICR suppression by drug candidates, which is based on human embryonic kidney (HEK 293) cells expressing a mutant RyR2 channel (R4496C).[7,8] This mutation results in spontaneous calcium release from the endoplasmic reticulum of the cells through the defective channel, with calcium efflux detected by the measurement of fluorescence from the Ca^{2+}-sensitive indicator dye fura 2/AM.

Moreover, the same R4496C mutation in mice renders them highly susceptible to stress-induced ventricular arrhythmias, which are easily triggered by stimulants such as caffeine and

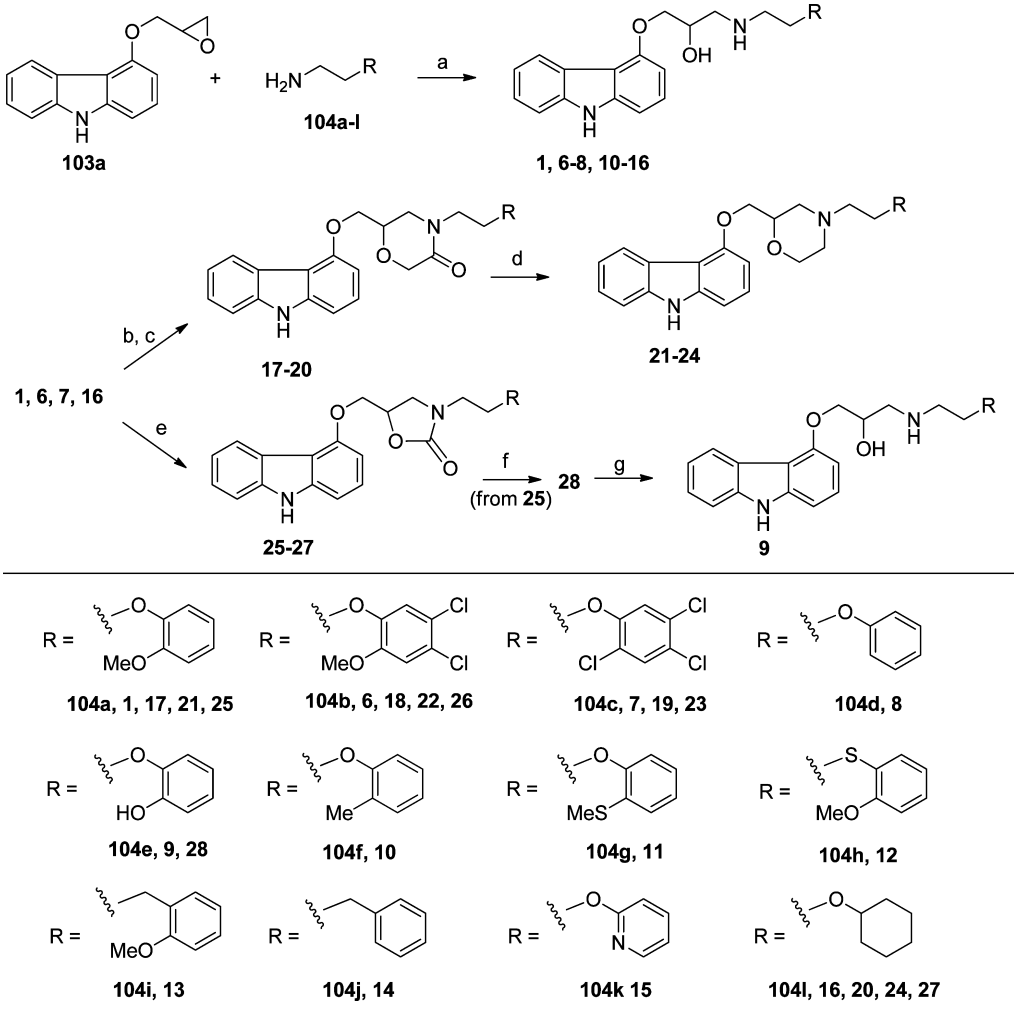
Received: July 18, 2013
Published: October 14, 2013

   dx.doi.org/10.1021/jm401090a | J. Med. Chem. 2013, 56, 8626−8655

Chart 1. Structures of Carvedilol and Some of Its Analogues



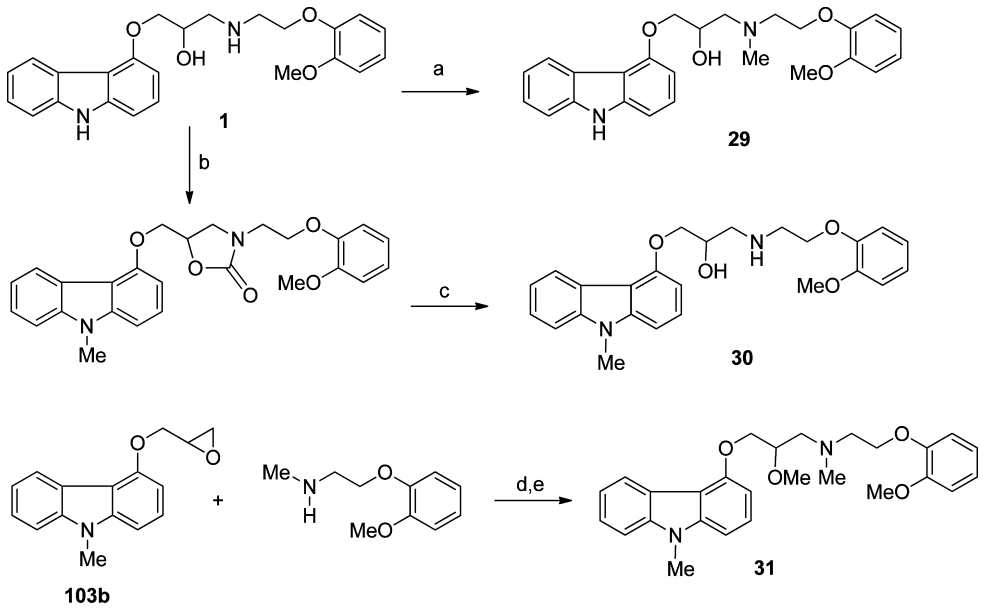
Scheme 1[a]



[a](a) LiBr, DME, 50 °C or *i*-PrOH, reflux. (b) Chloroacetyl chloride, Et_3N, $CHCl_3$, rt. (c) NaH, THF, rt. (d) $LiAlH_4$, THF, rt. (e) 1,1′-Carbonyldiimidazole, Et_3N, CH_2Cl_2, rt. (f) BBr_3, CH_2Cl_2, rt. (g) 2 M NaOH, EtOH, reflux.

dx.doi.org/10.1021/jm401090a | *J. Med. Chem.* 2013, 56, 8626−8655

Scheme 2[a]



[a](a) NaH, MeI, THF, rt. (b) $(MeO)_2C{=}O$, DABCO, DMF, 95 °C. (c) LiOH, EtOH, reflux. (d) *i*-PrOH, reflux. (e) NaH, MeI, DMF, rt.

epinephrine. This provides a useful animal model for evaluating potential antiarrhythmic drugs.[9−14]

Our initial efforts that led to the discovery of **2**−**4** were guided by the X-ray crystal structure of the complex of the carvedilol analogue carazolol (**5**) with the β-adrenergic receptor that had been previously reported by Stevens, Kobilka, and their coworkers.[33] Their results indicated that the carbazole amino group participates in hydrogen bonding with residue S203 of the receptor, whereas multiple hydrogen bonds occur between the secondary alcohol and the protonated amino group of the β-amino alcohol moiety with residues D113, Y316, and N312. Furthermore, a series of hydrophobic interactions were observed involving the aromatic rings of the carbazole and the *N*-isopropyl group of **5** with corresponding hydrophobic pockets in the receptor. Blocking, modifying, or relocating the key hydrogen-bonding functionalities and hydrophobic regions of carvedilol might therefore be expected to disrupt its binding to the β-adrenergic receptor. Similarly, a catechol moiety is a common structural motif in many α-blockers,[24] suggesting that manipulation of this group in **1** could result in diminished α-blockade. However, such structural changes might also interfere with binding to RyR2 and SOICR suppression. We now report the synthesis of a wide range of novel structures, in addition to the carvedilol analogues **2**−**4**, as part of a SAR investigation to determine how such structural modifications would affect the abilities of these compounds to decrease SOICR in the HEK 293 (R4496C) cell line.

RESULTS

The SOICR-suppressing ability of a series of carvedilol analogues, **2**−**94**, **97**, and **98**, as well as of reference compounds **1**, **95**, **96**, and **99**−**102** that were included for comparison is shown in Tables 1−8. All compounds were tested for SOICR inhibition in the RyR2-R4496C mutant HEK293 cell line, and the IC_{50} values along with the number of replicates and the total number of cells employed in the assay are provided in the tables.

Chemistry. The synthesis of compounds **1**, **6**−**8**, and **10**−**16** in Table 1 was achieved by reacting the commercially available epoxide **103a** with the corresponding amines **104a**-**l**, as shown in Scheme 1. Cyclization of amino alcohols **1**, **6**, **7**, and **16** with chloroacetyl chloride afforded lactams **17**−**20**, whereas the use of 1,1′-carbonyldiimidazole afforded products **25**−**27** in Table 2. The reduction of **17**−**20** with lithium aluminum hydride provided **21**−**24**. The free phenol **28** was obtained by demethylation of **25** with boron tribromide, whereas hydrolysis of **28** afforded the amino alcohol **9**.

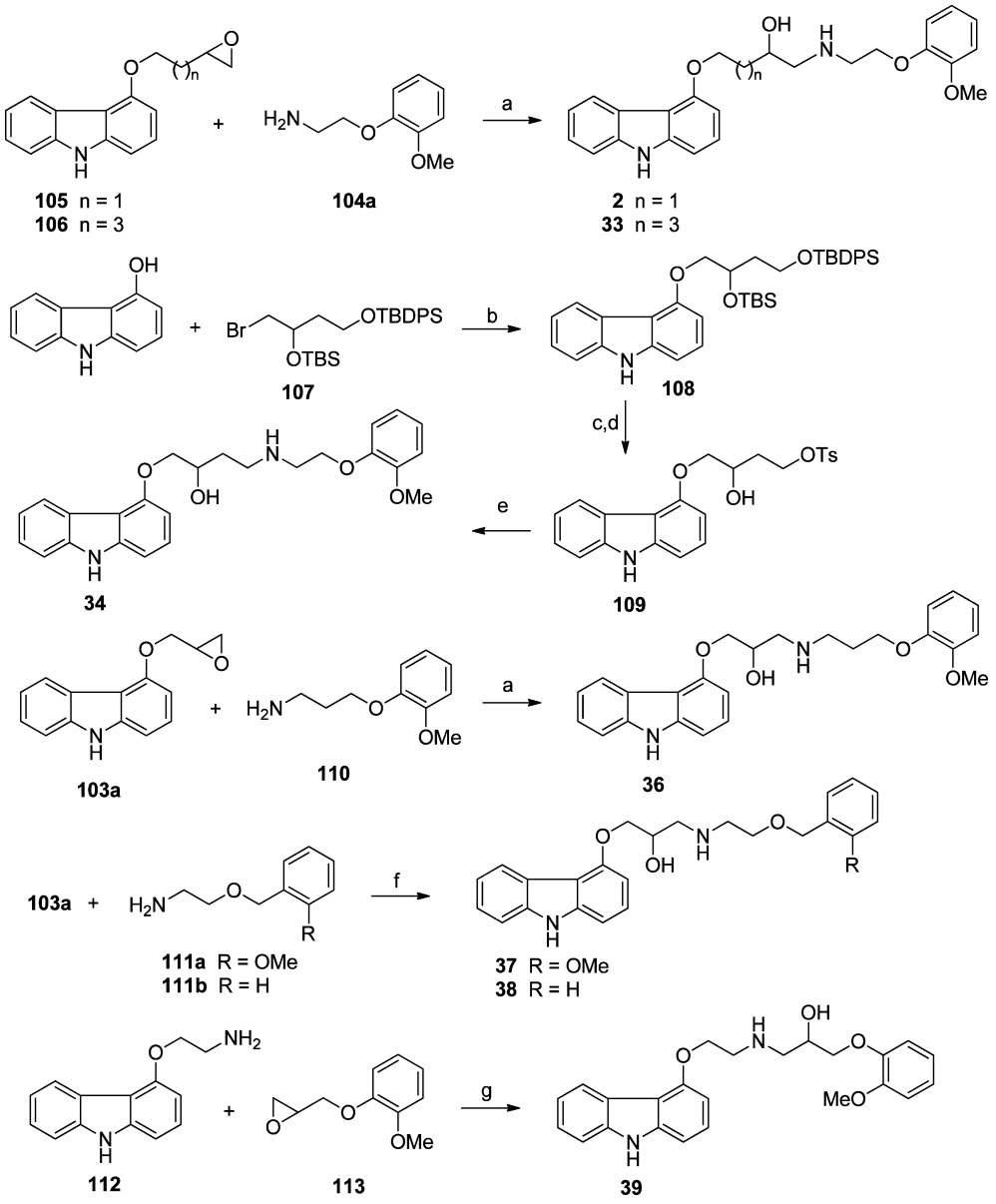
The methylated product **29** in Table 2 was prepared by methylation of **1** with iodomethane, whereas **30** was obtained from **1** by cyclization and *N*-methylation with dimethyl carbonate in one step followed by hydrolysis (Scheme 2). Compound **31** was produced from the reaction of epoxide **103b** with the *N*-methyl derivative of amine **104a** followed by *O*-methylation with iodomethane.

Products **2** and **33** in Table 3 were prepared from the reactions of amine **104a** with the homologated epoxides **105** and **106**, which were in turn obtained from 4-hydroxycarbazole and the corresponding homologated haloepoxides. Alternatively, **34** was produced from 4-hydroxycarbazole and amine **104a** via the monotosylate **109**. Compounds **36**−**38** were obtained from epoxide **103a** and amines **110** and **111a**,**b**, respectively, whereas product **39**, containing transposed alcohol and amine functionalities, was prepared from the carbazole derivative **112** and epoxide **113**. These processes are summarized in Scheme 3. Cyclizations to afford lactams **32**, **35**, and **40** were effected from the corresponding amino alcohols **2**, **34**, and **39**, respectively, with chloroacetyl chloride, as shown previously for **17**−**20** in Scheme 1.

Although the products in Tables 1−3 originated from 4-hydroxycarbazole, the syntheses of those in Table 4 were carried out similarly but by employing 3-hydroxycarbazole, its 6-fluoro derivative, or 3-aminocarbazole instead, as shown in Scheme 4. Compound **46** was obtained by alkylation of amine **104a** with bromide **115**, which was obtained as a byproduct in the preparation of epoxide **114b**. Similarly, compound **48** was obtained by alkylation of **104a** with chloride **116**, which was in turn obtained from 9-*t*-Boc-protected 3-aminocarbazole and epichlorohydrin. Furthermore, the products in Table 5 were obtained by analogous methods, employing 2-hydroxycarbazole, its 6-fluoro or 6,8-difluoro analogues, or 1-hydroxycarbazole as starting materials

dx.doi.org/10.1021/jm401090a | J. Med. Chem. 2013, 56, 8626−8655

Scheme 3[a]



[a](a) LiBr, DME, 60 °C. (b) K_2CO_3, DMF, 100 °C. (c) TBAF, THF, rt. (d) TsCl, Et_3N, $CHCl_3$, 0 °C. (e) **104a**, LiBr, DME, reflux. (f) *i*-PrOH, reflux. (g) LiBr, DME, reflux.

(Scheme 5). Lactams **41**, **49**, and **51** were again obtained by cyclization of the corresponding amino alcohols **3**, **4**, and **50**, respectively, with chloroacetyl chloride, whereas cyclizations to afford **42** and **52** from **3** and **50**, respectively, were effected with bromomethanesulfonyl chloride or 1,1′-carbonyldiimidazole.

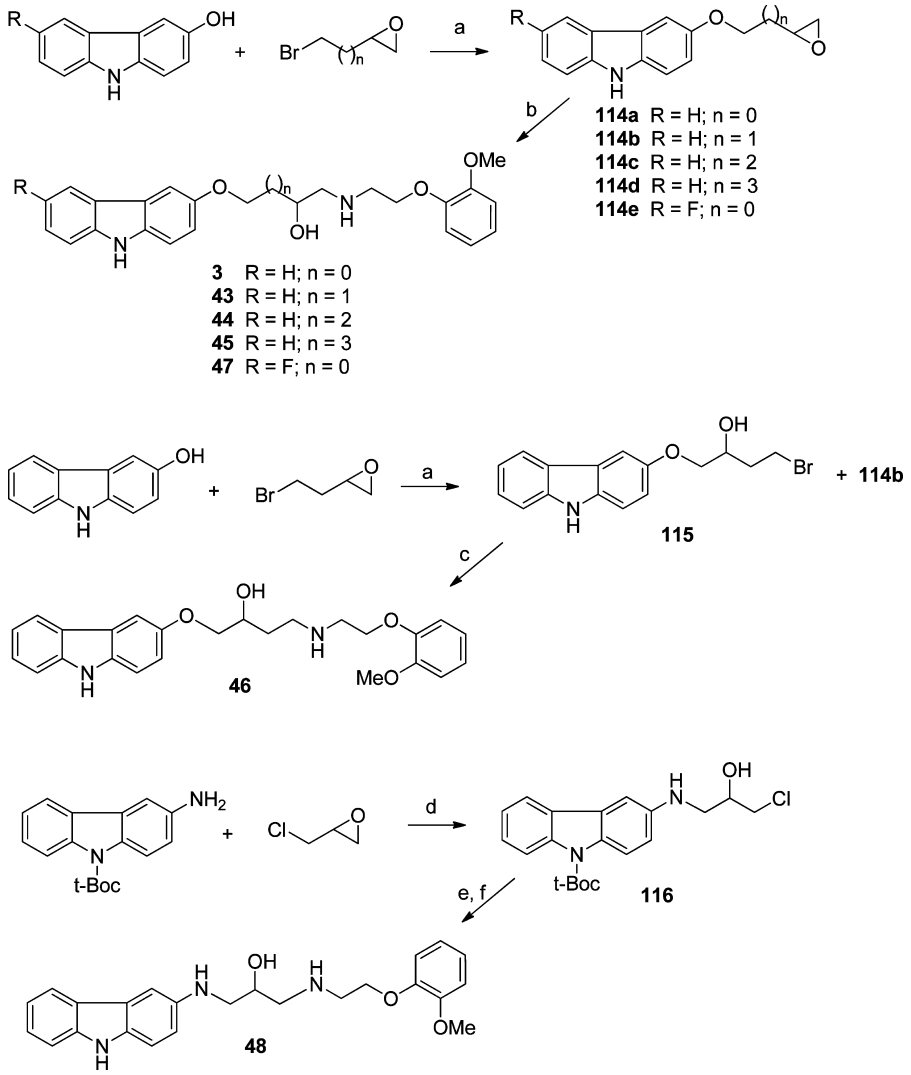
The *N*-acylated carbazole derivatives **59** and **60** in Table 6 were prepared as shown in Scheme 6. Although **60** was prepared by direct acylation of **17**, compound **59** was more easily obtained by prior acylation of epoxide **103a** followed by ring-opening with amine **104a** in the usual manner. The other compounds in Table 6 were prepared by alkylating the other indicated phenols or alcohols instead of 4-hydroxycarbazole with the corresponding haloalkyl epoxides followed by treatment with amine **104a**, as indicated in Scheme 6. Product **62** was obtained by Wolff–Kishner reduction of ketone **63**, whereas desulfurization of **66** with nickel boride[34] afforded **65**.

Products **83**–**90** and **92** in Table 7 were obtained by treating epoxides **103a** (entries 3, 4, 9, 10, and 12), **105** (entry 5), **114a** (entry 6), **117a** (entry 7), or **117c** (entry 8) with the corresponding amines **104a** or **118a**–**f**, as shown in Scheme 7. The benzofuran and benzoxazole derivatives **81** and **82** (entries 1 and 2) were produced by reductive amination or alkylation of amine **119** with aldehyde **121** or chloride **122**, respectively, followed by debenzylation of the intermediate benzylamines. Amides **93** and **94** (entries 13 and 14) were formed by amidation of carboxylic acid **120** with amines **104a** or **118f**, respectively, using *N*-(3-diethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDC hydrochloride) and 1-hydroxybenzotriazole hydrate (HOBT·H_2O) as coupling reagents.[35] Product **91** (entry 11) was prepared by cyclization of **94** with diethylaminosulfur trifluoride (DAST).[36]

Metoprolol (**95**) was obtained from commercial sources, whereas 4,6-dibromo-3-hydroxycarbazole (**96**) was prepared by a literature procedure.[37] The conversion of **96** to **97** and its further transformation to **98** was achieved via the same

dx.doi.org/10.1021/jm401090a | *J. Med. Chem.* 2013, 56, 8626–8655

Scheme 4[a]



[a]One molar NaOH, DMSO, rt or 40 °C. (b) **104a**, *i*-PrOH, reflux. (c) **104a**, Et_3N, MeOH, 60 °C. (d) EtOH, reflux. (e) **104a**, K_2CO_3, cat. KI, EtOH, reflux. (f) TFA, CH_2Cl_2, rt.

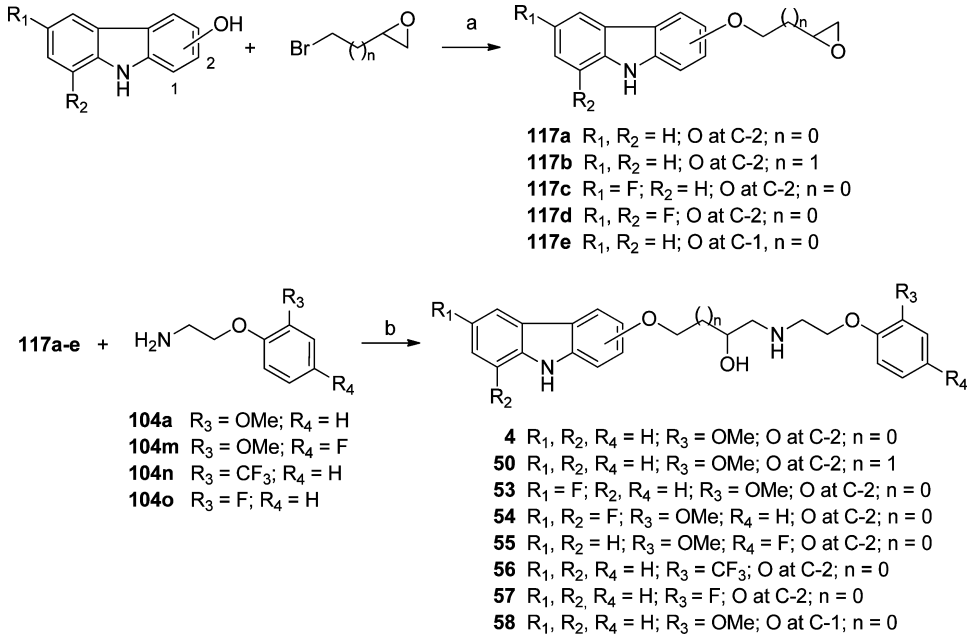
procedure that was employed for the preparation of **1** from 4-hydroxycarbazole and for the cyclization of **1** to **17**, as shown in Scheme 1. Products **99** and its hydrochloride salt **100**[38] as well as **102**[39] were obtained by known procedures. Alternatively, the regioisomer **101** of **99** was prepared, along with **101**, from the known thiapyrone **123**,[40] as shown in Scheme 8.

SOICR Inhibition. The benchmark compound **1** displayed an IC_{50} of 15.9 μM (Table 1, entry 1) in this assay. We first prepared and assayed several derivatives (**6**–**16**) with modified catechol groups, as shown in Table 1. Aromatic hydroxylation of the catechol moiety of carvedilol at the 4′- and 5′-positions is known to afford phenolic metabolites.[41] Modification of these sites to probe their effect on SOICR inhibition was therefore of particular interest (entries 2–4). The introduction of 4′- and 5′-chloro substituents in **6** slightly improved SOICR activity, but replacement of the methoxy group with a third chlorine atom in **7** diminished the potency significantly. Surprisingly, the simple phenyl derivative **8** proved comparable to **1**, whereas replacement of the methoxy substituent of **1** with a hydroxyl group in derivative **9** lowered the IC_{50} by half. The similar replacement by methyl or methylthio groups (**10** and **11**, respectively) had no effect on activity. When the other catechol oxygen atom was replaced with sulfur or a methylene group (**12** and **13**, respectively) or when the methoxy group was also absent, as in **14**, slightly higher activity compared to **1** was observed. However, replacement of the catechol moiety by a 2-pyridyl group (**15**) or by a cyclohexyl substituent (**16**) resulted in a 3- and 2-fold loss of activity, respectively.

We also investigated whether SOICR inhibition would be affected by manipulation of the β-amino alcohol moiety in the linker chain, which plays a critical role in the excessive β-blockade encountered with carvedilol. Entries 1–12 in Table 2 show the IC_{50} values for analogues where this functionality was incorporated into various rings with or without the previous modifications to the catechol region of the carvedilol molecule given in Table 1. In the case of δ-lactams **17**–**20**, there was a moderate loss of activity compared to **1** when either the intact catechol moiety was retained (**17**) or when it was replaced by a simple cyclohexyl group (**20**). Moreover, the chlorinated derivatives **18** and **19** were essentially devoid of activity when introduced together with lactamization (cf. the relatively active chlorinated compounds **6** and **7** in Table 1). The morpholine

dx.doi.org/10.1021/jm401090a | J. Med. Chem. 2013, 56, 8626–8655

Scheme 5[a]



[a](a) One molar NaOH, DMSO, rt or 40 °C. (b) *i*-PrOH, reflux.

analogues **21**–**24** revealed no consistent pattern of behavior when compared with the corresponding free β-amino alcohols **1**, **6**, **7**, and **16** and with the corresponding lactams **17**–**20**, respectively. Although a slight decrease in activity was observed in **17** and **21** compared to **1**, the chlorinated analogues **22** and **23** were intermediate between the corresponding amino alcohols **6** and **7** and the inactive lactams **18** and **19**. The cyclohexyl derivative **24** was devoid of activity, in contrast to the weakly active amino alcohol **16**. The cyclic carbamates **25**–**27** all showed poor SOICR inhibition compared to the corresponding amino alcohols **1**, **6**, and **16**, whereas the free phenol analogue **28** was comparable to carvedilol but less active than phenol **9** in this regard. Furthermore, alkylation of the aliphatic secondary amino group in **29** had little effect, whereas alkylation of the carbazole nitrogen in **30** resulted in diminished activity. Surprisingly, exhaustive alkylation of both nitrogens and of the secondary alcohol group in **31** produced a more strongly SOICR-inhibiting compound than either **1**, **29**, or **30**.

Attempts to determine the effects of homologation of the linker chain at various sites upon SOICR inhibition were also made (Table 3, entries 1–8). Homologation was effected by insertion of one or more extra methylene units between the carbazole ether and secondary alcohol of **1** to afford **2**, its cyclized derivative **32**, and **33**, respectively. Similarly, homologation between the alcohol and amino group provided **34** and the corresponding lactam **35**, whereas insertion of an extra methylene unit between the amino group and the catechol ether and between the catechol ether and aromatic ring afforded derivatives **36** and **37**, respectively. Products **2**, **32**, **33**, **34**, **37**, and **38** proved comparable to **1**, whereas **36** was slightly less potent. When homologation was combined with lactamization of the linker chain of **34** to afford **35**, activity diminished more than 6-fold. Removal of the methoxy group from homologue **37** to give **38** had essentially no effect on the activity. Transposition of the alcohol and secondary amino groups in the linker chain of **1** and **17** was also investigated (entries 9 and 10). Thus, **39** and its lactam analogue **40** were prepared and found to have IC_{50}'s ca. 1.7-fold those of **1**.

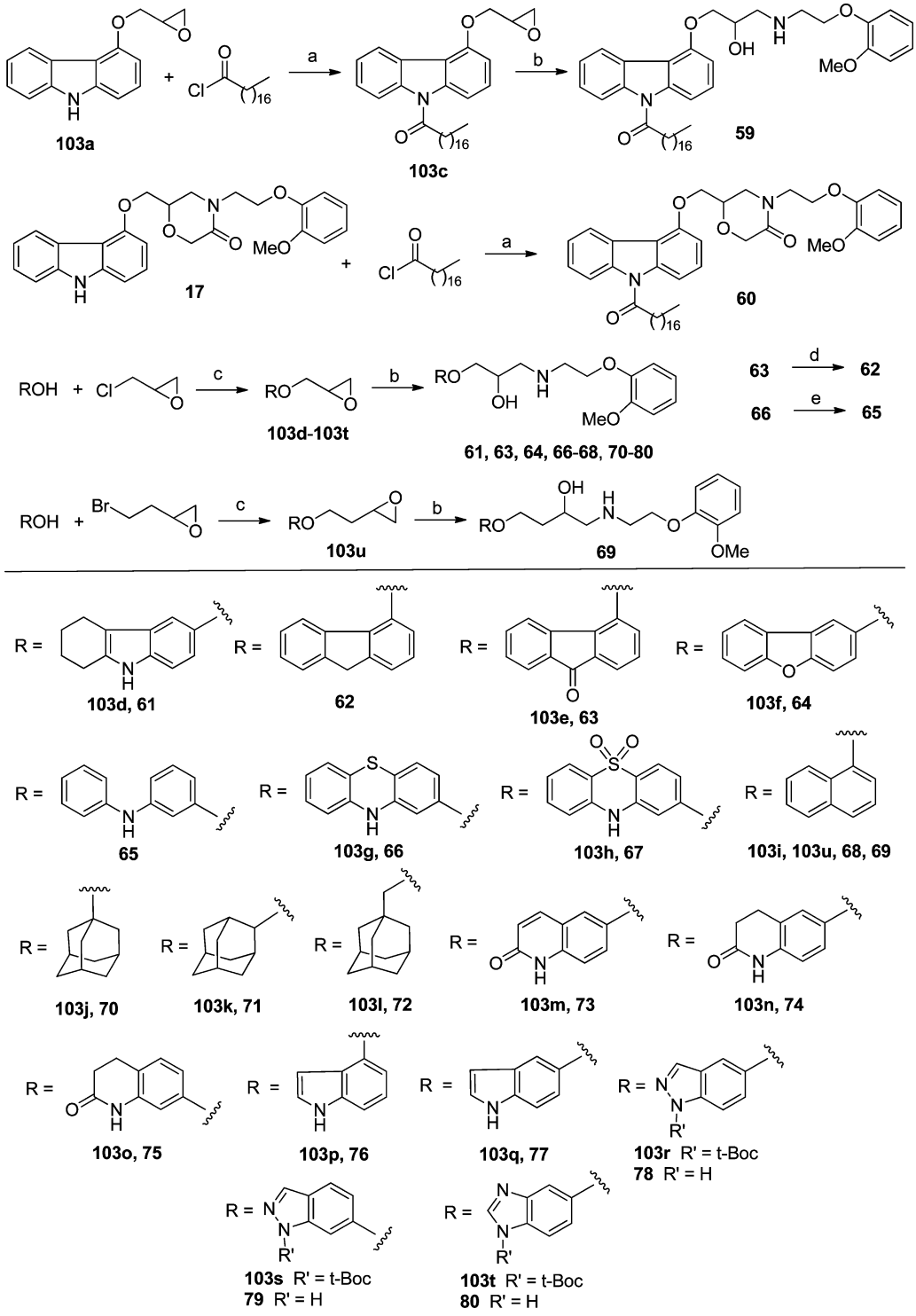
When the point of attachment of the linker was moved from the 4-position of the carbazole moiety (as in carvedilol) to the 3-position, a series of highly active compounds was obtained (Table 4, entries 1–7). Thus, compounds **3**, **41**, **43**, and **44** all proved superior to carvedilol in their inhibition of SOICR. Cyclization of **3** to afford lactam **41** retained the high activity of the parent amino alcohol, and only the sultam moiety of derivative **42** strongly impeded SOICR inhibition. Furthermore, homologation of **3** by one, two, or three methylene units between the carbazole and hydroxyl functions produced the highly active analogues **43**–**45**, respectively, with the lowest IC_{50} of 4.66 μM observed for the doubly homologated derivative **44**. Single homologation between the alcohol and amino functions in **46** also produced a more potent product than carvedilol, whereas the 6-fluoro derivative **47** showed essentially identical activity to that of the parent compound **3** of this series. Replacement of the ether oxygen with an amino group at C-3 of the carbazole moiety in **48** resulted in comparable activity to that of carvedilol.

