Inhibitors of Acyl-CoA:Cholesterol *O*-Acyltransferase. 2. Identification and Structure−Activity Relationships of a Novel Series of *N*-Alkyl-*N*-(heteroaryl-substituted benzyl)-*N*′-arylureas[1]

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A series of *N*-alkyl-*N*-(heteroaryl-substituted benzyl)-*N*′-arylurea and related derivatives represented by **2** and **3** have been prepared and evaluated for their ability to inhibit acyl-CoA: cholesterol *O*-acyltransferase in vitro and to lower plasma cholesterol levels in cholesterol-fed rats in vivo. Among these novel compounds, the type **3** series was superior. A pyrazol-3-yl group on the *N*-benzyl group of this trisubstituted urea (i.e. **3**, Ar_1 = pyrazol-3-yl) was identified as a heteroaromatic ring providing a good profile of biological activity. As a result of optimization of the combination with the *N*-alkyl group (R) and *N*-aryl group (Ar_3), compound **3aq** (FR186054) was identified as a new, orally efficacious ACAT inhibitor, which exhibited potent in vitro ACAT inhibitory activity (rabbit intestinal microsomes IC_{50} = 99 nM) and excellent hypocholesterolemic effects in cholesterol-fed rats, irrespective of administration mode (ED_{50} = 0.046 mg/kg dosed via the diet, ED_{50} = 0.44 mg/kg administered by gavage in PEG400 vehicle). Moreover, a toxicological study revealed compound **3aq** to be nontoxic to the adrenal glands of dogs when tested at a single dose of 10 mg/kg po.

Introduction

Since the pioneering results of the Framingham study were disclosed in 1971,[2] hypercholesterolemia has become well-known as one of the major risk factors for the development of coronary heart disease (CHD).[3] Considerable efforts have been directed toward the development of therapeutic agents to control plasma cholesterol levels.[4] Acyl-CoA:cholesterol *O*-acyltransferase (ACAT, EC 2.3.1.26)[5] is an intracellular enzyme responsible for catalyzing the esterification of free cholesterol with fatty acyl-CoA to produce cholesteryl esters. This enzyme plays an important role in the absorption of dietary cholesterol, the secretion of hepatic very low density lipoprotein (VLDL), and the accumulation of cholesteryl esters in arterial lesions. Inhibition of ACAT would be expected to reduce the absorption of cholesterol, lower serum lipid levels,[6] and arrest progression and promote regression of atherosclerotic plaques.[7] Therefore, ACAT inhibitors are very attractive targets for development of new treatments for hypercholesterolemia and atherosclerosis.[8]

In recent years, a number of classes of compounds have been shown to inhibit ACAT-catalyzed cholesterol esterification.[9] These include *N*-alkyl-*N*-benzyl-*N*′-phenylurea derivatives[10] such as CL 277,082[10a] which has been the subject of various animal and human studies (Figure 1).[11] However, despite intensive research attention on ACAT inhibitors, their hypocholesterolemic effects in human trials, including CL 277,082, have proved disappointing.[11c,12] As part of our research program directed at the development of potent ACAT inhibitors that are particularly effective in in vivo models of hypercholesterolemia, we have recently investigated and reported on a novel series of *N*-alkyl-*N*-(biphenylylmethyl)-*N*′-arylurea derivatives represented by **1** as a series related to CL 277,082.[13] From this series, FR182980 was identified as a potent ACAT inhibitor in vitro and an efficacious hypocholesterolemic agent in vivo. Due to the encouraging biological results, we have continued our efforts to develop novel ACAT inhibitors and opted to design, prepare, and evaluate the novel series of *N*-alkyl-*N*-(heteroaryl-substituted benzyl)-*N*′-arylureas and related derivatives represented by **2** and **3**, replacing one of the phenyl rings of the biphenyl moiety of **1** by a heteroaromatic ring as heterocyclic isosteres of **1**, since heterocyclic replacement might be expected to improve physicochemical characteristics such as aqueous solubility and influence biological activity as well as toxicity. In this paper, we disclose the synthesis, biological properties, and full details of the structure−activity relationships of this novel series of ACAT inhibitors.

Chemistry

The basic synthetic route to the novel trisubstituted urea compounds **2a**−**g** and **3a**−**bg** prepared in this work is summarized in Scheme 1 and Table 1. Reductive amination of benzaldehydes **4a**−**af** or benzylamine **5** with various alkylamines or carbonyl compounds (methods A and B) or monoalkylation of various amines with benzyl bromides **6a**−**c** (method C) provided the key

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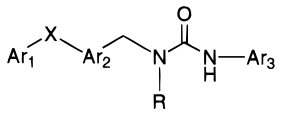
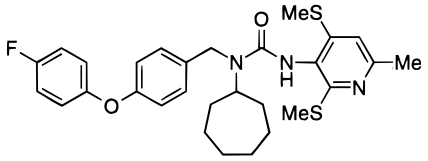
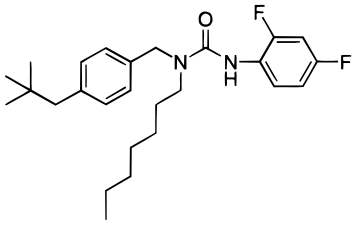


1, $Ar_1 = Ar_2 = Ph$, X = bond, O, S, etc.
2, $Ar_1 = Ph$, Ar_2 = Heteroaryl, X = bond
3, Ar_1 = Heteroaryl, $Ar_2 = Ph$, X = bond



FR182980



CL 277,082

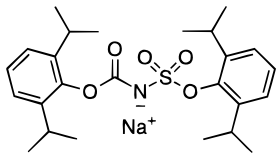


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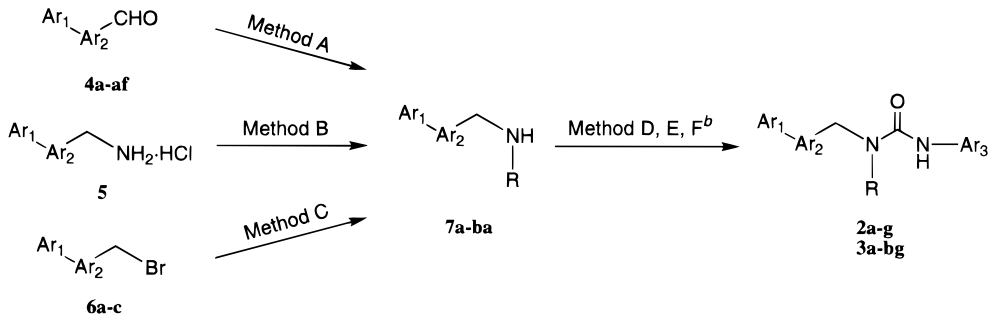
Figure 1. ACAT inhibitors.

Scheme 1. Preparation of Target Molecules[a]



[a] Reagents: Method A; (1) RNH_2; (2) $NaBH_4$, EtOH; Method B; (1) NaOH(aq), CH_2Cl_2; (2) carbonyl compound; (3) $NaBH_4$, EtOH; Method C; RNH_2; Method D; 2,4,6-Me_3PhNCO, CH_2Cl_2; Method E, 2,4,6-F_3PhNH_2, triphosgene, Et_3N, CH_2Cl_2; Method F; phenyl *N*-arylcarbamate, Et_3N, toluene. [b] When necessary, followed by a deprotection step; TFA, anisole or concentrated HCl, MeOH.

intermediate secondary amines **7a**−**ba**. Elaboration to the final hypocholesterolemic agents **2a**−**g** and **3a**−**bg** was performed by one of three methods: (1) treatment with 2,4,6-trimethylphenyl isocyanate (method D), (2) reaction with 2,4,6-trifluoroaniline utilizing triphosgene activation (method E), or (3) treatment with a phenyl *N*-arylcarbamate[13] (method F). For the syntheses of **3n**, **3o**, and **3ae**, deprotection of the *N*-trityl group was carried out with TFA−anisole or concentrated HCl in MeOH after urea formation.

The various benzaldehyde derivatives **4a**−**af** were prepared by several different methods as shown in Schemes 2−13. Phenylthiophenecarboxaldehydes **4a** and **4b** were synthesized by palladium-catalyzed cross-coupling reaction of the appropriate bromothiophenecarboxaldehyde **8a** or **8b** with phenylboric acid under modified Suzuki cross-coupling conditions.[14a] Phenylfurancarboxaldehyde **4c** was also prepared by a similar coupling reaction of bromofurancarboxaldehyde **10**, readily obtained from carboxylic acid **9** by amidation and $LiAlH_4$ reduction. Phenylpyridinecarboxaldehyde **4d** was prepared by the coupling reaction of methyl 6-chloronicotinate (**11**) with phenylboric acid followed by $LiAlH_4$ reduction and MnO_2 oxidation.

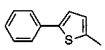
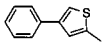
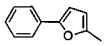
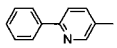
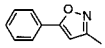
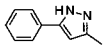
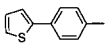
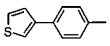
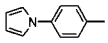
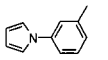
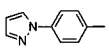
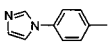
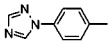
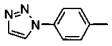
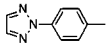
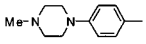
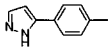
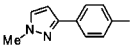
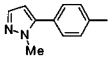
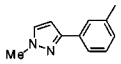
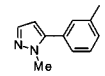
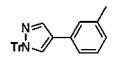
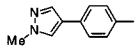
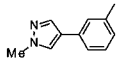
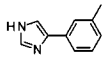
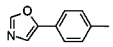
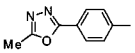
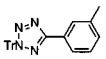
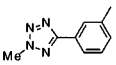
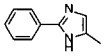
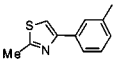
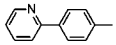
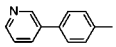
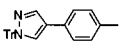
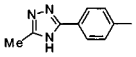
Isoxazole and pyrazole derivatives **4e**,**f** were prepared from acetophenone (**13**). Construction of the heteroaromatic ring was achieved by the reaction of diketo ester **14** with $NH_2OH{\cdot}HCl$ or $H_2NNH_2{\cdot}H_2O$, respectively. Subsequently, the ester function was transformed to aldehyde by reduction and oxidation (Scheme 3).

Thienylbenzaldehydes **4g**,**h** were prepared by Stille coupling reaction[15] of 4-bromobenzyl alcohol with the appropriate stannylthiophene **16a**,**b**, followed by MnO_2 oxidation (Scheme 4). (1*H*-Pyrrol-1-yl)benzaldehydes **4i**,**j** were obtained from the appropriate benzoic acid derivatives **18a**,**b**[16] by formation of the Weinreb amide and $LiAlH_4$ reduction to the aldehyde (Scheme 5).

Benzaldehyde derivatives with various heterocyclic substituents at the 4-position (**4k**−**o**,**p**) were prepared by the reaction of 4-fluorobenzaldehyde (**19**) with the appropriate azoles or 1-methylpiperazine in the presence of K_2CO_3. In the case of the reaction with 1,2,3-triazole, two regioisomers **4n**,**o** were obtained favoring **4n** (Scheme 6).

The synthetic routes to various pyrazolylbenzaldehydes are summarized in Schemes 7−9. (Pyrazol-3-yl)-benzaldehydes **4q**,**r** were prepared from ethyl 4-acetylbenzoate (**20a**) or 3-acetylbenzonitrile (**20b**) by treatment with *N*,*N*-dimethylformamide dimethyl acetal (simultaneous ester exchange occurred in the case of **20a**), followed by construction of the pyrazole ring with $H_2NNH_2{\cdot}H_2O$ and transformation of ester or nitrile functions by the usual methods. For the syntheses of **4s**−**v**, *N*-methylpyrazole ring systems were assembled by

Table 1. Structures and Synthetic Methods of Benzaldehydes (**4**), Benzylamines (**5**), Benzyl Bromides (**6**), and Secondary Amines (**7**)

no.	Ar_1-Ar_2-	R	Method
4a, 7a		c-C_7H_{13}	A
4b, 7b		c-C_7H_{13}	A
4c, 7c		c-C_7H_{13}	A
4d, 7d		c-C_7H_{13}	A
4e, 7e		c-C_7H_{13}	A
4f, 7f		c-C_7H_{13}	A
4g, 7g		c-C_7H_{13}	A
4h, 7h		c-C_7H_{13}	A
4i, 7i		c-C_7H_{13}	A
4j, 7j		c-C_7H_{13}	A
4k, 7k		c-C_7H_{13}	A
4l, 7l		c-C_7H_{13}	A
4m, 7m		c-C_7H_{13}	A
4n, 7n		c-C_7H_{13}	A
4o, 7o		c-C_7H_{13}	A
4p, 7p		c-C_7H_{13}	A
4q, 7q-r		c-C_7H_{13} (**7q**), Bn (**7r**)	A
4r, 7s-ab		c-C_7H_{13} (**7s**), c-C_6H_{11} (**7t**) c-C_5H_9 (**7u**), Bn (**7v**) 4-Me_2N-Bn (**7w**), 4-F-Bn (**7x**) 4-MeO-Bn (**7y**), 2-MeO-Bn (**7z**) 3-MeO-Bn (**7aa**), $PhCH_2CH_2$ (**7ab**)	A[a]
4s, 7ac-ad		c-C_7H_{13} (**7ac**), Bn (**7ad**)	A
4t, 7ae-af		c-C_7H_{13} (**7ae**), Bn (**7af**)	A
4u, 7ag-ah		c-C_7H_{13} (**7ag**), Bn (**7ah**)	A
4v, 7ai-aj		c-C_7H_{13} (**7ai**), Bn (**7aj**)	A
4w, 7ak		c-C_7H_{13} (**7ak**)	A
4x, 7al-am		c-C_7H_{13} (**7al**), Bn (**7am**)	A
4y, 7an-ao		c-C_7H_{13} (**7an**), Bn (**7ao**)	A
4z, 7ap		c-C_7H_{13}	A
4aa, 7aq		c-C_7H_{13}	A
4ab, 7ar		c-C_7H_{13}	A
4ac, 7as		c-C_7H_{13}	A
4ad, 7at		c-C_7H_{13}	A
4ae, 7au		c-C_7H_{13}	A
4af,[b] 7av		c-C_7H_{13}	A
5, 7aw		c-C_7H_{13}	B
6a, 7ax		c-C_7H_{13}	C
6b, 7ay		c-C_7H_{13}	C
6c, 7az		c-C_7H_{13}	C
7ba		c-C_7H_{13}	A

[a] In the case of **7w**, Et_3N was used to convert 4-(dimethylamino)benzylamine dihydrochloride to the free form. [b] Commercially available.

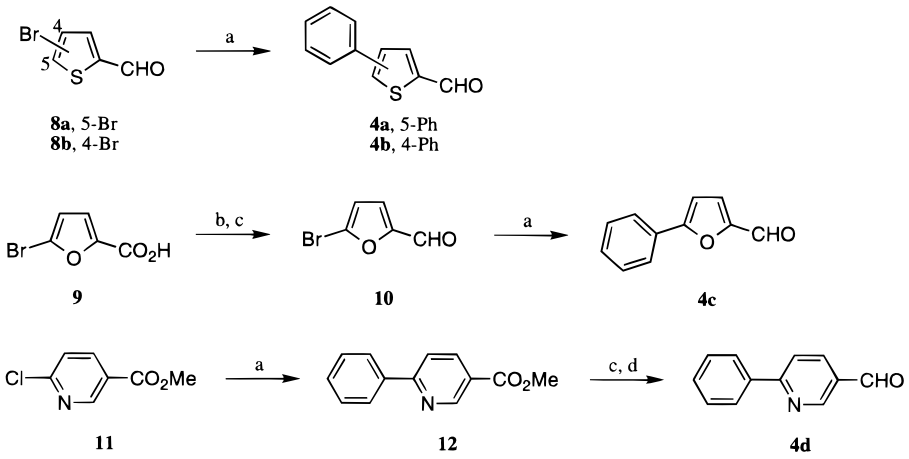
cyclization of **21a**,**b** with 1 equiv of $MeNHNH_2$ in AcOH to give chromatographically separable regioisomeric mixtures **23a**,**b** or **24a**,**b**. In both cases a 2:1 ratio was observed favoring **23a** or **24a**, respectively.[17] However, when the reaction was carried out with 1 equiv of $MeNHNH_2$ and AcOH in MeOH, in both cases the ratio was reversed to 1:4 favoring **23b** or **24b**. To obtain all isomers in synthetically useful amounts, we selected the former conditions. Transformation of ester or nitrile function to aldehyde gave *N*-methylpyrazolylbenzaldehydes **4s**−**v** (Scheme 7). 3-(1-Tritylpyrazol-4-yl)benzaldehyde (**4w**) was synthesized by Suzuki coupling reaction[14b,c] of 4-bromo-1-tritylpyrazole (**26**) and 3-formylphenylboric acid (**28**) which was obtained from bromobenzene derivative **27** (Scheme 8). (1-Methylpyrazol-4-yl)benzaldehydes **4x**,**y** were prepared by Stille coupling reaction of stannylpyrazole (**30**) which was readily obtained from 4-bromo-1-methylpyrazole (**29**)[18] and bromobenzaldehydes **31a**,**b** (Scheme 9).

Imidazolylbenzaldehyde **4z** was assembled from 3-acetylbenzonitrile (**20b**) via bromination and subsequent cyclization with $HCONH_2$, followed by conversion of the nitrile function to aldehyde (Scheme 10).