The 2-substituted carbazole series (Table 5, entries 1–10) was also investigated and revealed several highly active SOICR inhibitors. The parent compound **4** as well as its lactam and homologated counterparts **49** and **50**, respectively, proved similar to carvedilol. In contrast, the homologated lactam **51** and cyclic carbamate **52** were ineffective in SOICR inhibition. Monofluorination of the 6- position or 6,8-difluorination of the carbazole had a beneficial effect on activity, leading to the highly potent analogues **53** and **54**. Fluorination of the catechol moiety in compound **55** or fluoro or trifluoromethyl substitution of the methoxy group in **57** and **56**, respectively, had little effect compared to **1** or **4**. Finally, attachment of the linker chain to the 1-position of the carbazole unit in **58** (entry 11) also had little effect on activity.

It has been suggested that the carbazole moiety of carvedilol serves to embed the molecule in the lipid bilayer of cell membranes.[42] Furthermore, it provides a hydrophobic region and a

dx.doi.org/10.1021/jm401090a | J. Med. Chem. 2013, 56, 8626–8655

Scheme 6[a]



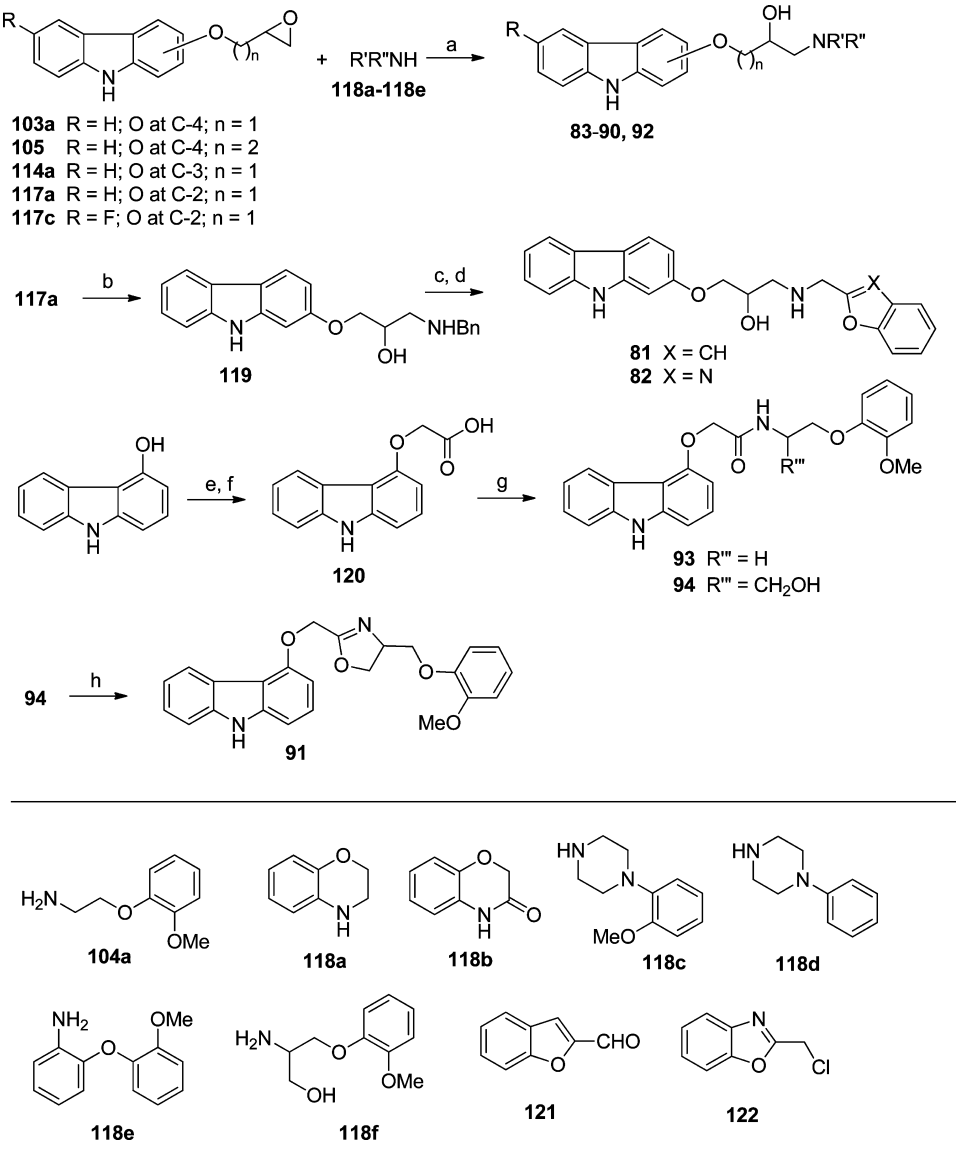
[a](a) NaH, THF, 0 °C. (b) **104a**, LiBr, DME, 60 °C or *i*-PrOH, reflux. (c) One molar NaOH, DMSO, 40 °C. (d) $NH_2NH_2.H_2O$, KOH, ethylene glycol, 100−160 °C. (e) $NiCl_2{\cdot}6H_2O$, $NaBH_4$ (Ni_2B), MeOH-THF-H_2O, rt.

hydrogen-bonding functionality that are key for binding to the *β*-adrenergic receptor.[33] To determine whether these structural features are also required for SOICR inhibition, we prepared a variety of analogues containing modified carbazole units (Table 6). In entries 1 and 2, amidation of the carbazole nitrogens of **1** and **17** with octadecanoic acid afforded **59** and the lactam derivative **60**, respectively. Unlike the *N*-methylated derivatives **30** and **31** in Table 2, which showed comparable activity to carvedilol (**1**), amides **59** and **60** unfortunately revealed negligible or significantly diminished activity relative to **1** and **17**.

Other carbazole modifications are shown in entries 3−22 of Table 6. The tetrahydrocarbazole **61**, the fluorene and fluorenone analogues **62** and **63**, respectively, that lack the

dx.doi.org/10.1021/jm401090a | J. Med. Chem. 2013, 56, 8626−8655

Scheme 7[a]



[a](a) *i*-PrOH, reflux. (b) $BnNH_2$, *i*-PrOH, reflux. (c) **121**, $NaBH(OAc)_3$, 1,2-dichloroethane or **122**, DIPEA, cat. KI, MeCN, 60 °C. (d) H_2, 10% Pd/C, MeOH. (e) Ethyl bromoacetate, NaOH, DMF, rt. (f) KOH, MeOH-H_2O. (g) **104a** or **118f**, EDC·HCl, HOBT·H_2O, Et_3N, THF, rt. (h) DAST, CH_2Cl_2-THF, −78 °C, 1 h; then K_2CO_3, rt, 2 h.

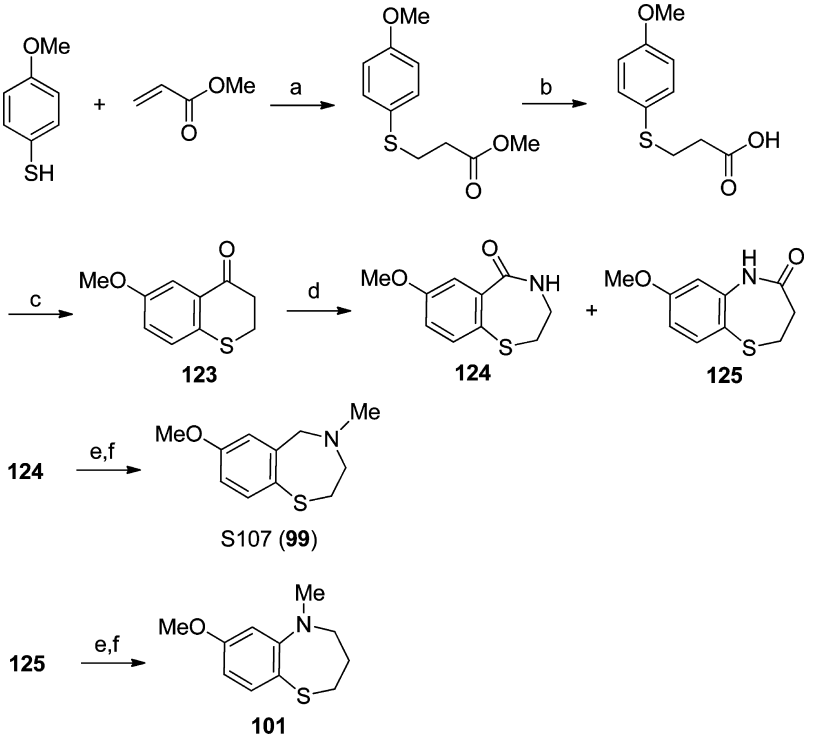
carbazole nitrogen atom, and the diphenylamine **65** all showed comparable or only slightly lower activity than carvedilol. However, the dibenzofuran **64** and the phenothiazine **66** were more strongly active than **1**, whereas oxidation of **66** to the corresponding sulfone **67** decreased activity by more than 10-fold. Replacement of the carbazole with naphthyl residues in **68** and its homologated analogue **69** afforded potent SOICR inhibitors. The adamantyl residues in **70**−**72** resulted in less efficacious compounds, and the quinolinone **73** and partially reduced quinolinones **74** and **75** were essentially inactive. The installation of indole (compounds **76** and **77**), benzodiazole (compounds **78** and **79**), and benzimidazole (compound **80**) residues in place of the carbazole also produced very weak or essentially inactive products.

We also introduced additional heterocyclic groups into the linker chain or in place of the catechol moiety (Table 7, entries 1−12), as well as amide instead of amino alcohol functionalities (entries 13−14). The benzofuran and benzoxazoles **81** and **82** were devoid of activity, but the benzomorpholine **83** proved more than twice as potent as carvedilol (**1**). The lactam derivative **84** and homologue **85** were comparable to **1**. Repositioning the linker chain of **85** to the 3- and 2-position of the carbazole moiety resulted in strong and negligible activities in **86** and **87**, respectively. Fluorination of the 6-position of **87** to afford **88** failed to improve the bioactivity. Piperazines **89** and **90**, as well as dihydrooxazole **91** and diaryl ether **92** displayed weaker activity than **1**. Surprisingly, replacement of the amino alcohol moiety of **1** with amide linkages in **93** and **94** afforded the most potent SOICR inhibitors of this investigation, with IC_{50} values of ca. 3.6 μM compared with 15.9 μM for carvedilol.

Several other classes of compounds have been reported to provide salutary effects in the treatment of cardiac arrhythmias. We therefore measured their SOICR inhibiting properties in order to compare them with the above carvedilol analogues (Table 8). The clinically useful β-blocker metoprolol (**95**) was devoid of any SOICR-inhibition in the mutant HEK293 single

dx.doi.org/10.1021/jm401090a | J. Med. Chem. 2013, 56, 8626−8655

Scheme 8[a]



[a](a) Borax, H_2O, rt. (b) MeOH, 2 M NaOH, rt. (c) TFA, TFAA, 60 °C. (d) $TMSN_3$, TFA, rt. (e) $LiAlH_4$, THF-Et_2O, reflux. (f) Formaldehyde, $NaBH_3CN$, MeOH, rt.

cell bioassay. This result is consistent with our previous finding[32] that carvedilol is unique in the family of β-blocker drugs in effectively suppressing SOICR in the HEK293 cell line and in the knock-in mouse model.

Furthermore, compound **96** has been reported to inhibit Ca^{2+}-induced Ca^{2+} release (CICR) in skeletal muscle sarcoplasmic reticulum.[37] In the RyR2-R4496C mutant HEK293 cell assay it exhibited negligible activity, which improved substantially when its structure was incorporated into the novel carvedilol derivative **97**, whereas further lactamization of the amino alcohol in **98** resulted in complete loss of activity. The thiazepine compounds **99**[38] and **102**[39] have been reported to suppress ventricular arrhythmias and sudden death in mice through enhanced binding of the 12.6 kDa FK506 binding protein (FKBP12.6) to the RyR2 channel. However, neither **99**, its hydrochloride salt **100**, nor its isomer **101** displayed any measurable activity in the present assay. On the other hand, the amide derivative **102** showed activity about one-half that of **1**.

DISCUSSION

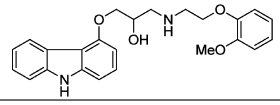
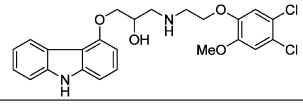
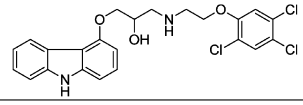
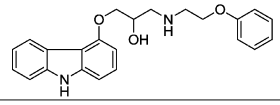
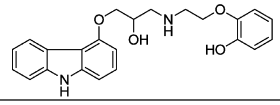
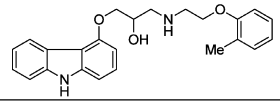
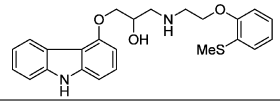
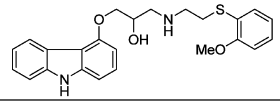
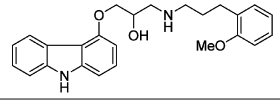
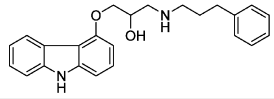
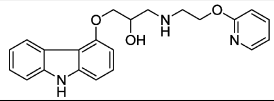
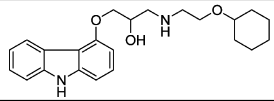
These results demonstrate that considerable variation in the structure of carvedilol is possible while retaining strong SOICR-suppressing activity in the RyR2-R4496C mutant HEK293 single cell assay. Thus, 34 of the above compounds (**3**, **6**, **9**, **10**, **12**−**14**, **31**−**34**, **37**, **38**, **41**, **43**−**47**, **50**, **53**−**56**, **58**, **64**, **66**, **68**, **69**, **83**, **84**, **86**, **93** and **94**) proved equal or superior to carvedilol (**1**) in this assay. This subset of highly potent analogues reveals that significant changes can be tolerated in the catechol, linker and carbazole moieties without loss of activity relative to the clinically useful drug **1**. All of the compounds in Table 1, where modifications to the catechol subunit are listed, show significant activity. Beneficial catechol modifications include chlorination of the 4′- and 5′-positions (compound **6**), which is expected to block metabolic oxidation at those sites and possibly retard clearance. The 2′-methoxy group can be replaced by H, OH, Me or MeS substituents (compounds **8**, **9**, **10** and **11**) and the 1′-ether oxygen can be replaced by S (compound **12**) or CH_2 (compounds **13** and **14**) without deleterious effects on SOICR inhibition. Remarkably, the simple phenyl derivative **14** is roughly twice as potent as **1**, whereas even the pyridyl and cyclohexyl analogues **15** and **16** show only a three- or 2-fold loss of activity. This suggests that the compounds in Table 1 may prove good candidates as SOICR inhibitors.

The β-amino alcohol functionality plays a key role in mediating β-adrenergic blockade via multiple hydrogen-bonding interactions with the β-receptor.[33] In order to determine whether or not this functionality plays a similar role in SOICR inhibition, we investigated the alkylation of these key groups via incorporation into cyclic structures or by simple methylation. However, Table 2 indicates mixed results with respect to the SOICR inhibition shown by such compounds. Although the lactam and morpholine derivatives of carvedilol (**17** and **21**, respectively), as well as the *O*- and *N*-methylated compounds **29**-**31** showed similar or slightly lower SOICR inhibition compared to **1**; further alteration of these structures was generally accompanied by severe or total loss of activity.

The variously homologated analogues in Table 3 (**2**, **32**−**34**, and **36**−**38**) and the compounds with transposed amino alcohol linkers (**39** and **40**) all showed strong SOICR suppression in the mutant HEK293 cells. Similarly, relocation of the point of attachment of the linker chain from the 4-position (as in **1**) to the 3-, 2-, or 1-positions of the carbazole subunit generally had a salutary effect on the compounds in Tables 4 and 5, except for the sultam derivative **42**, the lactam **51**, and the cyclic carbamate **52**.

dx.doi.org/10.1021/jm401090a | J. Med. Chem. 2013, 56, 8626−8655

Table 1. SOICR Inhibition by Modified Catechol Analogues of 1

entry	compound	structure	IC_{50} (μM) ± SEM	repeats (n)	no. of cells
1	carvedilol **1**		15.9 ± 2.5	6	375
2	**6**		11.2 ± 1.2	3	149
3	**7**		28.0 ± 0.6	3	191
4	**8**		16.8. ± 2.7	3	228
5	**9**		7.62 ± 0.44	3	159
6	**10**		15.1 ± 3.7	3	173
7	**11**		16.4 ± 4.2	3	235
8	**12**		11.6 ± 0.9	3	253
9	**13**		7.43 ± 0.65	3	202
10	**14**		8.52 ± 1.3	3	190
11	**15**		54.9 ± 5.7	3	255
12	**16**		35.2 ± 2.2	4	141

The alterations to the carbazole moiety shown in Table 6 produced mixed results. The relatively strong activity of several analogues lacking the carbazole nitrogen or other hydrogen-bonding functionalities is noteworthy. Thus, the fluorenyl derivative **62**, naphthyl derivatives **68** and **69**, and the weaker but still significantly active adamantyl analogues **70**−**72** demonstrate that the hydrogen-bonding carbazole NH functionality that participates in binding to the *β*-receptor is not required for SOICR inhibition. However, *N*-acylation of the carbazole nitrogen suppressed activity (compounds **59** and **60**), whereas other heterocyclic groups displayed IC_{50}'s ranging from 5.7 μM (compound **66**) to a complete loss of activity. The more extensive structural modifications to the compounds listed in Table 7 also had varied effects on SOICR suppression. Of special interest are the benzomorpholine derivative **83** and the amides **93** and **94**, with IC_{50}'s ranging from 3.55 to 5.76 μM compared to 15.9 μM for **1**.

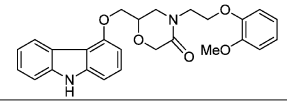
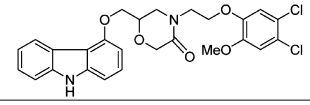
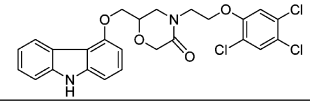
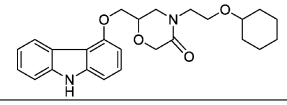
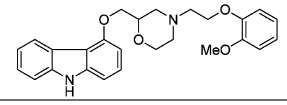
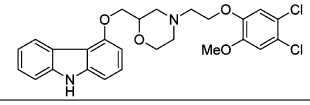
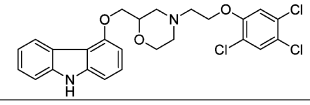
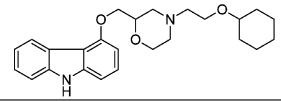
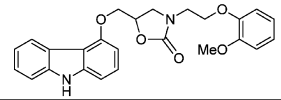
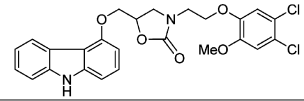
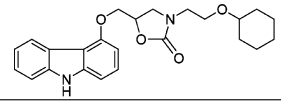
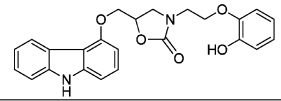
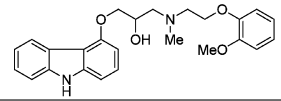
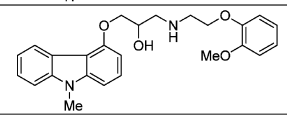
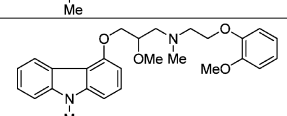
Finally, we note the striking contrast between the most active SOICR inhibitors described above and the SOICR-suppressing abilities of several conventional *β*-blockers and antiarrhythmic agents shown in Table 8. The complete absence of such activity in the case of metoprolol (**95**), the dibromocarbazole derivatives **96** and **98**, and the thiazepine derivatives **99**−**101** strongly suggest that the latter compounds express their antiarrhythmic effects through different mechanisms than the active compounds described in Tables 1−7. Only the carvedilol-resembling analogue **97** and the thiazepine **102** exhibited any measurable effect on SOICR suppression.

CONCLUSIONS

It was recently demonstrated that the effectiveness of carvedilol as an antiarrhythmic therapy for patients with heart failure was due in part to its ability to suppress SOICR by regulating calcium efflux through the RyR2 channel.[32] As a continuation of this

dx.doi.org/10.1021/jm401090a | J. Med. Chem. 2013, 56, 8626−8655

Table 2. SOICR Inhibition by Compounds with Cyclized or Alkylated Linker Chains

entry	compound	structure	IC_{50} (μM) ± SEM	repeats (n)	no. of cells
1	**17**		26.1 ± 3.6	14	410
2	**18**		>1000	3	206
3	**19**		>1000	3	197
4	**20**		52.9 ± 15	4	175
5	**21**		22.9 ± 2.7	3	133
6	**22**		86.7± 36	3	173
7	**23**		364 ± 91	3	234
8	**24**		>1000	3	248
9	**25**		86.3 ± 52	3	149
10	**26**		97.2 ± 63	2	186
11	**27**		113 ± 25	5	357
12	**28**		16.1 ± 7.2	3	191
13	**29**		18.3 ± 0.0	4	181
14	**30**		35.2 ± 5.2	3	139
15	**31**		11.7 ± 0.7	3	264

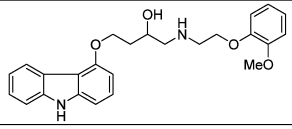
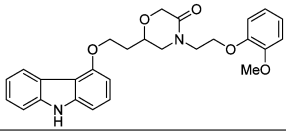
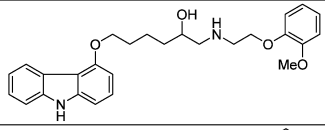
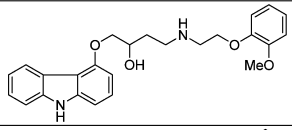
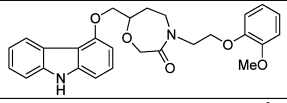
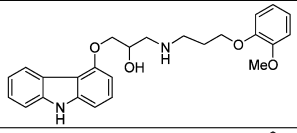
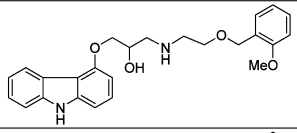
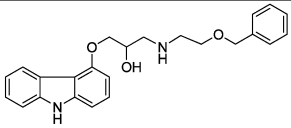
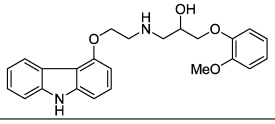
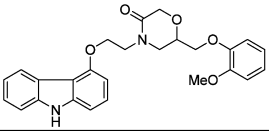
investigation, we screened ca. 100 mostly novel compounds for their SOICR-suppressing effects on the RyR2-R4496C mutant HEK293 cell line. The wide variety of modifications that are tolerated suggests that RyR2 is a promiscuous channel that accommodates a broad range of ligands, including ones with structural changes to the carbazole, linker chain, and catechol moieties of carvedilol.

EXPERIMENTAL SECTION

All compounds subjected to bioassay for which elemental analyses were not provided were of >95% purity as determined by HPLC analysis employing the following conditions: Novapak C_{18} reversed-phase column, 3.9 × 150 mm; solvent: acetonitrile/water, 70:30, 0.8 mL/min; UV detector: 254 nm. ^{1}H NMR spectra were obtained at 300 or 400 MHz. ^{13}C NMR spectra were obtained at 75 or 101 MHz. ^{19}F NMR

dx.doi.org/10.1021/jm401090a | J. Med. Chem. 2013, 56, 8626−8655

Table 3. Effects of Homologation and Transposition of Linker Chain on SOICR Inhibition

entry	compound	structure	IC_{50} (μM) ± SEM	repeats (n)	no. of cells
1	**2**		16.8 ± 3.3	4	206
2	**32**		14.6 ± 3.5	3	177
3	**33**		11.4 ± 0.8	3	245
4	**34**		13.5 ± 2.3	3	163
5	**35**		86.7 ± 53	3	204
6	**36**		20.0 ± 1.6	3	167
7	**37**		10.2 ± 0.5	3	168
8	**38**		9.51 ± 2.3	3	217
9	**39**		24.4 ± 3.1	4	365
10	**40**		26.7 ± 3.2	7	381

spectra were obtained at 376 MHz with hexafluorobenzene (−164 ppm) as the external standard relative to trichlorofluoromethane (0.00 ppm). Products **2**−**4** were prepared as described previously in the Supporting Information of ref 32.

Typical Procedure for the Preparation of Compounds 6−16. Preparation of 1-(9*H*-Carbazol-4-yloxy)-3-{[2-(4,5-dichloro-2-methoxyphenoxy)ethyl]amino}-2-propanol (6).[43] Epoxide **103a** (169 mg, 0.706 mmol) and amine **104b** (250 mg, 1.06 mmol) were refluxed for 2 h in isopropanol (4 mL). The solvent was then removed under vacuum, and the residue was purified by flash chromatography over silica gel (methanol/dichloromethane) to obtain 208 mg (62%) of product **6** as a white solid. mp 149−151 °C. IR (film): 3294, 1544, 1258, 1092 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.21 (d, J = 7.7 Hz, 1H), 8.06 (s, 1H), 7.46−7.14 (m, 4H), 7.06 (d, J = 7.7 Hz, 1H), 6.87 (s, 1H), 6.75 (s, 1H), 6.64 (d, J = 7.7 Hz, 1H), 4.29−3.91 (m, 5H), 3.57 (s, 3H), 3.30−3.12 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.2, 149.0, 147.5, 141.1, 138.8, 126.8, 125.2, 124.2, 123.5, 123.0, 122.6, 119.8, 115.3, 113.4, 112.8, 110.2, 104.0, 101.4, 70.4, 69.2, 68.5, 56.3, 52.1, 48.6. MS (ESI) m/z (relative intensity): 475 $[M + 1]^+$. HRMS (EI) calcd for $C_{24}H_{24}{}^{35}Cl_2N_2O_4$ $[M^+]$, 474.1113; found, 474.1123.

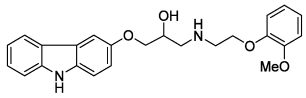
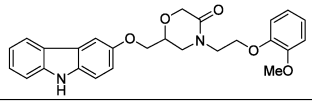
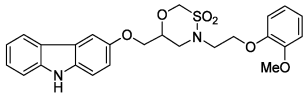
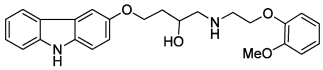
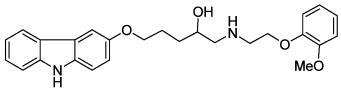
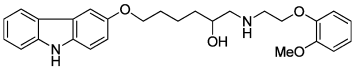
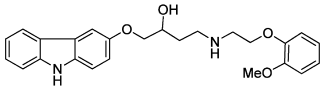
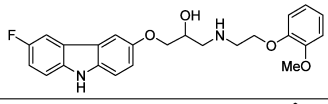
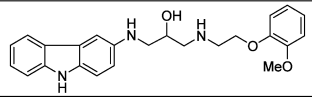
Compounds **7** and **8** and **10**−**16** were prepared similarly.

1-(9*H*-Carbazol-4-yloxy)-3-{[2-(2,4,5-trichlorophenoxy)-ethyl]amino}-2-propanol (7).[43] Yield: 66%, white solid. mp 146−148 °C. IR (film): 3285, 1452, 1095 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.24 (d, J = 7.8 Hz, 1H), 8.07 (s, 1H), 7.44−7.35 (m, 3H), 7.32 (dd, J = 8.0, 8.1 Hz, 1H), 7.20 (ddd, J = 1.6, 6.7, 8.1 Hz, 1H), 7.06 (dd, J = 0.5, 8.1 Hz, 1H), 6.96 (s, 1H), 6.68 (d, J = 7.6 Hz, 1H), 4.38−4.24 (m, 3H), 4.15−4.07 (m, 2H), 3.20−3.11 (m, 3H), 3.06 (dd, J = 6.9, 12.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.9, 153.2, 141.4, 139.1, 131.1, 130.7, 126.3, 124.6, 124.3, 122.5, 122.1, 118.8, 114.9, 112.3, 110.1, 104.1, 100.4, 70.1, 68.6, 68.4, 52.2, 48.0. MS (EI) m/z (relative intensity): 478 (4) $[M^+]$, 184 (14), 183 (100). HRMS (EI) calcd for $C_{23}H_{21}{}^{35}Cl_3N_2O_3$ $[M]^+$, 478.0618; found, 478.0619.

1-(9*H*-Carbazol-4-yloxy)-3-[2-(phenoxyethyl)amino]-2-propanol (8).[44,45] Yield: 76%, white solid. mp 109−111 °C. IR (film) 3407, 3244, 3055, 2924, 2873, 1597, 1506, 1453, 1242, 1095, 750, 725 cm^{-1}.

dx.doi.org/10.1021/jm401090a | J. Med. Chem. 2013, 56, 8626−8655

Table 4. SOICR Inhibition by 3-Carbazolyl Analogues

entry	compound	structure	IC_{50} (μM) ± SEM	repeats (n)	no. of cells
1	**3**		7.74 ± 1.1	7	367
2	**41**		6.20 ± 1.8	3	167
3	**42**		436 ± 330	3	150
4	**43**		9.72 ± 3.1	3	214
5	**44**		4.66 ± 0.13	3	164
6	**45**		15.9 ± 5.1	3	252
7	**46**		9.74 ± 2.8	3	185
8	**47**		6.26 ± 2.8	3	166
9	**48**		16.6 ± 4.3	3	235

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, J = 7.8 Hz, 1H), 8.07 (br s, 1H), 7.19−7.44 (m, 6H), 7.07 (d, J = 7.7 Hz, 1H), 6.95 (dd, J = 10.5, 4.2 Hz, 1H), 6.90 (dd, J = 8.7, 1.0 Hz, 2H), 6.68 (d, J = 7.9 Hz, 1H), 4.38−4.20 (m, 3H), 4.12 (t, J = 5.2 Hz, 2H), 3.19−3.10 (m, 3H), 3.05 (dd, J = 12.3, 7.3 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.9, 155.3, 141.1, 138.9, 129.6, 126.8, 125.2, 123.1, 122.7, 121.1, 119.9, 114.7, 112.9, 110.2, 104.0, 101.5, 70.5, 68.7, 67.3, 52.1, 49.0. MS (ESI) m/z (relative intensity): 377 (100) $[M + H]^+$. HRMS (ESI) calcd for $C_{23}H_{25}N_2O_3$ $[M + H]^+$, 377.1860; found, 377.1856.

1-(9*H*-Carbazol-4-yloxy)-3-{[2-(2-methylphenoxy)ethyl]-amino}-2-propanol (10).[44,45] Yield: 76%, white solid. mp 118−119 °C. IR (film) 3407, 3306, 3055, 2924, 1606, 1497, 1453, 1242, 1098, 750, 719 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, J = 7.7 Hz, 1H), 8.07 (br s, 1H), 7.36−7.44 (m, 2H), 7.32 (dd, J = 8.0, 7.9 Hz, 1H), 7.21 (ddd, J = 8.1, 6.5, 1.8 Hz, 1H), 7.04−7.17 (m, 3H), 6.91−6.79 (m, 2H), 6.68 (d, J = 7.9 Hz, 1H), 4.40−4.20 (m, 3H), 4.12 (t, J = 5.1 Hz, 2H), 3.22−3.12 (m, 3H), 3.06 (dd, J = 12.3, 7.1 Hz, 1H), 2.20 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.9, 155.2, 141.1, 138.8, 130.8, 127.0, 126.9, 126.8, 125.1, 123.0, 122.6, 120.7, 119.8, 112.9, 111.3, 110.1, 104.0, 101.4, 70.5, 68.6, 67.4, 52.0, 49.0, 16.3. MS (ESI) m/z (relative intensity): 391 (100) $[M + H]^+$. HRMS (ESI) calcd for $C_{24}H_{27}N_2O_3$ $[M + H]^+$, 391.2012; found, 391.2016.