Oxazolylbenzaldehyde **4aa** was synthesized from methyl 4-formylbenzoate (**33**) by treatment with tosylmethyl isocyanide (TosMIC) to construct the oxazole ring, followed by transformation of the ester function to aldehyde (Scheme 11).

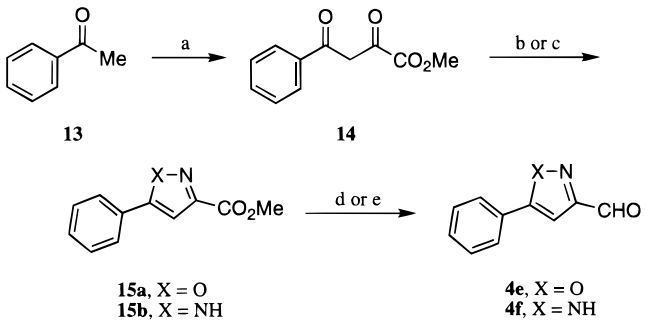
The synthetic route to (1,3,4-oxadiazol-2-yl)benzaldehyde **4ab** and 1,2,4-triazole compound **7ba** is depicted in Scheme 12. Methyl 4-formylbenzoate (**33**) was converted to hydrazide **35** in three steps and was then treated with ethyl acetimidate hydrochloride followed by thermal cyclization to provide 1,3,4-oxadiazole com-

Scheme 2[a]



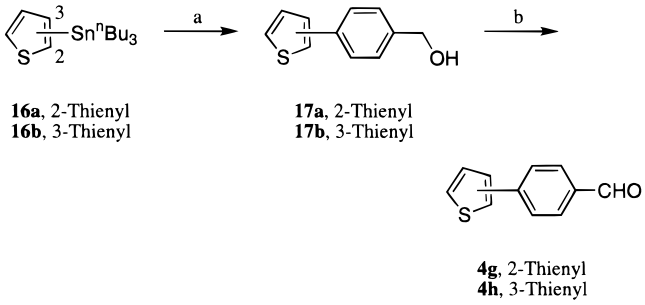
[a] Reagents: (a) $PhB(OH)_2$, $Pd(PPh_3)_4$, 2 M Na_2CO_3, DME; (b) Me(MeO)NH·HCl, HOBt, WSC, CH_2Cl_2; (c) $LiAlH_4$, THF; (d) MnO_2, $CHCl_3$.

Scheme 3[a]



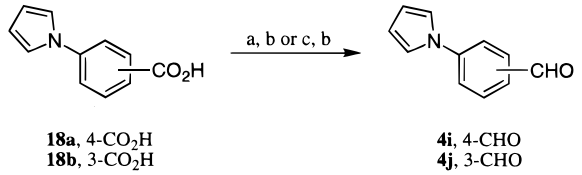
[a] Reagents: (a) $(CO_2Me)_2$, NaH, DMF; (b) NH_2OH·HCl, MeOH; (c) H_2NNH_2·H_2O, EtOH; (d) DIBAL, CH_2Cl_2; (e) (1) $LiAlH_4$, THF; (2) MnO_2, acetone.

Scheme 4[a]



[a] Reagents: (a) 4-$BrC_6H_4CH_2OH$, $Pd(PPh_3)_4$, xylene; (b) MnO_2, $CHCl_3$.

Scheme 5[a]



[a] Reagents: (a) Me(MeO)NH·HCl, WSC, CH_2Cl_2; (b) $LiAlH_4$, THF; (c) Me(MeO)NH·HCl, HOBt, WSC, CH_2Cl_2.

pound **36**. Subsequent desilylation and MnO_2 oxidation yielded (1,3,4-oxadiazolyl)benzaldehyde **4ab**. The 1,2,4-triazole ring system in amine **7ba** was prepared from a preexisting heterocyclic ring. Thus, 1,3,4-oxadiazole **36** was transformed to 4-benzyl-4*H*-1,2,4-triazole **37** by heating with benzylamine[19] and was then converted to benzaldehyde derivative **38**. Reductive amination and selective deprotection of the benzyl group on the triazole ring provided benzylamine **7ba**.

Tetrazolylbenzaldehydes **4ac**−**ae** were synthesized as shown in Scheme 13. 3-Cyanobenzoic acid **40** was esterified and treated with NaN_3 to provide methyl 3-(1*H*-tetrazol-5-yl)benzoate **41**. Subsequent transformation of the ester function to aldehyde followed by protection of the tetrazole moiety with a trityl group yielded **4ac**. Alkylation of **42** with MeI afforded a mixture of regioisomeric *N*-methyltetrazole compounds **4ad**,**ae** which were separated by column chromatography.[20]

2-Phenylimidazole-4-carboxaldehyde (**4af**) was commercially available.

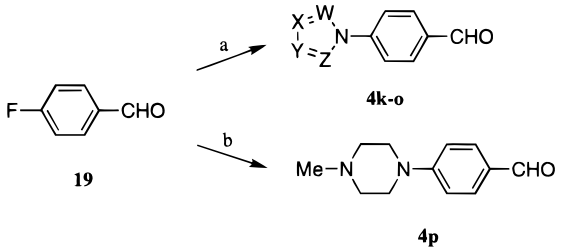
Thiazolylbenzylamine hydrochloride **5** was prepared from benzonitrile derivative **43** via conversion to methyl ketone **44**, bromination, construction of the thiazole ring with thioacetamide, and deacetylation (Scheme 14).

The syntheses of benzyl bromide derivatives bearing a heterocyclic ring **6a**−**c** were accomplished as shown in Scheme 15. Pyridylbenzyl bromides **6a**,**b** were obtained by bromination of the corresponding commercially available or known tolylpyridines **46a**,**b**[21] with NBS in the presence of a catalytic amount of benzoyl peroxide. Pyrazolylbenzyl bromide **6c** was prepared by coupling reaction of 4-methylphenylboric acid (**47**) and 4-bromo-1-tritylpyrazole (**26**) and subsequent bromination with NBS.

Results and Discussion

The compounds prepared were evaluated for their ability to inhibit intestinal ACAT in vitro by incubation with [1-^{14}C]oleoyl-CoA and the mucosal microsomes from the small intestine of cholesterol-fed rabbits according to the method of Heider et al.[22] with minor modifications.[13,23] In vivo hypocholesterolemic activity was assessed in cholesterol-fed rats by oral administration of the test compounds as a dietary admixture in a cholesterol-enriched diet.[13] The in vitro activity is expressed as the nanomolar concentration of a compound required to inhibit 50% of the enzyme activity (IC_{50}), the in vivo cholesterol-lowering activity is pre-

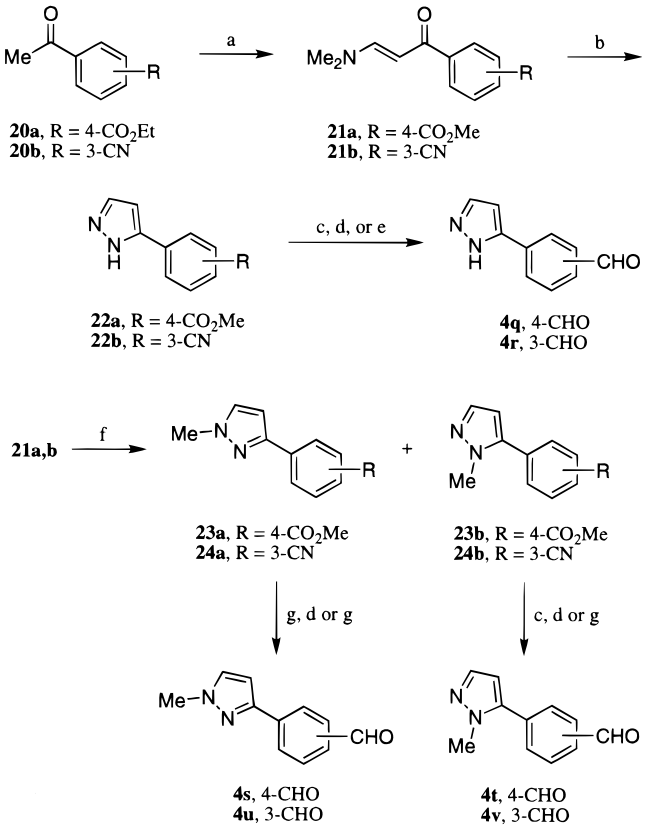
Scheme 6[a]



no.	W	X	Y	Z
4k	CH	CH	CH	N
4l	CH	N	CH	CH
4m	N	CH	N	CH
4n	N	N	CH	CH
4o	N	CH	CH	N

[a] Reagents: (a) azole, K_2CO_3, DMF; (b) 1-methylpiperazine, K_2CO_3, DMF.

Scheme 7[a]

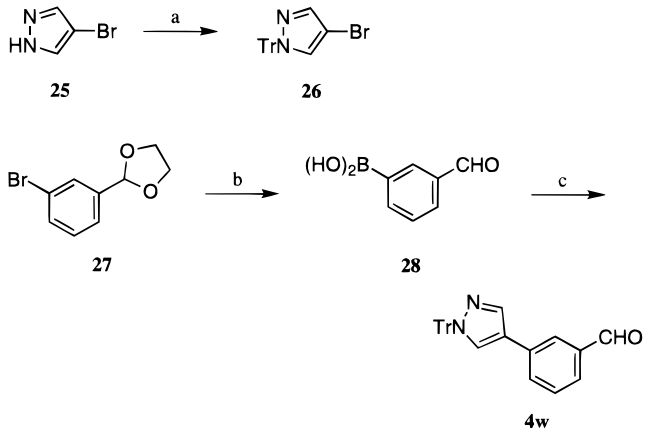


[a] Reagents: (a) $Me_2NCH(OMe)_2$; (b) $H_2NNH_2 \cdot H_2O$, AcOH, MeOH; (c) $LiAlH_4$, THF; (d) MnO_2, acetone; (e) Raney Ni, HCO_2H, H_2O; (f) $MeNHNH_2$, AcOH; (g) DIBAL, CH_2Cl_2.

sented in terms of percent reduction at the dose or ED_{50}, the effective dose to reduce plasma total cholesterol level by 50%.

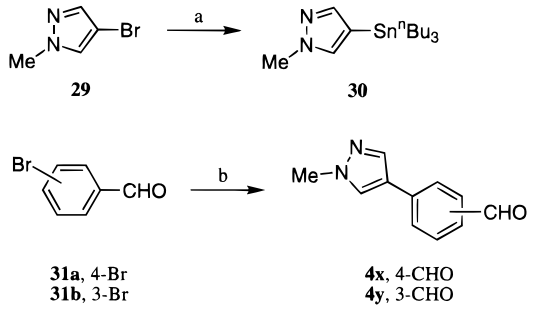
Biological data for the urea compounds represented by **2**, replacing the inner phenyl ring of the biphenyl moiety of **1** by a heteroaromatic ring, are shown in Table 2. To simplify the comparison, the *N*-alkyl (R) and *N*-aryl group (Ar_3) were kept constant to cycloheptyl and 2,4,6-trimethylphenyl groups, respectively, as these had been shown to give a good biological profile in our previous series **1**. Compared to the standard compound **1a**, which was one of our lead compounds,[13] no clearly superior compounds could be identified. Thus, conversion of phenyl to a nonpolar heteroaromatic ring, for example thiophene (**2a**, **2b**), furan (**2c**), and isoxazole (**2d**), reduced in vitro ACAT inhibitory activity by several orders and could not produce any significant improvement in cholesterol-lowering effects in vivo. Introduction of basic heteroaromatics, i.e. pyrazole (**2e**), imidazole (**2f**), and pyridine (**2g**), resulted in compounds

Scheme 8[a]



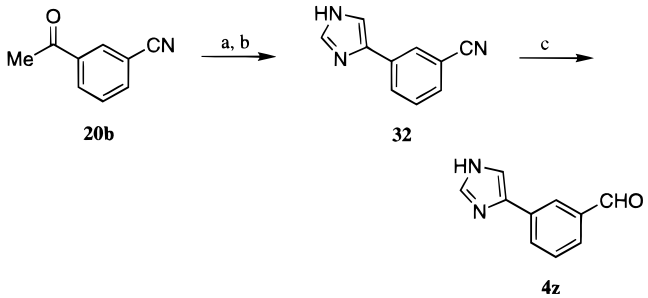
[a] Reagents: (a) TrCl, Et_3N, DMF; (b) (1) ^{n}BuLi, $B(OiPr)_3$, THF; (2) dil. HCl; (c) **26**, $Pd(PPh_3)_4$, K_2CO_3, toluene.

Scheme 9[a]



[a] Reagents: (a) ^{n}BuLi, $^n Bu_3SnCl$; (b) **30**, $Pd(PPh_3)_4$, xylene.

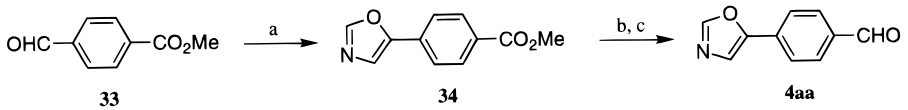
Scheme 10[a]



[a] Reagents: (a) Br_2, Et_2O, 1,4-dioxane; (b) $HCONH_2$; (c) Raney Ni, HCO_2H, H_2O.

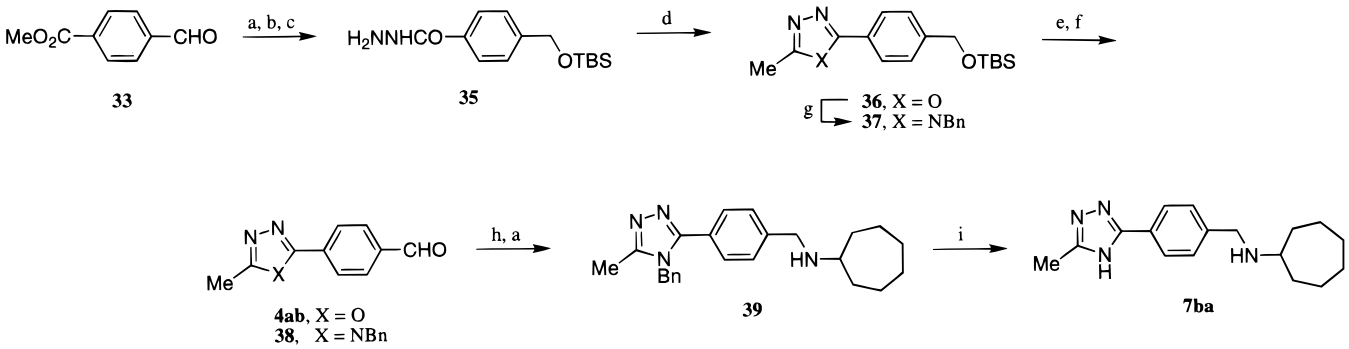
about 100-fold less active in vitro. In addition, compound **2f** was inactive at a dose of 1 mg/kg in vivo. On the basis of these results, it was considered that a heteroaromatic ring at this position may cause an unfavorable effect upon interaction with the enzyme and did not give any advantage over the parent compound **1a**.

Scheme 11[a]



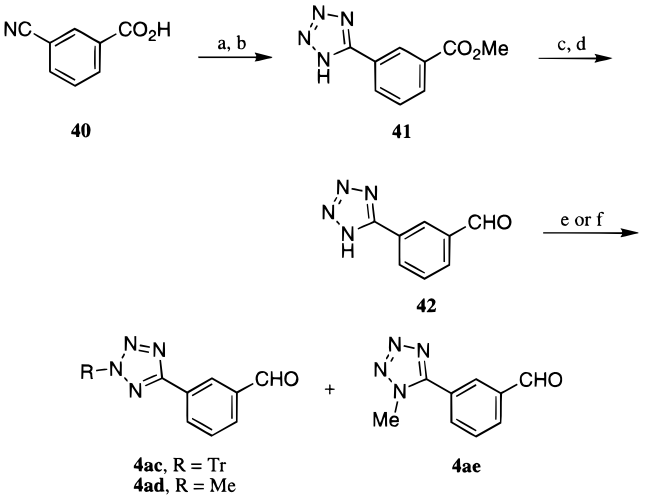
[a] Reagents: (a) TosMIC, K_2CO_3, MeOH; (b) $LiAlH_4$, THF; (c) Swern oxidation.

Scheme 12[a]



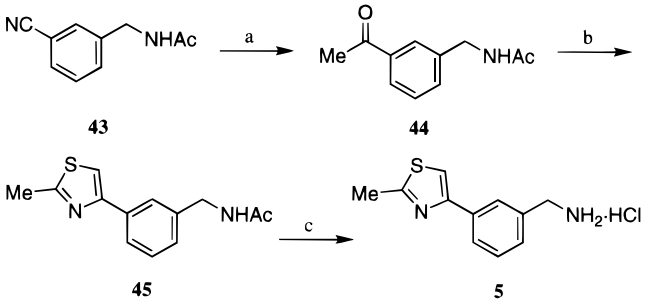
[a] Reagents: (a) $NaBH_4$, EtOH; (b) TBSCl, imidazole, DMF; (c) $H_2NNH_2 \cdot H_2O$, EtOH; (d) (1) MeC(=NH)OEt·HCl, Et_3N, EtOH; (2) 200 °C; (e) 1 N HCl, MeOH; (f) MnO_2, acetone; (g) $BnNH_2$; (h) cycloheptylamine; (i) Pd Black, HCO_2H, MeOH.

Scheme 13[a]



[a] Reagents: (a) DMF, $POCl_3$, MeOH, EtOAc; (b) NaN_3, NH_4Cl, DMF; (c) $LiAlH_4$, THF; (d) MnO_2, acetone; (e) TrCl, pyridine; (f) MeI, NaH, DMF.

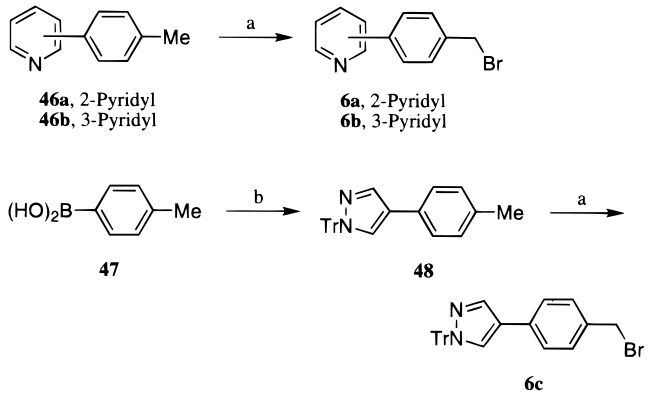
Scheme 14[a]



[a] Reagents: (a) MeMgBr, THF, Et_2O; (b) (1) Br_2, DME; (2) MeC(=S)NH_2, $NaHCO_3$, EtOH; (c) concentrated HCl, EtOH.

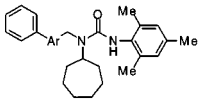
In contrast to the foregoing results, the structure–activity relationships of the urea series represented by **3**, replacing the terminal phenyl ring of the biphenyl moiety of **1** by a heteroaromatic ring, were quite different (Table 3). Our preliminary investigations involved replacing the phenyl by a thiophene or pyrrole ring (**3a**–**3g**). These compounds retained high in vitro activity, and several compounds (**3b**, **3d**, and **3g**) exhibited potent hypocholesterolemic activity in cholesterol-fed rats comparable to that of the parent compound **1a**. It is interesting that in the case of pyrrole compounds, the in vivo activity of **3g** substituted at position 3 was more potent than 4-substitution (**3f**), even though in vitro activity was equivalent. However, we decided that a breakthrough would not be expected by these very simple modifications. Moreover, most of the early ACAT inhibitors, designed to act in the intestine, preventing absorption of dietary cholesterol, are highly lipophilic and have poor bioavailability which translates into quite poor in vivo activity. Therefore, a major thrust of more recent approaches has been to functionalize lipophilic inhibitors to alter their physicochemical properties since this can be expected to dramatically affect not only biological activity but also systemic bioavailability.[9c] For instance, the recently reported CI-999, a relatively water soluble ACAT inhibitor, is weakly potent in vitro, but showed remarkable efficacy in vivo (Figure 1).[24] Therefore, we opted to examine introduction of more polar basic aromatic rings, which had been disappointing in the case of previous series. With regard to in vitro activity, pyridine (**3h**, **3i**), pyrazole (**3k**–**3m**, **3o**–**3u**),

Scheme 15[a]



[a] Reagents: (a) NBS, Bz_2O_2, CCl_4; (b) **26**, $Pd(PPh_3)_4$, K_2CO_3, toluene.

Table 2. Biological Activities of *N*-Alkyl-*N*-((phenyl-substituted heteroaryl)methyl)-*N*′-arylureas



no.	Ar	formula[a]	mp (°C)	yield[b] (method)	ACAT inhibitory activity[c] IC_{50} (nM)	hypocholesterolemic activity[d] ED_{50} (mg/kg)
1a[e]					24	0.29
2a		$C_{28}H_{34}N_2OS$	169-171	98 (D)	46	<1 (60)*
2b		$C_{28}H_{34}N_2OS$	185-186	82 (D)	36	<1 (69)***
2c		$C_{28}H_{34}N_2O_2$	131-132	76 (D)	44	<1 (68)*
2d		$C_{27}H_{33}N_3O_2$	149-150	92 (D)	61	>1 (28)
2e		$C_{27}H_{34}N_4O$	140-141	70 (D)	520	ND
2f		$C_{27}H_{34}N_4O$	208-209	55 (D)	750	>1 (inactive)
2g		$C_{29}H_{35}N_3O$	137-138	99 (D)	260	ND

[a] Satisfactory elemental analyses were obtained for C, H, N unless otherwise indicated. [b] Yield (%) of final step. [c] IC_{50} (nM) for the enzyme obtained from rabbit intestinal microsomes. [d] ED_{50} values are the effective dose to reduce plasma total cholesterol level by 50% of the control value. Compound was administered as a dietary admixture. Values in parentheses denotes percent reduction in total cholesterol at the dose indicated. [e] Analytical data and melting point previously published (see ref. 13). * Significantly different from control using unpaired, two-tailed Student's *t*-test, *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. ND denotes not determined.

imidazole (**3v**), and oxadiazole rings (**3ac**) were superior to oxazole (**3ab**) and thiazole (**3ad**). Triazole derivatives (**3x**−**3aa**) showed variable in vitro ACAT inhibitory activity but only weak in vivo activity. It is very interesting that a nonaromatic, highly basic, *N*-methylpiperazine ring compound (**3ah**) also possessed potent inhibitory activity, although its in vivo activity was not sufficient to justify further interest, possibly related to metabolism. These results suggest that both lipophilic and more polar basic components are acceptable at this position. Among the aromatic rings examined, pyrazole was attractive because of its moderate basicity. In the non-*N*-methylpyrazole series (**3k**−**3o**), dependence of the activity on the position of the pyrazole substituent on the phenyl ring was observed. That is, in the case of pyrazol-3-yl compounds, while in vitro activity was similar, with respect to in vivo efficacy, attachment to the 3-position on the phenyl ring was clearly superior (**3l** vs **3m**). On the other hand, in the case of the regioisomeric pyrazol-4-yl compounds, attachment to the 3-position was preferred for both in vitro and in vivo activity (**3n** vs **3o**). In the *N*-methylpyrazole series (**3p**−**3u**), a distinct tendency was not observed. Among these pyrazole compounds, **3m** in particular exhibited a very potent hypocholesterolemic effect ($ED_{50} = 0.097$ mg/kg). Although tetrazole compound **3ae** was also prepared and evaluated, it resulted in a complete loss of activity. Since N-methylation of the tetrazole ring restores the biological activity (**3af**, **3ag**), it can be concluded that an acidic functional unit is not acceptable to the enzyme site.

Having identified pyrazole as a heteroaromatic ring providing a good profile of biological activity, we next concentrated our efforts on varying *N*-alkyl group (R) and *N*-aryl group (Ar) (Tables 4 and 5). In the non-*N*-methylpyrazole series, the best compound **3m** was selected for further modification (Table 4). Conversion of 2,4,6-trimethylphenyl to 2,4,6-trifluorophenyl, which is one of the standard aromatic rings for ACAT inhibitors,[25] increased both in vitro and in vivo activity (**3ai**). However, introduction of 2,4-bis(methylthio)-6-methylpyridine, which afforded the best compound FR182980 in our previously reported series, significantly reduced activity (**3aj**). Although replacement of the cycloheptyl group of **3m** by smaller ring cycloalkyl groups (**3ak**, **3al**) retained in vitro activity, in vivo hypocholesterolemic activity was reduced; similar trends in the structure−activity relationships were observed for our previously disclosed biphenyl series, represented by structure **1**.[13] In the case of a benzyl group, although (2,4,6-trimethylphenyl)urea (**3am**) was not attractive, (2,4,6-trifluorophenyl)urea (**3an**) showed potent in vitro and in vivo activity. Furthermore, incorporation of 2,4-bis(methylthio)-6-methylpyridine, which was disappointing in the case of a cycloheptyl group, gave the compound with the best cholesterol-lowering effect (**3aq**, FR186054, $ED_{50} = 0.046$ mg/kg). These results suggest that the combination of the *N*-alkyl group (R) and *N*-aryl group (Ar) is very subtle and markedly influences biological activity.

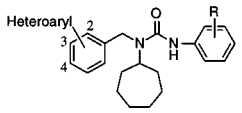
Introduction of a substituent to the 4-position of the *N*-benzyl group of **3aq** resulted in reduced in vitro activity (**3ar** and **3av**) irrespective of electronic and/or steric effects; however, cholesterol-lowering activity in vivo was retained. Although methoxy compound **3ar** possessed about the same level of activity as the parent compound **3aq**, a change in the position of the methoxy group markedly reduced the hypocholesterolemic activity (**3as**, **3at**). Additionally, a 2-phenylethyl group reduced in vivo activity (**3aw**). The best in vitro activity was obtained by introduction of a dimethylamino group to the 4-position of the *N*-benzyl group in **3an** (compound **3ao**, $IC_{50} = 12$ nM); however, its in vivo cholesterol-lowering effect was relatively reduced. As a consequence these modifications could not produce any significant improvement in the biological activity.

An attempt to apply the best combination, i.e. benzyl group and substituted pyridine, to compound **3l**, whose pyrazole ring is connected at the 4-position of the phenyl ring, improved in vivo activity (**3ay**), but it was inferior to compound **3aq**.

Similar modifications were performed on the *N*-methylpyrazole series (Table 5); however, a compound with potent in vivo biological activity was not identified. As a result of these investigations, **3m**, **3ai**, **3an**, and **3aq**, which all showed potent in vivo hypocholesterolemic activity, were selected for further studies.

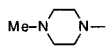
It has been shown previously that the bioavailability of ACAT inhibitors can be markedly influenced by modes of drug dosing.[13,26] Therefore, we next evaluated the hypocholesterolemic effects of the selected compounds (**3m**, **3ai**, **3an**, and **3aq**) in a different administration model, i.e. dosing of the test compound by gavage in poly(ethylene glycol) (PEG400) as a vehicle (Table 6).[13] Utilizing this model, **3an** which showed

Table 3. Biological Activities of *N*-Alkyl-*N*-(heteroaryl-substituted benzyl)-*N'*-arylureas



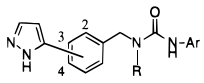
no.	Heteroaryl	R	position	formula[a]	mp (°C)	yield[b] (method)	ACAT inhibitory activity[c] IC_{50} (nM)	hypocholesterolemic activity[d] ED_{50} (mg/kg)
1a[e]		2,4,6-Me_3	4				24	0.29
3a		2,4,6-F_3	4	$C_{25}H_{25}F_3N_2OS$	136-137	80 (E)	18	>1 (33)
3b		2,4,6-Me_3	4	$C_{28}H_{34}N_2OS$	127-129	97 (D)	22	0.28
3c		2,4,6-F_3	4	$C_{25}H_{25}F_3N_2OS{\cdot}0.4H_2O$	amorphous solid	92 (E)	23	>1 (inactive)
3d		2,4,6-Me_3	4	$C_{28}H_{34}N_2OS$	120-122	100 (D)	19	0.51
3e		2,4,6-F_3	4	$C_{25}H_{26}F_3N_3O$	amorphous solid	97 (D)	27	>1 (21)
3f		2,4,6-Me_3	4	$C_{28}H_{35}N_3O$	160-161	84 (D)	28	<1 (51)
3g		2,4,6-Me_3	3	$C_{28}H_{35}N_3O$	161-163	94 (D)	20	0.17
3h		2,4,6-F_3	4	$C_{26}H_{26}F_3N_3O{\cdot}0.4H_2O$	amorphous solid	96 (E)	25	>1 (30)
3i		2,4,6-Me_3	4	$C_{29}H_{35}N_3O$	119-121	85 (D)	33	>1 (46)
3j		2,4,6-Me_3	4	$C_{29}H_{35}N_3O{\cdot}0.2H_2O$	amorphous solid	14 (D)	130	0.58
3k		2,4,6-Me_3	4	$C_{27}H_{34}N_4O$	136-137	74 (D)	70	>1 (inactive)
3l		2,4,6-Me_3	4	$C_{27}H_{34}N_4O{\cdot}0.1H_2O$	amorphous solid	61 (D)	52	>1 (17)
3m		2,4,6-Me_3	3	$C_{27}H_{34}N_4O$	180-181	65 (D)	65	0.097
3n		2,4,6-Me_3	4	$C_{27}H_{34}N_4O{\cdot}0.25H_2O$	amorphous solid	14[f] (D)	270	>1 (8)
3o		2,4,6-Me_3	3	$C_{27}H_{34}N_4O{\cdot}0.3H_2O$	amorphous solid	9[f] (D)	38	0.19
3p		2,4,6-Me_3	4	$C_{28}H_{36}N_4O$	amorphous solid	98 (D)	44	<1 (88)*** >0.32 (inactive)
3q		2,4,6-Me_3	3	$C_{28}H_{36}N_4O$	142-143	83 (D)	42	<1 (78)***
3r		2,4,6-Me_3	4	$C_{28}H_{36}N_4O$	190-191	65 (D)	24	<1 (64)*
3s		2,4,6-Me_3	3	$C_{28}H_{36}N_4O$	171-172	89 (D)	35	>1 (34)**
3t		2,4,6-Me_3	4	$C_{28}H_{36}N_4O$	114-117	82 (D)	47	0.31
3u		2,4,6-Me_3	3	$C_{28}H_{36}N_4O$	amorphous solid	91 (D)	44	<1 (74)**
3v		2,4,6-Me_3	4	$C_{27}H_{34}N_4O$	amorphous solid	94 (D)	47	>1 (26)
3w		2,4,6-Me_3	3	$C_{27}H_{34}N_4O$	amorphous solid	89 (D)	ND	<1 (84)*

Table 3. (Continued)

no.	Heteroaryl	R	position	formula[a]	mp (°C)	yield[b] (method)	ACAT inhibitory activity[c] IC_{50} (nM)	hypocholesterolemic activity[d] ED_{50} (mg/kg)
3x		2,4,6-Me_3	4	$C_{26}H_{33}N_5O$	amorphous solid	96 (D)	26	>1 (19)
3y		2,4,6-Me_3	4	$C_{26}H_{33}N_5O$	amorphous solid	93 (D)	42	>1 (19)
3z		2,4,6-Me_3	4	$C_{26}H_{33}N_5O$	157-158	87 (D)	130	>1 (11)
3aa		2,4,6-Me_3	4	$C_{27}H_{35}N_5O$	142-145	94 (D)	120	>1 (17)
3ab		2,4,6-Me_3	4	$C_{27}H_{33}N_3O_2$	113-114	87 (D)	200	>1 (13)
3ac		2,4,6-Me_3	4	$C_{27}H_{34}N_4O_2$	123-124	92 (D)	27	>0.32 (37)**
3ad		2,4,6-Me_3	3	$C_{28}H_{35}N_3OS$	87-90	73 (D)	180	ND
3ae		2,4,6-Me_3	3	$C_{25}H_{32}N_6O$	204-206	80[f] (D)	>1000	ND
3af		2,4,6-Me_3	3	$C_{26}H_{34}N_6O$	175-176	88 (D)	100	<1 (84)**
3ag		2,4,6-Me_3	3	$C_{26}H_{34}N_6O{\cdot}0.2H_2O$	171-173	95 (D)	ND	>1 (26)
3ah		2,4,6-Me_3	4	$C_{29}H_{42}N_4O$	amorphous solid	95 (D)	57	>1 (23)

[a-e,*] See corresponding footnotes of Table 2. [f] 2 steps, including a deprotection step, from amine **7ak**, **7as**, or **7az**. ND denotes not determined.