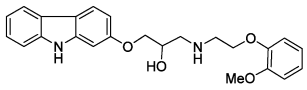
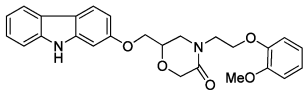
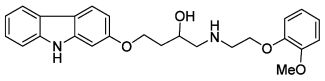
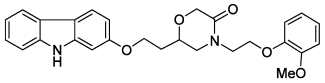
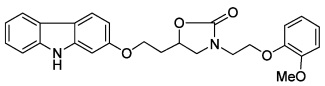
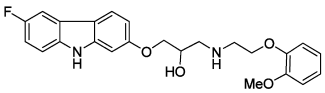
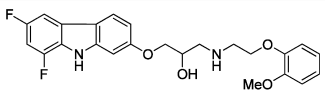
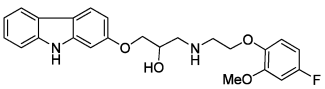
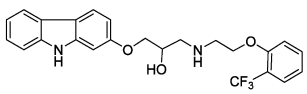
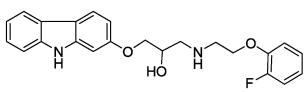
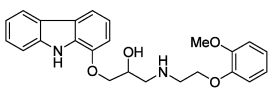
1-(9*H*-Carbazol-4-yloxy)-3-{[2-(2-methylthiophenoxy)ethyl]-amino}-2-propanol (11).[45] Yield: 65%, white solid. mp 103−104 °C. IR (film) 3407, 3297, 2917, 1606, 1456, 1435, 1236, 1095, 756, 722 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, J = 7.8 Hz, 1H), 8.08 (br s, 1H), 7.35−7.46 (m, 2H), 7.32 (dd, J = 8.0, 8.0 Hz, 1H), 7.21 (ddd, J = 8.0, 6.7, 1.6 Hz, 1H), 7.08−7.15 (m, 2H), 7.06 (d, J = 8.0 Hz, 1H), 6.97 (ddd, J = 7.6, 7.4, 1.2 Hz, 1H), 6.81−6.88 (m, 1H), 6.69 (d, J = 7.9 Hz, 1H), 4.15−4.39 (m, 5H), 3.14−3.22 (m, 3H), 3.06 (dd, J = 12.3, 7.0 Hz, 1H), 2.36 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.3, 155.2, 141.1, 138.8, 127.9, 126.7, 125.8 (2 signals), 125.1, 123.0, 122.6, 121.8, 119.8, 112.9, 112.0, 110.1, 103.9, 101.4, 70.3, 68.6, 68.4, 51.9, 48.7, 14.5. MS (EI) m/z (relative intensity): 422 (20) $[M^+]$, 196 (66), 182 (100), 153 (38). HRMS (EI) calcd for $C_{24}H_{26}N_2O_3S$ $[M]^+$, 422.1664; found, 422.1676.

1-(9*H*-Carbazol-4-yloxy)-3-{[2-[(2-methoxyphenylthio)-ethyl]amino}-2-propanol (12).[45] Yield: 69%, white solid. mp 48−49 °C. IR (film) 3407, 2930, 2833, 1603, 1581, 1456, 1098, 910, 750, 725 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, J = 7.8 Hz, 1H), 8.08 (s, 1H), 7.47−7.29 (m, 4H), 7.26−7.18 (m, 2H), 7.06 (d, J = 8.0 Hz, 1H), 6.90 (td, J = 7.5, 1.1 Hz, 1H), 6.86 (d, J = 8.2 Hz, 1H), 6.68 (d, J = 7.9 Hz, 1H), 4.40−4.15 (m, 3H), 3.88 (s, 3H), 3.14−3.01 (m, 3H), 2.99−2.85 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.1, 155.1, 141.0, 138.8, 131.3, 128.1, 126.7, 125.1, 123.2, 123.0, 122.6, 121.2, 119.8, 112.8, 110.8, 110.1, 104.0, 101.3, 70.3, 68.5, 55.9, 51.7, 48.2, 33.0. MS (EI) m/z (relative intensity): 422 (45) $[M^+]$, 269 (100), 195 (50), 182 (68), 153 (52), 120 (50). HRMS (EI) calcd for $C_{24}H_{26}N_2O_3S$ $[M]^+$, 422.1664; found, 422.1658.

1-(9*H*-Carbazol-4-yloxy)-3-{[3-(2-methoxyphenyl)propyl]-amino}-2-propanol (13).[45] Yield: 64%, white solid. mp 104−105 °C. IR (film) 3407, 2933, 2836, 1603, 1503, 1456, 1239, 1098, 907, 750, 719 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, J = 7.8 Hz, 1H), 8.09 (s, 1H), 7.47−7.35 (m, 2H), 7.32 (t, J = 8.0 Hz, 1H), 7.22 (ddd, J = 8.0, 6.6, 1.6 Hz, 1H), 7.17 (td, J = 8.0, 1.7 Hz, 1H), 7.12 (dd, J = 7.3, 1.5 Hz, 1H), 7.06 (d, J = 8.0 Hz, 1H), 6.88 (td, J = 7.4, 1.0 Hz, 1H), 6.84 (d, J = 8.1 Hz, 1H), 6.67 (d, J = 7.9 Hz, 1H), 4.47−4.09 (m, 3H), 3.80 (s, 3H), 3.06 (dd, J = 12.2, 3.5 Hz, 1H), 2.96 (dd, J = 12.2, 7.6 Hz, 1H), 2.86−2.61 (m, 4H), 1.81−1.91 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.6, 155.3, 141.1, 138.9, 130.4, 130.0, 127.2, 126.8, 125.1, 123.0, 122.7, 120.6, 119.8, 112.9, 110.4, 110.1, 104.0, 101.4, 70.6, 68.4, 55.4, 52.1, 49.5, 30.2, 27.8. MS (EI) m/z (relative intensity): 404 (40), 182 (100),

dx.doi.org/10.1021/jm401090a | J. Med. Chem. 2013, 56, 8626−8655

Table 5. SOICR Inhibition by 2- and 1-Carbazolyl Analogues

entry	compound	structure	IC_{50} (μM) ± SEM	repeats (n)	no. of cells
1	**4**		17.8 ± 3.6	5	174
2	**49**		19.8 ± 1.6	3	191
3	**50**		14.6 ± 2.4	3	275
4	**51**		>1000	3	279
5	**52**		354 ± 101	3	247
6	**53**		5.50 ± 2.3	3	206
7	**54**		4.37 ± 0.49	3	180
8	**55**		10.2 ± 0.9	3	165
9	**56**		15.4 ± 4.6	3	212
10	**57**		20.1 ± 4.5	2	229
11	**58**		12.4 ± 1.3	3	139

178 (88), 153 (50). HRMS (EI+) *m/z* calcd for $C_{25}H_{28}N_2O_3$ $[M]^+$, 404.2100; found, 404.2101.

1-(9*H*-Carbazol-4-yloxy)-3-[3-(phenylpropyl)amino]-2-propanol (14).[45] Yield: 64%, white solid. mp 110−111 °C. IR (film) 3407, 3084, 2917, 1603, 1450, 1095, 756, 716 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 7.8 Hz, 1H), 8.08 (s, 1H), 7.48−7.36 (m, 2H), 7.32 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.29−7.13 (m, 6H), 7.06 (d, *J* = 7.9 Hz, 1H), 6.67 (d, *J* = 7.9 Hz, 1H), 4.36−4.17 (m, 3H), 3.04 (dd, *J* = 12.2, 3.5 Hz, 1H), 3.00−2.89 (m, 1H), 2.85−2.61 (m, 4H), 1.87 (p, *J* = 7.2 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.2, 142.1, 141.1, 138.9, 128.5 (2C), 126.8, 125.9, 125.1, 123.0, 122.6, 119.8, 112.8, 110.2, 104.0, 101.4, 70.5, 68.5, 52.2, 49.5, 33.6, 31.7. MS (EI) *m/z* (relative intensity): 374 (18) $[M^+]$, 183 (100). HRMS (EI) calcd for $C_{24}H_{26}N_2O_2$ $[M]^+$, 374.1994; found, 374.1994.

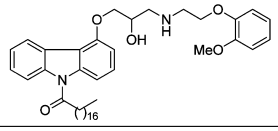
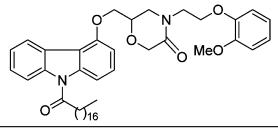
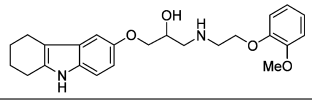
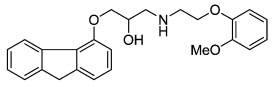
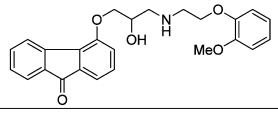
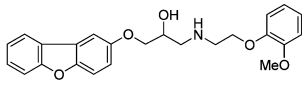
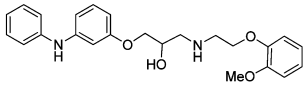
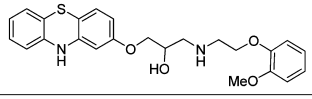
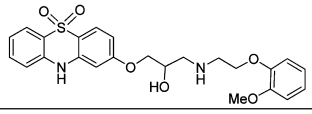
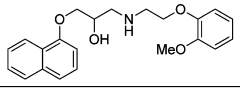
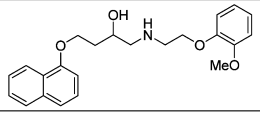
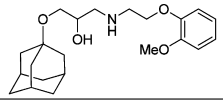
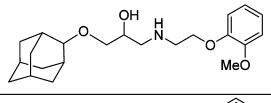
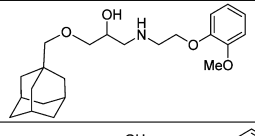
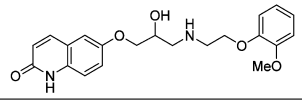
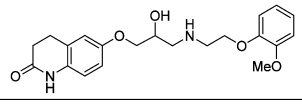
1-(9*H*-Carbazol-4-yloxy)-3-{2-(2-pyridyloxy)ethyl]amino}-2-propanol (15). Yield: 54%, white solid. mp 122−123 °C. IR (film) 3396, 3291, 2916, 1589, 1432, 1286, 1094, 783, 751, 720 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.0 Hz, 1H), 8.14 (ddd, *J* = 5.0, 2.0, 0.8 Hz, 1H), 8.08 (s, 1H), 7.55 (ddd, *J* = 8.3, 7.1, 2.0 Hz, 1H), 7.34−7.43 (m, 2H), 7.32 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.21 (ddd, *J* = 8.1, 6.8, 1.4 Hz, 1H), 7.06 (dd, *J* = 8.1, 0.5 Hz, 1H), 6.86 (ddd, *J* = 7.1, 5.1, 0.9 Hz, 1H), 6.72 (dt, *J* = 8.4, 0.9 Hz, 1H), 6.68 (d, *J* = 8.0 Hz, 1H), 4.43−4.52 (m, 2H), 4.20−4.38 (m, 3H), 2.98−3.25 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.8, 155.2, 146.9, 141.1, 138.8, 138.8, 126.8, 125.2, 123.1, 122.6, 119.9, 117.1, 112.9, 111.2, 110.1, 104.0, 101.4, 70.4, 68.5, 65.3, 52.1, 49.0. MS (ESI) *m/z* (relative intensity): 378 (100) $[M + H]^+$. HRMS (EI) calcd for $C_{22}H_{23}N_3O_3$ $[M]^+$, 377.1739; found, 377.1742.

1-(9*H*-Carbazol-4-yloxy)-3-{2-[(cyclohexyloxy)ethyl]amino}-2-propanol (16).[43] Yield: 68%, viscous oil. IR (neat) 3401, 3280, 3051, 1450, 1094 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.28 (d, *J* = 7.7 Hz, 1H), 8.14 (s, 1H), 7.41−7.22 (m, 4H), 7.06 (d, *J* = 7.7 Hz, 1H), 6.68 (d, *J* = 7.7 Hz, 1H), 4.32−4.22 (m, 3H), 3.62−3.59 (m, 2H), 3.27−3.24 (m, 1H), 3.12−3.07 (m, 1H), 3.01- 2.78 (m, 4H), 2.00−1.89 (m, 2H), 1.72−1.71 (m, 2H), 1.54−1.49 (m, 1H), 1.39−1.19 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.2, 141.1, 138.9, 126.8, 125.1, 123.1, 122.7, 119.8, 112.83, 110.2, 104.0, 101.4, 78.1, 70.4, 68.3, 66.6, 52.1, 49.6, 32.4, 25.9, 24.3. MS (EI) *m/z* (relative intensity): 382 (4) $[M^+]$, 269 (18), 183 (100). HRMS (EI) calcd for $C_{23}H_{30}N_2O_3$ $[M]^+$, 382.2256; found, 382.2270.

Typical Procedure for the Preparation of Compounds 17−20. Preparation of 6-[(9*H*-Carbazol-4-yloxy)methyl]-4-[2-(2-methoxyphenoxy)ethyl]-3-morpholinone (17).[43] Chloroacetyl chloride (113 mg, 1.00 mmol) was added to an ice-cooled solution of carvedilol (**1**) (406 mg, 1.00 mmol) and triethylamine (152 mg, 1.50 mmol) in chloroform. The reaction mixture was warmed to room temperature

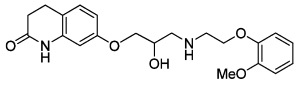
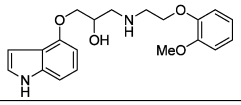
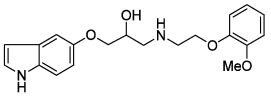
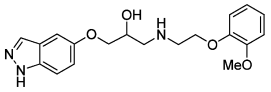
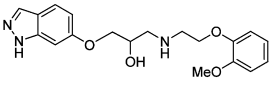
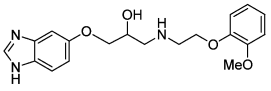
dx.doi.org/10.1021/jm401090a | *J. Med. Chem.* 2013, 56, 8626−8655

Table 6. Effect of Carbazole Modification or Replacement on SOICR Inhibition

entry	compound	structure	IC_{50} (μM) ± SEM	repeats (n)	no. of cells
1	**59**		>1000	3	180
2	**60**		86.5 ± 20	6	327
3	**61**		17.4 ± 1.1	3	261
4	**62**		17.0 ± 1.6	8	430
5	**63**		30.1 ± 2.6	17	982
6	**64**		11.0 ± 1.6	3	187
7	**65**		18.2 ± 2.7	5	392
8	**66**		5.7 ± 2.7	4	245
9	**67**		65.8 ± 6.5	3	140
10	**68**		15.1 ± 1.2	11	450
11	**69**		9.77 ± 2.0	3	188
12	**70**		75.6 ± 20	8	467
13	**71**		29.7 ± 11	2	206
14	**72**		28.0 ± 3.1	3	142
15	**73**		>1000	3	142
16	**74**		463 ± 129	3	185

dx.doi.org/10.1021/jm401090a | *J. Med. Chem.* 2013, 56, 8626−8655

Table 6. continued

entry	compound	structure	IC_{50} (μM) ± SEM	repeats (n)	no. of cells
17	**75**		>1000	3	167
18	**76**		213 ± 29	3	159
19	**77**		101 ± 16	3	189
20	**78**		>1000	3	179
21	**79**		545 ± 213	3	229
22	**80**		>1000	3	191

and stirred for 6 h. It was then quenched with water (10 mL) and extracted with chloroform. The combined organic layers were washed with saturated NH_4Cl solution (25 mL), dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by flash chromatography over silica gel (methanol/dichloromethane) to afford the corresponding chloroacetyl derivative. A suspension of NaH (1.1 mmol) in anhydrous THF was cooled to 0 °C. The above product was dissolved in THF and was added to the NaH mixture. The reaction mixture was stirred for 12 h at room temperature, quenched cautiously with water (10 mL), and extracted with ethyl acetate. The combined organic layers were washed with sat. NH_4Cl solution, dried over Na_2SO_4, and evaporated under reduced pressure. Flash chromatography of the residue over silica gel afforded 321 mg (72%) of **17** as a viscous oil. IR (neat): 3270, 1652, 1504, 1252 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.28−8.19 (m, 2H), 7.44−7.06 (m, 6H), 7.01−6.81 (m, 3H), 6.65 (d, J = 7.7 Hz, 1H), 4.45−4.21 (m, 7H), 3.96−3.79 (m, 4H), 3.69 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 154.9, 149.8, 148.1, 141.2, 138.9, 126.7, 125.3, 123.1, 122.5, 122.0, 121.0, 119.9, 114.1, 113.0, 112.0, 110.2, 104.4, 101.3, 72.2, 68.4, 68.0, 67.9, 55.8, 51.3, 47.1. MS (EI) m/z (relative intensity): 446 (17) [M^+], 323 (100). HRMS calcd for $C_{26}H_{26}N_2O_5$ [M^+], 446.1842; found 446.1844.

Compounds **18**−**20** were prepared similarly from the corresponding amino alcohols.

6-[(9*H*-Carbazol-4-yloxy)methyl]-4-[2-(4,5-dichloro-2-methoxyphenoxy)ethyl]-3-morpholinone (18).[43] Yield: 92%, viscous oil. IR (neat) 3275, 1650 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.20 (d, J = 7.7 Hz, 1H), 8.09 (s, 1H), 7.40−7.34 (m, 2H), 7.31 (t, J = 8.0 Hz, 1H), 7.12 (dd, J = 7.9, 4.5 Hz, 1H), 7.05 (d, J = 8.1 Hz, 1H), 6.92 (s, 1H), 6.78 (s, 1H), 6.66 (d, J = 7.7 Hz, 1H), 4.48−4.18 (m, 7H), 4.01−3.78 (m, 4H), 3.57 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2, 154.8, 148.9, 147.3, 141.1, 138.8, 128.5, 126.7, 125.4, 123.5, 123.0, 122.4, 119.9, 115.2, 113.3, 112.9, 110.2, 104.4, 101.3, 72.1, 68.3, 68.2, 67.9, 56.1, 51.3, 46.8. MS (EI) m/z (relative intensity): 514 (6) [M^+] 323 (100), 183 (18), 154 (48). HRMS calcd for $C_{26}H_{24}{}^{35}Cl_2N_2O_5$ [M^+], 514.1062; found, 514.1067.

6-[(9*H*-Carbazol-4-yloxy)methyl]-4-[(2,4,5-trichlorophenoxy)-ethyl]-3-morpholinone (19).[43] Yield: 77%, white solid. mp 106−108 °C. IR (film): 3268, 1652 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.22 (d, J = 7.7 Hz, 1H), 8.08 (s, 1H), 7.44−7.18 (m, 5H), 7.09 (d, J = 7.7 Hz, 1H), 6.96 (s, 1H), 6.67 (d, J = 7.7 Hz, 1H), 4.44−4.19 (m, 7H), 4.02−3.82 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.7, 154.5, 152.9, 141.3, 139.0, 131.3, 130.8, 126.3, 124.9, 124.6, 122.7, 122.1, 121.7, 119.2, 114.6, 112.5, 110.2, 104.4, 100.8, 71.9, 67.9, 67.8, 67.5, 51.0, 46.7. MS (EI) m/z (relative intensity): 518 (14) [M^+], 323 (33), 183 (100). HRMS calcd for $C_{25}H_{21}{}^{35}Cl_3N_2O_4$, 518.0567; found, 518.0599.

6-[(9*H*-Carbazol-4-yloxy)methyl]-4-[2-(cyclohexyloxy)ethyl]-3-morpholinone (20).[43] Yield: 41%, viscous oil. IR (neat) 3267, 1640 cm^{-1} . ^1H NMR (300 MHz $CDCl_3$) δ 8.24 (d, J = 7.7 Hz, 1H), 8.14 (s, 1H), 7.49−7.23 (m, 4H), 7.10 (d, J = 7.7 Hz, 1H), 6.68 (d, J = 7.7 Hz, 1H), 4.50−4.24 (m, 5H), 3.78 (d, J = 6.9 Hz, 2H), 3.66 (dd, J = 15.8, 4.6 Hz, 4H), 3.28−3.17 (m, 1H), 1.92−1.78 (m, 2H), 1.76−1.42 (m, 3H), 1.32−1.08 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 154.8, 141.2, 139.0, 126.7, 125.3, 123.1, 122.5, 119.8, 112.9, 110.3, 104.5, 101.3, 72.1, 68.3, 67.9, 66.2, 51.1, 47.7, 32.3, 29.9, 25.8, 24.1. MS (EI) m/z (relative intensity): 422 (24) [M^+], 296 (16), 183 (100). HRMS (EI) calcd for $C_{25}H_{30}N_2O_4$ [M^+], 422.2206; found, 422.2225.

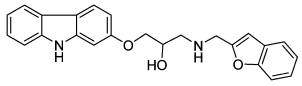
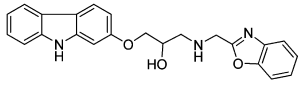
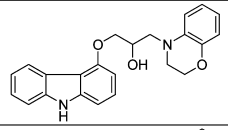
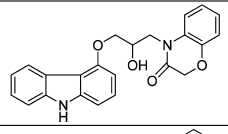
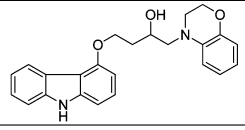
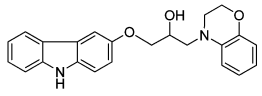
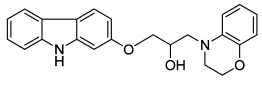
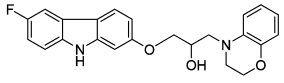
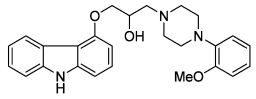
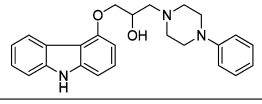
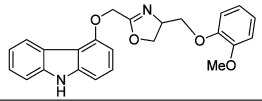
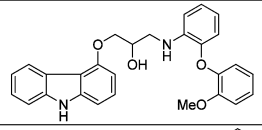
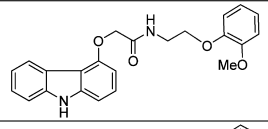
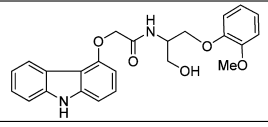
Typical Procedure for the Preparation of Compounds 21−24. Preparation of 4-{4-[2-(2-Methoxyphenoxy)ethyl]-2-morpholinyl]-methoxy}-9*H*-carbazole (21).[43] A solution of **17** (446 mg, 1.00 mmol) in THF was added to a suspension of $LiAlH_4$ (38 mg, 1.0 mmol) in THF, and the mixture was stirred at room temperature for 3 h. The reaction was quenched with ethyl acetate followed by saturated Na_2SO_4 solution. The crude mixture was filtered through Celite, and the residue was washed with ethyl acetate. The filtrate was dried over Na_2SO_4, evaporated under reduced pressure, and purified by flash chromatography over silica gel to afford 259 mg (60%) of **21** as a viscous oil. IR (neat) 3290 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.30 (d, J = 7.7 Hz, 1H), 8.09 (s, 1H), 7.46−7.17 (m, 4H), 7.06 (d, J = 7.7 Hz, 1H), 6.96−6.84 (m, 4H), 6.66 (d, J = 7.7 Hz, 1H), 4.40−4.05 (m, 5H), 4.04−3.93 (m, 1H), 3.91−3.76 (m, 1H), 3.78 (s, 3H), 3.34−3.22 (m, 1H), 3.04−2.84 (m, 3H), 2.58−2.31 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.3, 149.9, 148.4, 141.1, 138.9, 126.8, 125.1, 123.2, 122.7, 121.8, 121.1, 119.8, 114.2, 112.9, 112.2, 110.1, 104.0, 101.3, 74.2, 69.3, 67.0, 66.9, 57.7, 56.8, 56.0, 53.8. MS (EI) m/z (relative intensity): 432 (17) [M^+], 295 (100). HRMS (EI) calcd for $C_{26}H_{28}N_2O_4$ [M^+], 432.2049; found, 432.2017.

Compounds **22**−**24** were prepared similarly.

4-{[4-[2-(4,5-Dichloro-2-methoxyphenoxy)ethyl]-2-morpholinyl]-methoxy}-9*H*-carbazole (22).[43] Yield: 86%, viscous oil. IR (neat): 3280, 1600, 1503 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.29 (d, J = 7.7 Hz, 1H), 8.09 (s, 1H), 7.46−7.13 (m, 3H), 7.06 (d, J = 7.7 Hz, 1H), 6.98−6.80 (m, 3H), 6.67 (d, J = 7.7 Hz, 1H), 4.37−3.97 (m, 7H), 3.80 (s, 3H), 3.32−3.22 (m, 1H), 3.02−2.84 (m, 3H), 2.58−2.29 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.2, 149.9, 141.1, 138.9, 126.8, 125.1, 123.2, 122.7, 121.9,121.0, 120.5, 119.8, 114.5, 113.0, 112.7, 112.1, 110.1, 104.0, 101.4, 74.2, 69.2, 57.6, 56.1, 56.0, 53.8. MS (EI) m/z (relative

dx.doi.org/10.1021/jm401090a | J. Med. Chem. 2013, 56, 8626−8655

Table 7. Other Modified Carvedilol Derivatives as SOICR Inhibitors

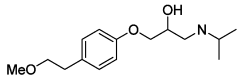
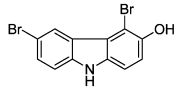
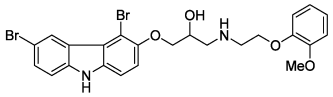
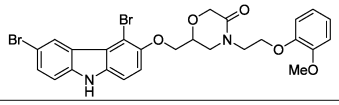
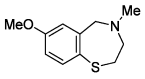
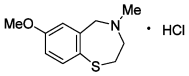
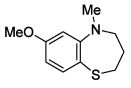
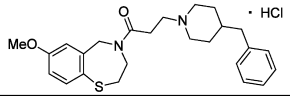
entry	compound	structure	IC_{50} (μM) ± SEM	repeats (n)	no. of cells
1	**81**		>1000	3	193
2	**82**		>1000	3	234
3	**83**		5.76 ± 1.3	4	299
4	**84**		15.8 ± 5.0	3	171
5	**85**		19.7 ± 9.0	3	188
6	**86**		8.61 ± 0.47	3	218
7	**87**		>1000	3	153
8	**88**		>1000	3	191
9	**89**		34.9 ± 3.7	3	148
10	**90**		62.7 ± 15	4	201
11	**91**		19.8 ± 1.7	3	187
12	**92**		94.5 ± 60	3	216
13	**93**		3.55 ± 0.30	3	158
14	**94**		3.63 ± 0.18	3	127

intensity): 500 (10) [M^+], 296 (20), 295 (100). HRMS (EI) calcd for $C_{26}H_{27}{}^{35}Cl_2N_2O_4$ [M^+], 500.1270; found, 500.1263.

4-{[4-[2-(2,4,5-Trichlorophenoxy)ethyl]-2-morpholinyl]-methoxy}-9*H*-carbazole (23).[43] Yield: 66%, viscous oil. IR (neat): 3308 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.25 (d, J = 7.7 Hz, 1H), 8.07 (s, 1H), 7.46−7.23, (m, 4H), 7.20−7.12 (m, 1H), 7.07 (d, J = 7.7 Hz, 1H), 7.00 (s, 1H), 6.67 (d, J = 7.7 Hz, 1H), 4.38−4.10 (m, 6H), 4.08−3.86 (m, 2H), 3.46−3.25 (m, 1H), 3.16−2.92 (m, 2H), 2.74−2.48 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.2, 153.3, 141.0, 138.8, 131.3, 131.0, 126.8, 125.2, 124.8, 123.1, 122.6, 122.3, 119.8, 115.1, 112.9, 110.1, 104.1, 101.4, 74.0, 69.1, 67.8, 66.8, 57.2, 56.6, 53.8. MS (EI) m/z (relative intensity): 504 (7) [M^+], 295 (44), 43 (100). HRMS (EI) calcd for $C_{25}H_{23}{}^{35}Cl_3N_2O_3$ [M^+], 504.0774; found, 504.0757.

dx.doi.org/10.1021/jm401090a | J. Med. Chem. 2013, 56, 8626−8655

Table 8. SOICR Inhibition by Other Types of Antiarrhythmic Agents

entry	compound	structure	IC_{50} (μM) ± SEM	repeats (n)	no. of cells
1	metoprolol **95**		>1000	3	185
3	**96**		>1000	3	146
4	**97**		69.8 ± 33	3	156
5	**98**		>1000	3	234
6	**99**		>1000	3	172
7	**100**		>1000	3	218
8	**101**		>1000	3	175
9	**102**		34.3 ± 6.7	4	187

4-{[4-[2-(Cyclohexyloxy)ethyl]-2-morpholinyl]methoxy}-9*H*-carbazole (24).[43] Yield: 60%, viscous oil. IR (neat) 3293, 1606, 1341, 1100 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.31 (d, J = 7.7 Hz, 1H), 8.11 (s, 1H),7.46–7.20 (m, 4H), 7.06 (d, J = 7.7 Hz, 1H), 6.66 (d, J = 7.7 Hz, 1H), 4.38–4.28 (m, 1H), 4.23–4.12 (m, 2H), 3.98 (d, J = 9.9 Hz, 1H), 3.84 (ddd, J = 11.3, 11.2, 2.3 Hz, 1H), 3.66 (t, J = 6.1 Hz, 2H), 3.28–3.17 (m, 2H), 2.85 (d, J = 11.6 Hz, 1H), 2.66 (t, J = 6.0 Hz, 2H), 2.37 (ddd, J = 11.4, 11.3, 3.3 Hz, 1H), 2.32–2.23 (m, 1H), 1.96–1.83 (m, 2H), 1.78–1.62 (m, 2H), 1.55–1.48 (m, 1H), 1.36–1.14 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.3, 141.1, 13.9, 126.8, 125.1, 123.3, 122.7, 119.8, 113.0, 110.1, 103.9, 101.3, 74.2, 69.4, 67.0, 65.5, 58.8, 56.9, 53.9, 32.4, 29.8, 25.9, 24.4. MS (EI) m/z (relative intensity): 408 (6) [M^+], 295 (100). HRMS (EI) calcd for $C_{25}H_{32}N_2O_3$ [M^+], 408.2413; found, 408.2415.

Typical Procedure for the Preparation of Compounds 25–27. Preparation of 5-[(9*H*-Carbazol-4-yloxy)methyl]-3-[2-(2-methoxyphenoxy)ethyl]-2-oxazolidinone (25).[43,46,47] A solution of carvedilol **1** (99 mg, 0.24 mmol), triethylamine (51 μL, 0.37 mmol), and 1,1′-carbonyldiimidazole (43 mg, 0.27 mmol) in 3 mL of dichloromethane was stirred at room temperature for 5 h. The mixture was diluted with dichloromethane and washed with water and saturated aqueous NH_4Cl solution, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash chromatography over silica gel (methanol/dichloromethane) to afford 96 mg (93%) of **25** as a white solid. mp >350 °C. IR (film) 3288, 1730, 1107 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.16 (d, J = 7.7 Hz, 1H), 8.08 (s, 1H), 7.46–7.19 (m, 4 H), 7.09 (d, J = 7.7 Hz, 1H), 6.98–6.79 (m, 4H), 6.64 (d, J = 7.7 Hz, 1H), 5.13–4.99 (m, 1H), 4.40 (dd, J = 10.0, 4.5 Hz, 1H), 4.33 (dd, J = 9.9, 5.7 Hz, 1H), 4.28–4.14 (m, 3H), 3.99 (dd, J = 9.0, 6.0 Hz, 1H), 3.88–3.72 (m, 2H), 3.68 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$–CD_3OD) δ 158.4, 154.5, 149.6, 147.7, 141.4, 139.1, 126.3, 125.0, 122.7, 122.1, 122.0, 121.0, 119.2, 114.1, 112.2, 112.0, 110.2, 104.6, 100.5, 71.9, 68.0, 67.9, 55.6, 43.9. MS (EI) m/z (relative intensity): 432 (58) [M^+], 183 (53), 44 (100). HRMS (EI) calcd for $C_{25}H_{24}N_2O_5$ [M^+], 432.1685; found, 432.1672.

Compounds **26** and **27** were prepared similarly.