Table 4. Biological Activities of *N*-Alkyl-*N*-(pyrazolylbenzyl)-*N′*-arylureas

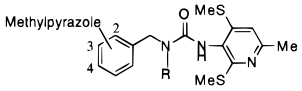


no.	R	Ar	position	formula[a]	mp (°C)	yield[b] (method)	ACAT inhibitory activity[c] IC_{50} (nM)	hypocholesterolemic activity[d] ED_{50} (mg/kg)
3m	cycloheptyl	2,4,6-Me_3Ph	3	$C_{27}H_{34}N_4O$	180−181	65 (D)	65	0.097
3ai	cycloheptyl	2,4,6-F_3Ph	3	$C_{24}H_{25}F_3N_4O$	158−159	52 (E)	22	0.062
3aj	cycloheptyl	Py-deriv	3	$C_{26}H_{33}N_5OS_2$[e]	amorphous solid	62 (F)	260	>0.32 (24)
3ak	cyclohexyl	2,4,6-Me_3Ph	3	$C_{26}H_{32}N_4O{\cdot}0.2H_2O$	amorphous solid	18 (D)	39	0.12
3al	cyclopentyl	2,4,6-Me_3Ph	3	$C_{25}H_{30}N_4O{\cdot}0.5H_2O$	amorphous solid	25 (D)	22	<1 (76)***
3am	benzyl	2,4,6-Me_3Ph	3	$C_{27}H_{28}N_4O$	amorphous solid	86 (D)	21	>1 (36)
3an	benzyl	2,4,6-F_3Ph	3	$C_{24}H_{19}F_3N_4O$	193−194	26 (E)	14	0.096
3ao	4-Me_2N-benzyl	2,4,6-F_3Ph	3	$C_{26}H_{24}F_3N_5O$	amorphous solid	98 (F)	12	<0.32 (68)*
3ap	4-F-benzyl	2,4,6-F_3Ph	3	$C_{24}H_{18}F_4N_4O{\cdot}0.25H_2O$	204−206	83 (F)	ND	<0.32 (64)*
3aq	benzyl	Py-deriv	3	$C_{26}H_{27}N_5OS_2$	209−210	78 (F)	99	0.046
3ar	4-MeO-benzyl	Py-deriv	3	$C_{27}H_{29}N_5O_2S_2$	170−173	68 (F)	200	<0.1 (81)**
3as	2-MeO-benzyl	Py-deriv	3	$C_{27}H_{29}N_5O_2S_2$	amorphous solid	74 (F)	ND	>0.1 (inactive)
3at	3-MeO-benzyl	Py-deriv	3	$C_{27}H_{29}N_5O_2S_2$	165−166	82 (F)	ND	>0.1 (13)
3au	4-Me_2N-benzyl	Py-deriv	3	$C_{28}H_{32}N_6OS_2$	185−188	76 (F)	72	<0.1 (61)*
3av	4-F-benzyl	Py-deriv	3	$C_{26}H_{26}FN_5OS_2$	166−168	61 (F)	250	<0.1 (66)**
3aw	2-phenylethyl	Py-deriv	3	$C_{27}H_{29}N_5OS_2$	amorphous solid	87 (F)	ND	>0.1 (inactive)
3l	cycloheptyl	2,4,6-Me_3Ph	4	$C_{27}H_{34}N_4O{\cdot}0.1H_2O$	amorphous solid	61 (D)	52	>1 (17)
3ax	cycloheptyl	Py-deriv	4	$C_{26}H_{33}N_5OS_2$	174−175	67 (F)	100	<0.32 (77)*
3ay	benzyl	Py-deriv	4	$C_{26}H_{27}N_5OS_2$	150−152	86 (F)	55	<0.32 (58)

[a-d,*] See corresponding footnotes of Table 2. [e] Satisfactory analytical data could not be obtained for this compound. Anal. N: calcd, 14.13; found, 13.25. Py-deriv denotes 2,4-bis(methylthio)-6-methylpyridin-3-yl. ND denotes not determined.

excellent activity when dosed as a dietary admixture, was only modestly potent. However, it was gratifying that the other three compounds were still efficacious even when dosed by gavage in PEG400. Among these

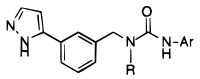
Table 5. Biological Activities of *N*-Alkyl-*N*-((methylpyrazolyl)benzyl)-*N'*-arylureas



no.	Methylpyrazole	R	position	formula[a]	mp (°C)	yield[b] (method)	ACAT inhibitory activity[c] IC_{50} (nM)	hypocholesterolemic activity[d] ED_{50} (mg/kg)
3az		benzyl	3	$C_{27}H_{29}N_5OS_2$	165-166	84 (F)	73	<1 (77)**
3ba		benzyl	3	$C_{27}H_{29}N_5OS_2$	amorphous solid	87 (F)	28	<1 (88)**
3bb		cycloheptyl	3	$C_{27}H_{35}N_5OS_2$	197-198	74 (F)	ND	>0.1 (44)*
3bc		benzyl	3	$C_{27}H_{29}N_5OS_2$	137-138	81 (F)	ND	>0.1 (43)
3bd		benzyl	4	$C_{27}H_{29}N_5OS_2 \cdot 0.25H_2O$	amorphous solid	96 (F)	29	>0.32 (inactive)
3be		benzyl	4	$C_{27}H_{29}N_5OS_2$	amorphous solid	90 (F)	27	<0.32 (86)*
3bf		cycloheptyl	4	$C_{27}H_{35}N_5OS_2$	247-248	92 (F)	ND	>0.1 (inactive)
3bg		benzyl	4	$C_{27}H_{29}N_5OS_2$	224-225	85 (F)	ND	>0.1 (29)

[a-d,*] See corresponding footnotes of Table 2. ND denotes not determined.

Table 6. Biological Activities of Selected Compounds and Effect of Administration Mode



no.	R	Ar	ACAT inhibitory activity[a] IC_{50} (nM)	foam cell formation inhibitory activity[b] IC_{50} (nM)	hypocholesterolemic activity[c] ED_{50} (mg/kg) administration mode: diet[d]	gavage[e]
3m	cycloheptyl	2,4,6-Me_3Ph	65	460	0.097	2.0
3ai	cycloheptyl	2,4,6-F_3Ph	22	580	0.062	0.79
3an	benzyl	2,4,6-F_3Ph	14	7400	0.096	8.6
3aq	benzyl	Py-deriv	99	350	0.046	0.44
FR182980			30	48	0.034	0.11
CL 277,082			33	ND	5.0	ND
CI-999			4000	55000	0.61	ND

[a] See footnote *c* of Table 2. [b] IC_{50} (nM) for acetylated LDL-induced accumulation of cholesteryl esters in mouse peritoneal macrophages. [c] ED_{50} values are the effective dose to reduce plasma total cholesterol level by 50% of the control value. [d] Compound was administered as a dietary admixture. [e] Compound was administered by gavage in PEG400 as a vehicle. Py-deriv denotes 2,4-bis(methylthio)-6-methylpyridin-3-yl.

compounds, **3aq** in particular showed the most potent cholesterol-lowering effect in both dosing models. Although the precise reasons why **3aq** exhibited such high potency are still unclear at this point, it may in part be presumably attributed to improved pharmacokinetics of this inhibitor as a result of incorporation of the substituted pyridine part which provides a protonation site to improve solubility and make the molecule more polar.

As previously stated, macrophage-derived foam cells play an important role in lesion progression. ACAT inhibition in arterial macrophages would be expected to exert an antiartherosclerotic effect by inhibiting foam cell formation in the arterial wall.[7,8] Furthermore, the possibility of the existence of isozymes of ACAT has been suggested.[27] Thus, selected compounds were further assessed for their ability to inhibit acetylated LDL-induced accumulation of cholesteryl esters in mouse peritoneal macrophages (Table 6). Compound **3aq** was found to be relatively less active in the macrophage assay than FR182980 but still retained a high level of activity. On the other hand, **3an** was found to have weak inhibitory activity, possibly related to its poor ability to penetrate the macrophage cell wall and/or essentially weak inhibitory activity of the macrophage ACAT.

Recently various classes of ACAT inhibitors have been

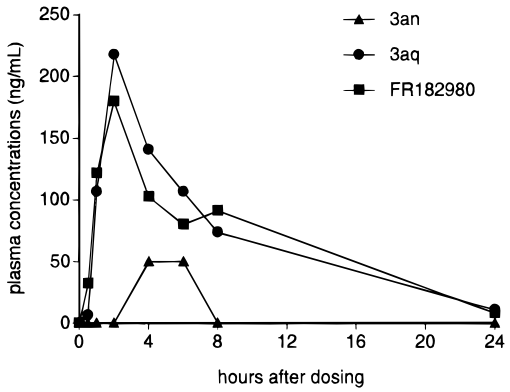


Figure 2. Plasma concentrations in fed dog (dose = 10 mg/kg, $n = 1$).

shown to induce toxicological effects on the adrenal glands of certain species.[26a,28−31] Therefore, **3an**, **3aq**, and FR182980 were assessed for adrenal toxicity in rabbits ($n = 3−4$) at a single dose of 5 mg/kg iv and/or dog ($n = 1$) at a single dose of 10 mg/kg po using PEG400 as a vehicle. Among these compounds, FR182980 showed a mild effect in rabbits, as indicated by slight alterations consisting of mononuclear cell infiltration in the adrenal cortex and, furthermore, significant adrenal toxicity in dog, as indicated by necrosis of cortical cells in the adrenal cortex. However drug-related histopathologic alterations to the adrenal glands of dogs were not observed for compounds **3an** and **3aq**. Figure 2 shows a time course for plasma drug levels in fed dog following oral administration of each compound at a dose of 10 mg/kg in this toxicological study. It should be noted that the plasma level of **3aq** was similar to that of FR182980, indicating that the intrinsic lack of adrenotoxicity is not related to serum concentration. On the other hand, poorly absorbed **3an**, predicted from its modest hypocholesterolemic activity when dosed by gavage, was essentially nontoxic in part due to the low systemic exposure. However, setting aside these plasma drug levels in dogs, **3an** was concluded to be nontoxic on the basis of the result of the toxicological study in rabbits after intravenous administration. It is unclear whether the observed adrenotoxicity is mechanism- or compound-related,[28b−e,29e,f,30,31] and additionally why our three compounds displayed such different effects on adrenal tissue. However, researchers at Parke-Davis have reported recently a tendency similar to that displayed in our results that toxicity was reduced significantly by making the molecule more polar and basic in nature.[26a] Furthermore, several reports including nontoxic analogues have appeared.[29c,d,f,32]

On the basis of the results discussed above, compound **3aq** (FR186054) bearing a novel pyrazole ring was identified as a potent, nonadrenotoxic, orally efficacious ACAT inhibitor, independent of the administration mode, and selected for further development as a new treatment for hypercholesterolemia and atherosclerosis.

Conclusion

In summary, we have prepared a novel series of *N*-alkyl-*N*-(heteroaryl-substituted benzyl)-*N′*-arylurea and related derivatives and evaluated them as ACAT inhibitors. The SAR study in this series of compounds revealed the following main features: (1) Replacing the inner phenyl ring of the biphenyl moiety of series **1** by basic heteroaromatic rings appears to be unfavorable for interaction with the enzyme. (2) Although introduction of basic heteroaromatic rings as the terminal aromatic ring of the biaryl moiety is acceptable, acidic rings such as tetrazole are unfavorable. Pyrazole was identified as the heteroaromatic ring providing the best balance of biological activity. (3) The position connecting the heteroaromatic ring and the inner phenyl ring can influence biological activity. (4) Combination with the *N*-alkyl group (R) and *N*-aryl group (Ar_3) is very subtle and has an enormous effect on the activity. On the basis of the main results described above, *N*-benzyl-*N*-[3-(pyrazol-3-yl)benzyl]-*N′*-[2,4-bis(methylthio)-6-methylpyridin-3-yl]urea (**3aq**, FR186054) was identified as a potent, nonadrenotoxic, orally efficacious ACAT inhibitor irrespective of dosing method and was selected for further development. The details of pharmacological studies on this compound and the results of further efforts to overcome the adrenal toxicity of FR182980, the best compound in our previous biphenyl series **1**, will be the subject of further communications from these laboratories.

Experimental Section

Chemistry. General Procedures. Melting points were measured on a Büchi 535 apparatus in open capillaries and are uncorrected. IR spectra were recorded on a Horiba Spectradesk FT-210 spectrometer as KBr disks, neat, or films as indicated. NMR spectra were measured on a Bruker AC200P (^{1}H, 200 MHz). Chemical shifts are given in parts per million, and tetramethylsilane was used as the internal standard for spectra obtained in DMSO-d_6 and $CDCl_3$. All *J* values are given in hertz. Mass spectra were measured on a Hitachi Model M-1000H mass spectrometer using APCI for ionization. Elemental analyses were carried out on a Perkin-Elmer 2400 CHN elemental analyzer. Reagents and solvents were used as obtained from commercial suppliers without further purification. Column chromatography was performed using silica gel, and reaction progress was determined by TLC analysis on silica gel coated glass plates. Visualization was with UV light (254 nm) or iodine. The term "evaporated" or "evaporation" refers to removal of solvent on a rotary evaporator at reduced pressure.

5-Phenylthiophene-2-carboxaldehyde (4a). To a solution of 5-bromothiophene-2-carboxaldehyde **8a** (2.00 g, 10.5 mmol) and phenylboric acid ($PhB(OH)_2$) (1.66 g, 13.6 mmol) in 1,2-dimethoxyethane (DME) (18 mL) were added a 2 M Na_2CO_3 solution (13.6 mL) and $Pd(PPh_3)_4$ (605 mg, 0.52 mmol), and the mixture was heated at 80 °C for 5 h. The reaction mixture was poured into a mixture of CH_2Cl_2 and ice water. The separated organic layer was washed with water and brine, dried ($MgSO_4$), and evaporated, and the residue was purified by silica gel column chromatography (hexane−EtOAc, 5:1 elution) to give **4a** (1.80 g, 91%) as a solid: ^{1}H NMR ($CDCl_3$) δ 7.33−7.50 (4H, m), 7.60−7.80 (3H, m), 9.90 (1H, s); IR (KBr) 1647, 1441, 1232, 754 cm^{-1}; MS *m/z* 189 (MH^+).

The following compound was prepared in a similar manner from 4-bromothiophene-2-carboxaldehyde **8b** (10.5 mmol) and $PhB(OH)_2$ (13.6 mmol).

4-Phenylthiophene-2-carboxaldehyde (4b): yield 1.97 g (100%); ^{1}H NMR ($CDCl_3$) δ 7.30−7.66 (5H, m), 7.82−7.90 (1H, m), 8.00−8.08 (1H, m), 9.98 (1H, d, $J = 1.2$ Hz); IR (KBr) 1676, 1539, 1429, 1173, 760 cm^{-1}; MS *m/z* 189 (MH^+).

5-Phenylfuran-2-carboxaldehyde (4c). To a suspension of 5-bromofuran-2-carboxylic acid **9** (10.0 g, 52.4 mmol), *N*,*O*-dimethylhydroxylamine hydrochloride (5.10 g, 52.4 mmol), and 1-hydroxybenzotriazole (HOBt) (7.07 g, 52.4 mmol) in CH_2Cl_2 (300 mL) was added dropwise a solution of 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide (WSC) (6.37 g, 52.4 mmol) in

CH_2Cl_2 (60 mL) at room temperature, and the mixture was stirred for 18 h. The reaction mixture was poured into water, the separated organic layer was washed with water and brine, dried ($MgSO_4$), and evaporated, and the residue was purified by silica gel column chromatography (hexane−EtOAc, 1:1 elution) to give *N*-methoxy-*N*-methyl-5-bromofuran-2-carboxamide (7.60 g, 62%) as a solid: ^{1}H NMR ($CDCl_3$) δ 3.34 (3H, s), 3.77 (3H, s), 6.45 (1H, d, J = 3.5 Hz), 7.09 (1H, d, J = 3.5 Hz); IR (KBr) 3107, 2981, 2937, 1637, 1564, 1466 cm^{-1}; MS m/z 234, 236 (MH^+).

To a suspension of $LiAlH_4$ (584 mg, 15.4 mmol) in THF (80 mL) was added dropwise a solution of the above amide (3.60 g, 15.4 mmol) in THF (35 mL) at 5 °C, and the mixture was stirred at the same temperature for 15 min. To the mixture were added anhydrous NaF (2.58 g, 61.5 mmol) and water (0.83 mL), followed by stirring at room temperature for 30 min. Insoluble materials were removed by filtration and washed with THF. The filtrate was evaporated and purified by silica gel column chromatography (hexane−EtOAc, 5:2 elution) to give 5-bromofuran-2-carboxaldehyde **10** (2.11 g, 78%) as a solid: ^{1}H NMR ($CDCl_3$) δ 6.57 (1H, d, J = 3.6 Hz), 7.19 (1H, d, J = 3.6 Hz), 9.54 (1H, s); IR (KBr) 1670, 1464, 1377, 1271 cm^{-1}.

To a solution of **10** (2.09 g, 11.9 mmol) and $PhB(OH)_2$ (1.89 g, 15.5 mmol) in DME (18 mL) were added a 2 M Na_2CO_3 solution (15.5 mL) and $Pd(PPh_3)_4$ (690 mg, 0.60 mmol), and the mixture was heated at 80 °C for 6 h. The reaction mixture was poured into a mixture of CH_2Cl_2 and ice water. The separated organic layer was washed with water and brine, dried ($MgSO_4$), evaporated, and purified by silica gel column chromatography (hexane−EtOAc, 5:1 elution) to give **4c** (1.88 g, 92%) as an oil: ^{1}H NMR ($CDCl_3$) δ 6.85 (1H, d, J = 3.7 Hz), 7.33 (1H, d, J = 3.7 Hz), 7.37−7.53 (3H, m), 7.80−7.92 (2H, m), 9.66 (1H, s); IR (neat) 1674, 1522, 1475, 1257 cm^{-1}; MS m/z 173 (MH^+).

6-Phenylpyridine-3-carboxaldehyde (4d). To a solution of methyl 6-chloronicotinate **11** (6.86 g, 40.0 mmol) and $PhB(OH)_2$ (5.85 g, 48.0 mmol) in DME (150 mL) were added a 2 M Na_2CO_3 solution (48 mL) and $Pd(PPh_3)_4$ (2.31 g, 2.0 mmol), and the mixture was refluxed for 16 h at 80 °C. The reaction mixture was poured into a mixture of EtOAc and ice water. The separated organic layer was washed with water and brine, dried ($MgSO_4$), evaporated, and purified by silica gel column chromatography (hexane−EtOAc, 2:1 elution) to give methyl 6-phenylnicotinate **12** (7.75 g, 91%) as a solid: ^{1}H NMR ($CDCl_3$) δ 3.98 (3H, s), 7.40−7.57 (3H, m), 7.82 (1H, dd, J = 8.3, 0.9 Hz), 8.00−8.10 (2H, m), 8.35 (1H, dd, J = 8.3, 2.2 Hz), 9.28 (1H, dd, J = 2.2, 0.9 Hz); IR (KBr) 3070, 3032, 2993, 2945, 2843, 1724, 1595, 1435 cm^{-1}; MS m/z 214 (MH^+).

To a suspension of $LiAlH_4$ (1.68 g, 44.2 mmol) in THF (200 mL) was added dropwise a solution of **12** (9.42 g, 44.2 mmol) in THF (120 mL) at 5 °C, and the mixture was stirred at room temperature for 4 h. To the mixture were added anhydrous NaF (7.42 g, 177 mmol) and water (2.39 mL) at 5 °C, and the mixture was stirred at room temperature for 30 min. Insoluble materials were removed by filtration and washed with THF. The filtrate was evaporated and purified by silica gel column chromatography (iPE−EtOAc, 1:1 elution) to give (6-phenylpyridin-3-yl)methanol (7.24 g, 89%) as an oil: ^{1}H NMR ($CDCl_3$) δ 4.74 (2H, s), 7.35−7.55 (3H, m), 7.67−7.85 (2H, m), 7.90−8.05 (2H, m), 8.62 (1H, d, J = 1.3 Hz); IR (neat) 3323 (br), 2866, 1601, 1564, 1477 cm^{-1}; MS m/z 186 (MH^+).

To a solution of (6-phenylpyridin-3-yl)methanol (7.24 g, 39.1 mmol) in $CHCl_3$ (100 mL) was added activated MnO_2 (34.0 g, 391 mmol), and the mixture was refluxed for 3.5 h. The cooled mixture was then filtered and evaporated to give **4d** (5.96 g, 83%) as a solid: ^{1}H NMR ($CDCl_3$) δ 7.42−7.60 (3H, m), 7.92 (1H, d, J = 8.3 Hz), 8.02−8.15 (2H, m), 8.24 (1H, dd, J = 8.3, 2.2 Hz), 9.13 (1H, dd, J = 2.2, 0.7 Hz), 10.14 (1H, s); IR (KBr) 3059, 2835, 2787, 2742, 1697, 1593, 1558 cm^{-1}; MS m/z 184 (MH^+).

5-Phenylisoxazole-3-carboxaldehyde (4e). To a solution of acetophenone **13** (20.0 g, 167 mmol) and dimethyl oxalate (23.6 g, 200 mmol) in DMF (160 mL) was added NaH (60% oil dispersion, 8.0 g, 200 mmol) at 5 °C. The mixture was stirred at room temperature for 1 h and then heated at 50 °C for 30 min. After cooling, the mixture was treated with 2.4 N HCl (70 mL) and extracted with EtOAc. The organic layer was washed with water and brine, dried ($MgSO_4$), evaporated, and purified by silica gel column chromatography (hexane−EtOAc, 4:1 to 1:1 elution) to give methyl 2,4-dioxo-4-phenylbutyrate **14** (20.3 g, 59%) as a semisolid: ^{1}H NMR ($CDCl_3$) δ 3.95 (3H, s), 7.10 (1H, s), 7.45−7.68 (3H, m), 7.95−8.06 (2H, m), 15.0−15.5 (1H, br); IR (KBr) 1732, 1622, 1601, 1574, 1444, 1269 cm^{-1}; MS m/z 207 (MH^+).

A solution of **14** (6.0 g, 29.1 mmol) and NH_2OH·HCl (6.07 g, 87.4 mmol) in MeOH (120 mL) was refluxed for 4 h. After evaporation and dilution with $CHCl_3$, the solution was washed with water and brine, dried ($MgSO_4$), evaporated, and purified by silica gel column chromatography (hexane−EtOAc, 3:1 elution) to give methyl 5-phenylisoxazole-3-carboxylate **15a** (5.25 g, 89%) as a solid: ^{1}H NMR ($CDCl_3$) δ 4.01 (3H, s), 6.94 (1H, s), 7.45−7.55 (3H, m), 7.75−7.88 (2H, m); IR (KBr) 1728, 1570, 1448, 1250 cm^{-1}; MS m/z 204 (MH^+).

To a solution of **15a** (4.73 g, 23.3 mmol) in CH_2Cl_2 (150 mL) was added dropwise diisobutylaluminum hydride (DIBAL) (1.02 M toluene solution, 45.7 mL, 46.6 mmol) at −60 °C, and the mixture was stirred at the same temperature for 1 h. To the mixture were added anhydrous NaF (7.83 g, 186.4 mmol) and water (2.52 mL), and the mixture was stirred at room temperature for 1 h. Insoluble materials were removed by filtration and washed with EtOAc. The filtrate was evaporated and purified by silica gel column chromatography (hexane−EtOAc, 3:1 elution) to give **4e** (1.94 g, 48%) as a solid: ^{1}H NMR ($CDCl_3$) δ 6.90 (1H, s), 7.35−7.68 (3H, m), 7.75−7.92 (2H, m), 10.20 (1H, s); IR (KBr) 3126, 1713, 1568, 1456, 1184 cm^{-1}; MS m/z 174 (MH^+).

5-Phenylpyrazole-3-carboxaldehyde (4f). A solution of **14** (6.0 g, 29.1 mmol) and H_2NNH_2·H_2O (1.42 mL, 29.1 mmol) in EtOH (48 mL) was refluxed for 5 h. After evaporation, the resulting solid was collected and washed with iPE to give methyl 5-phenylpyrazole-3-carboxylate **15b** (3.0 g, 51%) as a solid: ^{1}H NMR (DMSO-d_6) δ 3.83, 3.88 (total 3H, each s), 7.18−7.53 (4H, m), 7.78−7.94 (2H, m), 13.98, 14.08 (total 1H, each br s); IR (KBr) 3400−2500 (br), 1730, 1491, 1244 cm^{-1}; MS m/z 203 (MH^+).

To a suspension of $LiAlH_4$ (960 mg, 25.3 mmol) in THF (100 mL) was added dropwise a solution of **15b** (3.93 g, 19.5 mmol) in THF (40 mL) at 5 °C, and the mixture was stirred at room temperature for 3.5 h. To the mixture were added anhydrous NaF (4.25 g, 101.2 mmol) and water (1.37 mL) at 5 °C, and the mixture was stirred at room temperature for 2 h. Insoluble materials were removed by filtration and washed with THF. The filtrate was evaporated and the resulting precipitate collected by filtration and washed with iPE to give (5-phenylpyrazol-3-yl)methanol (1.30 g, 38%) as a solid: ^{1}H NMR (DMSO-d_6) δ 4.38−4.58 (2H, m), 4.95−5.37 (1H, m), 6.52−6.66 (1H, m), 7.20−7.53 (3H, m), 7.68−7.90 (2H, m), 12.75, 13.02 (total 1H, each br s); IR (KBr) 3500−2500 (br), 1471, 1360, 1030, 1001, 766 cm^{-1}; MS m/z 175 (MH^+).

To a solution of the above pyrazolylmethanol (1.30 g, 7.5 mmol) in acetone (130 mL) was added activated MnO_2 (6.5 g, 75 mmol), and the mixture was refluxed for 1.5 h. The cooled mixture was then filtered and the filtrate evaporated to give **4f** (1.16 g, 90%) as a solid: ^{1}H NMR (DMSO-d_6) δ 7.20−7.56 (4H, m), 7.75−7.95 (2H, m), 9.93 (1H, s), 14.05−14.30 (1H, br); IR (KBr) 3500−2400 (br), 1676, 1473, 1282, 1192 cm^{-1}; MS m/z 173 (MH^+).

4-(2-Thienyl)benzaldehyde (4g). A solution of 4-bromobenzyl alcohol (4.85 g, 25.9 mmol) and 2-(tri-*n*-butylstannyl)thiophene **16a** (11.6 g, 31.1 mmol) in xylene (60 mL) was treated with $Pd(PPh_3)_4$ (0.9 g, 0.78 mmol), and the mixture was heated at 140 °C for 1 h. After cooling, the resulting precipitate was collected and washed with hexane to give 4-(2-thienyl)benzyl alcohol **17a** (2.96 g, 60%) as a solid: ^{1}H NMR ($CDCl_3$) δ 1.70 (1H, t, J = 5.9 Hz), 4.71 (2H, d, J = 5.9 Hz), 7.08 (1H, dd, J = 5.1, 3.6 Hz), 7.22−7.42 (4H, m), 7.61 (2H, d,

J = 8.3 Hz); IR (KBr) 3334 (br), 1427, 1213, 1047, 806 cm^{-1}; MS m/z 173 ($MH^+ - H_2O$).

To a solution of **17a** (2.95 g, 15.5 mmol) in $CHCl_3$ (180 mL) was added activated MnO_2 (13.5 g, 155 mmol), and the mixture was refluxed for 1 h. The cooled mixture was then filtered, and the filtrate was evaporated to give **4g** (2.92 g, 100%) as a solid: ^1H NMR ($CDCl_3$) δ 7.14 (1H, dd, J = 5.1, 3.7 Hz), 7.40 (1H, dd, J = 5.1, 1.1 Hz), 7.47 (1H, dd, J = 3.7, 1.1 Hz), 7.77 (2H, d, J = 8.5 Hz), 7.89 (2H, d, J = 8.5 Hz), 10.00 (1H, s); IR (KBr) 1699, 1601, 1213, 1170 cm^{-1}; MS m/z 189 (MH^+).

4-(3-Thienyl)benzaldehyde (4h). To a solution of 4-bromobenzyl alcohol (4.85 g, 25.9 mmol) and 3-(tri-*n*-butylstannyl)thiophene **16b** (11.6 g, 31.1 mmol) in xylene (60 mL) was added $Pd(PPh_3)_4$ (0.9 g, 0.78 mmol), and the mixture was heated at 140 °C for 1 h. After cooling, the resulting precipitate was collected and washed with hexane to give 4-(3-thienyl)benzyl alcohol **17b** (2.67 g, 54%) as a solid: ^1H NMR ($CDCl_3$) δ 1.72 (1H, t, J = 5.9 Hz), 4.72 (2H, d, J = 5.9 Hz), 7.30−7.50 (5H, m), 7.60 (2H, d, J = 8.3 Hz); IR (KBr) 3310 (br), 1425, 1200, 1045, 1014, 777 cm^{-1}; MS m/z 173 ($MH^+ - H_2O$).

To a solution of **17b** (2.55 g, 13.4 mmol) in $CHCl_3$ (150 mL) was added activated MnO_2 (11.7 g, 134 mmol), and the mixture was refluxed for 1 h. The cooled mixture was then filtered, and the filtrate was evaporated to give **4h** (2.35 g, 93%) as a solid: ^1H NMR ($CDCl_3$) δ 7.41−7.47 (2H, m), 7.62 (1H, dd, J = 2.1, 2.1 Hz), 7.76 (2H, d, J = 8.3 Hz), 7.92 (2H, d, J = 8.3 Hz), 10.02 (1H, s); IR (KBr) 1689, 1601, 1211, 1167 cm^{-1}; MS m/z 189 (MH^+).

4-(1*H*-Pyrrol-1-yl)benzaldehyde (4i). To a suspension of 4-(1*H*-pyrrol-1-yl)benzoic acid **18a** (3.74 g, 20.0 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (1.95 g, 20.0 mmol) in CH_2Cl_2 (100 mL) was added dropwise a solution of WSC (2.43 g, 20.0 mmol) in CH_2Cl_2 (15 mL) at room temperature, and the mixture was stirred for 18 h. The reaction mixture was poured into water, and the separated organic layer was washed with water and brine, dried ($MgSO_4$), evaporated, and purified by silica gel column chromatography (hexane−EtOAc, 1:1 elution) to give 4-(1*H*-pyrrol-1-yl)-*N*-methoxy-*N*-methylbenzamide (2.12 g, 46%) as a solid: ^1H NMR ($CDCl_3$) δ 3.39 (3H, s), 3.58 (3H, s), 6.38 (2H, dd, J = 2.2, 2.2 Hz), 7.15 (2H, dd, J = 2.2, 2.2 Hz), 7.42 (2H, d, J = 8.8 Hz), 7.81 (2H, d, J = 8.8 Hz); IR (KBr) 3132, 2960, 2937, 1639, 1610, 1524 cm^{-1}; MS m/z 231 (MH^+).

To a suspension of $LiAlH_4$ (348 mg, 9.2 mmol) in THF (30 mL) was added dropwise a solution of the above benzamide (2.11 g, 9.2 mmol) in THF (40 mL) at 5 °C, and the mixture was stirred at the same temperature for 1.5 h. To the mixture were added anhydrous NaF (1.54 g, 36.6 mmol) and water (0.50 mL) at 5 °C, and the mixture was stirred at room temperature for 30 min. Insoluble materials were removed by filtration and washed with THF. The filtrate was evaporated and purified by silica gel column chromatography (hexane−EtOAc, 4:1 elution) to give **4i** (1.57 g, 100%) as a solid: ^1H NMR ($CDCl_3$) δ 6.41 (2H, dd, J = 2.2, 2.2 Hz), 7.19 (2H, dd, J = 2.2, 2.2 Hz), 7.54 (2H, d, J = 8.6 Hz), 7.95 (2H, d, J = 8.6 Hz), 9.99 (1H, s); IR (KBr) 3130, 2805, 2745, 1689, 1605, 1520 cm^{-1}; MS m/z 172 (MH^+).

3-(1*H*-Pyrrol-1-yl)benzaldehyde (4j). To a suspension of 3-(1*H*-pyrrol-1-yl)benzoic acid **18b** (5.62 g, 30.0 mmol), *N*,*O*-dimethylhydroxylamine hydrochloride (2.93 g, 30.0 mmol), and HOBt (4.05 g, 30.0 mmol) in CH_2Cl_2 (150 mL) was added dropwise a solution of WSC (3.65 g, 30.0 mmol) in CH_2Cl_2 (30 mL) at room temperature, and the mixture was stirred for 20 h. The reaction mixture was poured into water. The separated organic layer was washed with water and brine, dried ($MgSO_4$), evaporated, and purified by silica gel column chromatography (hexane−EtOAc, 1:1 elution) to give 3-(1*H*-pyrrol-1-yl)-*N*-methoxy-*N*-methylbenzamide (5.19 g, 75%) as an oil: ^1H NMR ($CDCl_3$) δ 3.39 (3H, s), 3.57 (3H, s), 6.36 (2H, dd, J = 2.2, 2.2 Hz), 7.12 (2H, dd, J = 2.2, 2.2 Hz), 7.40−7.62 (3H, m), 7.70−7.75 (1H, m); IR (neat) 3130, 2935, 1645, 1608, 1587, 1500 cm^{-1}; MS m/z 231 (MH^+).

To a suspension of $LiAlH_4$ (855 mg, 22.5 mmol) in THF (100 mL) was added dropwise a solution of the above benzamide (5.19 g, 22.5 mmol) in THF (100 mL) at 5 °C, and the mixture was stirred at the same temperature for 2 h. To the mixture were added anhydrous NaF (3.78 g, 90.0 mmol) and water (1.22 mL) at 5 °C, and the mixture was stirred at room temperature for 30 min. Insoluble materials were removed by filtration and washed with THF. The filtrate was evaporated and purified by silica gel column chromatography (hexane−EtOAc, 4:1 elution) to give **4j** (2.93 g, 76%) as an oil: ^1H NMR ($CDCl_3$) δ 6.40 (2H, dd, J = 2.2, 2.2 Hz), 7.16 (2H, dd, J = 2.2, 2.2 Hz), 7.55−7.80 (3H, m), 7.90−7.95 (1H, m), 10.06 (1H, s); IR (neat) 3130, 1699, 1651, 1591, 1502 cm^{-1}; MS m/z 172 (MH^+).

4-(1*H*-Pyrazol-1-yl)benzaldehyde (4k). To a solution of 4-fluorobenzaldehyde **19** (1.0 g, 8.06 mmol) and pyrazole (0.66 g, 9.67 mmol) in DMF (10 mL) was added powdered K_2CO_3 (1.34 g, 9.67 mmol), and the mixture was stirred at 120 °C for 5 h. After cooling, the reaction mixture was diluted with EtOAc (60 mL), washed with water and brine, dried ($MgSO_4$), evaporated, and purified by silica gel column chromatography (hexane−EtOAc, 3:1 elution) to give **4k** (1.09 g, 78%) as a solid: ^1H NMR ($CDCl_3$) δ 6.54 (1H, dd, J = 2.5, 1.8 Hz), 7.79 (1H, d, J = 1.5 Hz), 7.85−8.10 (5H, m), 10.02 (1H, s); IR (KBr) 1695, 1605, 1390, 1200 cm^{-1}; MS m/z 173 (MH^+).

The following compounds (**4l**−**m**) were prepared in a similar manner from 4-fluorobenzaldehyde **19** and the appropriate azole compound.

4-(Imidazol-1-yl)benzaldehyde (4l): yield 758 mg (55%); ^1H NMR ($CDCl_3$) δ 7.27 (1H, s), 7.38 (1H, s), 7.59 (2H, d, J = 8.5 Hz), 8.00 (1H, s), 8.03 (2H, d, J = 8.5 Hz), 10.05 (1H, s); IR (KBr) 3109, 1686, 1605, 1524, 1483 cm^{-1}; MS m/z 173 (MH^+).