5-[(9*H*-Carbazol-4-yloxy)methyl]-3-[2-(4,5-dichloro-2-methoxyphenoxy)ethyl]-2-oxazolidinone (26).[43] Yield: 65%, white solid. mp 104–106 °C. IR (film): 3290, 1749 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.12–8.05 (m, 2H), 7.44–7.20 (m, 4H), 7.13 (d, J = 7.7 Hz, 1H), 6.83 (d, J = 7.7 Hz, 1H), 6.67 (m, 2H), 5.08–5.02 (m, 1H), 4.43–4.39 (m, 2H), 4.14–4.04 (m, 4H), 3.85–3.62 (m, 2H), 3.52 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.6, 154.4, 148.5, 146.9, 139.7, 137.5, 128.2, 126.8, 124.9, 124.6, 124.4, 123.5, 123.4, 115.5, 114.8, 113.8, 112.9, 107.9, 105.9, 71.3, 68.5, 68.3, 56.0, 48.6, 43.8. MS (EI) m/z (relative intensity): 500 (6) [M^+], 222 (10), 68 (100). HRMS (EI) calcd for $C_{25}H_{22}{}^{35}Cl_2N_2O_5$ [M^+], 500.0906; found, 500.0936.

5-[(9*H*-Carbazol-4-yloxy)methyl]-3-[2-(cyclohexyloxy)ethyl]-2-oxazolidinone (27).[43] Yield: 74%, white solid. mp 146–148 °C. IR (neat) 3290, 1732 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.22–8.14 (m, 2H), 7.45–7.19 (m, 4H), 7.10 (d, J = 7.7 Hz, 1H), 6.66 (d, J = 7.7 Hz, 1H), 5.08–4.98 (m, 1H), 4.46–4.36 (m, 2H), 4.08–4.00 (m, 1H) 3.94–3.83 (m, 2H), 3.68–3.45 (m, 3H), 3.24–3.16 (m, 1H), 1.85–1.39 (m, 6H), 1.28–1.04 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.8, 154.7, 141.1, 138.9, 126.7, 125.3, 123.1, 122.5, 120.0, 112.9, 110.2, 104.5, 101.2, 77.9, 71.2, 68.2, 66.5, 48.8, 44.8, 32.2, 25.8, 24.0. MS (EI) m/z (relative intensity): 408 (100) [M^+], 183 (87). HRMS (EI) calcd for $C_{24}H_{28}N_2O_4$ [M^+], 408.2049; found 408.2027.

Preparation of 5-[(9*H*-Carbazol-4-yloxy)methyl]-3-[2-(2-hydroxyphenoxy)ethyl]-2-oxazolidinone (28). A solution of 25 (160 mg, 0.37 mmol) in dry dichloromethane (7 mL) was cooled in an ice bath and a 1.0 M solution of BBr_3 in dichloromethane (1.2 mL) was added dropwise. After 1 h, the reaction was warmed to room temperature and stirred an additional 1 h. The reaction was cooled in an ice bath and slowly quenched with water and diluted further with ethyl acetate. The organic phase was separated and washed with water and brine, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by flash chromatography over silica gel (ethyl acetate/hexanes) to afford 131 mg (85%) of 28 as a white solid. mp 194–196 °C.

dx.doi.org/10.1021/jm401090a | J. Med. Chem. 2013, 56, 8626–8655

IR (film) 3423, 3270, 2919, 2847, 1709, 1505, 1114, 746, 742 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 11.28 (s, 1H), 8.91 (s, 1H), 8.06 (d, J = 7.8 Hz, 1H), 7.45 (d, J = 8.1 Hz, 1H), 7.30–7.37 (m, 1H), 7.30 (dd, J = 8.0, 8.0 Hz, 1H), 7.15–7.07 (m, 2H), 6.91 (dd, J = 7.9, 1.3 Hz, 1H), 6.84–6.75 (m, 2H), 6.74–6.67 (m, 2H), 5.15–5.02 (m, 1H), 4.43 (dd, J = 10.8, 3.1 Hz, 1H), 4.34 (dd, J = 10.8, 4.8 Hz, 1H), 4.16 (t, J = 5.4 Hz, 2H), 4.02 (t, J = 9.2 Hz, 1H), 3.80–3.68 (m, 2H), 3.59 (dt, J = 14.5, 5.4 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 157.2, 154.2, 147.1, 146.3, 141.0, 138.8, 126.3, 124.6, 122.1, 121.7, 121.4, 119.1, 118.6, 115.8, 114.7, 111.4, 110.3, 104.2, 100.4, 68.1, 68.2, 66.8, 46.6, 43.2. MS (EI) m/z (relative intensity): 418 (100) [M^+], 222 (57), 154 (23). HRMS (EI) calcd for $C_{24}H_{22}N_2O_5$ [M]$^+$, 418.1529; found, 418.1524.

Preparation of 1-(9*H*-Carbazol-4-yloxy)-3-{[2-(2-hydroxyphenoxy)ethyl]amino}-2-propanol (9).[44,45] Compound **28** (77 mg, 0.18 mmol) was dissolved in ethanol (1 mL) and a 2 M NaOH solution (1.5 mL) and refluxed for 3.5 h. The mixture was cooled to room temperature, neutralized with a 1 M HCl solution, and extracted with ethyl acetate. The combined extracts were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography over silica gel (methanol/dichloromethane) to afford 56 mg (78%) of **9** as an off-white solid. mp 160–162 °C. IR (KBr) 3415, 1605, 1503, 1263, 1100, 755, 722 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 11.24 (s, 1H), 8.21 (d, J = 7.6 Hz, 1H), 7.43 (d, J = 8.1 Hz, 1H), 7.32 (ddd, J = 7.1, 7.0, 1.2 Hz, 1H), 7.27 (d, J = 8.0 Hz, 1H), 7.09 (ddd, J = 8.0, 7.0, 1.0, 1H), 7.06 (d, J = 8.0 Hz, 1H), 6.91 (dd, J = 8.1, 1.3 Hz, 1H), 6.82–6.74 (m, 2H), 6.73–6.68 (m, 1H), 6.68 (d, J = 8.1 Hz, 1H), 4.22–4.08 (m, 3H), 4.06–3.97 (m, 2H), 2.96–2.86 (m, 3H), 2.80 (dd, J = 12.3, 6.9 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 154.9, 148.0, 146.6, 141.0, 138.8, 126.4, 124.4, 122.4, 122.0, 121.6, 119.0, 118.5, 116.0, 115.8, 111.5, 110.2, 103.7, 100.3, 70.4, 69.2, 68.3, 52.1, 48.2. MS (EI) m/z (relative intensity): 392 (69) [M^+], 183 (100), 166 (30). HRMS (EI) calcd for $C_{23}H_{24}N_2O_4$ [M]$^+$, 392.1736; found, 392.1731.

Preparation of 1-(9*H*-Carbazol-4-yloxy)-3-{[2-(2-methoxyphenoxy)ethyl]methylamino}-2-propanol (29).[45] A suspension of NaH (60% in oil) (10 mg, 0.25 mmol) in anhydrous THF was cooled to 0 °C. A solution of carvedilol (**1**) (100 mg, 0.246 mmol) in THF was added and stirred for 20 min at the same temperature followed by iodomethane (35 mg, 0.25 mmol). The reaction mixture was stirred for 4 h at room temperature, quenched with water, and extracted with ethyl acetate. The combined organic layers were washed with saturated NH_4Cl solution, dried over Na_2SO_4, and evaporated under reduced pressure, and the residue was purified by flash chromatography over silica gel to obtain 57 mg (54%) of **29** as a viscous oil. IR (film) 3233, 2923, 1600, 1504, 1452, 1252, 732 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.29–8.20 (m, 2H), 7.41–7.31 (m, 3H), 7.28–7.26 (m, 1H), 7.06 (d, J = 8.1 Hz, 1H), 6.93–6.87 (m, 4H), 6.66 (d, J = 8.1 Hz, 1H), 4.36–4.21 (m, 5H), 3.78 (s, 3H), 3.27–3.13 (m, 4H), 2.72 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.9, 149.7, 147.6, 141.0, 138.8, 126.7, 125.0, 122.9, 122.5, 122.1, 120.9, 119.7, 114.3, 112.7, 111.9, 110.1, 104.0, 101.3, 69.9, 66.1, 66.0, 61.2, 56.4, 55.7, 43.0. MS (EI) m/z (relative intensity): 420 (5) [M^+], 283 (41), 194 (100). HRMS (EI) calcd for $C_{25}H_{28}N_2O_4$ [M^+], 420.2049; found 420.2038.

Preparation of 1-{[2-(2-Methoxyphenoxy)ethyl]amino}-3-[(9-methyl-9*H*-carbazol-4-yl)oxy]-2-propanol (30).[43,48] A solution of carvedilol (**1**) (50 mg, 0.12 mmol) and DABCO (2 mg) in dimethyl carbonate (4 mL) and DMF (1 mL) was heated at 95 °C for 18 h. The reaction mixture was partitioned between ether and water. The ether layer was washed with water and brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel to give (41 mg, 77%) of the *N*-methyl derivative of **25** as an oil. The latter product was dissolved in ethanol, 2 N NaOH (2 mL) was added, and the mixture was refluxed for 6 h. The ethanol was removed under vacuum, and the residue was taken up in ethyl acetate and washed with 1 M HCl. The aqueous layer was extracted with ethyl acetate, and the combined organic layer was washed with water, brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by flash chromatography over silica gel to obtain 38 mg (73% overall from **1**) of **30** as a white solid. mp 130–132 °C. IR (film) 3300, 1587, 1504, 1252 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.30 (d, J = 8.2 Hz, 1H), 7.48–7.36 (m, 3H), 7.24 (dd, J = 12.8, 5.1 Hz, 1H), 7.06 (d, J = 8.2 Hz, 1H), 6.98–6.88 (m, 4H), 6.70 (d, J = 8.2 Hz, 1H), 4.36–4.22 (m, 3H), 4.17 (t, J = 5.1 Hz, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 3.18–3.06 (m, 3H), 3.00 (dd, J = 12.2, 6.9 Hz, 1H), 2.72 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.3, 149.9, 148.3, 142.7, 140.4, 126.6, 125.0, 123.1, 122.2, 121.8, 121.0, 119.3, 114.4, 112.1, 112.0, 108.1, 101.9, 101.1, 70.5, 69.0, 68.6, 56.0, 52.1, 48.8, 29.4. MS (EI) m/z (relative intensity): 420 (13) [M^+], 197 (100). HRMS (EI) calcd for $C_{25}H_{28}N_2O_4$ [M^+], 420.2049; found, 420.2085.

Preparation of 2-Methoxy-*N*-[2-(2-methoxyphenoxy)ethyl]-*N*-methyl-3-[(9-methyl-9*H*-carbazol-4-yl)oxy]-1-propanamine (31).[43] A solution of epoxide **103a** (307 mg, 1.28 mmol) in DMF (5 mL) was added dropwise to a mixture of 60% NaH (101 mg, 2.50 mmol) in DMF (5 mL) and was cooled in an ice bath. After 5 min, iodomethane (87 μL, 1.4 mmol) was added, and the mixture was stirred at room temperature for 4 h. The reaction was quenched with water and brine, and diluted with ethyl acetate. The organic phase was separated and washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was subjected to flash chromatography over silica gel (ethyl acetate/hexanes) to afford 300 mg (92%) of the corresponding *N*-methyl derivative **103b** as a white solid. mp 76–77 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 8.21 (d, J = 7.4 Hz, 1H), 7.57 (d, J = 8.2 Hz, 1H), 7.44 (ddd, J = 8.3, 7.2, 1.2 Hz, 1H), 7.39 (dd, J = 8.1, 8.1 Hz, 1H), 7.27–7.17 (m, 2H), 6.77 (d, J = 7.9 Hz, 1H), 4.58 (dd, J = 11.3, 2.6 Hz, 1H), 4.12 (dd, J = 11.3, 6.3 Hz, 1H), 3.86 (s, 3H), 3.58–3.51 (m, 1H), 2.94 (dd, J = 5.0, 4.3 Hz, 1H), 2.85 (dd, J = 5.1, 2.7 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 154.4, 142.0, 139.8, 126.6, 124.8, 122.3, 121.1, 118.9, 110.9, 108.67, 102.4, 101.1, 68.8, 49.9, 43.8, 29.1.

The above product (90 mg, 0.36 mmol) was refluxed with the *N*-methyl derivative of amine **104a** (72 mg, 0.40 mmol) in isopropanol for 2 h. The solution was evaporated, and the residue was purified by flash chromatography over silica gel (methanol/dichloromethane) to obtain 117 mg (76%) of the corresponding *N*,*N*-methylated product as a colorless oil. IR (film) 3496, 3059, 1589, 1503, 1466, 1252 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.35 (d, J = 7.7 Hz, 1H), 7.49–7.34 (m, 3H), 7.28–7.19 (m, 1H), 7.03 (d, J = 8.1 Hz, 1H), 7.00–6.84 (m, 4H), 6.71 (d, J = 7.9 Hz, 1H), 4.58 (dd, J = 11.3, 2.6 Hz, 1H), 4.41–4.22 (m, 3H), 4.16 (t, J = 5.7 Hz, 2H), 3.85 (s, 3H), 3.83 (s, 3H), 3.18–3.03 (m, 1H), 3.00–2.84 (m, 3H), 2.51 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.4, 149.8, 148.4, 142.6, 140.4, 126.6, 124.8, 123.1, 122.2, 121.5, 120.9, 119.2, 113.7, 112.1, 112.0, 108.0, 101.8, 101.0, 70.4, 67.2, 67.0, 61.1, 56.8, 55.9, 43.5, 29.4. MS (EI) m/z (relative intensity): 434 (4) [M^+], 297 (10), 194 (100). HRMS (EI) m/z calcd for $C_{26}H_{30}N_2O_4$ [M^+], 434.2206; found, 434.2206.

The above carvedilol derivative (186 mg, 0.428 mmol) in DMF (5 mL) was cooled in an ice bath, and 60% NaH (34 mg, 0.85 mmol) was added. After 20 min, iodomethane (30 μL, 0.47 mmol) was added, and the mixture stirred at room temperature for 5 h. The reaction was quenched with water and brine and diluted with ethyl acetate. The organic phase was separated and washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was subjected to flash chromatography over silica gel (methanol/dichloromethane) to afford 151 mg (79%) of **31** as a viscous, colorless oil. IR (film) 3062, 1591, 1465, 1249, 1104, 1026 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, J = 8.0 Hz, 1H), 7.45 (ddd, J = 8.2, 7.1, 1.2, 1H), 7.42–7.32 (m, 2H), 7.23 (ddd, J = 8.0, 7.1, 1.1, 1H), 7.03 (d, J = 8.0 Hz, 1H), 6.95–6.74 (m, 4H), 6.70 (d, J = 7.8 Hz, 1H), 4.44–4.30 (m, 2H), 4.13 (t, J = 6.3 Hz, 2H), 3.97–3.89 (m, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 3.61 (s, 3H), 2.99 (t, J = 6.3 Hz, 2H), 2.96–2.81 (m, 2H), 2.50 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.5, 149.6, 148.4, 142.6, 140.3, 126.5, 124.8, 123.2, 122.3, 121.2, 120.9, 119.3, 113.4, 112.1, 111.9, 107.9, 101.6, 100.9, 78.5, 68.5, 67.2, 59.2, 58.1, 57.1, 55.9, 44.3, 29.4. MS (EI) m/z (relative intensity): 448 (2) [M^+], 194 (100). HRMS (EI) calcd for $C_{27}H_{32}N_2O_4$ [M^+], 448.2362; found, 448.2345.

Preparation of 6-[2-(9*H*-Carbazol-4-yloxy)ethyl]-4-[2-(2-methoxyphenoxy)ethyl]-3-morpholinone (32). Compound **32** was obtained from **2** by the same procedure used to obtain **17** from **1**. Yield: 56%, white solid, mp 157–160 °C. IR (KBr) 3256, 1634, 1507, 1452, 1257, 1122, 1098, 722 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.36 (br s, 1H), 8.26 (d, J = 7.8 Hz, 1H), 7.39–7.36 (m, 2H), 7.32

(d, J = 8.1 Hz, 1H), 7.19−7.12 (m, 1H), 7.04 (d, J = 8.1 Hz, 1H), 6.98−6.90 (m, 4H), 6.69 (d, J = 8.0 Hz, 1H), 4.44−4.05 (m, 7H), 3.81 (s, 3H), 3.8 −3.74 (m, 2H), 3.70−3.66 (m, 2H), 2.26−2.12 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 155.1, 149.4, 147.9, 141.0, 138.7, 126.6, 124.9, 122.7, 122.5, 121.6, 120.9, 119.5, 113.5, 112.6, 111.8, 110.0, 103.7, 101.0, 70.7, 67.8, 67.6, 63.6, 55.7, 53.6, 46.6, 32.7. MS (EI) m/z (relative intensity): 460 (14) [M^+], 338 (20), 337 (100). HRMS (EI) calcd for $C_{27}H_{28}N_2O_5$ [M^+], 460.1998; found, 460.2005.

Preparation of 6-(9*H*-Carbazol-4-yloxy)-1-{[2-(2-methoxyphenoxy)ethyl]amino}-2-hexanol (33). The product was obtained from epoxide **106** and amine **104a** by the same procedure as used to obtain **6**. Yield: 54%, solid white foam. IR (film) 3398, 3227, 3055, 2935, 1608, 1501, 1453, 1250, 1092, 787, 749, 720 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, J = 7.7 Hz, 1H), 8.28 (s, 1H), 7.42−7.20 (m, 4H), 7.01 (d, J = 8.0 Hz, 1H), 6.99−6.88 (m, 4H), 6.65 (d, J = 8.0 Hz, 1H), 4.22 (t, J = 6.3 Hz, 2H), 4.09 (t, J = 5.1 Hz, 2H), 3.85 (s, 3H), 3.69−3.58 (m, 1H), 3.06−2.93 (m, 2H), 2.75 (dd, J = 12.0, 2.8 Hz, 1H), 2.47 (dd, J = 12.0, 9.5 Hz, 1H), 2.20−2.80 (br s, 2H), 2.05−1.96 (m, 2H), 1.82−1.48 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.8, 149.8, 148.4, 141.2, 138.9, 126.8, 125.0, 123.2, 122.9, 121.8, 121.1, 119.7, 114.3, 112.9, 112.1, 110.1, 103.5, 101.2, 69.4, 68.9, 67.9, 56.0, 55.2, 48.6, 34.8, 29.6, 22.5. MS (CI) m/z (relative intensity): 449 (100) [M + H]$^+$. HRMS (CI) calcd for $C_{27}H_{33}N_2O_4$ [M + H]$^+$, 449.2440; found, 449.2460.

Preparation of 1-(9*H*-Carbazol-4-yloxy)-4-[[2-(2-methoxyphenoxy)ethyl]amino]-2-butanol (34). 4-Hydroxycarbazole (56 mg, 0.31 mmol), **107** (160 mg, 0.31 mmol), and K_2CO_3 (85 mg, 0.62 mmol) were heated in DMF (10 mL) at 100 °C for 12 h. The reaction mixture was diluted with water (50 mL) and extracted with dichloromethane. The combined organic layers were dried over Na_2SO_4, and the residue was purified by flash chromatography over silica gel to afford 120 mg (63%) of **108** as a colorless oil. The latter product (70 mg, 0.11 mmol) was dissolved in THF, TBAF in THF (0.22 mL, 1 M) was added, and the mixture was stirred at room temperature overnight. The solvent was removed under vacuum, and the residue was chromatographed similarly to afford 24 mg (80%) of the corresponding diol as colorless oil. The diol (735 mg, 2.71 mmol), triethylamine (1.5 mL, 10.8 mmol), p-toluenesulfonyl chloride (1.03 g, 5.4 mmol), and DMAP (5 mol %) were stirred in dry chloroform at room temperature for 2 days. Concentration and flash chromatography afforded 200 mg (17%) of tosylate **109** along with 500 mg of recovered starting material. The tosylate (200 mg, 0.471 mmol), amine **104a** (400 mg, 2.40 mmol), and LiBr (104 mg, 1.20 mmol) were heated briefly at 100 °C in DME (1 mL). The reaction mixture was then stirred for 2 days at room temperature, diluted with water (20 mL), and extracted with chloroform. The combined organic layers were dried over Na_2SO_4, concentrated, and subjected to flash chromatography over silica gel to afford 100 mg (51%) of **34** as solid foam. IR (KBr) 3345, 2919, 1605, 1502, 1454, 1255, 1123, 1100, 749, 718 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, J = 7.7 Hz, 1H), 8.15 (br s, 1H), 7.43−7.38 (m, 2H), 7.33 (t, J = 8.0 Hz, 1H), 7.23 (ddd, J = 8.0, 6.7, 1.5 Hz, 1H), 7.06 (d, J = 8.0 Hz, 1H), 7.00−6.90 (m, 4H), 6.70 (d, J = 8.0 Hz, 1H), 4.48−4.42 (m, 1H), 4.29 (dd, J = 9.2, 5.2 Hz, 1H), 4.18−4.12 (m, 2H), 3.87 (s, 3H), 3.22−2.98 (m, 5H), 2.10−2.03 (m, 1H), 1.94−1.84 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.3, 149.8, 148.1, 141.0, 138.8, 126.7, 124.9, 123.0, 122.6, 121.9, 121.0, 119.6, 114.5, 112.7, 111.9, 110.0, 103.7, 101.2, 71.6, 71.5, 68.4, 55.8, 48.4, 47.8, 31.8. MS (EI) m/z (relative intensity): 420 (11) [M^+], 238 (46), 154 (100). HRMS (EI) calcd for $C_{25}H_{28}N_2O_4$ [M^+], 420.2049; found, 420.2069.

Preparation of 7-[(9*H*-Carbazol-4-yloxy)methyl]-4-[2-(2-methoxyphenoxy)ethyl]-1,4-oxazepan-3-one (35). Compound **35** was obtained from **34** by the same procedure used to obtain **17** from **1**. Yield: 23% (overall), viscous oil. IR (KBr): 3285, 2920, 1647, 1504, 1455, 1252, 1221, 1123, 1032, 752 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (br s, 1H), 8.24 (d, J = 7.4 Hz, 1H), 7.41−7.39 (m, 2H), 7.32 (t, J = 8.0 Hz, 1H), 7.23 (ddd, J = 8.1, 6.7, 4.0 Hz, 1H), 7.06 (d, J = 8.1 Hz, 1H), 6.97−6.87 (m, 4H), 6.65 (d, J = 8.0 Hz, 1H), 4.57 (d, J = 15.5 Hz, 1H), 4.36−4.31 (m, 2H), 4.27−4.10 (m, 4H), 3.98−3.83 (m, 3H), 3.80 (s, 3H), 3.76−3.70 (m, 1H), 2.39−2.25 (m, 1H), 2.15−2.08 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.1, 154.9, 149.4, 148.0, 140.9, 138.7, 126.6, 125.0, 122.8, 122.4, 121.5, 120.9, 119.6, 113.2, 112.7, 111.7, 110.03, 103.9, 101.2, 78.6, 72.3, 69.8, 67.7, 55.7, 49.0, 47.8, 31.9. MS (EI) m/z (relative intensity): 460 (16) [M^+], 337 (100). HRMS (EI) calcd for $C_{27}H_{28}N_2O_5$ [M^+], 460.1998; found, 460.1990.

Preparation of 1-(9*H*-Carbazol-4-yloxy)-3-{[3-(2-methoxyphenyl)propyl]amino}-2-propanol (36).[43] Epoxide **103a** (100 mg, 0.418 mmol) and amine **110** (151 mg, 0.836 mmol) were stirred for 24 h at 50 °C in anhydrous DME (6 mL) in the presence of a catalytic amount of LiBr. The solvent was then removed under vacuum, and the residue was taken up in ether (10 mL) and washed with water. The aqueous layer was extracted with ether, and the combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by flash chromatography over silica gel (ethyl acetate/hexanes) to obtain 86 mg (49%) of product **36** as a viscous oil. IR (film) 3352, 1504, 1452 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29−8.24 (m, 2H), 7.42−7.28 (m, 2H), 7.22−7.18 (m, 1H), 7.06 (d, J = 8.2 Hz, 1H), 6.96−6.82 (m, 5H), 6.65 (d, J = 8.2 Hz, 1H), 4.39−4.09 (m, 2H), 4.12 (t, J = 5.1 Hz, 2H), 3.88−3.79 (m, 1H), 3.85 (s 3H), 3.60−3.20 (m, 2H), 3.20−2.93 (m, 3H), 2.15−2.05 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6, 149.7, 148.3, 141.1, 138.9, 126.9, 125.0, 123.0, 122.8, 121.8, 121.1, 119.7, 114.2, 112.7, 112.0, 110.2, 103.7, 101.3, 70.3, 68.1, 68.0, 56.1, 52.1, 47.7, 28.6. MS (EI) m/z (relative intensity): 420 (12) [M^+], 183 (44), 154 (70), 45 (100). HRMS (EI) calcd for $C_{25}H_{28}N_2O_4$, 420.2049; found 420.2088.

Preparation of 1-(9*H*-Carbazol-4-yloxy)-3-{[2-(2-methoxybenzyloxy)ethyl]amino}-2-propanol (37). The product was obtained from epoxide **103a** and amine **111a** by the same procedure used to obtain **6**. Yield: 82%, off-white solid. mp 94−95 °C. IR (film) 3402, 3291, 3050, 1606, 1455, 1243, 1100 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, J = 7.8 Hz, 1H), 8.15 (s, 1H), 7.42−7.19 (m, 6H), 7.04 (d, J = 8.0 Hz, 1H), 6.93 (td, J = 7.4, 0.9 Hz, 1H), 6.86 (d, J = 8.2 Hz, 1H), 6.66 (d, J = 7.9 Hz, 1H), 4.59 (s, 2H), 4.33−4.15 (m, 3H), 3.82 (s, 3H), 3.67 (t, J = 5.1 Hz, 2H), 3.05 (dd, J = 12.3, 3.5 Hz, 1H), 3.02−2.86 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.4, 155.3, 141.1, 138.9, 129.4, 129.0, 126.8, 126.6, 125.1, 123.1, 122.7, 120.6, 119.8, 112.9, 110.5, 110.1, 104.0, 101.4, 70.4, 69.6, 68.5, 68.2, 55.5, 52.1, 49.4. MS (EI) m/z (relative intensity): 420 (8) [M^+], 194 (46), 183 (100), 154 (48), 121 (92), 91 (50). HRMS (EI) calcd for $C_{25}H_{28}N_2O_4$ [M]$^+$, 420.2049; found, 420.2056.

Preparation of 1-(9*H*-Carbazol-4-yloxy)-3-{[2-(benzyloxy)-ethyl]amino}-2-propanol (38). The product was obtained from epoxide **103a** and amine **111b** by the same procedure used to obtain **6**. Yield: 72%, solid white foam. IR (film) 3405, 3299, 3056, 2919, 2856, 1603, 1455, 1100, 751, 720 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, J = 7.8 Hz, 1H), 8.09 (s, 1H), 7.46−7.18 (m, 9H), 7.06 (d, J = 8.0 Hz, 1H), 6.68 (d, J = 8.0 Hz, 1H), 4.52 (s, 2H), 4.34−4.18 (m, 3H), 3.63 (t, J = 5.1 Hz, 2H), 3.06 (dd, J = 12.2, 3.4 Hz, 1H), 3.01−2.86 (m, 3H), 2.67 (br s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.2, 141.1, 138.8, 138.2, 128.5, 127.9, 127.8, 126.7, 125.0, 123.0, 122.6, 119.7, 112.7, 110.1, 104.0, 101.3, 73.3, 70.4, 69.5, 68.5, 52.1, 49.4. MS (EI) m/z (relative intensity): 390 (5) [M^+], 154 (38), 149 (86), 91 (100). HRMS (EI) calcd for $C_{24}H_{26}N_2O_3$ [M^+], 390.1943; found, 390.1939.

Preparation of 1-{-2-[(9*H*-Carbazol-4-yloxy)ethyl]amino}-3-(2-methoxyphenyloxy)-2-propanol (39). The product was obtained from epoxide **113** and amine **112** by the same procedure used to obtain **36**. Yield: 55%, solid off-white foam. IR (KBr) 3399, 1606, 1586, 1455, 1254, 1119, 751 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, J = 7.8 Hz, 1H), 8.17 (br s, 1H), 7.40−7.35 (m, 2H), 7.31 (t, J = 8.0 Hz, 1H), 7.20 (ddd, J = 8.1, 6.4, 1.9 Hz, 1H), 7.04 (d, J = 8.0 Hz, 1H), 6.97−6.85 (m, 4H), 6.66 (d, J = 8.0 Hz, 1H), 4.35 (t, J = 5.3 Hz, 2H), 4.19−4.13 (m, 1H), 4.09−4.01 (m, 2H), 3.81 (s, 3H), 3.26 (dd, J = 5.8, 4.4 Hz, 2H), 3.22 (br s, 1H), 3.06 (dd, J = 12.2, 4.1 Hz, 1H), 2.97 (dd, J = 12.2, 7.3 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.2, 149.9, 148.2, 140.9, 138.7, 126.6, 125.0, 122.9, 122.5, 122.0, 120.9, 119.7, 115.0, 112.3, 111.9, 110.0, 103.8, 101.2, 72.7, 68.2, 67.2, 55.8, 51.7, 48.9. MS (EI) m/z (relative intensity): 406 (5) [M^+], 238 (100). HRMS (EI) calcd for $C_{24}H_{26}N_2O_4$ [M^+], 406.1893; found, 406.1904.

Preparation of 4-[2-(9*H*-Carbazol-4-yloxy)ethyl]-6-(2-methoxyphenoxymethyl)morpholine-3-one (40). Compound **40** was obtained from **39** by the same procedure used to obtain **17**

dx.doi.org/10.1021/jm401090a | J. Med. Chem. 2013, 56, 8626−8655

from **1**. Yield: 52% (overall), solid white foam. IR (KBr) 3257, 1646, 1501, 1450, 768, 717 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.50 (br s, 1H), 8.27 (d, J = 7.8 Hz, 1H), 7.36−7.33 (m, 2H), 7.29 (d, J = 8.0 Hz, 1H), 7.15 (ddd, J = 8.0, 5.1, 3.1 Hz, 1H), 7.02 (d, J = 8.0 Hz, 1H), 6.97 (dd, J = 7.0, 1.3 Hz, 1H), 6.89−6.86 (m, 2H), 6.79 (td, J = 7.8, 1.8 Hz, 1H), 6.63 (d, J = 8.0 Hz, 1H), 4.44−4.38 (m, 2H), 4.36 (d, J = 16.7 Hz, 1H), 4.21 (d, J = 16.6 Hz, 1H), 4.10−3.99 (m, 3H), 3.91−3.82 (m, 2H), 3.77 (s, 3H), 3.80−3.72 (m, 1H), 3.62 (dd, J = 11.9, 2.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.0, 154.7, 149.8, 147.6, 141.0, 138.7, 126.6, 125.0, 122.6, 122.3, 120.8, 119.5, 114.8, 112.4, 111.9, 110.1, 104.0, 101.0, 71.8, 69.4, 67.6, 65.9, 55.6, 50.1, 46.6. MS (CI) m/z (relative intensity): 464 (23) $[M + NH_4]^+$, 447 (100) $[M + H]^+$. HRMS (CI) calcd for $C_{26}H_{27}N_2O_5$ $[M + H]^+$, 447.1920; found, 447.1942.

Preparation of 6-[(9*H*-Carbazol-3-yloxy)methyl]-4-[2-(2-methoxyphenoxy)ethyl]morpholine-3-one (41). Compound **41** was obtained from **3** by the same procedure used to obtain **17** from **1**. Yield: 49% (overall), white solid. mp 63−65 °C. IR (KBr) 3458, 3378, 2922, 2834, 1507, 1452, 1253, 1222, 1186, 1121, 745 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, J = 7.8 Hz, 1H), 7.96 (br s, 1H), 7.54 (d, J = 2.4 Hz, 1H), 7.43−7.36 (m, 2H), 7.32 (d, J = 8.7 Hz, 1H), 7.23−7.15 (m, 1H), 7.05 (dd, J = 8.7, 2.4 Hz, 1H), 6.95−6.82 (m, 4H), 4.40−4.03 (m, 7H), 3.78 (s, 3H), 3.92−3.76 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.1, 152.7, 149.7, 148.1, 140.5, 135.0, 126.2, 123.9, 123.3, 121.9, 120.4, 119.3, 115.6, 113.8, 112.1, 111.5, 111.0, 104.9, 72.2, 69.5, 68.0, 67.9, 56.0, 51.0, 47.0. MS (EI) m/z (relative intensity): 445 (20), 322 (100). HRMS (EI) calcd for $C_{26}H_{26}N_2O_5$ $[M^+]$, 446.1842; found, 446.1861.