4-(1*H*-1,2,4-Triazol-1-yl)benzaldehyde (4m): yield 1.95 g (47%); ^1H NMR ($CDCl_3$) δ 7.92 (2H, d, J = 8.6 Hz), 8.06 (2H, d, J = 8.6 Hz), 8.16 (1H, s), 8.70 (1H, s), 10.07 (1H, s); IR (KBr) 3130, 2856, 1709, 1603, 1518, 1441, 1275 cm^{-1}; MS m/z 174 (MH^+).

4-(1*H*-1,2,3-Triazol-1-yl)benzaldehyde (4n) and 4-(2*H*-1,2,3-Triazol-2-yl)benzaldehyde (4o). To a solution of 4-fluorobenzaldehyde **19** (5.0 g, 40.3 mmol) and 1,2,3-triazole (3.33 g, 48.3 mmol) in DMF (50 mL) was added powdered K_2CO_3 (6.68 g, 48.3 mmol), and the mixture was stirred at 120 °C for 1 h. After cooling, the reaction mixture was diluted with EtOAc (300 mL), washed with water and brine, dried ($MgSO_4$), and evaporated to about 50 mL. The resulting precipitate was collected and washed with hexane to give pure **4n** (3.44 g, 49%) as a solid. The mother liquor was then evaporated to about 10 mL and the resulting precipitate collected by a similar procedure to give pure **4o** (297 mg, 4%) as a solid. **4n**: ^1H NMR ($CDCl_3$) δ 7.91 (1H, s), 7.99 (2H, d, J = 8.5 Hz), 8.08 (2H, d, J = 8.5 Hz), 8.12 (1H, s), 10.09 (1H, s); IR (KBr) 3138, 3116, 2845, 1695, 1603, 1516, 1419, 1389 cm^{-1}; MS m/z 174 (MH^+). **4o**: ^1H NMR ($CDCl_3$) δ 7.89 (2H, s), 8.02 (2H, d, J = 8.6 Hz), 8.29 (2H, d, J = 8.6 Hz), 10.06 (1H, s); IR (KBr) 3114, 3084, 2715, 1699, 1603, 1508, 1408, 1383 cm^{-1}; MS m/z 174 (MH^+).

4-(4-Methylpiperazin-1-yl)benzaldehyde (4p). To a solution of 4-fluorobenzaldehyde **19** (6.21 g, 50 mmol) and 1-methylpiperazine (6.01 g, 60 mmol) in DMF (100 mL) was added powdered K_2CO_3 (8.29 g, 60 mmol), and the mixture was stirred at 150 °C for 4.5 h. After cooling, the reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with water and brine, dried ($MgSO_4$), evaporated, and purified by silica gel column chromatography (CH_2Cl_2−MeOH, 10:1 elution) to give **4p** (5.31 g, 52%) as a solid: ^1H NMR (DMSO-d_6) δ 2.22 (3H, s), 2.35−2.48 (4H, m), 3.30−3.42 (4H, m), 7.04 (2H, d, J = 8.8 Hz), 7.70 (2H, d, J = 8.8 Hz), 9.71 (1H, s); IR (KBr) 2935, 2839, 2791, 2748, 1691, 1599, 1518, 1448 cm^{-1}; MS m/z 205 (MH^+).

4-(Pyrazol-3-yl)benzaldehyde (4q). A mixture of ethyl 4-acetylbenzoate **20a** (10 g, 52.1 mmol) and *N*,*N*-dimethylformamide dimethyl acetal (41.8 mL, 312.6 mmol) was heated at 85 °C for 18 h. After cooling, the resulting solid was

collected and washed with iPE to give methyl 4-(3-(dimethylamino)-1-oxo-2(*E*)-propenyl)benzoate **21a** (10.4 g, 86%) as a solid: ^{1}H NMR (DMSO-d_6) δ 2.94 (3H, s), 3.17 (3H, s), 3.88 (3H, s), 5.85 (1H, d, J = 12.2 Hz), 7.77 (1H, d, J = 12.2 Hz), 7.90−8.05 (4H, m); IR (KBr) 1718, 1637, 1578, 1541, 1425 cm^{-1}; MS m/z 234 (MH$^+$).

To a suspension of **21a** (5.0 g, 21.5 mmol) in MeOH (150 mL) were added AcOH (1.84 mL, 32.2 mmol) and $H_2NNH_2 \cdot H_2O$ (1.56 mL, 32.2 mmol). After 10 h of stirring at room temperature, solvents were evaporated. The residue was dissolved in EtOAc, washed with water and brine, dried ($MgSO_4$), and evaporated to give methyl 4-(pyrazol-3-yl)benzoate **22a** (4.21 g, 97%) as a solid: ^{1}H NMR (DMSO-d_6) δ 3.86 (3H, s), 6.85 (1H, d, J = 2.2 Hz), 7.84 (1H, br s), 7.85−8.10 (4H, m), 13.10, 13.55 (total 1H, each br s); IR (KBr) 3500−2800 (br), 1709, 1610, 1537, 1439, 1414 cm^{-1}; MS m/z 203 (MH$^+$).

To a suspension of $LiAlH_4$ (1.02 g, 26.9 mmol) in THF (120 mL) was added dropwise a solution of **22a** (4.18 g, 20.7 mmol) in THF (60 mL) at 5 °C, and the mixture was stirred at 50 °C for 4 h. After cooling, anhydrous NaF (4.52 g, 107.6 mmol) and water (1.45 mL) were added at 5 °C, and the mixture was stirred at room temperature for 1 h. Insoluble materials were removed by filtration and washed with THF, and the filtrate was evaporated to give 4-(pyrazol-3-yl)benzyl alcohol (3.33 g, 93%) as a solid: ^{1}H NMR (DMSO-d_6) δ 4.51 (2H, d, J = 5.7 Hz), 5.07−5.27 (1H, m), 6.60−6.74 (1H, br s), 7.20−7.85 (5H, m), 12.82, 13.24 (total 1H, each br s); IR (KBr) 3178 (br), 1522, 1456, 1419, 1032, 841, 762 cm^{-1}; MS m/z 175 (MH$^+$).

To a solution of the above benzyl alcohol (3.23 g, 18.6 mmol) in acetone (300 mL) was added activated MnO_2 (32.3 g, 371 mmol), and the mixture was refluxed for 1 h. The cooled mixture was then filtered and evaporated to give **4q** (2.98 g, 93%) as an oil: ^{1}H NMR (DMSO-d_6) δ 6.90 (1H, d, J = 2.3 Hz), 7.83 (1H, br s), 7.85−8.12 (4H, m), 10.00 (1H, s), 13.13 (1H, br); IR (neat) 3700−2400 (br), 1697, 1606, 1211, 1171, 837 cm^{-1}; MS m/z 173 (MH$^+$).

3-(Pyrazol-3-yl)benzaldehyde (4r). A mixture of 3-acetylbenzonitrile **20b** (90 g, 0.62 mol) and *N*,*N*-dimethylformamide dimethyl acetal (164 mL, 1.24 mol) was heated at 90 °C for 2 h. After cooling, excess reagent was removed by evaporation, and the resulting solid was collected and washed with iPE to give 3-(3-(dimethylamino)-1-oxo-2(*E*)-propenyl)benzonitrile **21b** (98.4 g, 79%) as a solid: ^{1}H NMR (DMSO-d_6) δ 2.96 (3H, s), 3.17 (3H, s), 5.92 (1H, d, J = 12.1 Hz), 7.65 (1H, dd, J = 7.8, 7.8 Hz), 7.78 (1H, d, J = 12.1 Hz), 7.88−8.00 (1H, m), 8.14−8.26 (1H, m), 8.34 (1H, s); IR (KBr) 3070, 2910, 2800, 2226, 1643, 1599, 1551, 1417, 1360, 1111, 762 cm^{-1}; MS m/z 201 (MH$^+$).

To a solution of **21b** (108.7 g, 0.54 mol) in MeOH (1.0 L) were added AcOH (46.6 mL, 0.81 mol) and $H_2NNH_2 \cdot H_2O$ (39.4 mL, 0.81 mol) at 5 °C. After 24 h of stirring at room temperature, solvent was evaporated. The residue was dissolved in EtOAc (1 L), washed with saturated $NaHCO_3$ solution, water, and brine, dried ($MgSO_4$), and evaporated to give 3-(pyrazol-3-yl)benzonitrile **22b** (91.8 g, 100%) as a solid: ^{1}H NMR (DMSO-d_6) δ 6.89 (1H, dd, J = 2.0, 2.0 Hz), 7.61 (1H, dd, J = 7.8, 7.8 Hz), 7.68−7.80 (1H, m), 7.84 (1H, dd, J = 2.3, 1.5 Hz), 8.12−8.30 (3H, m), 13.08, 13.46 (total 1H, each br); IR (KBr) 3470−2330 (br), 2227, 1558, 1466, 1356, 1055, 760 cm^{-1}; MS m/z 170 (MH$^+$).

To a suspension of **22b** (91.8 g, 0.54 mol) in HCO_2H (730 mL) was added a suspension of Raney nickel (NDT-90) (180 mL) in water (140 mL), and the mixture was refluxed for 3 h. After the mixture was cooled to room temperature, Raney nickel was filtered off and washed with HCO_2H (500 mL). The filtrate was evaporated to 200 mL, and CH_2Cl_2 (1.0 L) was added thereto. The mixture was adjusted to pH 8−9 with 5 N NaOH solution under ice cooling. The resulting insoluble materials were removed by filtration. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with water and brine, dried ($MgSO_4$), evaporated, and purified by silica gel column chromatography (CH_2Cl_2−MeOH, 20:1 elution) to give **4r** (80.4 g, 86%) as an oil: ^{1}H NMR (DMSO-d_6) δ 6.84 (1H, d, J = 2.2 Hz), 7.64 (1H, dd, J = 7.5, 7.5 Hz), 7.70−7.95 (2H, m), 8.15 (1H, d, J = 7.5 Hz), 8.34 (1H, s), 10.07 (1H, s), 13.03 (1H, br s); IR (neat) 3680−2460 (br), 1693, 1606, 1587, 1188, 768 cm^{-1}; MS m/z 173 (MH$^+$).

4-(1-Methyl-1*H*-pyrazol-3-yl)benzaldehyde (4s) and 4-(2-Methyl-2*H*-pyrazol-3-yl)benzaldehyde (4t). To a solution of **21a** (5.23 g, 22.5 mmol) in AcOH (50 mL) was added $MeNHNH_2$ (1.31 mL, 24.7 mmol), and the mixture was stirred at room temperature for 3 h. To the solution was added 5 N NaOH solution (180 mL) under ice cooling, and the mixture was extracted with EtOAc. The organic layer was washed with saturated $NaHCO_3$ solution, water, and brine, dried ($MgSO_4$), evaporated, and purified by silica gel column chromatography (CH_2Cl_2−MeOH, 120:1 elution) to give first methyl 4-(1-methyl-1*H*-pyrazol-3-yl)benzoate **23a** (3.14 g, 65%) as a solid and then methyl 4-(2-methyl-2*H*-pyrazol-3-yl)benzoate **23b** (1.63 g, 34%) as a solid. **23a**: ^{1}H NMR ($CDCl_3$) δ 3.92 (3H, s), 3.97 (3H, s), 6.61 (1H, d, J = 2.2 Hz), 7.41 (1H, d, J = 2.2 Hz), 7.86 (2H, d, J = 8.3 Hz), 8.06 (2H, d, J = 8.3 Hz); IR (KBr) 3134, 2949, 1705, 1612, 1439, 1344, 1281 cm^{-1}; MS m/z 217 (MH$^+$). **23b**: ^{1}H NMR ($CDCl_3$) δ 3.93 (3H, s), 3.96 (3H, s), 6.38 (1H, d, J = 2.0 Hz), 7.51 (2H, d, J = 8.3 Hz), 7.54 (1H, d, J = 2.0 Hz), 8.13 (2H, d, J = 8.3 Hz); IR (KBr) 3135, 2960, 1718, 1614, 1464, 1425, 1286 cm^{-1}; MS m/z 217 (MH$^+$).

To a solution of **23a** (2.5 g, 11.6 mmol) in CH_2Cl_2 (80 mL) was added dropwise DIBAL (1.02 M toluene solution, 25.0 mL, 25.5 mmol) at −50 °C, and the mixture was stirred at the same temperature for 30 min. To the mixture were added anhydrous NaF (4.28 g, 102.0 mmol) and water (1.38 mL), and the mixture was stirred at room temperature for 1 h. Insoluble materials were removed by filtration and washed with CH_2Cl_2, and the filtrate was evaporated to give 4-(1-methyl-1*H*-pyrazol-3-yl)benzyl alcohol (1.74 g, 80%) as a solid: ^{1}H NMR ($CDCl_3$) δ 1.90 (1H, t, J = 5.7 Hz), 3.95 (3H, s), 4.70 (2H, d, J = 5.7 Hz), 6.54 (1H, d, J = 2.2 Hz), 7.33−7.43 (3H, m), 7.78 (2H, d, J = 8.2 Hz); IR (KBr) 3250 (br), 1508, 1462, 1431, 1360, 1302 cm^{-1}; MS m/z 189 (MH$^+$).

To a solution of the above benzyl alcohol (1.50 g, 8.0 mmol) in acetone (150 mL) was added activated MnO_2 (13.9 g, 160 mmol), and the mixture was refluxed for 1 h. The cooled mixture was then filtered and evaporated to give **4s** (1.45 g, 98%) as a solid: ^{1}H NMR ($CDCl_3$) δ 3.99 (3H, s), 6.64 (1H, d, J = 2.3 Hz), 7.43 (1H, d, J = 2.3 Hz), 7.86−8.03 (4H, m), 10.01 (1H, s); IR (KBr) 1695, 1603, 1566, 1431, 1306 cm^{-1}; MS m/z 187 (MH$^+$).

To a suspension of $LiAlH_4$ (264 mg, 6.94 mmol) in THF (40 mL) was added dropwise a solution of **23b** (1.50 g, 6.94 mmol) in THF (25 mL) at 5 °C, and the mixture was stirred at the same temperature for 30 min. To the mixture were added anhydrous NaF (1.17 g, 27.8 mmol) and water (0.38 mL), and the mixture was stirred at room temperature for 1.5 h. Insoluble materials were removed by filtration and washed with THF, and the filtrate was evaporated to give 4-(2-methyl-2*H*-pyrazol-3-yl)benzyl alcohol (1.30 g, 99%) as a solid: ^{1}H NMR ($CDCl_3$) δ 2.12 (1H, t, J = 5.7 Hz), 3.88 (3H, s), 4.77 (2H, d, J = 5.7 Hz), 6.30 (1H, d, J = 1.9 Hz), 7.35−7.52 (4H, m), 7.51 (1H, d, J = 1.9 Hz); IR (KBr) 3298 (br), 1495, 1460, 1425, 1385, 1273 cm^{-1}; MS m/z 189 (MH$^+$).

To a solution of the above benzyl alcohol (1.27 g, 6.8 mmol) in acetone (130 mL) was added activated MnO_2 (11.8 g, 135 mmol), and the mixture was refluxed for 1 h. The cooled mixture was then filtered, and the filtrate was evaporated to give **4t** (1.17 g, 93%) as a solid: ^{1}H NMR ($CDCl_3$) δ 3.95 (3H, s), 6.41 (1H, d, J = 1.9 Hz), 7.56 (1H, d, J = 1.9 Hz), 7.61 (2H, d, J = 8.2 Hz), 7.98 (2H, d, J = 8.2 Hz), 10.08 (1H, s); IR (KBr) 1695, 1608, 1568, 1390, 1215, 1184 cm^{-1}; MS m/z 187 (MH$^+$).

3-(1-Methyl-1*H*-pyrazol-3-yl)benzaldehyde (4u) and 3-(2-Methyl-2*H*-pyrazol-3-yl)benzaldehyde (4v). To a solution of **21b** (8.0 g, 40.0 mmol) in AcOH (80 mL) was added $MeNHNH_2$ (2.23 mL, 42.0 mmol), and the mixture was stirred at room temperature for 3.5 h. A 5 N NaOH solution was added under ice cooling, and the mixture was extracted with EtOAc. The organic layer was washed with saturated $NaHCO_3$ solution, water, and brine, dried ($MgSO_4$), and evaporated,

and the residue was purified by silica gel column chromatography (CH_2Cl_2−MeOH, 120:1 to 60:1 elution) to give first 3-(1-methyl-1*H*-pyrazol-3-yl)benzonitrile **24a** (4.45 g, 61%) as a solid and then 3-(2-methyl-2*H*-pyrazol-3-yl)benzonitrile **24b** (2.09 g, 29%) as a solid. **24a**: ^{1}H NMR ($CDCl_3$) δ 3.97 (3H, s), 6.56 (1H, d, J = 2.3 Hz), 7.38−7.60 (3H, m), 7.95−8.10 (2H, m); IR (KBr) 3115, 2935, 2220, 1602, 1471, 1352, 1246 cm^{-1}; MS m/z 184 (MH^+). **24b**: ^{1}H NMR ($CDCl_3$) δ 3.92 (3H, s), 6.37 (1H, d, J = 1.5 Hz), 7.50−7.75 (5H, m); IR (KBr) 3066, 2951, 2231, 1475, 1416, 1335, 1236 cm^{-1}; MS m/z 184 (MH^+).