Preparation of 6-[(9*H*-Carbazol-3-yloxy)methyl]-4-[2-(2-methoxyphenoxy)ethyl]-1,3λ^6,4-oxathiazinane-3,3-dione (42). A suspension of **3** (101 mg, 0.249 mmol) and Et_3N (60 μL, 0.4 mmol) in dry dichloromethane (3 mL) was cooled in an ice bath. After 5 min, a solution of bromomethanesulfonyl chloride[49] (84 mg, 0.43 mmol) in dry dichloromethane (0.5 mL) was added dropwise. The ice bath was removed, and the reaction was stirred at room temperature for 24 h. The reaction was concentrated under vacuum, and the residue was purified by flash chromatography over silica gel (ethyl acetate/hexanes) to afford the intermediate sulfonamide as a solid white foam. A solution of the sulfonamide (48 mg, 0.086 mmol) in dry THF (2 mL) was cooled to 10 °C and treated with NaH (6 mg, 60% dispersion in oil, 0.15 mmol). The reaction was stirred for 20 h at room temperature, quenched with water, and extracted with ethyl acetate. The combined organic extracts were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography over silica gel (ethyl acetate/hexanes) to afford 28 mg (24% overall) of **42** as an off-white solid. mp 71−73 °C. IR (film) 3396, 3007, 2919, 1503, 1452, 1329, 1253, 1160, 1120, 745 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 11.05 (s, 1H), 8.06 (d, J = 7.6 Hz, 1H), 7.72 (d, J = 1.6 Hz, 1H), 7.47−7.29 (m, 3H), 7.15−6.83 (m, 6H), 5.02 (d, J = 11.7 Hz, 1H), 4.94 (d, J = 11.7 Hz, 1H), 4.44−4.37 (m, 1H), 4.16−4.10 (m, 4H), 3.72 (s, 3H), 3.92−3.55 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.6, 149.7, 147.8, 140.5, 135.0, 126.2, 124.0, 123.3, 122.2, 121.1, 120.4, 119.4, 115.6, 114.0, 112.1, 111.5, 111.0, 105.0, 81.4, 74.5, 68.9, 68.7, 55.9, 54.2, 47.2. MS (CI) m/z (relative intensity): 500 $[M + NH_4]^+$ (100), 418 (30), 354 (20). HRMS (EI) calcd for $C_{25}H_{26}N_2O_6S$ $[M^+]$, 482.1512; found, 482.1499.

Preparation of 4-(9*H*-Carbazol-3-yloxy)-1-{[2-(2-methoxyphenoxy)ethyl]amino}-2-butanol (43). Compound **43** was obtained from epoxide **114b** and amine **104a** by the same procedure as used to obtain **6**. Yield: 62%, off-white solid. mp 126−128 °C. IR (KBr) 3408, 3299, 3060, 2940, 2877, 2834, 1588, 1495, 1459, 1250, 1183, 1123, 1024, 745 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 11.00 (s, 1H), 8.07 (d, J = 7.7 Hz, 1H), 7.67 (d, J = 2.3 Hz, 1H), 7.42 (d, J = 8.0 Hz, 1H), 7.39−7.29 (m, 2H), 7.09 (dd, J = 7.5, 7.4 Hz, 1H), 7.04−6.80 (m, 5H), 4.75 (d, J = 5.0 Hz, 1H), 4.15 (t, J = 6.3 Hz, 2H), 4.02 (t, J = 5.5 Hz, 2H), 3.85−3.77 (m, 1H), 3.74 (s, 3H), 2.92 (t, J = 5.5 Hz, 2H), 2.74−2.53 (m, 2H), 1.96−1.75 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 152.2, 149.1, 148.0, 140.3, 134.4, 125.2, 122.7, 122.4, 121.0, 120.7, 120.2, 117.8, 115.1, 113.6, 112.2, 111.4, 110.9, 103.9, 68.2, 66.3, 65.2, 55.5, 55.4, 48.2, 34.8. MS (EI) m/z (relative intensity): 420 (100) $[M^+]$, 419 (32), 389 (17), 388 (53). HRMS (EI) calcd for $C_{25}H_{28}N_2O_4$ $[M^+]$, 420.2049; found, 420.2044.

Preparation of 5-(9*H*-Carbazol-3-yloxy)-1-{[2-(2-methoxyphenoxy)ethyl]amino}-2-pentanol (44). Compound **44** was obtained from epoxide **114c** and amine **104a** by the same procedure as used to obtain **6**. Yield: 56%, white solid. mp 116−118 °C. IR (film) 3402, 3236, 2942, 1500, 1449, 1249, 1180, 742 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 11.00 (s, 1H), 8.07 (d, J = 7.6 Hz, 1H), 7.66 (d, J = 2.3 Hz, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.36 (d, J = 8.7 Hz, 1H), 7.33 (dd, J = 7.2, 7.0 Hz, 1H), 7.09 (dd, J = 7.6, 7.1 Hz, 1H), 7.00−6.81 (m, 5H), 4.67 (d, J = 4.1 Hz, 1H), 4.08−3.99 (m, 4H), 3.74 (s, 3H), 3.70−3.60 (m, 1H), 2.92 (t, J = 5.5 Hz, 2H), 2.71−2.49 (m, 2H), 1.95−1.45 (m, 4H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 152.2, 149.1, 148.0, 140.3, 134.4, 125.2, 122.7, 122.4, 121.0, 120.7, 120.2, 117.8, 115.1, 113.6, 112.2, 111.4, 110.8, 103.9, 68.9, 68.3, 68.2, 55.6, 55.4, 48.2, 31.6, 25.4. MS (EI) m/z (relative intensity): 434 (50) $[M^+]$, 252 (77), 180 (100), 154 (14). HRMS (EI) calcd for $C_{26}H_{30}N_2O_4$ $[M^+]$, 434.2206; found, 434.2203.

Preparation of 6-(9*H*-Carbazol-3-yloxy)-1-{[2-(2-methoxyphenoxy)ethyl]amino}-2-hexanol (45). Compound **45** was obtained from epoxide **114d** and amine **104a** by the same procedure as used to obtain **6**. Yield: 54%, solid white foam. IR (film) 3406, 3234, 3060, 2938, 1502, 1250, 743 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, J = 8.1 Hz, 1H), 7.98 (br s, 1H), 7.53 (d, J = 2.3 Hz, 1H), 7.40−7.33 (m, 2H), 7.30 (d, J = 8.7 Hz, 1H), 7.20−7.14 (m, 1H), 7.03 (dd, J = 8.7, 2.4 Hz, 1H), 6.96−6.86 (m, 4H), 4.10 (t, J = 5.2 Hz, 2H), 4.05 (t, J = 6.4 Hz, 2H), 3.83 (s, 3H), 3.70−3.60 (m, 1H), 3.08−2.98 (m, 2H), 2.81 (dd, J = 12.1, 2.9 Hz, 1H), 2.77−2.53 (br s, 2H), 2.51 (dd, J = 12.0, 9.5 Hz, 1H), 1.90−1.80 (m, 2H), 1.77−1.42 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.4, 149.8, 148.3, 140.5, 134.6, 125.9, 123.9, 123.5, 121.9, 121.1, 120.4, 119.1, 115.8, 114.4, 112.0, 111.4, 110.9, 104.5, 69.3, 68.0, 68.8, 56.0, 55.1, 48.5, 34.8, 29.7, 22.5. MS (CI) m/z (relative intensity): 449 (100) $[M + H]^+$. HRMS (CI) calcd for $C_{27}H_{33}N_2O_4$ $[M + H]^+$, 449.2440; found, 449.2437.

Preparation of 1-(9*H*-Carbazol-3-yloxy)-4-{[2-(2-methoxyphenoxy)ethyl]amino}-2-butanol (46). A solution of bromoalcohol **115** (151 mg, 0.452 mmol), amine **104a** (149 mg, 0.892 mmol), and Et_3N (0.14 mL, 0.98 mmol) in methanol (2 mL) was heated at 60 °C for 18 h. The reaction mixture was diluted with water and extracted with dichloromethane. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash chromatography over silica gel (methanol/dichloromethane) to afford 94 mg (49%) of **46** as a white solid. mp 134−136 °C. IR (film) 3402, 3351, 2927, 2839, 1500, 1452, 1252, 1180, 1026, 745 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 11.01 (s, 1H), 8.07 (d, J = 7.8 Hz, 1H), 7.67 (d, J = 2.4 Hz, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.37 (d, J = 8.8 Hz, 1H), 7.33 (ddd, J = 8.0, 7.9, 1.2 Hz, 1H), 7.09 (ddd, J = 8.0, 7.9, 1.0 Hz, 1H), 7.02 (dd, J = 8.8, 2.5 Hz, 1H), 6.99−6.82 (m, 4H), 4.00 (t, J = 5.7 Hz, 2H), 3.98−3.90 (m, 3H), 3.74 (s, 3H), 2.90 (t, J = 5.7 Hz, 2H), 2.79 (t, J = 6.9 Hz, 2H), 1.80−1.75 (m, 1H), 1.65−1.58 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 152.3, 149.2, 148.0, 140.3, 134.5, 125.2, 122.7, 122.4, 121.1, 120.7, 120.2, 117.9, 115.2, 113.8, 112.2, 111.4, 110.8, 104.0, 73.1, 68.1, 67.7, 55.4, 48.1, 46.1, 33.4. MS (EI) m/z (relative intensity): 420 (1) $[M^+]$, 238 (100), 180 (30). HRMS (EI) calcd for $C_{25}H_{28}N_2O_4$ $[M^+]$, 420.2049; found, 420.2032.

Preparation of 1-(6-Fluoro-9*H*-carbazol-3-yloxy)-3-{[2-(2-methoxyphenoxy)ethyl]amino}-2-propanol (47). Compound **47** was obtained from epoxide **114e** and amine **104a** by the same procedure as used to obtain **6**. Yield: 53%, white solid. mp 62−64 °C. IR (KBr) 3382, 2927, 2836, 1575, 1497, 1456, 1286, 1249, 11955, 1120, 1023, 794, 756 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 11.05 (s, 1H), 7.91 (dd, J = 9.5, 2.6 Hz, 1H), 7.70 (d, J = 2.4 Hz, 1H), 7.42 (dd, J = 8.8, 4.4 Hz, 1H), 7.37 (d, J = 8.8 Hz, 1H), 7.18 (ddd, J = 9.4, 8.8, 2.6 Hz, 1H), 7.05 (dd, J = 8.8, 2.5 Hz, 1H), 6.99−6.93 (m, 2H), 6.92−6.81 (m, 2H), 5.07 (d, J = 2.6 Hz, 1H), 4.06−3.93 (m, 5H), 3.73 (s, 3H), 2.93 (t, J = 5.5 Hz, 2H), 2.83 (dd, J = 11.4, 3.7 Hz, 1H), 2.71 (dd, J = 11.8, 6.4 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 155.9 (d, $^1J_{C-F}$ = 230 Hz), 152.1, 149.1, 148.0, 136.7, 135.6, 122.7 (d, $^3J_{C-F}$ = 10 Hz), 122.4 (d, $^4J_{C-F}$ = 4 Hz), 121.0, 120.6, 116.1, 113.6, 113.0 (d, $^2J_{C-F}$ = 25 Hz), 112.2, 111.8, 111.7 (CH, d, $^3J_{C-F}$ = 9 Hz), 105.6 (d, $^2J_{C-F}$ = 23 Hz), 104.1, 71.4, 68.2, 55.4, 52.4, 48.4. ^{19}F NMR (376 MHz, DMSO-d_6) δ −125.6. MS (EI) m/z (relative intensity): 424 (18) $[M^+]$, 201 (97), 180 (100), 172 (28),

dx.doi.org/10.1021/jm401090a | J. Med. Chem. 2013, 56, 8626−8655

44 (39). HRMS (EI) calcd for $C_{24}H_{25}FN_2O_4$ [M^+], 424.1798; found, 424.1790.

Preparation of 1-[(9*H*-Carbazol-3-yl)amino]-3-{[2-(2-methoxyphenoxy)ethyl]amino}-2-propanol (48). A mixture of 9-*t*-butyloxycarbonyl-3-aminocarbazole (576 mg, 2.04 mmol) and epichlorohydrin (0.11 mL, 1.4 mmol) in absolute ethanol (3.5 mL) was refluxed for 6 h. The reaction mixture was cooled to room temperature and concentrated under vacuum, and the residue was purified by flash chromatography over silica gel (methanol/dichloromethane) to afford 369 mg (70%) of **116** as a yellow foam. A mixture of **116** (201 mg, 0.536 mmol), **104a** (177 mg, 1.06 mmol), K_2CO_3 (91 mg, 0.66 mmol), and catalytic KI in absolute ethanol (3.5 mL) was refluxed for 3 h. The reaction mixture was cooled to room temperature, filtered, and washed with dichloromethane. The filtrate was concentrated under vacuum, and the residue was purified by flash chromatography over silica gel (methanol/dichloromethane) to afford 177 mg (66%) of *t*-Boc-protected **48** as a yellow solid foam. A solution of the latter product (100 mg, 0.198 mmol) in dichloromethane (2.5 mL) was stirred in TFA (0.38 mL, 4.9 mmol) at room temperature for 3.5 h. The reaction mixture was treated with 1 M NaOH and extracted with dichloromethane. The combined organic extracts were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography over silica gel (methanol/dichloromethane) to afford 52 mg (65%) of **48** as a white solid. mp 135−137 °C. IR (KBr) 3408, 3299, 3060, 2940, 2877, 2834, 1588, 1495, 1459, 1250, 1183, 1123, 1024, 745 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 10.75 (s, 1H), 7.94 (d, J = 7.6 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.32−7.20 (m, 3H), 7.12−6.80 (m, 6H), 4.92 (br s, 1H), 4.03 (t, J = 4.8 Hz, 2H), 3.89−3.80 (m, 1H), 3.74 (s, 3H), 3.20 (dd, J = 12.2, 5.1 Hz, 1H), 3.05 (dd, J = 12.2, 6.4 Hz, 1H), 2.93 (t, J = 5.0 Hz, 2H), 2.79 (dd, J = 11.6, 3.9 Hz, 1H), 2.68 (dd, J = 11.6, 7.3 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 149.1, 148.0, 142.4, 140.0, 132.6, 124.7, 123.0, 122.3, 121.0, 120.6, 119.8, 117.4, 114.5, 113.7, 112.2, 111.3, 110.6, 101.0, 68.2, 68.1, 55.4, 53.6, 49.1, 48.3. MS (EI) m/z (relative intensity): 405 (100) [M^+], 220 (50), 195 (80), 182 (40), 167 (33). HRMS (EI) calcd for $C_{24}H_{27}N_3O_3$ [M^+], 405.2052; found, 405.2038.

Compounds **49**−**58** were prepared in the usual manner by conversion of the corresponding hydroxycarbazoles to the epoxides **117a**−**e** followed by epoxide-opening with amines **104a** or **104m**−**o**, as shown in Scheme 5. The lactams **49** and **51** and the oxazolidinone **52** were obtained by cyclization of the corresponding amino alcohols with chloroacetyl chloride and 1,1-carbonyldiimidazole, respectively.

6-[(9*H*-Carbazol-2-yloxy)methyl]-4-[2-(2-methoxyphenoxy)ethyl]morpholine-3-one 49. Yield: 57% (overall from **4**), white solid. mp 69−71 °C. IR (KBr) 3407, 3063, 2929, 2873, 1647, 1607, 1500, 1460, 1250, 1175, 1022, 747 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 11.12 (s, 1H), 7.99 (d, J = 7.6 Hz, 1H), 7.97 (d, J = 8.5 Hz, 1H), 7.42 (d, J = 8.0 Hz, 1H), 7.28 (dd, J = 7.9, 7.2 Hz, 1H), 7.10 (dd, J = 7.5, 7.2 Hz, 1H), 7.04−6.83 (m, 5H), 6.80 (dd, J = 8.5, 2.1 Hz, 1H), 4.28−4.10 (m, 7H), 3.77 (s, 3H), 3.86−3.58 (m, 4H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.9, 157.3, 149.2, 147.7, 140.9, 139.7, 124.2, 122.5, 121.4, 120.9, 120.7, 119.2, 118.5, 116.5, 113.7, 112.4, 110.6, 107.8, 95.4, 71.5, 68.1, 66.8, 66.4, 55.6, 49.1, 45.6. MS (EI) m/z (relative intensity): 445 (15), 322 (75), 181 (49), 153 (100), 77 (21). HRMS (EI) m/z calcd for $C_{26}H_{26}N_2O_5$ [M^+], 446.1842; found, 446.1824.

4-(9*H*-Carbazol-2-yloxy)-1-{[2-(2-methoxyphenoxy)ethyl]-amino}-2-butanol (50). Yield: 65% from epoxide **117b** and amine **104a**; 39% overall from 2-hydroxycarbazole. mp 93−95 °C. IR (KBr) 3415, 3052, 2928, 2871, 1605, 1503, 1263, 1100, 755, 722 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 11.07 (s, 1H), 7.97 (d, J = 7.8 Hz, 1H), 7.94 (d, J = 8.5 Hz, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.27 (ddd, J = 8.2, 7.1, 1.2 Hz, 1H), 7.09 (ddd, J = 7.9, 7.8, 1.0 Hz, 1H), 6.99−6.93 (m, 3H), 6.92−6.82 (m, 2H), 6.76 (dd, J = 8.5, 2.2 Hz, 1H), 4.75 (d, J = 4.1 Hz, 1H), 4.14 (t, J = 6.6 Hz, 2H), 4.01 (t, J = 5.6 Hz, 2H), 3.85−3.75 (m, 1H), 3.74 (s, 3H), 2.90 (t, J = 5.6 Hz, 2H), 2.64 (dd, J = 11.8, 4.2 Hz, 1H), 2.63 (dd, J = 11.8, 7.4 Hz, 1H), 1.99− 1.88 (m, 1H), 1.84−1.78 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 157.8, 149.1, 148.0, 141.0, 139.6, 124.0, 122.6, 121.0, 120.8, 120.7, 119.1, 118.4, 116.0, 113.6, 112.2, 110.5, 108.0, 95.0, 68.3, 66.3, 64.7, 55.6, 55.4, 48.3, 34.7. MS (EI) m/z (relative intensity): 238 (100), 180 (45), 100 (16). HRMS (EI) calcd for $C_{25}H_{28}N_2O_4$ [M^+], 420.2049; found, 420.2029.

6-[2-(9*H*-Carbazol-2-yloxy)ethyl]-4-[2-(2-methoxyphenoxy)-ethyl]-3-morpholinone (51). Yield: 61% overall from **50**, white solid. mp 160−161 °C. IR (film) 3396, 3002, 2932, 2876, 1641, 1503, 1460, 1255, 1219, 768 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 11.07 (s, 1H), 7.97 (d, J = 7.8 Hz, 1H), 7.95 (d, J = 8.6 Hz, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.27 (dd, J = 8.0, 7.1 Hz, 1H), 7.09 (dd, J = 7.5, 7.4 Hz, 1H), 7.01−6.94 (m, 5H), 6.76 (dd, J = 8.5, 1.9 Hz, 1H), 4.20−4.05 (m, 6H), 4.03−3.95 (m, 1H), 3.77−3.68 (m, 1H), 3.73 (s, 3H), 3.66−3.49 (m, 3H), 2.08−1.94 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.0, 157.5, 149.1, 147.7, 140.9, 139.7, 124.1, 122.5, 121.3, 120.8, 120.7, 119.2, 118.4, 116.2, 113.6, 112.3, 110.5, 107.9, 95.2, 70.1, 67.0, 66.3, 63.7, 55.5, 52.1, 45.4, 32.0. MS (EI) m/z (relative intensity): 460 (24) [M^+], 337 (100). HRMS (EI) calcd for $C_{27}H_{28}N_2O_5$ [M^+], 460.1998; found, 460.1988.

5-[2-(9*H*-Carbazol-2-yloxy)ethyl]-3-[2-(2-methoxyphenoxy)-ethyl]-2-oxazolidinone (52). Yield: 87% overall from **50**, white solid. mp 61−63 °C. IR (film) 3399, 3320, 3002, 2926, 1739, 1500, 1460, 1249, 749 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 11.09 (s, 1H), 7.98 (d, J = 7.8 Hz, 1H), 7.95 (d, J = 8.5 Hz, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.28 (dd, J = 7.8, 7.3 Hz, 1H), 7.10 (dd, J = 7.6, 7.3 Hz, 1H), 7.01−6.83 (5H, m), 6.76 (dd, J = 8.5, 1.9 Hz, 1H), 4.80−4.70 (m, 1H), 4.21−4.11 (m, 2H), 4.09 (t, J = 5.3 Hz, 2H), 3.88 (t, J = 8.6 Hz, 1H), 3.73 (s, 3H), 3.58−3.50 (m, 3H), 2.19−2.11 (2H, m). ^{13}C NMR (101 MHz, DMSO-d_6) δ 157.4, 157.1, 149.3, 147.6, 140.9, 139.7, 124.1, 122.5, 121.5, 120.8, 120.7, 119.2, 118.4, 116.3, 114.1, 112.4, 110.5, 107.9, 95.2, 70.9, 66.6, 63.7, 55.5, 50.1, 43.1, 33.9. MS (EI) m/z (relative intensity): 446 (100) [M^+], 236 (48). HRMS (EI) calcd for $C_{26}H_{26}N_2O_5$ [M^+], 446.1842; found, 446.1835.

1-(6-Fluoro-9*H*-carbazol-2-yloxy)-3-{[2-(2-methoxyphenoxy)-ethyl]amino}-2-propanol (53). Yield: 54% from epoxide **117c** and amine **104a**; 38% overall from 6-fluoro-2-hydroxycarbazole, white solid. mp 157−159 °C. IR (KBr) 3388, 3059, 2924, 2855, 1631, 1503, 1487, 1456, 1249, 1164, 1104, 1035, 819, 747 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 11.10 (s, 1H), 7.97 (d, J = 7.8 Hz, 1H), 7.81 (dd, J = 9.5, 2.6 Hz, 1H), 7.40 (dd, J = 8.8, 4.4 Hz, 1H), 7.11 (ddd, J = 9.5, 8.8, 2.6 Hz, 1H), 6.99−6.81 (m, 5H), 6.77 (dd, J = 8.6, 2.2 Hz, 1H), 5.08 (br s, 1H), 4.07−3.94 (m, 5H), 3.74 (s, 3H), 2.93 (t, J = 5.5 Hz, 2H), 2.82 (dd, J = 12.0, 4.2 Hz, 1H), 2.71 (dd, J = 11.7, 6.2 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 158.2, 156.4 (d, $^1J_{C-F}$ = 230 Hz), 149.1, 148.0, 142.1, 136.1, 123.2 (d, $^3J_{C-F}$ = 10 Hz), 121.3, 121.0, 120.6, 115.9 (d, $^4J_{C-F}$ = 4.0 Hz), 113.7, 112.2, 111.3 (d, $^2J_{C-F}$ = 33 Hz), 111.2, 108.3, 104.9 (d, $^2J_{C-F}$ = 24 Hz), 95.2, 70.9, 68.2, 68.1, 55.4, 52.3, 48.3. ^{19}F NMR (376 MHz, DMSO-d_6) δ −125.2. MS (EI) m/z (relative intensity): 424 (5) [M^+], 368 (10), 201 (34), 180 (100), 56 (34). HRMS (EI) calcd for $C_{24}H_{25}N_2O_4F$ [M^+], 424.1798; found, 424.1807.

1-(6,8-Difluoro-9*H*-carbazol-2-yloxy)-3-{[2-(2-methoxyphenoxy)-ethyl]amino}-2-propanol (54). Yield: 55% from epoxide **117d** and amine **104a**; 33% overall from 6,8-difluoro-2-hydroxycarbazole, white solid. mp 136−138 °C. IR (KBr) 3309, 3176, 2927, 2860, 1652, 1632, 1592, 1505, 1256, 1117, 984, 838, 815, 735 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 11.55 (s, 1H), 7.99 (d, J = 8.6 Hz, 1H), 7.71 (d, J = 7.7 Hz, 1H), 7.17 (t, J = 9.5 Hz, 1H), 7.05−6.80 (m, 6H), 5.10 (br s, 1H), 4.09−3.92 (m, 5H), 3.73 (s, 3H), 2.92 (t, J = 5.1 Hz, 2H), 2.87−2.66 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 158.9, 155.5 (dd, J_{C-F} = 233, 9.9 Hz), 149.2, 148.0, 147.3 (dd, J_{C-F} = 242, 13.9 Hz), 142.3, 125.7 (dd, J_{C-F} = 11.3, 7.2 Hz), 123.8 (d, J_{C-F} = 12.6 Hz), 121.8, 121.1, 120.7, 116.0 (dd, J_{C-F} = 4.2, 4.1 Hz), 113.7, 112.2, 109.2, 101.2 (dd, J_{C-F} = 23, 3.7 Hz), 98.9 (dd, J_{C-F} = 29, 21 Hz), 95.4, 71.0, 68.3, 68.2, 55.5, 52.3, 48.4. ^{19}F NMR (376 MHz, DMSO-d_6) δ −122.5, −130.4. MS (EI) m/z (relative intensity): 442 (9) [M^+], 219 (13), 180 (100). HRMS (EI^+) calcd for $C_{24}H_{24}F_2N_2O_4$ [M^+], 442.1704; found, 442.1715.

1-(9*H*-Carbazol-2-yloxy)-3-{[2-(4-fluoro-2-methoxyphenoxy)-ethyl]amino}-2-propanol (55). Yield: 60% from epoxide **117a** and amine **104m**; 37% overall from 2-hydroxycarbazole, white solid. mp 141−143 °C. IR (KBr) 3400, 3303, 3247, 3081, 2927, 2839, 1609, 1503, 1462, 1173, 1032, 948, 750, 728 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) 11.07 (s, 1H), 7.97 (d, J = 7.8 Hz, 1H), 7.94 (d, J = 8.6 Hz, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.27 (td, J = 8.2, 1.2 Hz, 1H), 7.09 (td, J = 7.9, 1.0 Hz, 1H), 6.99−6.92 (m, 2H), 6.88 (dd, J = 10.7, 3.0 Hz, 1H), 6.77 (dd, J = 8.6, 2.2 Hz, 1H), 6.65 (td, J = 8.6, 3.0 Hz, 1H), 5.08 (d, J = 4.0 Hz, 1H),

dx.doi.org/10.1021/jm401090a | J. Med. Chem. 2013, 56, 8626−8655

4.06−3.92 (m, 5H), 3.75 (s, 3H), 2.90 (t, J = 5.5 Hz, 2H), 2.80 (dd, J = 11.8, 4.0 Hz, 1H), 2.69 (dd, J = 11.8, 6.4 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 157.8, 156.8 (d, $^1J_{C-F}$ = 235 Hz), 150.2 (d, $^3J_{C-F}$ = 10 Hz), 144.4 (d, $^4J_{C-F}$ = 2.0 Hz), 141.0, 139.6, 124.0, 122.6, 120.8, 119.1, 118.4, 116.1, 114.4 (d, $^3J_{C-F}$ = 10 Hz), 110.5, 108.0, 105.5 (d, $^2J_{C-F}$ = 22 Hz), 100.6 (d, $^2J_{C-F}$ = 27 Hz), 95.2, 70.9, 69.1, 68.2, 55.8, 52.3, 48.4. ^{19}F NMR (376 MHz, DMSO-d_6) δ −120.4. MS (EI) m/z (relative intensity): 424 (28) [M$^+$], 198 (39), 183 (100), 154 (65), 56 (37). HRMS (EI) calcd for $C_{24}H_{25}N_2O_4F$ [M$^+$], 424.1798, found: 424.1792.

1-(9*H*-Carbazol-2-yloxy)-3-{[2-(2-trifluoromethylphenoxy)-ethyl]amino}-2-propanol (56). Yield: 52% from epoxide **117a** and amine **104n**; 32% overall from 2-hydroxycarbazole, white solid. mp 138−140 °C. IR (film) 3400, 3292, 1607, 1455, 1319, 1131, 1034, 766, 749 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.05 (s, 1H), 7.97 (d, J = 7.7 Hz, 1H), 7.94 (d, J = 8.6 Hz, 1H), 7.57−7.65 (m, 2H), 7.40 (d, J = 8.0 Hz, 1H), 7.32−7.23 (m, 2H), 7.14−7.03 (m, 2H), 6.95 (d, J = 2.2 Hz, 1H), 6.76 (dd, J = 8.5, 2.2 Hz, 1H), 5.03 (d, J = 4.6 Hz, 1H), 4.17 (t, J = 5.2 Hz, 2H), 4.07−3.90 (m, 3H), 2.96 (t, J = 5.5 Hz, 2H), 2.86−2.65 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 157.8, 156.3, 140.9, 139.6, 134.1, 126.6 (q, $^3J_{C-F}$ = 5 Hz), 124.0 (CH), 123.7 (q, $^1J_{C-F}$ = 270 Hz), 122.5, 120.7, 120.1, 119.1, 118.4, 117.1 (q, $^2J_{C-F}$ = 30 Hz), 116.1, 113.6, 110.5, 108.0, 95.2, 70.8, 68.5, 68.2, 52.2, 48.0. ^{19}F NMR (376 MHz, DMSO-d_6) δ −60.7. MS (EI) m/z (relative intensity): 444 (10) [M$^+$], 198 (25), 183 (100). HRMS (EI) calcd for $C_{24}H_{23}N_2O_3F_3$ [M$^+$], 444.1661; found, 444.1663.

1-(9*H*-Carbazol-2-yloxy)-3-{[2-(2-fluorophenoxy)ethyl]-amino}-2-propanol (57). Yield: 58% from epoxide **117a** and amine **104o**; 36% overall from 2-hydroxycarbazole, white solid. mp 160−162 °C. IR (KBr) 3397, 3303, 3068, 2924, 2848, 1609, 1509, 1456, 1311, 1286, 1199, 1173, 1108, 738, 722 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.05 (s, 1H), 7.97 (d, J = 7.8 Hz, 1H), 7.94 (d, J = 8.6 Hz, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.27 (ddd, J = 8.2, 7.1, 1.2 Hz, 1H), 7.23−7.06 (m, 4H), 6.96 (d, J = 2.1 Hz, 1H), 6.95−6.90 (m, 1H), 6.77 (dd, J = 8.5, 2.2 Hz, 1H), 5.05 (d, J = 4.5 Hz, 1H), 4.11 (t, J = 5.6 Hz, 2H), 4.07−3.90 (m, 3H), 2.95 (t, J = 5.5 Hz, 2H), 2.81 (dd, J = 11.8, 3.9 Hz, 1H), 2.71 (dd, J = 11.8, 6.5 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 157.8, 151.7 (d, $^1J_{C-F}$ = 241 Hz), 146.5 (d, $^3J_{C-F}$ = 10 Hz), 141.0, 139.6, 124.7 (d, $^4J_{C-F}$ = 3.0 Hz), 124.0, 122.6, 121.0 (d, $^3J_{C-F}$ = 7.0 Hz), 120.7, 119.1, 118.4, 116.1, 115.9 (d, $^2J_{C-F}$ = 18 Hz), 115.0, 110.5, 108.0, 95.2, 70.9, 68.6, 68.2, 52.3, 48.2. ^{19}F NMR (376 MHz, DMSO-d_6) δ −134.9. MS (EI) m/z (relative intensity): 394 (20) [M$^+$], 183 (100), 168 (46), 154 (40), 56 (27). HRMS (EI) calcd for $C_{23}H_{23}FN_2O_3$ [M$^+$], 394.1693; found, 394.1679.