To a solution of **24a** (3.81 g, 20.8 mmol) in CH_2Cl_2 (120 mL) was added dropwise DIBAL (1.01 M toluene solution, 41.2 mL, 41.6 mmol) at −60 °C, and the mixture was stirred at the same temperature for 30 min. To the mixture were added anhydrous NaF (7.0 g, 166.6 mmol) and water (2.25 mL), and the mixture was stirred at room temperature for 3 h. Insoluble materials were removed by filtration and washed with CH_2Cl_2. The filtrate was evaporated, and the residue was dissolved in THF (20 mL). Then 1 N HCl (40 mL) was added and the solution stirred at room temperature for 3 h. A 5 N NaOH solution (8 mL) was then added and the mixture was extracted with CH_2Cl_2. The organic layer was washed with water and brine, dried ($MgSO_4$), evaporated, and purified by silica gel column chromatography (hexane−EtOAc, 1:2 elution) to give **4u** (3.24 g, 84%) as an oil: ^{1}H NMR ($CDCl_3$) δ 3.98 (3H, s), 6.62 (1H, d, J = 2.2 Hz), 7.42 (1H, d, J = 2.2 Hz), 7.51−7.62 (1H, m), 7.77−7.86 (1H, m), 8.05−8.13 (1H, m), 8.25−8.32 (1H, m), 10.07 (1H, s); IR (neat) 2941, 2829, 2730, 1695, 1606, 1585, 1439, 1242 cm^{-1}; MS m/z 187 (MH^+).

To a solution of **24b** (1.99 g, 10.9 mmol) in CH_2Cl_2 (60 mL) was added dropwise DIBAL (1.01 M toluene solution, 21.5 mL, 21.8 mmol) at −60 °C, and the mixture was stirred at the same temperature for 30 min. To the mixture were added anhydrous NaF (3.65 g, 87.0 mmol) and water (1.17 mL), and the mixture was stirred at room temperature for 2 h. Insoluble materials were removed by filtration and washed with CH_2Cl_2. The filtrate was evaporated, and the residue was dissolved in THF (10 mL). Then 1 N HCl (20 mL) was added and the solution stirred at room temperature for 2 h. A 5 N NaOH solution (4 mL) was then added, and the mixture was extracted with CH_2Cl_2. The organic layer was washed with water and brine, dried ($MgSO_4$), evaporated, and purified by silica gel column chromatography (hexane−EtOAc, 1:2 elution) to give **4v** (1.47 g, 73%) as a solid: ^{1}H NMR ($CDCl_3$) δ 3.94 (3H, s), 6.39 (1H, d, J = 1.4 Hz), 7.56 (1H, d, J = 1.4 Hz), 7.58−7.74 (2H, m), 7.89−7.97 (2H, m), 10.09 (1H, s); IR (KBr) 3041, 2831, 2733, 1697, 1579, 1462, 1377 cm^{-1}; MS m/z 187 (MH^+).

3-(1-Trityl-1*H*-pyrazol-4-yl)benzaldehyde (4w). To a solution of 4-bromopyrazole **25** (5.00 g, 34.0 mmol) and Et_3N (4.52 mL, 32.4 mmol) in DMF (45 mL) was added trityl chloride (9.03 g, 32.4 mmol) at 5 °C, and the mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with $CHCl_3$, washed with water and brine, dried ($MgSO_4$), and evaporated. The resulting solid was collected and washed with iPE to give 4-bromo-1-trityl-1*H*-pyrazole **26** (9.00 g, 71%) as a solid: ^{1}H NMR ($CDCl_3$) δ 7.07−7.23 (6H, m), 7.23−7.42 (9H, m), 7.38 (1H, d, J = 0.6 Hz), 7.62 (1H, d, J = 0.6 Hz); MS m/z 243 (Ph_3C^+).

To a solution of 2-(3-bromophenyl)-1,3-dioxolane **27** (4.58 g, 20.0 mmol) and triisopropyl borate (5.27 g, 28.0 mmol) in THF (100 mL) was added dropwise *n*-BuLi (1.70 M hexane solution, 16.5 mL, 28.0 mmol) at −70 °C over 50 min. The mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was poured into 2 N HCl (40 mL), stirred for 40 min, and extracted with EtOAc. The organic layer was washed with water and brine, dried ($MgSO_4$), evaporated, and purified by silica gel column chromatography (EtOAc elution) to give 3-formylphenylboric acid **28** (620 mg, 21%) as a solid: ^{1}H NMR (DMSO-d_6) δ 7.58 (1H, dd, J = 7.5, 7.5 Hz), 7.94 (1H, d, J = 7.5 Hz), 8.11 (1H, d, J = 7.5 Hz), 8.33 (3H, br s), 10.03 (1H, s); IR (KBr) 3363, 1678, 1603, 1581 cm^{-1}; MS m/z 151 (MH^+).

To a suspension of **26** (19.0 g, 48.7 mmol) and **28** (14.6 g, 97.4 mmol) in toluene (400 mL) were added powdered K_2CO_3 (10.1 g, 73.1 mmol) and $Pd(PPh_3)_4$ (2.8 g, 2.4 mmol), and the mixture was refluxed for 6 h. The reaction mixture was poured into a mixture of EtOAc and ice water. The separated organic layer was washed with water and brine, dried ($MgSO_4$), evaporated, and purified by silica gel column chromatography (hexane−EtOAc, 5:1 elution) to give **4w** (2.65 g, 13%) as a solid: ^{1}H NMR (DMSO-d_6) δ 7.00−7.15 (6H, m), 7.30−7.45 (9H, m), 7.52 (1H, s), 7.76 (1H, s), 7.76 (1H, dd, J = 7.7, 7.7 Hz), 7.97 (1H, d, J = 7.7 Hz), 8.13 (1H, d, J = 7.7 Hz), 8.31 (1H, s), 10.13 (1H, s); IR (KBr) 3057, 3024, 1699, 1603, 1585, 1491, 1444 cm^{-1}; MS m/z 243 (Ph_3C^+).

4-(1-Methyl-1*H*-pyrazol-4-yl)benzaldehyde (4x). To a solution of 4-bromo-1-methyl-1*H*-pyrazole **29** (1.0 g, 6.2 mmol) in ether (15 mL) was added dropwise *n*-BuLi (1.63 M hexane solution, 4.2 mL, 6.83 mmol), keeping the temperature below −60 °C, and the mixture was stirred at the same temperature for 30 min. To the anion solution was added tri-*n*-butyltin chloride (1.85 mL, 6.83 mmol) in ether (1.85 mL) dropwise, followed by stirring for 1 h. The mixture was then warmed to room temperature over 30 min and stirred for an additional 1 h. The reaction mixture was diluted with ether, washed with water and brine, dried ($MgSO_4$), and evaporated to give crude 1-methyl-4-(tri-*n*-butylstannyl)-1*H*-pyrazole **30** (2.3 g, 100%) as an oil that was used directly in the next reaction: ^{1}H NMR ($CDCl_3$) δ 0.75−1.70 (27H, m), 3.93 (3H, s), 7.23 (1H, s), 7.42 (1H, s); IR (neat) 2930, 1504, 1460, 1120 cm^{-1}.

To a solution of 4-bromobenzaldehyde **31a** (462 mg, 2.5 mmol) and **30** (1.1 g, 3.0 mmol) in xylene (6 mL) was added $Pd(PPh_3)_4$ (87 mg, 0.075 mmol), and the mixture was heated at 140 °C for 3 h. After cooling, the reaction mixture was diluted with toluene (6 mL), and an aqueous solution (5 mL) of KF (1.74 g, 30 mmol) was added thereto. After 1 h of stirring at room temperature, insoluble materials were filtered off. The filtrate was washed with water and brine, dried ($MgSO_4$), evaporated, and purified by silica gel column chromatography (hexane−EtOAc, 1:2 elution) to give **4x** (427 mg, 92%) as a solid: ^{1}H NMR ($CDCl_3$) δ 3.98 (3H, s), 7.62 (2H, d, J = 8.3 Hz), 7.73 (1H, s), 7.85 (1H, s), 7.87 (2H, d, J = 8.3 Hz), 9.98 (1H, s); IR (KBr) 1693, 1605, 1169, 831 cm^{-1}; MS m/z 187 (MH^+).

The following compound was prepared in a similar manner from 3-bromobenzaldehyde **31b** (6.74 mmol) and **30** (8.09 mmol).

3-(1-Methyl-1*H*-pyrazol-4-yl)benzaldehyde (4y): yield 978 mg (78%); ^{1}H NMR ($CDCl_3$) δ 3.98 (3H, s), 7.47−7.58 (1H, m), 7.65−7.78 (3H, m), 7.83 (1H, s), 7.93−7.98 (1H, m), 10.04 (1H, s); IR (neat) 2943, 2818, 1686, 1608, 1230, 1174 cm^{-1}; MS m/z 187 (MH^+).

3-(Imidazol-4-yl)benzaldehyde (4z). A suspension of 3-acetylbenzonitrile **20b** (25.4 g, 0.175 mol) in ether−1,4-dioxane (10:1, 275 mL) was treated dropwise with bromine (9.0 mL, 0.175 mol) at room temperature and then stirred for 40 min. The mixture was then treated with an aqueous solution (200 mL) of $NaHCO_3$ (15 g, 0.18 mol) under ice cooling and extracted with EtOAc. The organic layer was washed with saturated $NaHCO_3$ solution, water, and brine, dried ($MgSO_4$), and evaporated to give crude 3-(bromoacetyl)benzonitrile (39.2 g, 100%) as a solid: ^{1}H NMR ($CDCl_3$) δ 4.42 (2H, s), 7.66 (1H, dd, J = 8.1, 8.1 Hz), 7.85−7.95 (1H, m), 8.18−8.32 (2H, m); IR (KBr) 3103, 3068, 2941, 2229, 1707, 1599, 1429, 1279, 1223, 1149 cm^{-1}.

A mixture of 3-(bromoacetyl)benzonitrile (38.2 g, 0.17 mol) and $HCONH_2$ (190 mL) was heated at 185 °C for 30 min. After being cooled to room temperature, the reaction mixture was poured into saturated $NaHCO_3$ solution (400 mL) and extracted with EtOAc (1.8 L). The organic layer was washed with water and brine, dried ($MgSO_4$), and evaporated. The resulting precipitate was collected and washed with EtOAc−iPE (2:1) to give 3-(imidazol-4-yl)benzonitrile **32** (14.8 g, 51%) as a solid: ^{1}H NMR (DMSO-d_6) δ 7.50−7.68 (2H, m), 7.70−7.87 (2H, m), 8.12 (1H, d, J = 7.4 Hz), 8.18 (1H, s), 12.32 (1H,

br s); IR (KBr) 3240−2250 (br), 2224, 1606, 1477, 1333, 1070, 970, 824, 789 cm^{-1}; MS *m/z* 170 (MH^+).

To a suspension of **32** (7.0 g, 41.4 mmol) in HCO_2H (56 mL) was added a suspension of Raney nickel (NDT-90) (14 mL) in water (11 mL), and the mixture was refluxed for 3 h. After cooling, Raney nickel was filtered off and washed with HCO_2H, and the filtrate was evaporated. The residue was dissolved in THF−water, and the mixture was adjusted to pH 8−9 with 5 N NaOH solution under ice cooling. The resulting insoluble materials were removed by filtration. The organic layer was separated, and the aqueous layer was extracted with THF. The combined organic layer was washed with water and brine, dried ($MgSO_4$), and evaporated. The resulting solid was collected and washed with THF−EtOAc to give **4z** (5.27 g, 74%) as a solid: ^1H NMR (DMSO-d_6) δ 7.59 (1H, dd, J = 7.6, 7.6 Hz), 7.67−7.80 (3H, m), 8.05−8.15 (1H, m), 8.31 (1H, s), 10.04 (1H, s), 12.30 (1H, br); IR (KBr) 3390−2080 (br), 1691, 1606, 1479, 1327, 1186, 1066, 978, 781 cm^{-1}; MS *m/z* 173 (MH^+).

4-(Oxazol-5-yl)benzaldehyde (4aa). To a solution of methyl 4-formylbenzoate **33** (4.0 g, 24.4 mmol) and tosylmethyl isocyanide (TosMIC) (5.0 g, 25.6 mmol) in MeOH (40 mL) was added powdered K_2CO_3 (3.54 g, 25.6 mmol), and the mixture was refluxed for 3.5 h. After cooling, the reaction mixture was diluted with EtOAc (300 mL), washed with water and brine, dried ($MgSO_4$), evaporated, and purified by silica gel column chromatography (hexane−EtOAc, 2:1 to 1:1 elution) to give methyl 4-(oxazol-5-yl)benzoate **34** (4.04 g, 82%) as a solid: ^1H NMR ($CDCl_3$) δ 3.94 (3H, s), 7.48 (1H, s), 7.73 (2H, d, J = 8.7 Hz), 7.97 (1H, s), 8.10 (2H, d, J = 8.7 Hz); IR (KBr) 3118, 1726, 1614, 1275, 1109 cm^{-1}; MS *m/z* 204 (MH^+).

To a suspension of $LiAlH_4$ (826 mg, 21.8 mmol) in THF (100 mL) was added dropwise a solution of **34** (4.42 g, 21.8 mmol) in THF (40 mL) at 5 °C, and the mixture was stirred at the same temperature for 30 min. To the mixture were added anhydrous NaF (3.66 g, 87.1 mmol) and water (1.18 mL), and the mixture was stirred at room temperature for 30 min. Insoluble materials were removed by filtration and washed with THF. The filtrate was evaporated to give 4-(oxazol-5-yl)benzyl alcohol (3.32 g, 87%) as a solid: ^1H NMR ($CDCl_3$) δ 4.74 (2H, s), 7.34 (1H, s), 7.43 (2H, d, J = 8.1 Hz), 7.65 (2H, d, J = 8.1 Hz), 7.91 (1H, s); IR (KBr) 3330 (br), 1510, 1491, 1041, 818 cm^{-1}; MS *m/z* 176 (MH^+).

To a solution of oxalyl chloride (1.5 mL, 17.2 mmol) in CH_2Cl_2 (30 mL) was added a solution of DMSO (1.83 mL, 25.7 mmol) in CH_2Cl_2 (4 mL), keeping the temperature below −60 °C, and the mixture was stirred for 20 min. To the mixture was added a solution of 4-(oxazol-5-yl)benzyl alcohol (2.5 g, 14.3 mmol) in CH_2Cl_2 (25 mL) and DMSO (2 mL) at the same temperature, and the mixture was then stirred for 1 h. To the reaction mixture was added Et_3N (8 mL, 57.2 mmol), and the mixture was then stirred for 30 min and warmed to room temperature over 30 min. After 1 h of stirring, the mixture was diluted with EtOAc, washed with water and brine, dried ($MgSO_4$), evaporated, and purified by silica gel column chromatography (hexane−EtOAc, 1:1 elution) to give **4aa** (2.20 g, 89%) as a solid: ^1H NMR ($CDCl_3$) δ 7.54 (1H, s), 7.83 (2H, d, J = 8.5 Hz), 7.96 (2H, d, J = 8.5 Hz), 8.00 (1H, s), 10.03 (1H, s); IR (KBr) 3124, 1693, 1610, 1211, 1111, 829 cm^{-1}; MS *m/z* 174 (MH^+).

4-(5-Methyl-1,3,4-oxadiazol-2-yl)benzaldehyde (4ab). To a solution of methyl 4-formylbenzoate **33** (5.0 g, 30.5 mmol) in EtOH (50 mL) was added carefully $NaBH_4$ (576 mg, 15.3 mmol) at 5 °C, followed by stirring at the same temperature for 30 min. The mixture was poured into water and extracted with CH_2Cl_2. The organic layer was washed with water and brine, dried ($MgSO_4$), and evaporated to give methyl 4-hydroxymethylbenzoate (5.06 g, 100%) as a solid: ^1H NMR ($CDCl_3$) δ 1.89 (1H, t, J = 5.9 Hz), 3.92 (3H, s), 4.77 (2H, d, J = 5.9 Hz), 7.44 (2H, d, J = 8.2 Hz), 8.03 (2H, d, J = 8.2 Hz); IR (KBr) 3304 (br), 1722, 1614, 1437, 1286, 1111, 1047, 1016, 756 cm^{-1}; MS *m/z* 167 (MH^+).

A solution of methyl 4-hydroxymethylbenzoate (5.0 g, 30.1 mmol) and imidazole (4.1 g, 60.2 mmol) in DMF (25 mL) was treated with TBDMSCl (4.77 g, 31.6 mmol) at 5 °C, and then the mixture was stirred at ambient temperature for 1.5 h. The mixture was poured into 0.1 N HCl (100 mL) and extracted with EtOAc. The organic layer was washed with water and brine, dried ($MgSO_4$), and evaporated to give methyl 4-(((*tert*-butyldimethylsilyl)oxy)methyl)benzoate (8.43 g, 100%) as an oil: ^1H NMR ($CDCl_3$) δ 0.11 (6H, s), 0.95 (9H, s), 3.91 (3H, s), 4.79 (2H, s), 7.39 (2H, d, J = 8.2 Hz), 8.01 (2H, d, J = 8.2 Hz); IR (neat) 2954, 2859, 1724, 1464, 1281, 1107, 841 cm^{-1}; MS *m/z* 281 (MH^+).