1-(9*H*-Carbazol-1-yloxy)-3-{[2-(2-methoxyphenoxy)ethyl]-amino}-2-propanol (58).[50] Yield: 66% from epoxide **117e** and amine **104a**; 44% overall from 1-hydroxycarbazole, white solid. mp 58−60 °C. IR (film) 3215, 3057, 2927, 2833, 1576, 1502, 1452, 1250, 738 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.17 (s, 1H), 8.06 (d, J = 7.8 Hz, 1H), 7.68 (d, J = 7.7 Hz, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.36 (dd, J = 7.2, 7.2 Hz, 1H), 7.13 (dd, J = 7.4, 7.3 Hz, 1H), 7.05 (dd, J = 7.8, 7.8 Hz, 1H), 6.99−6.80 (5H, m), 5.07 (d, J = 4.0 Hz, 1H), 4.20−4.00 (m, 5H), 3.73 (s, 3H), 2.95 (t, J = 5.4 Hz, 2H), 2.99−2.73 (m, 2H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 149.1, 148.0, 144.8, 139.4, 129.8, 125.2, 123.5, 122.6, 121.0, 120.7, 120.1, 119.0, 118.4, 113.7, 112.6, 112.2, 111.3, 107.1, 70.7 (2 signals), 68.2, 55.4, 52.1, 48.3. MS (EI) m/z (relative intensity): 405 (45), 223 (18), 182 (55), 181 (63), 179 (98), 153 (100), 123 (34), 77 (30), 56 (63). HRMS (EI) calcd for $C_{24}H_{26}N_2O_4$ [M$^+$], 406.1893; found, 406.1880.

Preparation of 1-[4-(2-Hydroxy-3-{[2-(2-methoxyphenoxy)-ethyl]amino}propoxy-9*H*-carbazol-9-yl]octadecan-1-one (59). Epoxide **103a** (700 mg, 2.93 mmol) was dissolved in dry THF and cooled to 0 °C. Sodium hydride (220 mg, 60% dispersion in oil, 5.5 mmol) was added, and the mixture was stirred for 45 min and then warmed to room temperature. Octadecanoyl chloride (1.26 g, 4.16 mmol) in THF was added, and the reaction mixture was stirred for 1 h at room temperature and quenched with water, and the aqueous phase was extracted with chloroform and ethyl acetate. The combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by flash chromatography over silica gel (dichloromethane/hexanes) to afford 1.26 g (85%) of epoxide **103c**.

Epoxide **103c** (200 mg, 0.396 mmol) and amine **104a** (132 mg, 0.792 mmol) were reacted in the usual manner to afford 88 mg (33%) of **59** as a white solid. mp 94−95 °C. IR (KBr) 3451, 2922, 2836, 1705, 1594, 1507, 1441, 1237, 739, 717 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.31 (d, J = 7.4 Hz, 1H), 8.20 (d, J = 8.3 Hz, 1H), 7.80 (d, J = 8.4 Hz, 1H), 7.45−7.31 (m, 3H), 6.95−6.81 (m, 5H), 4.28−4.13 (m, 5H), 3.82 (s, 3H), 3.14−2.95 (m, 6H), 1.97−1.87 (m, 2H), 1.28 (br s, 28H), 0.90 (t, J = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 173.5, 154.6, 149.6, 148.0, 139.7, 137.8, 127.7, 126.2, 125.5, 123.6, 123.1, 121.6, 120.8, 115.7, 115.3, 114.0, 111.7, 109.1, 105.6, 70.5, 68.6, 68.2, 55.7, 51.9, 48.6, 39.2, 31.9, 29.6, 29.6, 29.5, 29.3, 29.2, 24.7, 22.6, 14.1. MS (EI) m/z (relative intensity): 672 (2) [M]$^+$, 549 (10), 183 (60), 180 (100). HRMS (EI) calcd for $C_{42}H_{60}N_2O_5$ [M$^+$], 672.4502; found, 672.4504.

4-[2-(2-Methoxyphenoxy)ethyl]-6-{[(9-octadecanoyl-9*H*-carbazol-4-yl)oxy]methyl}morpholin-3-one (60). The product was prepared by the acylation of **17** with octadecanoyl chloride, as in the preceding procedure. Yield: 80%, white solid. mp 98−99 °C. IR (KBr) 1704, 1639, 1500, 1257, 1160, 752, 739, 721 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.29 (d, J = 7.7 Hz, 1H), 8.20 (d, J = 8.4 Hz, 1H), 7.90 (d, J = 8.4 Hz, 1H), 7.45 (d, J = 8.9 Hz, 1H), 7.39 (d, J = 8.5 Hz, 1H), 7.28−7.24 (m, 1H), 6.98−6.91 (m, 3H), 6.84 (t, J = 7.3 Hz, 2H), 4.45−4.23 (m, 7H), 3.99−3.80 (m, 4H), 3.68 (s, 3H), 3.14 (t, J = 7.4 Hz, 2H), 1.98−1.88 (d, J = 7.2 Hz, 2H), 1.27 (br s 28H), 0.89 (t, J = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 173.6, 166.8, 154.3, 149.5, 147.9, 140.00, 137.9, 127.8, 126.5, 125.3, 123.7, 123.2, 121.8, 120.9, 115.7, 115.6, 113.8, 111.8, 109.7, 105.6, 72.0, 68.4, 68.0, 67.8, 55.6, 51.0, 46.9, 39.3, 31.9, 29.7 (2 signals), 29.6, 29.5, 29.4, 29.3, 24.7, 22.7, 14.1. MS (CI) m/z 713 (71) [M + H]$^+$, 447 (100). HRMS (EI) calcd for $C_{44}H_{60}N_2O_6$, 712.4451; found, 712.4418 [M$^+$].

Compounds **61**, **63**, **64**, and **66**−**80** were prepared by alkylation of the corresponding phenols or alcohols with 3-chloro-1,2-epoxypropane or 4-bromo-1,2-epoxybutane followed by epoxide opening with amine **104a**, as in the preparation of **6**.

1-{[2-(2-Methoxyphenoxy)ethyl]amino}-3-(2,3,4,9-tetrahydro-1*H*-carbazol-6-yloxy)- 2-propanol (61). Yield: 75% from epoxide **103d**; 53% overall from the corresponding phenol, white solid. mp 114−116 °C. IR (film) 3388, 3309, 3060, 2930, 2837, 1592, 1505, 1456, 1253, 1123, 1024, 908, 738 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.55 (br s, 1H), 7.12 (d, J = 8.4 Hz, 1H), 6.96−6.84 (m,5H), 6.75 (dd, J = 8.7, 2.5 Hz, 1H), 4.13 (t, J = 5.3 Hz, 2H), 4.13−4.07 (m, 1H), 4.02 (d, J = 5.2 Hz, 2H), 3.82 (s, 3H), 3.08 (t, J = 5.3 Hz, 2H), 2.98 (dd, J = 12.2, 3.9 Hz, 1H), 2.88 (dd, J = 12.2, 7.8 Hz, 1H), 2.69 (t, J = 5.9 Hz, 2H), 2.63 (t, J = 5.8 Hz, 2H), 1.93−1.80 (m, 4H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 153.1, 150.1, 148.4, 135.4, 131.2, 128.5, 122.0, 121.1, 114.7, 112.2, 111.1, 110.3, 102.0, 71.7, 69.0, 68.7, 56.1, 52.0, 48.9, 23.6, 23.5, 23.4, 21.1. MS (EI) m/z (relative intensity): 410 (30) [M$^+$], 187 (100), 180 (25), 158 (24). HRMS (EI) calcd for $C_{24}H_{30}N_2O_4$ [M]$^+$, 410.2266; found, 410.2208.

4-(2-Hydroxy-3-{[2-(2-methoxyphenoxy)ethyl]amino}-propoxy)-9*H*-fluoren-9-one (63). Yield: 40% from epoxide **103e**; 53% overall from the corresponding phenol, yellow solid. mp 97−99 °C. IR (KBr) 3326, 1710, 1598, 1505, 1251, 726 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.81 (d, J = 7.4 Hz, 1H), 7.63 (d, J = 7.3 Hz, 1H), 7.42 (t, J = 7.5 Hz, 1H), 7.30 (d, J = 7.2 Hz, 1H), 7.25 (d, J = 8.0 Hz, 1H), 7.21 (d, J = 7.3 Hz, 1H), 7.06 (d, J = 8.2 Hz, 1H), 6.95−6.87 (m, 4H), 4.21−4.15 (m, 6H), 3.83 (s, superimposed on m, 4H), 3.14−3.11 (m, 2H), 3.07 (dd, J = 12.2, 3.2 Hz, 1H), 2.96−2.89 (m, 1H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 194.1, 154.5, 149.6, 148.0, 143.7, 135.8, 134.9, 133.5, 131.4, 130.4, 128.1, 124.2, 124.0, 121.7, 120.9, 118.8, 116.9, 114.0, 111.8, 70.7, 68.7, 68.1, 55.7, 51.7, 48.6. MS (CI) m/z (relative intensity): 420 (100) [M + H]$^+$. HRMS (CI) calcd for $C_{25}H_{26}NO_5$ [M + H]$^+$, 420.1811; found, 420.1815.

1-{[2-(2-Methoxyphenoxy)ethyl]amino}-1-{8-oxatricyclo-[7.4.0.0^{2,7}]trideca-1(9),2(7),3,5,10,12-hexaen-4-yloxy}-2-propanol (64). Yield: 56% from epoxide **103f**; 42% overall from the corresponding phenol, white solid. mp 110−112 °C. IR (nujol) 3257, 1461, 1371, 1247, 1171, 738 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12 (dd, J = 7.8, 1.9 Hz, 1H), 7.73 (d, J = 2.5 Hz, 1H), 7.65 (dd, J = 8.2, 0.8 Hz, 1H), 7.58 (d, J = 8.9 Hz, 1H), 7.49 (ddd, J = 8.6, 8.4, 1.4 Hz, 1H), 7.36 (ddd, J = 7.7,

7.5, 1.0 Hz, 1H), 7.10 (dd, J = 8.9, 2.7 Hz, 1H), 6.99−6.93 (m, 2H), 6.92−6.82 (m, 2H), 5.09 (d, J = 4.4 Hz, 1H), 4.09−3.93 (m, 5H), 3.73 (s, 3H), 2.93 (t, J = 5.5 Hz, 2H), 2.82 (dd, J = 11.9, 4.3 Hz, 1H), 2.72 (dd, J = 11.9, 6.7 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 156.1, 155.1, 150.0, 149.2, 148.1, 127.4, 124.1, 123.9, 122.7, 121.2, 121.0, 120.7, 115.9, 113.7, 112.2, 112.1, 111.6, 105.1, 71.5, 68.4, 68.3, 55.4, 52.4, 48.5. MS (EI) m/z (relative intensity): 284 (6), 270 (7), 210 (8), 180 (100). HRMS (EI) calcd for $C_{24}H_{25}NO_5$ [M$^+$], 407.1733; found, 407.1733.

1-{[2-(2-Methoxyphenoxy)ethyl]amino}-1-(10*H*-phenothiazin-2-yloxy)-2-propanol (66). Yield: 63% from epoxide **103g**; 33% overall from the corresponding phenol, off-white solid. mp 48−50 °C. IR (KBr) 3388, 3059, 2924, 2855, 1631, 1503, 1487, 1456, 1249, 1164, 1104, 1035, 819, 747 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.54 (s, 1H), 7.02−6.82 (m, 5H), 6.79 (d, J = 8.4 Hz, 1H), 6.74 (ddd, J = 7.5, 7.5, 1.0 Hz, 1H), 6.67 (dd, J = 7.9, 0.8 Hz, 1H), 6.38 (dd, J = 8.4, 2.5 Hz, 1H), 6.34 (d, J = 2.5 Hz, 1H), 5.03 (br s, 1H), 4.00 (t, J = 5.5 Hz, 2H), 3.93−3.75 (m,3H), 3.73 (s, 3H), 2.89 (t, J = 5.5 Hz, 2H), 2.73 (dd, J = 11.8, 4.1 Hz, 1H), 2.64 (dd, J = 11.8, 6.2 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 158.6, 149.1, 148.0, 143.2, 141.7, 127.2, 126.7, 126.1, 121.6, 121.0, 120.6, 116.9, 114.3, 113.6, 112.2, 107.8, 107.0, 101.2, 70.6, 68.3, 68.0, 55.4, 52.2, 48.4. MS (EI) m/z (relative intensity): 438 (100) [M$^+$], 224 (22), 215 (82). HRMS (EI) calcd for $C_{24}H_{26}N_2O_4S$ [M$^+$], 438.1613; found, 438.1600.

2-(2-Hydroxy-3-{[2-(2-methoxyphenoxy)ethyl]amino}-propoxy)-10*H*-5λ6,10-phenothiazine-5,5-dione (67). Yield: 54% from epoxide **103h**; 28% overall from the corresponding phenol, white solid. mp 67−69 °C. IR (film) 3518, 3309, 3183, 3076, 2930, 2834, 2249, 1622, 1260, 1024, 911, 725 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (s, 1H), 7.94 (dd, J = 8.0, 1.1 Hz, 1H), 7.77 (d, J = 8.9 Hz, 1H), 7.31 (t, J = 8.4 Hz, 1H), 7.07 (t, J = 7.4 Hz, 1H), 6.96 (d, J = 8.3 Hz, 1H), 6.94−6.81 (m, 4H), 6.57 (dd, J = 8.9, 2.1 Hz, 1H), 6.34 (d, J = 2.0 Hz, 1H), 4.09 (t, J = 4.9 Hz, 2H), 4.07−3.98 (m, 1H), 3.90−3.78 (m, 2H), 3.76 (s, 3H), 3.27 (br s, 2H), 3.03 (t, J = 4.9 Hz, 2H), 2.87 (dd, J = 12.3, 4.0 Hz, 1H), 2.76 (dd, J = 12.3, 7.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.2, 149.6, 148.1, 139.9, 138.1, 133.0, 124.9, 123.0, 122.0, 121.8, 121.6, 121.3, 116.8, 114.3, 114.2, 112.2, 110.6, 100.3, 70.8, 68.5, 68.1, 56.0, 51.5, 48.8. MS (EI) m/z (relative intensity): 470 (3) [M$^+$], 347 (10), 333 (13), 247 (13), 180 (100), 178 (25), 148 (12), 56 (20). HRMS (EI) calcd for $C_{24}H_{26}N_2O_6S$ [M+], 470.1512; found, 470.1490.

1-{[2-(2-Methoxyphenoxy)ethyl]amino}-3-(naphthalen-1-yloxy)-2-propanol (68). Yield: 38% from epoxide **103i**; 32% overall from the corresponding phenol, white solid. mp 110−112 °C. IR (KBr) 3435, 1504, 1256, 782, 773, 743 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.24 (d, J = 7.5 Hz, 1H), 7.85 (d, J = 7.5 Hz, 1H), 7.35−7.55 (m, 4H), 6.80−7.04 (m, 5H), 5.16 (d, J = 3.9 Hz, 1H), 3.97−4.19 (m, 5H), 3.72 (s, 3H), 2.92 (t, J = 5.5 Hz, 2H), 2.87 (dd, J = 11.7, 3.7 Hz, 1H), 2.77 (dd, J = 12.0, 6.3 Hz, 1H), 1.98 (br s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 154.2, 149.2, 148.1, 134.0, 127.4, 126.4, 126.2, 125.1, 125.0, 121.8, 121.0, 120.7, 119.8, 113.6, 112.2, 105.1, 70.9, 68.4, 68.4, 55.4, 52.5, 48.5. MS (CI) m/z (relative intensity): 368 (100) [M + H]$^+$. HRMS (EI) calcd for $C_{22}H_{25}NO_4$ [M$^+$], 367.1784; found, 367.1797.

1-{[2-(2-Methoxyphenoxy)ethyl]amino}-4-(naphthalen-1-yloxy)-2-butanol (69). Yield: 51% from **103u**; 12% overall from the corresponding phenol, white solid. mp 65−67 °C. IR (KBr) 3310, 2917, 1591, 1578, 1504, 1454, 1391, 1252, 1127, 1098, 770 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (ddd, J = 6.7, 1.7, 0.7 Hz, 1H), 7.82−7.80 (m, 1H), 7.50−7.46 (m, 2H), 7.44 (d, J = 8.3 Hz, 1H), 7.38 (t, J = 8.3 Hz, 1H), 6.97−6.84 (m, 5H), 4.38−4.29 (m, 2H), 4.12 (t, J = 5.2 Hz, 2H), 4.07−4.01 (m, 1H), 3.85 (s, 3H), 3.12−3.02 (m, 2H), 2.94 (dd, J = 12.1, 3.2 Hz, 1H), 2.68 (dd, J = 12.1, 9.2 Hz, 1H), 2.14−1.99 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.5, 149.7, 148.2, 134.4, 127.4, 126.3, 125.9, 125.6, 125.1, 121.9, 121.6, 120.9, 120.1, 114.1, 111.8, 104.70, 68.7, 66.9, 65.00, 55.7, 55.1, 48.4, 34.5. MS (EI) m/z (relative intensity): 381 (<1) [M$^+$] 238 (100), 180 (74). HRMS (EI) calcd for $C_{23}H_{27}NO_4$ [M$^+$], 381.1940; found, 381.1941.

1-(Adamantan-1-yloxy)-3-{[2-(2-methoxyphenoxy)ethyl]-amino}-2-propanol (70). Yield: 50% from epoxide **103j**; 13% overall from 1-adamantanol, viscous oil. IR (KBr) 3428, 2904, 1498, 1252, 1119, 742 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.93−6.87 (m, 4H), 4.12 (t, J = 5.3 Hz, 2H), 3.85 (s, 3H), 3.85−3.77 (m, 1H), 3.47−3.38 (m, 2H), 3.05 (t, J = 5.3 Hz, 2H), 2.82 (dd, J = 12.0, 4.0 Hz, 1H), 2.72 (dd, J = 12.1, 7.6 Hz, 1H), 2.60 (br s, 1H), 2.09−2.17 (m, 3H), 1.69−1.78 (m, 6H), 1.54−1.68 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.6, 148.2, 121.4, 120.8, 114.0, 111.8, 72.2, 69.3, 68.7, 62.5, 55.8, 52.1, 48.7, 41.4, 36.3, 30.4. MS (CI) m/z (relative intensity): 376 (100) [M + H]$^+$. HRMS (CI) calcd for $C_{22}H_{34}NO_4$ [M + H]$^+$, 376.2488; found, 376.2475.

1-(Adamantan-2-yloxy)-3-{[2-(2-methoxyphenoxy)ethyl]-amino}-2-propanol (71). Yield: 50% from epoxide **103k**; 32% overall from 2-adamantanol, white solid. mp 53−57 °C. IR (KBr) 3334, 2896, 1509, 1256, 740 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.97−6.86 (m, 4H), 4.13 (t, J = 5.4 Hz, 2H), 3.86 (s, 3H), 3.92−3.84 (m, 1H), 3.52−3.42 (m, 3H), 3.07 (t, J = 5.4 Hz, 2H), 2.85 (dd, J = 12.1, 4.2 Hz, 1H), 2.77 (dd, J = 12.1, 7.5 Hz, 1H), 1.96−2.07 (m, 4H), 1.73−1.88 (m, 4H), 1.70−1.62 (m, 4H), 1.43−1.52 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.7, 148.2, 121.5, 120.8, 114.1, 111.8, 82.0, 70.00, 69.1, 68.8, 55.8, 52.2, 48.7, 37.5, 36.4, 31.63, 31.59, 31.5, 27.3. MS (CI) m/z (relative intensity): 376 (100) [M + H]$^+$. HRMS (CI) calcd for $C_{22}H_{34}NO_4$ [M + H]$^+$, 376.2488; found, 376.2501.

1-(Adamantan-1-ylmethoxy)-3-{[2-(2-methoxyphenoxy)-ethyl]amino}-2-propanol (72). Yield: 87% overall from (1-adamantyl)methanol via epoxide **103l**, viscous oil. IR (KBr) 3211, 1596, 1509, 1452, 1254, 1125, 1029, 744 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.96−6.88 (m, 4H), 4.12 (t, J = 5.3 Hz, 2H), 3.86 (s, 3H), 3.90−3.83 (m, 1H), 3.37−3.47 (m, 2H), 3.05 (t, J = 5.4 Hz, 2H), 2.97−3.07 (m, 2H), 2.82 (dd, J = 12.1, 4.1 Hz, 1H), 2.73 (dd, J = 12.1, 7.7 Hz, 1H), 1.91−2.02 (m, 3H), 1.58−1.78 (m, 6H), 1.49−1.56 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.7, 148.1, 121.6, 120.9, 114.3, 111.8, 82.5, 74.0, 68.6, 68.5, 55.8, 52.0, 48.6, 39.6, 37.1, 34.1, 28.2. MS (CI) m/z (relative intensity): 390 (100) [M + H]$^+$. HRMS (CI) calcd for $C_{23}H_{36}NO_4$ [M + H]$^+$, 390.2644; found, 390.2631.

6-(2-Hydroxy-3-{[2-(2-methoxyphenoxy)ethyl]amino}-propoxy)-1,2-dihydroquinolin-2-one (73). Yield: 40% from epoxide **103m**; 9% overall from the corresponding phenol, white solid. mp 154−155 °C. IR (film) 3283, 2909, 1654, 1502, 1249, 1119 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.60 (br s, 1H), 7.82 (d, J = 9.6 Hz, 1H), 7.10−7.25 (m, 3H), 6.80−6.99 (m, 4H), 6.47 (d, J = 9.5 Hz, 1H), 5.05 (br s, 1H), 3.87−4.05 (m, 5H), 3.73 (s, 3H), 2.91 (t, J = 5.4 Hz, 2H), 2.78 (dd, J = 11.8, 3.6 Hz, 1H), 2.68 (dd, J = 11.7, 6.0 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.4, 153.5, 149.2, 148.1, 139.7, 133.3, 122.2, 121.0, 120.7, 119.9, 119.6, 116.3, 113.7, 112.3, 110.2, 71.1, 68.3, 68.1, 55.5, 52.3, 48.4. MS (ESI) m/z (relative intensity): 385 (100) [M + H]$^+$. HRMS (ESI) calcd for $C_{21}H_{25}N_2O_5$ [M + H]$^+$, 385.1758; found, 385.1754.

6-(2-Hydroxy-3-{[2-(2-methoxyphenoxy)ethyl]amino}-propoxy)-1,2,3,4-tetrahydroquinolin-2-one (74). Yield: 29% from epoxide **103n**; 10% overall from the corresponding phenol, white solid. mp 126−128 °C. IR (film) 3302, 3167, 2920, 2830, 1625, 1593, 1503, 1450, 1252, 1121, 1022, 743 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.87 (br s, 1H), 6.96 (d, J = 7.6, 2.1 Hz, 2H), 6.93−6.83 (m, 2H), 6.81−6.68 (m, 3H), 4.98 (br s, 1H), 4.00 (t, J = 5.6 Hz, 2H), 3.92−3.80 (m, 3H), 3.74 (s, 3H), 2.90 (t, J = 5.5 Hz, 2H), 2.82 (t, J = 7.5 Hz, 2H), 2.75 (dd, J = 12.0, 3.7 Hz, 1H), 2.65 (dd, J = 11.8, 6.1 Hz, 1H), 2.39 (dd, J = 8.3, 6.8 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 169.7, 153.8, 149.2, 148.1, 131.7, 124.8, 121.0, 120.7, 115.7, 114.0, 113.7, 113.0, 112.3, 71.0, 68.3, 68.1, 55.5, 52.3, 48.4, 30.3, 25.1. MS (ESI) m/z (relative intensity): 387 (100) [M + H]$^+$. HRMS (ESI) m/z (relative intensity): calcd for $C_{21}H_{27}N_2O_5$ [M + H]$^+$, 387.1914; found, 387.1910.

7-(2-Hydroxy-3-{[2-(2-methoxyphenoxy)ethyl]amino}-propoxy)-1,2,3,4-tetrahydroquinolin-2-one (75). Yield: 65% from epoxide **103o**; 13% overall from the corresponding phenol, white solid. mp 161−163 °C. IR (film) 3584, 3183, 2914, 2831, 1678, 1588, 1223, 1123, 1027, 738 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.96 (br s, 1H), 7.14−6.78 (m, 5H), 6.62−6.37 (m, 2H), 5.03 (br s, 1H), 4.01 (t, J = 5.3 Hz, 2H), 3.95−3.76 (m, 3H), 3.74 (s, 3H), 2.91 (t, J = 5.3 Hz, 2H), 2.78 (t, J = 7.3 Hz, 2H), 2.79−2.71 (m, 1H), 2.66 (dd, J = 11.7, 6.2 Hz, 1H), 2.41 (t, J = 7.4 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 170.2, 157.9, 149.2, 148.0, 139.1, 128.3, 121.1, 120.7, 115.5, 113.8, 112.3, 107.5, 101.7, 70.6, 68.3, 68.0, 55.5, 52.2, 48.4, 30.7, 24.0. MS (ESI) m/z

(relative intensity): 387 (100) $[M + H]^+$. HRMS (ESI) calcd for $C_{21}H_{27}N_2O_5$ $[M + H]^+$, 387.1914; found, 387.1909.

1-(1*H*-Indol-4-yloxy)-3-{[2-(2-methoxyphenoxy)ethyl]amino}-2-propanol (76).[51] Yield: 63% from epoxide **103p**; 43% overall from 4-hydroxyindole, white solid. mp 98−100 °C. IR (film) 3378, 3066, 2924, 2868, 2834, 1586, 1506, 1453, 1249, 1122, 1091, 1051, 1027, 909, 742 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (br s, 1H), 7.11−7.00 (m, 3H), 6.97−6.83 (m, 4H), 6.65−6.59 (m, 1H), 6.51 (dd, J = 7.6, 0.7 Hz, 1H), 4.24−4.08 (m, 5H), 3.81 (s, 3H), 3.20−3.10 (br s, 1H), 3.10 (t, J = 5.2 Hz, 2H), 3.02 (dd, J = 12.4, 3.5 Hz, 1H), 2.93 (dd, J = 12.4, 7.5 Hz, 1H), 2.96−2.92 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.6, 150.1, 148.4, 137.6, 123.0, 122.9, 122.0, 121.2, 119.0, 114.7, 112.2, 105.0, 101.1, 100.1, 70.6, 69.0, 68.5, 56.1, 52.0, 48.9. MS (EI) m/z (relative intensity): 356 (25) $[M^+]$, 180 (100), 133 (35). HRMS (EI) calcd for $C_{20}H_{24}N_2O_4$ $[M^+]$, 356.1736; found, 356.1727.

1-(1*H*-Indol-5-yloxy)-3-{[2-(2-methoxyphenoxy)ethyl]amino}-2-propanol (77). Yield: 58% from epoxide **103q**; 44% overall from 5-hydroxyindole, white solid. mp 109−110 °C. IR (film) 3375, 2930, 2867, 1592, 1505, 1456, 1253, 1220, 1157, 1123, 1027, 748, 727 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 10.89 (s, 1H), 7.28−7.24 (m, 2H), 7.03 (d, J = 2.4 Hz, 1H), 6.98−6.93 (m, 2H), 6.92−6.82 (m, 2H), 6.73 (dd, J = 8.7, 2.4 Hz, 1H), 6.32−6.30 (m, 1H), 5.00 (br s, 1H), 4.01 (t, J = 5.6 Hz, 2H), 3.95−3.85 (m, 3H), 3.73 (s, 3H), 3.32 (br s, 1H), 2.92 (t, J = 5.6 Hz, 2H), 2.80 (dd, J = 11.9, 3.9 Hz, 1H), 2.68 (dd, J = 11.9, 6.4 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 152.5, 149.2, 148.0, 131.0, 127.9, 125.7, 121.0, 120.7, 113.7, 112.2, 111.8, 111.6, 102.8, 100.8, 71.3, 68.3, 68.2, 55.4, 52.5, 48.4. MS (ESI) m/z (relative intensity): 357 (100%) $[M + H]^+$. HRMS (ESI) calcd for $C_{20}H_{24}N_2O_4$ $[M + H]^+$, 357.1809; found, 357.1819.

Preparation of 1-(1*H*-Indazol-5-yloxy)-3-{[2-(2-methoxyphenoxy)ethyl]amino}-2-propanol (78). The reaction of the *N*-*t*-Boc-protected epoxide derivative **103r** with amine **104a** was carried out as in the preparation of **6** followed by deprotection with TFA in dichloromethane at room temperature to afford **78** in 43% overall yield, white solid. mp 114−116 °C. IR (film) 3000−3600 (br), 3062, 2924, 2848, 1591, 1500, 1450, 1249, 1221, 1123, 1026, 948, 744 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (br s, 1H), 7.37 (d, J = 8.8 Hz, 1H), 7.15−7.04 (m, 2H), 6.84−7.02 (m, 4H), 4.17 (t, J = 5.1 Hz, 2H), 4.20−4.11 (m, 1H), 4.04 (d, J = 5.1 Hz, 2H), 3.84 (s, 3H), 3.13 (t, J = 5.0 Hz, 2H), 3.03 (dd, J = 12.3, 3.7 Hz, 1H), 2.91 (dd, J = 12.2, 8.0 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.9, 150.0, 148.3, 135.9, 134.6, 123.5, 122.1, 121.1, 119.5, 114.8, 112.2, 110.8, 101.6, 71.2, 68.9, 68.2, 56.0, 51.8, 48.8. MS (ESI) m/z (relative intensity): 358 (100%) $[M + H]^+$. HRMS (ESI) calcd for $C_{19}H_{24}N_3O_4$ $[M + H]^+$, 358.1761; found, 358.1756.

Products **79** and **80** were prepared similarly.

1-(1*H*-Indazol-6-yloxy)-3-{[2-(2-methoxyphenoxy)ethyl]amino}-2-propanol (79). Overall yield from **103s**: 47%, white solid. mp 131−133 °C. IR (film) 3300, 3018, 2933, 2870, 1628, 1503, 1456, 1252, 1123, 1026, 941, 741 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (br s, 1H), 7.56 (d, J = 8.8 Hz, 1H), 7.02−6.77 (m, 6H), 4.30−4.22 (m, 1H), 4.20 (t, J = 5.1 Hz, 2H), 4.10−4.01 (m, 2H), 3.83 (s, 3H), 3.20 (dd, J = 8.1, 4.8 Hz, 2H), 3.14 (dd, J = 12.3, 3.9 Hz, 1H), 3.01 (dd, J = 12.3, 8.2 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.6, 149.6, 147.9, 141.3, 134.2, 122.1, 121.6, 121.2, 118.1, 114.5, 113.4, 112.2, 91.9, 70.6, 68.0, 67.7, 55.9, 51.7, 48.4. MS (ESI) m/z (relative intensity): 358 (100) $[M^+]$. HRMS (ESI) calcd for $C_{19}H_{24}N_3O_4$ $[M + H]^+$, 358.1761; found, 358.1752.

1-(1*H*-Benzodiazol-5-yloxy)-3-{[2-(2-methoxyphenoxy)ethyl]amino}-2-propanol (80). Overall yield from **103t**: 20%, white solid. mp 125−127 °C. IR (film) 3302, 3167, 2920, 2830, 1625, 1593, 1503, 1450, 1252, 1121, 1022, 743 cm^{-1}. ^1H NMR (400 MHz, CD_3OD) δ 8.05 (s, 1H), 7.48 (d, J = 8.8 Hz, 1H), 7.13 (s, 1H), 7.03−6.84 (m, 5H), 6.51 (dd, J = 7.6, 0.7 Hz, 1H), 4.18−4.01 (m, 5H), 3.80 (s, 3H), 3.03 (t, J = 5.0 Hz, 2H), 2.96 (dd, J = 12.2, 4.0 Hz, 1H), 2.85 (dd, J = 12.2, 8.0 Hz, 1H), 2.96−2.92 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.3, 148.3, 146.7, 139.2, 120.1, 119.2, 119.0, 112.9, 111.2, 110.5, 100.0, 69.6, 67.0, 66.8, 53.5, 50.3, 46.7. MS (EI) m/z (relative intensity): 179 (100), 133 (35). HRMS (ESI) calcd for $C_{19}H_{24}N_3O_4$ $[M + H]^+$, 358.1761; found, 358.1760.

Preparation of 3-(9*H*-Fluoren-4-yloxy)-1-{[2-(2-methoxyphenoxy)ethyl]amino}-2-propanol (62). The product was prepared by the Wolff−Kishner reduction of **63** in 54% yield, white solid. mp 104.5−106.0 °C. IR (KBr) 3290, 2922, 1582, 1503, 1457, 1274, 1253, 1221, 738 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.14 (d, J = 7.5 Hz, 1H), 7.53 (d, J = 7.3 Hz, 1H), 7.36 (t, J = 7.1 Hz, 1H), 7.30−7.28 (m, 1H), 7.24 (d, J = 7.8 Hz, 1H), 7.18 (d, J = 7.3 Hz, 1H), 6.98−6.88 (m, 5H), 4.30−4.14 (m, 5H), 3.92 (s, 2H), 3.84 (s, 3H), 3.14−3.07 (m, 3H), 2.97 (dd, J = 7.7, 12.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.9, 149.7, 148.2, 145.3, 142.5, 140.8, 129.9, 127.6, 126.7, 125.8, 124.3, 123.6, 121.6, 120.9, 117.6, 114.1, 111.8, 109.6, 70.4, 68.8, 68.4, 55.7, 51.9, 48.6, 37.2. MS (EI) m/z (relative intensity): 405 (3) $[M^+]$, 268 (25), 180 (100). HRMS (EI) calcd for $C_{25}H_{27}NO_4$ $[M^+]$, 405.1940; found, 405.1945.

Preparation of 3-(2-Hydroxy-3-{[2-(2-methoxyphenoxy)ethyl]amino}propoxy-*N*-phenylaniline (65). A mixture of **66** (88 mg, 0.20 mmol) and $NiCl_2 \cdot 6H_2O$ (337 mg, 1.41 mmol) in methanol/THF/H_2O (8 mL; 1:2:1) at room temperature was treated with small portions of $NaBH_4$ (162 mg, 4.28 mmol) over 1 h.[34] Stirring was continued for an additional 2 h, the mixture was filtered through a pad of Celite, and the filtrate was concentrated under vacuum. The residue was purified by flash chromatography over silica gel (methanol/dichloromethane) to afford 29 mg (36%) of **65** as a yellow oil. IR (film) 3355, 3279, 3061, 2928, 2835, 1588, 1495, 1251, 745 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.28−7.21 (m, 3H), 7.11 (t, J = 8.0 Hz, 1H), 7.08−7.02 (m, 2H), 6.97−6.83 (m, 5H), 6.66−6.58 (m, 2H), 6.44 (dd, J = 8.2, 2.0 Hz, 1H), 4.14 (t, J = 5.1 Hz, 2H), 4.15−4.07 (m, 1H), 4.00−3.92 (m, 2H), 3.81 (s, 3H), 3.10 (t, J = 5.1 Hz, 2H), 3.00 (dd, J = 12.3, 3.7 Hz, 1H), 2.88 (dd, J = 12.3, 8.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.9, 150.0, 148.2, 144.9, 142.9, 130.3, 129.5, 122.2, 121.5, 121.2, 118.6, 115.0, 112.2, 110.6, 106.9, 104.1, 70.4, 68.7, 68.0, 56.0, 51.7, 48.7. MS (EI) m/z (relative intensity): 408 (40) $[M^+]$, 368 (19), 285 (19), 186 (19), 185 (100), 180 (73). HRMS (EI) calcd for $C_{24}H_{28}N_2O_4$ $[M^+]$, 408.2049; found, 408.2030.

Preparation of 1-[(Benzofuran-2-ylmethyl)amino]-3-(9*H*-carbazol-2-yloxy)-2-propanol (81). A mixture of **117a** (304 mg, 1.27 mmol) and benzylamine (0.42 mL, 3.84 mmol) were refluxed for 2 h in isopropanol (3 mL). The solvent was removed under vacuum, and the residue was purified by flash chromatography over silica gel (methanol/dichloromethane) to afford 211 mg (48%) of amino alcohol **119** as an off-white solid. mp 160−161 °C. IR (film) 3392, 3043, 2919, 2847, 1607, 1455, 749, 724 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 11.06 (s, 1H), 7.97 (d, J = 8.2 Hz, 1H), 7.94 (d, J = 9.2 Hz, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.38−7.20 (m, 6H), 7.09 (dd, J = 7.7, 7.2 Hz, 1H), 6.96 (s, 1H), 6.76 (d, J = 8.6 Hz, 1H), 4.09−3.93 (m, 3H), 3.77 (s, 2H), 2.73 (dd, J = 11.7, 3.5 Hz, 1H), 2.65 (dd, J = 11.6, 5.9 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 157.8, 141.0, 140.3, 139.7, 128.1, 128.0, 126.6, 124.1, 122.6, 120.8, 119.2, 118.5, 116.2, 110.5, 108.1, 95.3, 70.9, 68.1, 52.9, 51.6. MS (EI) m/z (relative intensity): 346 (32) $[M^+]$, 183 (100), 154 (20), 120 (18), 91 (48). HRMS (EI) calcd for $C_{22}H_{22}N_2O_2$ $[M^+]$, 346.1681; found, 346.1686.

A mixture of **119** (188 mg, 0.542 mmol), aldehyde **121** (85 mg, 0.58 mmol), and $NaBH(OAc)_3$ (168 mg, 0.792 mmol) in 1,2-dichloroethane (5 mL) was stirred at room temperature for 4 h. The mixture was partitioned between water and dichlormethane, and the aqueous phase was extracted with dichloromethane. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by flash chromatography over silica gel (methanol/dichloromethane) to furnish 196 mg (76%) of the *N*-benzyl derivative of **81** as a white solid foam. ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 7.7 Hz, 1H), 7.88 (d, J = 8.4 Hz, 1H), 7.87 (br s, 1H), 7.54−7.50 (m, 1H), 7.48−7.44 (m, 1H), 7.40−7.31 (m, 6H), 7.29−7.16 (m, 4H), 6.84−6.76 (m, 2H), 6.58 (s, 1H), 4.14−4.23 (m, 1H), 4.03 (d, J = 5.1 Hz, 2H), 3.90 (d, J = 15.1 Hz, 1H), 3.89 (d, J = 13.5 Hz, 1H), 3.84 (d, J = 15.1 Hz, 1H), 3.70 (d, J = 13.5 Hz, 1H), 3.31 (s, 1H), 2.77−2.92 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.3, 155.3, 155.1, 140.9, 139.7, 138.4, 129.3, 128.7, 128.4, 127.6, 124.8, 124.2, 123.6, 122.9, 121.1, 121.0, 119.8, 119.7, 117.6, 111.4, 110.5, 108.8, 106.0, 95.8, 70.9, 67.0, 58.7, 56.5, 50.7.

A solution of the above *N*-benzyl derivative (50 mg, 0.10 mmol) in a 2:1 mixture of methanol/dichloromethane (1.5 mL) was added to 10%

dx.doi.org/10.1021/jm401090a | J. Med. Chem. 2013, 56, 8626−8655

palladium on charcoal (27 mg). The mixture was heated at 45 °C for 4 h under positive pressure of hydrogen (balloon). The reaction was cooled to room temperature and filtered through Celite. The filtrate was concentrated under vacuum, and the residue was purified by flash chromatography over silica gel (methanol/dichloromethane) to provide 27 mg (68%) of **81** as a white solid. mp 159−160 °C. IR (film) 3355, 3279, 3061, 2928, 2835, 1588, 1495, 1251, 745 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 11.04 (s, 1H), 7.97 (d, J = 7.6 Hz, 1H), 7.94 (d, J = 8.6 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.31−7.17 (m, 3H), 7.09 (dd, J = 7.7, 7.2 Hz, 1H), 6.96 (d, J = 2.2 Hz, 1H), 6.76 (dd, J = 8.5, 2.2 Hz, 1H), 6.73 (s, 1H), 5.03 (d, J = 4.5 Hz, 1H), 3.92−4.09 (m, 2H), 3.91 (s, 3H), 2.79 (dd, J = 11.8, 4.3 Hz, 1H), 2.70 (dd, J = 11.8, 6.0 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 157.8, 157.7, 154.1, 140.9, 139.6, 128.1, 124.0, 123.5, 122.6, 122.5, 120.7, 120.6, 119.1, 118.4, 116.1, 110.7, 110.4, 108.0, 103.1, 95.2, 70.8, 68.2, 51.7, 46.0. MS (EI) m/z (relative intensity): 386 (74) [M^+], 183 (100), 131 (82), 43 (54). HRMS (EI) calcd for $C_{24}H_{22}N_2O_3$ [M^+], 386.1630; found, 386.1626.

Preparation of 1-[(Benzoxazol-2-ylmethyl)amino]-3-(9*H*-carbazol-2-yloxy)-2-propanol (82). A mixture of amino alcohol **119** (88 mg, 0.25 mmol), chloride **122** (47 mg, 0.28 mmol), *N*,*N*-diisopropylethylamine (71 μL, 0.41 mmol), and a catalytic amount of KI in acetonitrile (2 mL) was stirred at 60 °C for 16 h. The reaction was cooled to room temperature and partitioned between water and ethyl acetate. The aqueous phase was separated and extracted with ethyl acetate. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash chromatography over silica gel (methanol/dichloromethane) to provide 101 mg (85%) of the *N*-benzyl derivative of **82** as an off-white solid. mp 77−79 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 11.07 (s, 1H), 7.98 (d, J = 7.8 Hz, 1H), 7.92 (d, J = 8.5 Hz, 1H), 7.79−7.73 (m, 1H), 7.72−7.66 (m, 1H), 7.46−7.21 (m, 9H), 7.15−7.06 (m, 1H), 6.91 (d, J = 2.1 Hz, 1H), 6.67 (dd, J = 8.5, 2.2 Hz, 1H), 5.01 (d, J = 4.8 Hz, 1H), 4.13−4.01 (m, 4H), 3.94−3.89 (m, 1H), 3.90 (d, J = 16.0 Hz, 1H), 3.83 (d, J = 16.0 Hz, 1H), 2.85 (dd, J = 13.3, 5.9 Hz, 1H), 2.77 (dd, J = 13.3, 5.8 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.0, 157.8, 150.2, 141.0, 140.6, 139.7, 138.7, 128.8, 128.2, 127.0, 125.0, 124.3, 124.0, 122.6, 120.7, 119.6, 119.2, 118.5, 116.1, 110.7, 110.5, 108.0, 95.2, 70.9, 67.5, 58.4, 56.3, 50.5. MS (EI) m/z (relative intensity): 477 (7) [M^+], 345 (21), 252 (20), 251 (100), 91 (79). HRMS (EI) calcd for $C_{30}H_{27}N_3O_3$ [M^+], 477.2052; found, 477.2068.

A solution of the *N*-benzyl derivative of **82** (79 mg, 0.17 mmol) in methanol (1.5 mL) was added to 10% palladium on charcoal (21 mg). The mixture was hydrogenated as in the preceding procedure for 48 h. The reaction was cooled to room temperature and filtered through Celite. The filtrate was concentrated under vacuum, and the residue was purified by flash chromatography over silica gel (methanol/dichloromethane) to obtain 22 mg (34%) of **82** as a beige solid. mp 136−138 °C. IR (film) 3355, 3279, 3061, 2928, 2835, 1588, 1495, 1251, 745 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 11.05 (s, 1H), 7.97 (d, J = 7.7 Hz, 1H), 7.93 (d, J = 8.5 Hz, 1H), 7.75−7.65 (m, 2H), 7.43−7.32 (m, 3H), 7.27 (t, J = 7.2 Hz, 1H), 7.10 (t, J = 7.3 Hz, 1H), 6.96 (d, J = 2.0 Hz, 1H), 6.75 (dd, J = 8.5, 2.1 Hz, 1H), 5.07 (d, J = 4.2 Hz, 1H), 4.09−3.93 (m, 3H), 4.07 (s, 2H), 2.83 (dd, J = 12.0, 3.7 Hz, 1H), 2.75 (dd, J = 11.5, 5.6 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.8, 157.8, 150.2, 141.0, 140.7, 139.7, 124.9, 124.3, 124.1, 122.6, 120.8, 119.5, 119.2, 118.5, 116.2, 110.7, 110.5, 108.1, 70.9, 68.4, 51.9, 46.2. MS (EI) m/z (relative intensity): 387 (82) [M^+], 183 (100), 161 (25), 133 (32), 132 (39). HRMS (EI) calcd for $C_{23}H_{21}N_3O_3$ [M^+], 387.1583; found, 387.1587.

Compounds **83**−**90** and **92** were prepared by the treatment of the corresponding epoxides **103a**, **105**, **114a**, **117a**, or **117c** with the appropriate amines by means of the same procedure as for the preparation of **6** except for the variation described below for **84**.

1-(9*H*-Carbazol-4-yloxy)-3-(3,4-dihydro-2*H*-1,4-benzoxazin-4-yl)-2-propanol (83). From **103a** and **118a**.Yield: 67%, off-white solid. mp 68−70 °C. IR (film) 3398, 3056, 2930, 2870, 1605, 1502, 1452, 1343, 1097, 722 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.30 (d, J = 7.8 Hz, 1H), 8.08 (s, 1H), 7.47−7.37 (m, 2H), 7.33 (dd, J = 8.0, 7.9 Hz, 1H), 7.30−7.21 (m, 1H), 7.06 (d, J = 8.0 Hz, 1H), 6.90−6.79 (m, 3H), 6.75−6.61 (m, 2H), 4.57−4.45 (m, 1H), 4.40−4.24 (m, 2H), 4.21 (t, J = 4.4 Hz, 2H), 3.69 (dd, J = 14.8, 5.4 Hz, 1H), 3.57 (dd, J = 14.8, 7.1 Hz, 1H), 3.53−3.34 (m, 2H), 2.61 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.9, 144.4, 141.1, 138.9, 135.4, 126.9, 125.3, 122.9, 122.5, 121.9, 119.9, 118.5, 116.8, 113.0, 112.8, 110.3, 104.3, 101.4, 69.8, 68.4, 64.4, 55.2, 49.0. MS (ESI) m/z (relative intensity): 375 (100) [$M + H$]$^+$. HRMS (ESI) calcd for $C_{23}H_{23}N_2O_3$ [$M + H$]$^+$, 375.1709; found, 375.1708.

Preparation of 4-[3-(9*H*-Carbazol-4-yloxy)-2-hydroxypropyl]-3,4-dihydro-2*H*-1,4-benzoxazin-3-one (84). A mixture of epoxide **103a** (179 mg, 0.748 mmol), **118b** (101 mg, 0.677 mmol), and Cs_2CO_3 (309 mg, 0.948 mmol) in DMF (2 mL) was heated at 80 °C for 20 h. The reaction was then partitioned between ethyl acetate and water. The organic phase was separated, washed with brine, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash chromatography over silica gel (ethyl acetate/hexanes) to afford 94 mg (36%) of **84**, off-white solid. mp 133−135 °C. IR (film) 3402, 3342, 3050, 2925, 2870, 1663, 1497, 1094, 748, 720 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 11.25 (s, 1H), 8.30 (d, J = 7.8 Hz, 1H), 7.44 (d, J = 8.1 Hz, 1H), 7.41−7.47 (m, 1H), 7.33 (ddd, J = 8.8, 7.5, 1.5 Hz, 1H), 7.28 (dd, J = 8.0, 7.9 Hz, 1H), 7.10 (ddd, J = 8.0, 7.2, 1.0 Hz, 1H), 7.08 (dd, J = 8.0, 0.5 Hz, 1H), 6.97−7.03 (m, 3H), 6.66 (d, J = 7.6 Hz, 1H), 5.49 (d, J = 5.3 Hz, 1H), 4.67 (d, J = 14.8 Hz, 1H), 4.61 (d, J = 14.8 Hz, 1H), 4.32−4.40 (m, 1H), 4.09−4.31 (m, 4H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.3, 154.7, 145.0, 141.1, 138.9, 129.3, 126.4, 124.5, 123.4, 122.6, 122.4, 121.6, 118.5, 116.5, 116.1, 111.5, 110.3, 104.0, 100.4, 70.2, 67.1, 66.4, 44.5. MS (EI) m/z (relative intensity): 388 (25) [M^+], 206 (100). HRMS (EI) calcd for $C_{23}H_{20}N_2O_4$ [M^+], 388.1423; found, 388.1417.

4-(9*H*-Carbazol-4-yloxy)-1-(3,4-dihydro-2*H*-1,4-benzoxazin-4-yl)-2-butanol (85). From **105** and **118a**.Yield: 20% (35% based on recovered starting material), off-white solid. mp 172−174 °C. IR (film) 3516, 3319, 2945, 2879, 1600, 1500, 1091, 734, 720 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 11.21 (s, 1H), 8.07 (d, J = 7.8 Hz, 1H), 7.42 (d, J = 8.1 Hz, 1H), 7.25−7.35 (m, 2H), 6.97−7.10 (m, 2H), 6.76 (dd, J = 8.1, 1.5 Hz, 1H), 6.62−6.73 (m, 3H), 6.48 (ddd, J = 7.9, 7.2, 1.5 Hz, 1H), 4.99 (d, J = 5.6 Hz, 1H), 4.06−4.40 (m, 5H), 3.52−3.58 (m, 1H), 3.37−3.43 (m, 2H), 3.22 (dd, J = 14.6, 7.5 Hz, 1H), 2.13−2.23 (m, 1H), 1.82−1.94 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.0, 143.3, 141.0, 138.8, 135.4, 126.5, 124.4, 122.2, 121.7, 121.3, 118.5, 116.1, 115.7, 111.7, 111.4, 110.3, 103.7, 100.3, 64.6, 64.1, 63.9, 57.5, 48.3, 34.7. MS (EI) m/z (relative intensity): 388 (26) [M^+], 148 (100). HRMS (EI) calcd for $C_{24}H_{24}N_2O_3$ [M^+], 388.1787; found, 388.1786.

1-(9*H*-Carbazol-3-yloxy)-3-(3,4-dihydro-2*H*-1,4-benzoxazin-4-yl)-2-propanol (86). From **114a** and **118a**. Yield: 76%, white solid. mp 61−62 °C. IR (film) 3402, 3056, 2925, 2862, 1500, 1183, 745 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, J = 7.8 Hz, 1H), 7.95 (s, 1H), 7.59 (d, J = 2.4 Hz, 1H), 7.38−7.44 (m, 2H), 7.35 (d, J = 8.7 Hz, 1H), 7.17−7.25 (m, 1H), 7.10 (dd, J = 8.7, 2.5 Hz, 1H), 6.76−6.87 (m, 3H), 6.66 (ddd, J = 8.1, 6.2, 2.4 Hz, 1H), 4.31−4.50 (m, 1H), 4.24 (t, J = 4.4 Hz, 2H), 4.07−4.22 (m, 2H), 3.59 (dd, J = 14.8, 5.6 Hz, 1H), 3.40−3.57 (m, 3H), 2.53 (d, J = 4.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.8, 144.4, 140.5, 135.5, 134.9, 126.1, 124.0, 123.3, 121.8, 120.4, 119.3, 118.3, 116.8, 115.5, 112.9, 111.5, 110.9, 104.9, 71.0, 68.5, 64.5, 54.8, 49.0. MS (EI) m/z (relative intensity): 374 (42) [M^+], 148 (100). HRMS (EI+) m/z calcd for $C_{23}H_{22}N_2O_3$ [M^+], 374.1630; found, 374.1621.

1-(9*H*-Carbazol-2-yloxy)-3-(3,4-dihydro-2*H*-1,4-benzoxazin-4-yl)-2-propanol (87). From **117a** and **118a**. Yield: 61%, beige solid. mp 172−174 °C. IR (film) 3402, 3053, 2930, 2870, 1602, 1502, 1097, 908, 725 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 11.08 (s, 1H), 7.98 (d, J = 8.0 Hz, 1H), 7.97 (d, J = 8.0 Hz, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.28 (ddd, J = 8.2, 7.2, 1.2 Hz, 1H), 7.18−7.05 (ddd, J = 8.0, 7.0, 1.0 Hz, 1H), 6.99 (d, J = 2.1 Hz, 1H), 6.81 (dd, J = 8.5, 2.2 Hz, 1H), 6.76 (dd, J = 8.1, 1.5 Hz, 1H), 6.71 (ddd, J = 8.1, 7.1, 1.5 Hz, 1H), 6.65 (dd, J = 7.9, 1.5 Hz, 1H), 6.47 (ddd, J = 7.8, 7.2, 1.5 Hz, 1H), 5.26 (s, 1H), 4.23−4.08 (m, 3H), 4.04 (d, J = 5.1 Hz, 2H), 3.56 (dd, J = 14.7, 4.9 Hz, 1H), 3.53−3.40 (m, 2H), 3.28 (dd, J = 14.7, 6.8 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 157.7, 143.4, 141.0, 139.7, 135.4, 124.1, 122.6, 121.3, 120.9, 119.2, 118.5, 116.4, 116.3, 115.8, 111.9, 110.6, 108.1, 95.3, 70.4, 66.8, 63.9, 54.0, 48.2. MS (EI) m/z (relative intensity): 374 (40) [M^+], 148 (100). HRMS (EI) calcd for $C_{23}H_{22}N_2O_3$ [M^+], 374.1630; found, 374.1613.

dx.doi.org/10.1021/jm401090a | J. Med. Chem. 2013, 56, 8626−8655

1-(3,4-Dihydro-2*H*-1,4-benzoxazin-4-yl)-3-(6-fluoro-9*H*-carbazol-2-yloxy)-2-propanol (88). From **117c** and **118a**. Yield: 86%, white solid. mp 180−181 °C. IR (film) 3392, 2917, 2850, 1605, 1502, 1163, 911, 738 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 11.12 (s, 1H), 7.98 (d, J = 8.6 Hz, 1H), 7.82 (dd, J = 9.5, 2.6 Hz, 1H), 7.40 (dd, J = 8.8, 4.5 Hz, 1H), 7.11 (ddd, J = 9.5, 9.4, 2.6 Hz, 1H), 6.98 (d, J = 2.1 Hz, 1H), 6.82 (dd, J = 8.6, 2.2 Hz, 1H), 6.76 (dd, J = 8.1, 1.4 Hz, 1H), 6.70 (ddd, J = 8.1, 7.6, 1.5 Hz, 1H), 6.65 (dd, J = 7.8, 1.5 Hz, 1H), 6.47 (ddd, J = 7.9, 7.8, 1.5 Hz, 1H), 5.24 (d, J = 4.8 Hz, 1H), 4.23−4.07 (m, 3H), 4.04 (d, J = 4.9 Hz, 2H), 3.55 (dd, J = 14.7, 4.8 Hz, 1H), 3.54−3.46 (m, 1H), 3.44−3.35 (m, 1H), 3.35−3.23 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 158.1, 156.5 (d, $^1J_{C-F}$ = 231 Hz), 143.4, 142.1, 136.1, 135.4, 123.2 (d, $^3J_{C-F}$ = 10 Hz), 121.4, 121.3, 116.4, 116.1 (d, $^4J_{C-F}$ = 4.0 Hz), 115.8, 111.9, 111.5 (d, $^2J_{C-F}$ = 27 Hz), 111.3 (d, $^3J_{C-F}$ = 12 Hz), 108.3, 104.9 (d, $^2J_{C-F}$ = 24 Hz), 95.3, 70.4, 66.8, 63.8, 54.0, 48.2. ^{19}F NMR (376 MHz, DMSO-d_6) δ −127.1. MS (EI) m/z (relative intensity): 392 (24%) [M^+], 148 (100%). HRMS (EI) calcd for $C_{23}H_{21}N_2O_3F$ [M^+], 392.1536; found, 392.1523.

1-(9*H*-Carbazol-4-yloxy)-3-[4-(2-methoxyphenyl)piperazin-1-yl]-2-propanol (89). From **103a** and **118c**. Yield: 87%, white solid. mp 88−89 °C. IR (film) 3406, 3273, 3060, 2943, 2828, 1502, 1240, 1098, 909, 751, 724 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, J = 7.9 Hz, 1H), 8.12 (s, 1H), 7.42−7.37 (m, 2H), 7.33 (t, J = 8.0 Hz, 1H), 7.29−7.21 (m, 1H), 7.08−6.92 (m, 4H), 6.88 (dd, J = 8.0, 1.1 Hz, 1H), 6.70 (d, J = 7.8 Hz, 1H), 4.43−4.31 (m, 2H), 4.29−4.22 (m, 1H), 3.88 (s, 3H), 3.16 (br s, 4 H), 3.02−2.91 (m, 2H), 2.86−2.79 (m, 2H), 2.79−2.68 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.4, 152.4, 141.3, 141.1, 138.9, 126.8, 125.1, 123.2, 123.1, 122.7, 121.2, 119.8, 118.4, 112.9, 111.4, 110.1, 103.9, 101.4, 70.5, 65.9, 61.3, 55.5, 53.8, 50.9. MS (EI) m/z (relative intensity): 431 (25) [M^+], 205 (100). HRMS (EI) calcd for $C_{26}H_{29}N_3O_3$ [M]$^+$, 431.2209; found, 431.2220.

1-(9*H*-Carbazol-4-yloxy)-3-(4-phenylpiperazin-1-yl]-2-propanol (90). From **103a** and **118d**. Yield: 97%, off-white solid. mp 75−77 °C. IR (film) 3405, 3295, 3056, 2940, 2824, 1598, 1505, 1449, 1094, 908, 752, 725 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, J = 7.9 Hz, 1H), 8.08 (s, 1H), 7.44−7.37 (m, 2H), 7.37−7.22 (m, 4H), 7.05 (d, J = 7.9 Hz, 1H), 7.01−6.92 (m, 2H), 6.89 (dd, J = 7.3, 7.2 Hz, 1H), 6.70 (d, J = 7.9 Hz, 1H), 4.43−4.30 (m, 2H), 4.31−4.21 (m, 1H), 3.57 (br s, 1H), 3.34−3.18 (m, 4H), 2.97−2.86 (m, 2H), 2.86−2.74 (m, 2H), 2.75−2.64 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.3, 151.3, 141.1, 138.9, 129.3, 126.8, 125.2, 123.1, 122.7, 120.0, 119.8, 116.3, 112.9, 110.2, 104.0, 101.4, 70.4, 66.0, 61.2, 53.6, 49.4. MS (EI) m/z (relative intensity): 401 (30) [M^+], 175 (100). HRMS (EI) calcd for $C_{25}H_{27}N_3O_2$ [M]$^+$, 401.2103; found, 401.2114.

***N*-[3-(9*H*-Carbazol-4-yloxy)-2-hydroxypropyl]-2-(2-methoxyphenoxy)aniline (92).** From **103a** and **118e**. Yield: 88%, white solid. mp 62−64 °C. IR (film) 3407, 3059, 2930, 1603, 1497, 1261, 1208, 725 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, J = 7.6 Hz, 1H), 8.08 (s, 1H), 7.46−7.36 (m, 2H), 7.32 (t, J = 8.0 Hz, 1H), 7.24 (ddd, J = 8.0, 6.5, 1.8 Hz, 1H), 7.12−7.05 (m, 2H), 7.04−6.98 (m, 1H), 6.99−6.91 (m, 3H), 6.88 (ddd, J = 8.0, 7.3, 1.5 Hz, 1H), 6.78 (dd, J = 8.0, 1.4 Hz, 1H), 6.72−6.66 (m, 1H), 6.64 (d, J = 8.0 Hz, 1H), 5.31 (br s, 1H), 4.53−4.43 (m, 1H), 4.31 (d, J = 5.2 Hz, 2H), 3.82 (s, 3H), 3.68 (dd, J = 13.4, 4.5 Hz, 1H), 3.53 (dd, J = 13.3, 7.3 Hz, 1H), 2.70 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.1, 150.9, 145.7, 144.9, 141.1, 139.4, 138.9, 126.8, 125.2, 124.4, 124.3, 123.0, 122.6, 121.2, 119.9, 119.7, 117.8, 117.7, 112.8, 112.2, 110.2, 104.2, 101.5, 70.1, 69.1, 56.1, 47.2. MS (EI) m/z (relative intensity): 454 (78) [M^+], 228 (100), 183 (40), 120 (25). HRMS (EI) calcd for $C_{28}H_{26}N_2O_4$ [M^+], 454.1893; found, 454.1885.

Preparation of 2-(9*H*-Carbazol-4-yloxy)-*N*-[2-(2-methoxyphenoxy)ethyl]acetamide (93). A mixture of amine **104a** (208 mg, 1.24 mmol) in dry THF (12 mL) was cooled in an ice bath and treated with Et_3N (0.34 mL, 2.4 mmol). After 15 min, acid **120**[52] (292 mg, 1.21 mmol), *N*-(3-diethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDC hydrochloride) (356 mg, 1.86 mmol), and 1-hydroxybenzotriazole hydrate (HOBT·H_2O) (280 mg, 1.8 mmol) were added sequentially, and the reaction mixture was stirred at room temperature for 3 h. It was partitioned between ethyl acetate and water, and the organic phase was separated and washed with saturated aqueous NH_4Cl and $NaHCO_3$, H_2O, and brine, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash chromatography over silica gel (ethyl acetate/hexanes) to afford 318 mg (67%) of **93** as a white solid. mp 155−156 °C. IR (film) 3425, 3292, 3053, 2937, 2827, 1671, 1502, 1256, 752, 722 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 11.29 (s, 1H), 8.28 (t, J = 5.5 Hz, 1H), 8.22 (d, J = 7.8 Hz, 1H), 7.45 (d, J = 8.1 Hz, 1H), 7.33 (t, J = 8.0 Hz, 1H), 7.26 (t, J = 8.0 Hz, 1H), 7.10 (d, J = 7.9 Hz, 1H), 7.06 (t, J = 8.0 Hz, 1H), 6.82−7.02 (m, 4H), 6.61 (d, J = 7.9 Hz, 1H), 4.76 (s, 2H), 4.05 (t, J = 5.8 Hz, 2H), 3.70 (s, 3H), 3.57 (q, J = 5.7 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.0, 154.0, 149.3, 147.8, 141.1, 138.9, 126.3, 124.6, 122.6, 121.4 (2C), 120.7, 118.5, 114.2, 112.4, 111.7, 110.3, 104.5, 100.8, 67.3, 67.2, 55.4, 38.2. MS (EI) m/z (relative intensity): 390 (64) [M^+], 267 (100), 196 (42), 154 (57). HRMS (EI) calcd for $C_{23}H_{22}N_2O_4$ [M^+], 390.1580; found, 390.1577.

Preparation of 2-(9*H*-Carbazol-4-yloxy)-*N*-[1-hydroxy-3-(2-methoxyphenoxy)propan-2-yl]acetamide (94). A solution of **118f**·HCl (354 mg, 1.51 mmol) in dry THF (20 mL) was cooled in an ice bath and treated with Et_3N (0.65 mL, 4.5 mmol). After 15 min, acid **120**[52] (365 mg, 1.51 mmol), EDC hydrochloride (435 mg, 2.26 mmol), and HOBT·H_2O (348 mg, 2.3 mmol) were added sequentially, and the reaction mixture was stirred at room temperature for 4 h. It was worked up and purified as in the preceding procedure to afford 481 mg (76%) of **94** as a white solid. mp 169−170 °C. IR (film) 3412, 3285, 3056, 2933, 1661, 1502, 1253, 1216, 1107, 722 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 11.27 (s, 1H), 8.21 (d, J = 7.8 Hz, 1H), 7.97 (d, J = 8.1 Hz, 1H), 7.45 (d, J = 8.1 Hz, 1H), 7.32 (t, J = 7.2 Hz, 1H), 7.27 (t, J = 8.0 Hz, 1H), 7.11 (d, J = 8.0 Hz, 1H), 7.08−7.00 (m, 2H), 6.83−7.00 (m, 3H), 6.64 (d, J = 7.9 Hz, 1H), 4.99 (t, J = 5.4 Hz, 1H), 4.77 (s, 2H), 4.28−4.16 (m, 1H), 4.15−4.00 (m, 2H), 3.70 (s, 3H), 3.69−3.63 (m, 1H), 3.63−3.55 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.6, 153.9, 149.3, 148.0, 141.1, 138.9, 126.3, 124.6, 122.5, 121.4, 121.3, 120.7, 118.6, 114.1, 112.6, 111.5, 110.4, 104.5, 100.9, 67.3, 67.2, 59.8, 55.6, 50.1. MS (EI) m/z (relative intensity): 420 (40) [M^+], 297 (100), 196 (42), 154 (44). HRMS (EI) calcd for $C_{24}H_{24}N_2O_5$ [M^+], 420.1685; found, 420.1667.

Preparation of 4-{[4-(2-Methoxyphenoxymethyl)-4,5-dihydro-1,3-oxazol-2-yl]methoxy}-9*H*-carbazole (91). A solution of **94** (75 mg, 0.18 mmol) in a 2:1 mixture of dichloromethane/THF (4 mL) was cooled to −78 °C and treated with diethylaminosulfur trifluoride[41] (DAST) (32 μL, 0.24 mmol). After 1 h, K_2CO_3 (38 mg, 0.26 mmol) was added, and the cold bath was removed. The reaction mixture was stirred at room temperature for 2 h, diluted with saturated aqueous $NaHCO_3$ solution, and extracted with dichloromethane. The combined organic extracts were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography over silica gel (ethyl acetate/hexanes) to afford 44 mg (62%) of **91** as a white solid. mp 152−154 °C. IR (film) 3402, 3062, 2936, 1669, 1606, 1583, 1500, 1452, 1252, 1117, 751, 722 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 11.28 (s, 1H), 8.22 (d, J = 7.8 Hz, 1H), 7.45 (d, J = 8.1 Hz, 1H), 7.34 (ddd, J = 8.2, 7.2, 1.2 Hz, 1H), 7.27 (t, J = 8.0 Hz, 1H), 7.10−7.15 (m, 1H), 7.11 (d, J = 7.7 Hz, 1H), 6.82−7.05 (m, 4H), 6.75 (d, J = 7.7 Hz, 1H), 5.02 (s, 2H), 4.43−4.62 (m, 2H), 4.27−4.35 (m, 1H), 4.09 (dd, J = 9.7, 4.4 Hz, 1H), 3.98 (dd, J = 9.7, 5.4 Hz, 1H), 3.75 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 163.8, 153.9, 149.3, 148.0, 141.1, 138.9, 126.3, 124.7, 122.5, 121.5, 121.4, 120.8, 118.6, 114.5, 112.7, 111, 110.4, 104.5, 100.8, 70.6, 69.9, 65.2, 62.3, 55.7. MS (EI) m/z (relative intensity): 402 (100) [M^+], 182 (38), 154 (72). HRMS (EI) calcd for $C_{24}H_{22}N_2O_4$ [M^+], 402.1580; found, 402.1560.

Preparation of 1-(4,6-Dibromo-9*H*-carbazol-3-yloxy)-3-{[2-(2-methoxyphenoxy)ethyl]amino}-2-propanol (97). Compound **97** was obtained from 4,6-dibromo-3-hydroxycarbazole (**96**) by treatment with epichlorohydrin followed by amine **104a** by the same procedure as employed for the preparation of **3**.[32] Yield: 42%, off-white solid. mp 141−143 °C. IR (KBr) 3458, 3378, 2922, 2834, 1507, 1452, 1253, 1222, 1186, 1121, 745 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.90 (d, J = 1.8 Hz, 1H), 8.22 (br s, 1H), 7.55 (dd, J = 8.6, 2.0 Hz, 1H), 7.31 (d, J = 8.7, 2.6 Hz, 1H), 7.30 (d, J = 8.7 Hz, 1H), 6.98−6.90 (m, 4H), 4.20−4.10 (m, 5H), 3.86 (s, 3H), 3.13 (dd, J = 5.8, 5.7 Hz, 2H), 2.99 (dd, J = 6.4, 4.7 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.9, 149.5, 148.4, 139.2, 136.3, 129.5, 125.5, 125.1, 121.8, 121.1, 115.2, 114.4, 112.1,

dx.doi.org/10.1021/jm401090a | J. Med. Chem. 2013, 56, 8626−8655

112.07, 112.02, 110.1, 110.0, 107.4, 74.1, 69.0, 68.6, 56.0, 51.7, 49.0. MS (CI) m/z (relative intensity): 566 (52) [M^+ ($^{81}Br_2$)], 564 (100) [M^+ ($^{81}Br^{79}Br$)], 562 (47) [M^+ ($^{79}Br_2$)], 487 (40), 485 (41), 407 (18), 224 (36). HRMS (EI) m/z calcd for $C_{24}H_{24}{}^{81}Br^{79}BrN_2O_4$ [M^+], 564.0082; found, 564.0099.

Preparation of 6-[(-(4,6-Dibromo-9*H*-carbazol-3-yloxy)-methyl]-4-[2-(2-methoxyphenoxy)ethyl]morpholin-3-one (98). Compound **98** was prepared from **97** by the same procedure as employed for the preparation of **17**. Yield: 34%, white solid. mp 208−209 °C. IR (KBr) 3430, 3277, 2926, 2875, 1634, 1504, 1290, 1255, 751 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 11.63 (s, 1H), 8.72 (d, J = 2.0 Hz, 1H), 7.59 (dd, J = 8.6, 2.0 Hz, 1H), 7.51 (d, J = 8.8 Hz, 1H), 7.50 (d, J = 8.8 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H), 7.02−6.83 (m, 4H), 4.28−4.10 (m, 7H), 3.72 (s, 3H), 3.85−3.61 (m, 4H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.9, 149.2, 148.3, 147.7, 139.3, 136.5, 128.6, 123.6, 121.4, 120.7, 120.4, 115.6, 113.8, 113.2, 112.3, 111.0, 110.0, 105.5, 104.4, 71.6, 71.0, 66.9, 66.4, 55.5, 49.0, 45.6. MS (EI) m/z (relative intensity): 482 (39), 480 (100), 478 (44). HRMS (EI) calcd for $C_{26}H_{24}{}^{81}Br^{79}BrN_2O_5$ [M^+], 604.0031; found, 604.0007.

Preparation of 7-Methoxy-5-methyl-2,3,4,5-tetrahydro-1,5-benzothiazepine (101). Thiapyrone **123**[40] (1.00 g, 5.15 mmol) was dissolved in TFA (5 mL). Trimethylsilyl azide (0.68 mL, 5.2 mmol) was added at room temperature, the mixture was stirred for 2 days, and the reaction was quenched with water and basified with NaOH. The mixture was extracted with dichloromethane, the combined organic phase was dried over Na_2SO_4, the solvent was evaporated under reduced pressure, and the residue was purified by flash chromatography over silica gel (ethyl acetate/hexanes) to afford lactams **124**[53] (260 mg, 24%) and **125**[54] (500 mg, 47%). Product **125** had the following properties: ^1H NMR (300 MHz, $CDCl_3$) δ 8.25 (br s, 1H), 7.50 (d, J = 8.5 Hz, 1H), 6.73 (dd, J = 8.5, 2.6 Hz, 1H), 6.67 (d, J = 2.6 Hz, 1H), 3.82 (s, 3H), 3.39 (t, J = 7.0 Hz, 2H), 2.62 (t, J = 6.9 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9, 161.0, 142.7, 136.4, 117.6, 112.1, 109.2, 55.6, 34.4, 33.6. MS (EI) m/z (relative intensity): 209 (100) [M^+], 154 (75). HRMS (EI) calcd for $C_{10}H_{11}NO_2S$ [M^+], 209.0511; found, 209.0507.

To lactam **125** (500 mg, 2.39 mmol) in dry THF/ether (15 mL, 1:1), $LiAlH_4$ (181 mg, 4.77 mmol) was added at 0 °C, and the mixture was then heated at 40 °C overnight. The reaction was carefully quenched with 0.5 mL of water and filtered through Celite. The solid was washed repeatedly with ether, the filtrate was evaporated, and the crude product was purified by flash chromatography over silica gel to give the corresponding amine (260 mg, 56%) as an oil that solidified upon standing. mp 71.5−72.5 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J = 8.5 Hz, 1H), 6.41 (dd, J = 8.5, 2.6 Hz, 1H), 6.34 (d, J = 2.6 Hz, 1H), 3.76 (s, 3H), 3.24−3.22 (m, 2H), 2.76−2.73 (m, 2H), 2.12−2.06 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.8, 153.3, 134.1, 117.0, 106.6, 105.9, 55.3, 47.7, 33.5, 32.1. MS (EI) m/z (relative intensity): 195 (97) [M^+], 166 (100). HRMS (EI) calcd for $C_{10}H_{13}NOS$ [M^+], 195.0718; found, 195.0710.

The above amine (250 mg, 1.28 mmol) was dissolved in 10 mL of methanol and 1.1 mL of 37% formaldehyde. Sodium cyanoborohydride (476 mg, 7.57 mmol) was added at room temperature, and the mixture was stirred for 30 min, during which the pH was maintained between 4 and 5 by the addition of a few drops of 1 N HCl. The solvent was removed under reduced pressure, and the residue was dissolved in dichloromethane, washed with water, and dried over Na_2SO_4. The solvent was evaporated, and the residue was purified by flash chromatography over silica gel (ether/pentane) to afford 245 mg (91%) of **101**, colorless oil. IR 2933, 2822, 1593, 1555, 1478, 1107, 1074, 1032 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.33 (d, J = 8.4 Hz, 1H), 6.50 (d, J = 2.6 Hz, 1H), 6.40 (dd, J = 8.4, 2.6 Hz, 1H), 3.78 (s, 3H), 3.17−3.13 (m, 2H), 2.91 (s, 3H), 2.78−2.74 (m, 2H), 2.07−2.00 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.9, 155.1, 133.7, 117.9, 105.3, 104.4, 55.6, 55.2, 42.6, 30.5, 30.3. MS (EI) m/z (relative intensity): 209 (77) [M^+], 180 (100). HRMS (EI) calcd for $C_{11}H_{15}NOS$ [M^+], 209.0874; found, 209.0875.

Bioassay: Single-cell Ca^{2+} Imaging of HEK293 Cells. Stable, inducible HEK293 cells expressing a CPVT-causing RyR2 mutant, R4496C, display robust spontaneous Ca^{2+} oscillations (SOICR), but parental HEK293 cells do not.[55,56] These RyR2-R4496C cells were used to assess the impact of carvedilol, carvedilol analogues, beta-blockers, and other compounds on SOICR. SOICR was measured using single-cell Ca^{2+} imaging and the fluorescent Ca^{2+} indicator dye fura-2/AM (Invitrogen) as described previously[55,56] Briefly, cells grown on glass coverslips for 18−22 h after induction by 1 μg/mL of tetracycline were loaded with 5 μM fura 2/AM in KRH (Krebs−Ringer−Hepes) buffer (125 mM NaCl, 5 mM KCl, 1.2 mM KH_2PO_4, 6 mM glucose, 1.2 mM $MgCl_2$, and 25 mM Hepes, pH 7.4) plus 0.02% pluronic F-127 and 0.1 mg/mL BSA for 20 min at room temperature (23 °C). The coverslips were then mounted in a perfusion chamber (Warner Instruments) on an inverted microscope (Nikon TE2000-S). The Ca^{2+} concentration was then stepped to 0.5 mM for 5 min before increasing to 1 mM. The cells were continuously perfused with KRH buffer containing 1 mM $CaCl_2$ and different drugs for 8−10 min. Caffeine (10 mM) was applied at the end of each experiment to confirm the expression of active RyR2 channels. Time-lapse images (0.25 frame/s) were captured and analyzed with the Compix Simple PCI 6 software (Compix Inc.). Fluorescence intensities were measured from regions of interest centered on individual cells. Only cells that responded to caffeine were used in analyses. All chemicals were obtained from Sigma unless otherwise specified.

■ ASSOCIATED CONTENT

Supporting Information

Elemental analyses of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Tel.: 1-403-220-6256. E-mail: tgback@ucalgary.ca.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by a grant (R01HL75210) from the U.S. National Institutes of Health to S.R.W.C. and T.G.B. and by the Heart and Stroke Foundation/Libin Cardiovascular Institute Professorship in Cardiovascular Research to S.R.W.C. We thank the King family and the Libin Cardiovascular Institute of Alberta for their generous donations.

■ ABBREVIATIONS USED

SOICR, store-overload-induced calcium release; RyR, ryanodine receptor; DAD, delayed after-polarization; CPVT, catecholaminergic polymorphic ventricular tachycardia; EDC, *N*-(3-diethylaminopropyl)-*N*′-ethylcarbodiimide; HOBT·H_2O, 1-hydroxybenzotriazole hydrate; DAST, diethylaminosulfur trifluoride; TBDPS, *t*-butyldiphenylsilyl

■ REFERENCES

(1) Waldo, A. L.; Camm, A. J.; deRuyter, H.; Friedman, P. L.; MacNeil, D. J.; Pauls, J. F.; Pitt, B.; Pratt, C. M.; Schwartz, P. J.; Veltri, E. P. Effect of *d*-sotalol on mortality in patients with left ventricular dysfunction after recent and remote myocardial infarction. The SWORD investigators. Survival with oral d-sotalol. *Lancet* **1996**, *348*, 7−12.

(2) Miller, L. W. Limitations of current medical therapies for the treatment of heart failure. *Rev. Cardiovasc. Med.* **2003**, *4*, S21−S29.

(3) Kamath, G. S.; Mittal, S. The role of antiarrhythmic drug therapy for the prevention of sudden cardiac death. *Prog. Cardiovasc. Dis.* **2008**, *50*, 439−448.

(4) Bers, D. M. Calcium and cardiac rhythms: Physiological and pathophysiological. *Circ. Res.* **2002**, *90*, 14−17.

(5) Pogwizd, S. M.; Bers, D. M. Cellular basis of triggered arrhythmias in heart failure. *Trends Cardiovasc. Med.* **2004**, *14*, 61−66.

(6) Engelhardt, S.; Hein, L.; Dyachenkow, V.; Kranias, E. G.; Isenberg, G.; Lohse, M. J. Altered calcium handling is critically involved in the cardiotoxic effects of chronic β-adrenergic stimulation. *Circulation* **2004**, *109*, 1154−1160.

(7) Jiang, D.; Xiao, B.; Yang, D.; Wang, R.; Choi, P.; Zhang, L.; Cheng, H.; Chen, S. R. W. RyR2 mutations linked to ventricular tachycardia and sudden death reduce the threshold for store-overload-induced Ca^{2+} release (SOICR). *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 13062−13067.
(8) Jiang, D.; Wang, R.; Xiao, B.; Kong, H.; Hunt, D. J.; Choi, P.; Zhang, L.; Chen, S. R. W. Enhanced store overload-induced Ca^{2+} release and channel sensitivity to luminal Ca^{2+} activation are common defects of RyR2 mutations linked to ventricular tachycardia and sudden death. *Circ. Res.* **2005**, *97*, 1173−1181.
(9) Cerrone, M.; Colombi, B.; Santoro, M.; Raffaele di Barletta, M.; Scelsi, M.; Villani, L.; Napolitano, C.; Priori, S. G. Bidirectional ventricular tachycardia and fibrillation elicited in a knock-in mouse model carrier of a mutation in the cardiac ryanodine receptor. *Circ. Res.* **2005**, *96*, e77−e82.
(10) Liu, N.; Colombi, B.; Memmi, M.; Zissimopoulos, S.; Rizzi, N.; Negri, S.; Imbriani, M.; Napolitano, C.; Lai, F. A.; Priori, S. G. Arrhythmogenesis in catecholaminergic polymorphic ventricular tachycardia: Insights from a RyR2 R4496C knock-in mouse model. *Circ. Res.* **2006**, *99*, 292−298.
(11) Cerrone, M.; Noujaim, S. F.; Tolkacheva, E. G.; Talkachou, A.; O'Connell, R.; Berenfeld, O.; Anumonwo, J.; Pandit, S. V.; Vikstrom, K.; Napolitano, C.; Priori, S. G.; Jalife, J. Arrhythmogenic mechanisms in a mouse model of catecholaminergic polymorphic ventricular tachycardia. *Circ. Res.* **2007**, *101*, 1039−1048.
(12) Paavola, J.; Viitasalo, M.; Laitinen-Forsblom, P. J.; Pasternack, M.; Swan, H.; Tikkanen, I.; Toivonen, L.; Kontula, K.; Laine, M. Mutant ryanodine receptors in catecholaminergic polymorphic ventricular tachycardia generate delayed afterdepolarizations due to increased propensity to Ca^{2+} waves. *Eur. Heart J.* **2007**, *28*, 1135−1142.
(13) Kannankeril, P. J.; Mitchell, B. M.; Goonasekera, S. A.; Chelu, M. G.; Zhang, W.; Sood, S.; Kearney, D. L.; Danila, C. I.; De Biasi, M.; Wehrens, X. H. T.; Pautler, R. G.; Roden, D. M.; Taffet, G. E.; Dirksen, R. T.; Anderson, M. E.; Hamilton, S. L. Mice with the R176Q cardiac ryanodine receptor mutation exhibit catecholamine-induced ventricular tachycardia and cardiomyopathy. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 12179−12184.
(14) Uchinoumi, H.; Yano, M.; Suetomi, T.; Ono, M.; Xu, X.; Tateishi, H.; Oda, T.; Okuda, S.; Doi, M.; Kobayashi, S.; Yamamoto, T.; Ikeda, Y.; Ohkusa, T.; Ikemoto, N.; Matsuzaki, M. Catecholaminergic polymorphic ventricular tachycardia is caused by mutation-linked defective conformational regulation of the ryanodine receptor. *Circ. Res.* **2010**, *106*, 1413−1424.
(15) Kass, R. S.; Tsien, R. W. Fluctuations in membrane current driven by intracellular calcium in cardiac Purkinje fibers. *Biophys. J.* **1982**, *38*, 259−269.
(16) Orchard, C. H.; Eisner, D. A.; Allen, D. G. Oscillations of intracellular Ca^{2+} in mammalian cardiac muscle. *Nature* **1983**, *304*, 735−738.
(17) Stern, M. D.; Kort, A. A.; Bhatnagar, G. M.; Lakatta, E. G. Scattered-light intensity fluctuations in diastolic rat cardiac muscle caused by spontaneous Ca^{+2}-dependent cellular mechanical oscillations. *J. Gen. Physiol.* **1983**, *82*, 119−153.
(18) Wier, W. G.; Kort, A. A.; Stern, M. D.; Lakatta, E. G.; Marban, E. Cellular calcium fluctuations in mammalian heart: Direct evidence from noise analysis of aequorin signals in Purkinje fibers. *Proc. Natl. Acad. Sci. U.S.A.* **1983**, *80*, 7367−7371.
(19) Marban, E.; Robinson, S. W.; Wier, W. G. Mechanisms of arrhythmogenic delayed and early afterdepolarizations in ferret ventricular muscle. *J. Clin. Invest.* **1986**, *78*, 1185−1192.
(20) Schlotthauer, K.; Bers, D. M. Sarcoplasmic reticulum Ca^{2+} release causes myocyte depolarization. Underlying mechanism and threshold for triggered action potentials. *Circ. Res.* **2000**, *87*, 774−780.
(21) Xie, L.-H.; Weiss, J. N. Arrhythmogenic consequences of intracellular calcium waves. *Am. J. Physiol.: Heart Circ. Physiol.* **2009**, *297*, 997−1002.
(22) Vermeulen, J. T.; McGuire, M. A.; Opthof, T.; Coronel, R.; de Bakker, J. M; Klopping, C.; Janse, M. J. Triggered activity and automaticity in ventricular trabeculae of failing human and rabbit hearts. *Cardiovasc. Res.* **1994**, *28*, 1547−1554.
(23) Shannon, T. R.; Pogwizd, S. M.; Bers, D. M. Elevated sarcoplasmic reticulum Ca^{2+} leak in intact ventricular myocytes from rabbits in heart failure. *Circ. Res.* **2003**, *93*, 592−594.
(24) (a) Hieble, J. P.; Bondinell, W.; Ruffolo, R. R., Jr. α- and β-Adrenoceptors: From the gene to the clinic. 1. Molecular biology and adrenoceptor subclassification. *J. Med. Chem.* **1995**, *38*, 3415−3444. (b) Ruffolo, R. R., Jr.; Bondinell, W.; Hieble, J. P. α- and β-Adrenoceptors: From the gene to the clinic. 2. Structure-activity relationships and therapeutic applications. *J. Med. Chem.* **1995**, *38*, 3681−3716.
(25) (a) Mochizuki, M.; Yano, M.; Oda, T.; Tateishi, H.; Kobayashi, S.; Yamamoto, T.; Ikeda, Y.; Ohkusa, T.; Ikemoto, N.; Matsuzaki, M. Scavenging free radicals by low-dose carvedilol prevents redox-dependent Ca^{2+} leak via stabilization of ryanodine receptor in heart failure. *J. Am. Coll. Cardiol.* **2007**, *49*, 1722−1732. (b) Nakamura, K.; Kusano, K.; Nakamura, Y.; Kakishita, M.; Ohta, K.; Nagase, S.; Yamamoto, M.; Miyaji, K.; Saito, H.; Morita, H.; Emori, T.; Matsubara, H.; Toyokuni, S.; Ohe, T. Carvedilol decreases elevated oxidative stress in human failing myocardium. *Circulation* **2002**, *105*, 2867−2871. (c) Kukin, M. L.; Kalman, J.; Charney, R. H.; Levy, D. K.; Buchholz-Varley, C.; Ocampo, O. N.; Eng, C. Prospective, randomized comparison of effect of long-term treatment with metoprolol or carvedilol on symptoms, exercise, ejection fraction, and oxidative stress in heart failure. *Circulation* **1999**, *99*, 2645−2651. (d) Yue, T. L.; Cheng, H. Y.; Lysko, P. G.; McKenna, P. J.; Feuerstein, R.; Gu, J. L.; Lysko, K. A.; Davis, L. L.; Feuerstein, G. Carvedilol, a new vasodilator and beta-adrenoceptor antagonist, is an antioxidant and free radical scavenger. *J. Pharmacol. Exp. Ther.* **1992**, *263*, 92−98.
(26) Kramer, J. H.; Weglicki, W. B. A hydroxylated analog of the β-adrenoceptor antagonist, carvedilol, affords exceptional antioxidant protection to postischemic rat hearts. *Free Radical Biol. Med.* **1996**, *21*, 813−825.
(27) Poole-Wilson, P. A.; Swedberg, K.; Cleland, J. G. F.; Di Lenarda, A.; Hanrath, P.; Komajda, M.; Lubsen, J.; Lutiger, B.; Metra, M.; Remme, W. J.; Torp-Pedersen, C.; Scherhag, A.; Skene, A. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol or Metoprolol European Trial (COMET): Randomised controlled trial. *Lancet* **2003**, *362*, 7−13.
(28) Stroe, A. F.; Gheorghiade, M. Carvedilol: Beta-blockade and beyond. *Rev. Cardiovasc. Med.* **2004**, *5*, S18−S27.
(29) Greenberg, B. Nonselective versus selective beta-blockers in the management of chronic heart failure: Clinical implications of the Carvedilol or Metoprolol European Trial. *Rev. Cardiovasc. Med.* **2004**, *5*, S10−S17.
(30) Remme, W J. Which beta-blocker is most effective in heart failure? *Cardiovasc. Drugs Ther.* **2010**, *24*, 351−358.
(31) Ko, D. T.; Hebert, P. R.; Coffey, C. S.; Curtis, J. P.; Foody, J. M.; Sedrakyan, A.; Krumholz, H. M. Adverse effects of β-blocker therapy for patients with heart failure: A quantitative overview of randomized trials. *Arch. Intern. Med.* **2004**, *164*, 1389−1394.
(32) Zhou, Q.; Xiao, J.; Jiang, D.; Wang, R.; Vembaiyan, K.; Wang, A.; Smith, C. D; Xie, C.; Chen, W.; Zhang, J.; Tian, X.; Jones, P. P.; Zhong, X.; Guo, A.; Chen, H.; Zhang, L.; Zhu, W.; Yang, D.; Li, X.; Chen, J.; Gillis, A. M.; Duff, H. J.; Cheng, H.; Feldman, A. M.; Song, L.-S.; Fill, M.; Back, T. G.; Chen, S. R. W. Carvedilol and its new analogs suppress arrhythmogenic store overload-induced Ca^{2+} release. *Nat. Med.* **2011**, *17*, 1003−1010.
(33) Rosenbaum, D. M.; Cherezov, V.; Hanson, M. A.; Rasmussen, S. G. F.; Thian, F. S.; Kobilka, T. S.; Choi, H.-J.; Yao, X.-J.; Weis, W. I.; Stevens, R. C.; Kobilka, B. K. GPCR engineering yields high-resolution structural insights into β_2-adrenegic receptor function. *Science* **2007**, *318*, 1266−1273.
(34) Back, T. G.; Yang, K.; Krouse, H. R. Desulfurization of benzo- and dibenzothiophenes with nickel boride. *J. Org. Chem.* **1992**, *57*, 1986−1990.
(35) (a) Sheehan, J. C.; Cruickshank, P. A.; Boshart, G. L. A convenient synthesis of water-soluble carbodiimides. *J. Org. Chem.* **1961**, *26*, 2525−2528. (b) Windridge, G.; Jorgensen, E. C. 1-Hydroxybenzotriazole as a

racemization-suppressing reagent for the incorporation of Im-benzyl-L-histidine into peptides. *J. Am. Chem. Soc.* **1971**, *17*, 6318−6319.
(36) Phillips, A. J.; Uto, Y.; Wipf, P.; Reno, M. J.; Williams, D. R. Synthesis of functionalized oxazolines and oxazoles with DAST and deoxo-fluor. *Org. Lett.* **2000**, *2*, 1165−1168.
(37) Takahashi, Y.; Furukawa, K.-I.; Kozutsumi, D.; Ishibashi, M.; Kobayashi, J.; Ohizumi, Y. 4,6-Dibromo-3-hydroxycarbazole (an analogue of caffeine-Like Ca^{2+} releaser), a novel type of inhibitor of Ca^{2+}-induced Ca^{2+} release in skeletal muscle sarcoplasmic reticulum. *Br. J. Pharmacol.* **1995**, *114*, 941−948.
(38) (a) Lehnart, S. E.; Mongillo, M.; Bellinger, A.; Lindegger, N.; Chen, B.-X.; Hsueh, W.; Reiken, S.; Wronska, A.; Drew, L. J.; Ward, C. W.; Lederer, W. J.; Kass, R. S.; Morley, G.; Marks, A. R. Leaky Ca^{2+} release channel/ryanodine receptor 2 causes seizures and sudden cardiac death in mice. *J. Clin. Invest.* **2008**, *118*, 2230−2245. (b) Bellinger, A. M.; Reiken, S.; Dura, M.; Murphy, P. W.; Deng, S.-X.; Landry, D. W.; Nieman, D.; Lehnart, S. E.; Samaru, M.; LaCampagne, A.; Marks, A. R. Remodeling of ryanodine receptor complex causes "leaky" channels: A molecular mechanism for decreased exercise capacity. *Proc. Natl. Acad. Sci. U.S.A.* **2008**, *105*, 2198−2202.
(39) Wehrens, X. H. T.; Lehnart, S. E.; Reiken, S. R.; Deng, S.-X.; Vest, J. A.; Cervantes, D.; Coromilas, J.; Landry, D. W.; Marks, A. R. Protection from cardiac arrhythmia through ryanodine receptor-stabilizing protein calstabin2. *Science* **2004**, *304*, 292−296.
(40) Krollpfeiffer, F.; Schultze, H.; Schlumbohm, E.; Sommermeyer, E. Ober thiochromanone und umwandlungsgrodukte (II). *Ber. Dtsch. Chem. Ges.* **1925**, *58B*, 1654−76.
(41) (a) Senderoff, S. G.; Villani, A. J.; Landvatter, S. W.; Garnes, K. T.; Heys, J. R. Synthesis of the enantiomers and three racemic metabolites of carvedilol labeled to high specific activity with tritium. *J. Labelled Compd. Radiopharm.* **1993**, *33*, 1091−1105. (b) Schaefer, W. H.; Politowski, J.; Hwang, B.; Dixon, F., Jr.; Goalwin, A.; Gutzait, L.; Anderson, K.; Debrosse, C.; Bean, M.; Rhodes, G. R. Metabolism of carvedilol in dogs, rats, and mice. *Drug Metab. Dispos.* **1998**, *26*, 958−969. (c) Senthilkumar, N.; Somannavar, Y. S.; Reddy, S. B.; Sinha, B. K.; Narayan, G. K. A. S. S.; Dandala, R.; Mukkanti, K. Synthesis of active metabolites of carvedilol, an antihypertensive drug. *Synth. Commun.* **2011**, *41*, 268−276. (d) Reiff, K. High-performance liquid chromatographic method for the determination of carvedilol and its desmethyl metabolite in body fluids. *J. Chromatogr., B: Biomed. Sci. Appl.* **1987**, *413*, 355−362.
(42) Butler, S.; Wang, R.; Wunder, S. L.; Cheng, H.-Y.; Randall, C. S. Perturbing effects of carvedilol on a model membrane system: role of lipophilicity and chemical structure. *Biophys. Chem.* **2006**, *119*, 307−315.
(43) Chen, S. R. W; Back, T. G.; Jiang, D.; Vembaiyan, K. Preparation of carbazoles as ryanodine receptor type 2 (RyR2) antagonists for treatment of cardiac conditions. U.S. Patent US 20070254849, 2007.
(44) Strein, K.; Sponer, G.; Mueller-Beckmann, B.; Bartsch, W. Pharmacological profile of carvedilol, a compound with [beta]-blocking and vasodilating properties. *J. Cardiovasc. Pharmacol.* **1987**, *10*, S33−S41.
(45) Wiedemann, F.; Kampe, W.; Thiel, M.; Sponer, G.; Roesch, E.; Dietmann, K. Carbazolyl-4-oxypropanolamine derivatives. Patent DE 19792815926, 1979.
(46) Pittelkow, T.; Fischer, E.; Treppendahl, S. P. Process and intermediates for the preparation of 1-(9H-carbazol-4-yloxy)-3-[2-(2-methoxyphenoxy)ethylamino]propan-2-ol (carvedilol) or acid addition salts thereof. *PCT International Patent* WO2001087837, 2001.
(47) Kumar, B. A.; Ashrafuddin, M.; Rajesh, V.; Parveen, S.; Madhusudhan, G. Convenient synthesis of carvedilol utilizing 3-(9H-carbazol-4-yloxy)-1-chloropropan-2-yl phenyl carbonate as a key intermediate. *Indian J. Chem., Sect. B* **2012**, *51B*, 780−784.
(48) Ramadoss, S.; Jaggi, M.; Dixit, G.; Sharma, A. K. Novel carvedilol derivatives and their use in treatment of cancer. *Indian Patent* IN 2001DE00001, 2005.
(49) Gao, F.; Yan, X.; Zahr, O.; Larsen, A.; Vong, K.; Auclair, K. Synthesis and use of sulfonamide-, sulfoxide-, or sulfone-containing aminoglycoside−CoA bisubstrates as mechanistic probes for aminoglycoside N-6′-acetyltransferase. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5518−5522.
(50) Yuan, C.; Lei, X.; Liu, Y.; Su, X. Liniment for lowering hypertension and its application. Faming Zhuanli Shenqing Gongkai Shuomingshu, Chinese Patent CN 1457787, 2003.
(51) (a) Groszek, G.; Bednarski, M.; Dybala, M.; Filipek, B. Synthesis and adrenolytic activity of 1-(1*H*-indol-4-yloxy)-3-{[2-(2-methoxyphenoxy)ethyl]amino}propan-2-ol and its enantiomers. *Eur. J. Med. Chem.* **2009**, *44*, 809−817. (b) Bednarski, M.; Filipek, B.; Groszek, G.; Maciag, D. Preparation of new derivative of 2-aminopropanol and its salt. *Pol. Patent* PL 195413, 2007.
(52) Neugebauer, G.; Neubert, P. Metabolism of carvedilol in man. *Eur. J. Drug Metab. Pharmacokinet.* **1991**, *16*, 257−260.
(53) Marks, A. R.; Landry, D. W.; Deng, S. X.; Cheng, Z. Z. Novel anti-arrhythmic and heart failure drugs that target the leak in the ryanodine receptor (ryr2). *U.S. Patent* US 20050215540, 2005.
(54) Ambrogi, V.; Grandolini, G. A convenient one-pot synthesis of 2,3-dihydro-1,5-benzothiazepin-4(5H)-ones. *Synthesis* **1987**, 724−726.
(55) Jiang, D.; Xiao, B.; Yang, D.; Wang, R.; Choi, P.; Zhang, L.; Cheng, H.; Chen, S. R. W. RyR2 mutations linked to ventricular tachycardia and sudden death reduce the threshold for store-overload-induced Ca^{2+} release (SOICR). *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 13062−13067.
(56) Jiang, D.; Wang, R.; Xiao, B.; Kong, H.; Hunt, D. J.; Choi, P.; Zhang, L.; Chen, S. R. W. Enhanced store overload-induced Ca^{2+} release and channel sensitivity to luminal Ca^{2+} activation are common defects of RyR2 mutations linked to ventricular tachycardia and sudden death. *Circ. Res.* **2005**, *97*, 1173−1181.