A mixture of the above ester (1.0 g, 3.57 mmol) and $H_2NNH_2 \cdot H_2O$ (0.87 mL, 17.9 mmol) in EtOH (0.8 mL) was refluxed for 1 h. After cooling, the reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with water and brine, dried ($MgSO_4$), and evaporated to give 4-(((*tert*-butyldimethylsilyl)oxy)methyl)-benzoic acid hydrazide **35** (1.0 g, 100%) as a solid: ^1H NMR (DMSO-d_6) δ 0.08 (6H, s), 0.91 (9H, s), 4.47 (2H, s), 4.75 (2H, s), 7.36 (2H, d, J = 8.2 Hz), 7.79 (2H, d, J = 8.2 Hz), 9.72 (1H, s); IR (KBr) 3273 (br), 2954, 2858, 1662, 1599, 1539, 1335, 1254, 1093, 841 cm^{-1}; MS *m/z* 281 (MH^+).

To a mixture of **35** (8.0 g, 28.6 mmol) and ethyl acetimidate hydrochloride (4.24 g, 34.3 mmol) in EtOH (160 mL) was added Et_3N (4.8 mL, 34.3 mmol) at room temperature, and the mixture was stirred for 30 min. After evaporation, the residue was dissolved in EtOAc (120 mL), washed with water and brine, dried ($MgSO_4$), and evaporated. The resulting residue was then heated neat at 200 °C for 10 min, cooled to room temperature, and purified by silica gel column chromatography (hexane−EtOAc, 2:1 elution) to give 2-[4-(((*tert*-butyldimethylsilyl)oxy)methyl)phenyl]-5-methyl-1,3,4-oxadiazole **36** (6.35 g, 73%) as a solid: ^1H NMR (DMSO-d_6) δ 0.10 (6H, s), 0.92 (9H, s), 2.58 (3H, s), 4.80 (2H, s), 7.52 (2H, d, J = 8.2 Hz), 7.95 (2H, d, J = 8.2 Hz); IR (KBr) 2956, 2933, 2897, 2860, 1576, 1502, 1257, 1086, 843 cm^{-1}; MS *m/z* 305 (MH^+).

A solution of **36** (2.0 g, 6.6 mmol) in MeOH (20 mL) was treated dropwise with 1 N HCl (13 mL, 13.0 mmol) at 5 °C, and the mixture was then stirred at room temperature for 1 h. The reaction mixture was then recooled to 5 °C, $NaHCO_3$ (1.15 g, 13.7 mmol) was added carefully, and the mixture was extracted with CH_2Cl_2. The organic layer was washed with water and brine, dried ($MgSO_4$), and evaporated. The resulting solid was collected and washed with hexane to give 4-(5-methyl-1,3,4-oxadiazol-2-yl)benzyl alcohol (0.75 g, 60%) as a solid: ^1H NMR (DMSO-d_6) δ 2.58 (3H, s), 4.59 (2H, d, J = 5.4 Hz), 5.39 (1H, t, J = 5.4 Hz), 7.53 (2H, d, J = 8.1 Hz), 7.93 (2H, d, J = 8.1 Hz); IR (KBr) 3323 (br), 2877, 2819, 1614, 1576, 1416, 1257, 1053, 833, 729 cm^{-1}; MS *m/z* 191 (MH^+).

To a solution of the above benzyl alcohol (723 mg, 3.81 mmol) in acetone (75 mL) was added activated MnO_2 (6.62 g, 76.1 mmol), and the mixture was refluxed for 1 h. The cooled mixture was then filtered, and the filtrate was evaporated to give **4ab** (645 mg, 90%) as a solid: ^1H NMR ($CDCl_3$) δ 2.66 (3H, s), 8.02 (2H, d, J = 8.3 Hz), 8.22 (2H, d, J = 8.3 Hz), 10.10 (1H, s); IR (KBr) 2829, 1701, 1610, 1590, 1550, 1421 cm^{-1}; MS *m/z* 189 (MH^+).

***N*-Cycloheptyl-4-(5-methyl-1,2,4-triazol-3-yl)benzylamine (7ba).** A mixture of **36** (5.05 g, 16.6 mmol) and benzylamine (18 mL, 166 mmol) was heated at 150 °C for 2 days. After cooling, the mixture was purified by silica gel column chromatography (CH_2Cl_2−MeOH, 20:1 elution) to give 4-benzyl-3-[4-(((*tert*-butyldimethylsilyl)oxy)methyl)phenyl]-5-methyl-4*H*-1,2,4-triazole **37** (5.04 g, 77%) as a solid: ^1H NMR ($CDCl_3$) δ 0.08 (6H, s), 0.94 (9H, s), 2.37 (3H, s), 4.77 (2H, s), 5.16 (2H, s), 6.90−7.03 (2H, m), 7.27−7.40 (5H, m), 7.50 (2H, d, J = 8.2 Hz); IR (KBr) 2953, 2929, 2885, 2854, 1524, 1460, 1431, 1255, 1101, 1003, 835 cm^{-1}; MS *m/z* 394 (MH^+).

A solution of **37** (3.50 g, 8.9 mmol) in MeOH (35 mL) was treated dropwise with 1 N HCl (17.8 mL, 17.8 mmol) at 5 °C, and the mixture was then stirred at room temperature for 1 h. The reaction mixture was then recooled to 5 °C, $NaHCO_3$ (1.57 g, 18.7 mmol) was added carefully, and the mixture was extracted with CH_2Cl_2. The organic layer was washed with water and brine, dried ($MgSO_4$), and evaporated. The resulting solid was collected and washed with hexane to give 4-(4-

benzyl-5-methyl-4*H*-1,2,4-triazol-3-yl)benzyl alcohol (2.35 g, 95%) as a solid: ^{1}H NMR ($CDCl_3$) δ 2.36 (3H, s), 3.10−3.25 (1H, m), 4.65−4.77 (2H, m), 5.14 (2H, s), 6.90−7.03 (2H, m), 7.25−7.50 (7H, m); IR (KBr) 3188 (br), 1535, 1487, 1425, 1363, 1039, 854, 739 cm^{-1}; MS *m*/*z* 280 (MH^+).

To a solution of the above benzyl alcohol (1.18 g, 4.23 mmol) in acetone (120 mL) was added activated MnO_2 (7.35 g, 84.6 mmol), and the mixture was refluxed for 2 h. The cooled mixture was then filtered, and the filtrate was evaporated to give 4-(4-benzyl-5-methyl-4*H*-1,2,4-triazol-3-yl)benzaldehyde **38** (1.14 g, 97%) as a solid: ^{1}H NMR ($CDCl_3$) δ 2.44 (3H, s), 5.22 (2H, s), 6.93−7.07 (2H, m), 7.30−7.47 (3H, m), 7.73 (2H, d, J = 8.3 Hz), 7.94 (2H, d, J = 8.3 Hz), 10.05 (1H, s); IR (KBr) 3450 (br), 1689, 1608, 1572, 1531, 1207 cm^{-1}; MS *m*/*z* 278 (MH^+).

A mixture of **38** (1.16 g, 4.19 mmol) and cycloheptylamine (0.64 mL, 5.03 mmol) in toluene (20 mL) was heated at 120 °C for 3 h and then cooled to room temperature and evaporated. The residue was dissolved in EtOH (25 mL). To the solution was added carefully $NaBH_4$ (159 mg, 4.19 mmol), and the mixture was stirred at ambient temperature for 2 h. The mixture was poured into water and extracted with CH_2Cl_2. The organic layer was washed with water and brine, dried ($MgSO_4$), evaporated, and purified by silica gel column chromatography (CH_2Cl_2−MeOH, 8:1 elution) to give *N*-cycloheptyl-4-(4-benzyl-5-methyl-4*H*-1,2,4-triazol-3-yl)benzylamine **39** (1.37 g, 87%) as an oil: ^{1}H NMR ($CDCl_3$) δ 1.30−1.93 (12H, m), 2.38 (3H, s), 2.60−2.77 (1H, m), 3.81 (2H, s), 5.16 (2H, s), 6.90−7.05 (2H, m), 7.27−7.44 (5H, m), 7.49 (2H, d, J = 8.2 Hz); IR (neat) 3298, 2924, 2852, 1612, 1527, 1458, 1358 cm^{-1}; MS *m*/*z* 375 (MH^+).

A solution of **39** (500 mg, 1.34 mmol) in MeOH (25 mL) was treated with palladium black (500 mg) and HCO_2H (1.25 mL) and stirred at room temperature for 4.5 h, monitoring by TLC carefully. The catalyst was then filtered off, and the filtrate was basified with 1 N NaOH solution under ice cooling and evaporated to dryness. The residue was dissolved in CH_2Cl_2−MeOH (5:1), dried ($MgSO_4$), evaporated, and purified by silica gel column chromatography (CH_2Cl_2−MeOH, 4:1 elution) to give **7ba** (220 mg, 58%) as an amorphous solid: ^{1}H NMR ($CDCl_3$) δ 1.30−2.00 (12H, m), 2.48 (3H, s), 2.65−2.80 (1H, m), 3.83 (2H, s), 4.60−5.15 (2H, br), 7.36 (2H, d, J = 8.2 Hz), 7.94 (2H, d, J = 8.2 Hz); IR (KBr) 3172 (br), 2926, 2854, 1564, 1458, 1099 cm^{-1}; MS *m*/*z* 285 (MH^+).

3-(2-Trityl-2*H*-tetrazol-5-yl)benzaldehyde (4ac). To a solution of DMF (17.1 mL, 0.22 mol) in EtOAc (50 mL) was added $POCl_3$ (20.3 mL, 0.22 mol) at 5 °C, and the mixture was stirred at room temperature for 1 h. The mixture was diluted with EtOAc (200 mL) and 3-cyanobenzoic acid **40** (25.0 g, 0.17 mol) added thereto at 5 °C. After 30 min of stirring at the same temperature, the mixture was added dropwise to MeOH (100 mL) at 5 °C and stirred at room temperature for 18 h. The reaction mixture was quenched with water (200 mL), adjusted to pH 7 with powdered K_2CO_3, and then extracted with EtOAc. The organic layer was washed with water and brine, dried ($MgSO_4$), evaporated, and purified by silica gel column chromatography (hexane−EtOAc, 5:1 elution) to give methyl 3-cyanobenzoate (18.0 g, 66%) as a solid: ^{1}H NMR (DMSO-d_6) δ 3.90 (3H, s), 7.76 (1H, dd, J = 7.8, 7.8 Hz), 8.15 (1H, ddd, J = 7.8, 1.5, 1.5 Hz), 8.26 (1H, ddd, J = 7.8, 1.5, 1.5 Hz), 8.33 (1H, dd, J = 1.5, 1.5 Hz); IR (neat) 2953, 2229, 1720, 1600, 1444, 1294 cm^{-1}; MS *m*/*z* 162 (MH^+).

A mixture of methyl 3-cyanobenzoate (8.0 g, 49.7 mmol), NaN_3 (19.4 g, 298 mmol), and NH_4Cl (16.0 g, 298 mmol) in DMF (32 mL) was heated at 120 °C for 2.5 h. After cooling, the mixture was poured into a mixture of ice water (300 mL) and EtOAc (100 mL). To the mixture was added $NaNO_2$ (20.5 g, 298 mmol) (to decompose excess NaN_3), followed by 6 N HCl until the pH was adjusted to 1−2 under ice cooling. After 30 min of stirring at room temperature, the mixture was extracted with a mixture of EtOAc and THF. The organic layer was washed with water and brine, dried ($MgSO_4$), and evaporated to give methyl 3-(1*H*-tetrazol-5-yl)benzoate **41** (10.0 g, 99%) as a solid: ^{1}H NMR (DMSO-d_6) δ 3.93 (3H, s), 7.78 (1H, dd, J = 7.9, 7.9 Hz), 8.10−8.20 (1H, m), 8.25−8.38 (1H, m), 8.60−8.70 (1H, m); IR (KBr) 3151 (br), 1705, 1684, 1618, 1562 cm^{-1}; MS *m*/*z* 205 (MH^+).

To a suspension of $LiAlH_4$ (3.71 g, 98.0 mmol) in THF (280 mL) was added dropwise a solution of **41** (10.0 g, 49.0 mmol) in THF (150 mL) at 5 °C, and the mixture was stirred at 50 °C for 4 h. After cooling, 6 N HCl was added at 5 °C and the mixture extracted with EtOAc. The organic layer was washed with water and brine, dried ($MgSO_4$), and evaporated to give 3-(1*H*-tetrazol-5-yl)benzyl alcohol (6.88 g, 80%) as a solid: ^{1}H NMR (DMSO-d_6) δ 4.61 (2H, s), 5.20−5.60 (1H, br), 7.48−7.65 (2H, m), 7.85−7.98 (1H, m), 8.05 (1H, s); IR (KBr) 3600−2100 (br), 1562, 1485, 1419, 1219 cm^{-1}; MS *m*/*z* 177 (MH^+).

To a solution of the above benzyl alcohol (6.75 g, 38.4 mmol) in acetone (680 mL) was added activated MnO_2 (66.7 g, 767 mmol), and the mixture was refluxed for 8 h. The cooled mixture was filtered, and the filtrate was evaporated to give 3-(1*H*-tetrazol-5-yl)benzaldehyde **42** (5.22 g, 78%) as a solid: ^{1}H NMR (DMSO-d_6) δ 7.86 (1H, dd, J = 7.7, 7.7 Hz), 8.08−8.20 (1H, m), 8.30−8.42 (1H, m), 8.57 (1H, dd, J = 1.5, 1.5 Hz), 10.13 (1H, s); IR (KBr) 3500−2400 (br), 1674, 1612, 1560, 1373, 1207 cm^{-1}; MS *m*/*z* 175 (MH^+).

To a solution of **42** (1.0 g, 5.75 mmol) in pyridine (15 mL) was added trityl chloride (1.76 g, 6.32 mmol) at 5 °C, and the mixture was stirred at room temperature for 4 h. The reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with 1 N HCl, water, and brine, dried ($MgSO_4$), and then evaporated to give crude **4ac** (2.51 g, 100%) as a solid: ^{1}H NMR (DMSO-d_6) δ 7.05−7.20 and 7.38−7.53 (15H, m), 7.80 (1H, dd, J = 7.7, 7.7 Hz), 8.05−8.14 (1H, m), 8.30−8.40 (1H, m), 8.50−8.55 (1H, m), 10.12 (1H, s); IR (KBr) 1699, 1516, 1491, 1446, 1201 cm^{-1}; MS *m*/*z* 243 (Ph_3C^+).

3-(2-Methyl-2*H*-tetrazol-5-yl)benzaldehyde (4ad) and 3-(1-Methyl-1*H*-tetrazol-5-yl)benzaldehyde (4ae). To a solution of **42** (600 mg, 3.45 mmol) in DMF (6 mL) was added NaH (60% oil dispersion, 138 mg, 3.45 mmol) at 5 °C. After 15 min of stirring at the same temperature, MeI (0.43 mL, 6.9 mmol) was added to the mixture, followed by stirring at room temperature for 3 h and at 40 °C for 30 min. The reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with water and brine, dried ($MgSO_4$), evaporated, and purified by silica gel column chromatography (hexane−EtOAc, 1:1 elution) to give first **4ad** (511 mg, 79%) as a solid and then **4ae** (82 mg, 13%) as a solid. **4ad**: ^{1}H NMR (DMSO-d_6) δ 4.47 (3H, s), 7.81 (1H, dd, J = 7.7, 7.7 Hz), 8.05−8.10 (1H, m), 8.33−8.40 (1H, m), 8.55−8.58 (1H, m), 10.14 (1H, s); IR (KBr) 3072, 2839, 1691, 1587, 1520, 1443 cm^{-1}; MS *m*/*z* 189 (MH^+). **4ae**: ^{1}H NMR (DMSO-d_6) δ 4.22 (3H, s), 7.87 (1H, dd, J = 7.7, 7.7 Hz), 8.13−8.25 (2H, m), 8.38−8.40 (1H, m), 10.14 (1H, s); IR (KBr) 1699, 1608, 1535, 1450, 1394 cm^{-1}; MS *m*/*z* 189 (MH^+).

3-(2-Methylthiazol-4-yl)benzylamine Hydrochloride (5). To a solution of methylmagnesium bromide (3 M in Et_2O, 200 mL, 0.6 mol) in THF (400 mL) was added dropwise a solution of *N*-(3-cyanobenzyl)acetamide **43** (34.8 g, 0.2 mol) in THF (400 mL) at room temperature, and the mixture was then stirred at 60 °C for 5 h. After cooling, water (400 mL) was added to the reaction mixture at 5 °C, the pH was adjusted to 7 with 6 N HCl, and the mixture was then extracted with EtOAc. The organic layer was washed with water and brine, dried ($MgSO_4$), evaporated, and purified by silica gel column chromatography (EtOAc−MeOH, 20:1 elution) to give *N*-(3-acetylbenzyl)acetamide **44** (36.1 g, 95%) as an oil: ^{1}H NMR (DMSO-d_6) δ 1.89 (3H, s), 2.57 (3H, s), 4.31 (2H, d, J = 6.0 Hz), 7.40−7.90 (4H, m), 8.30−8.50 (1H, m); IR (neat) 3292, 3072, 2927, 1684, 1541, 1431 cm^{-1}; MS *m*/*z* 192 (MH^+).

To a solution of **44** (9.56 g, 50.0 mmol) in DME (150 mL) was added dropwise at room temperature bromine (2.56 mL, 50.0 mmol), and the mixture was stirred at the same temperature for 1.5 h. The resulting precipitate was dissolved by addition of EtOH (150 mL), thioacetamide (4.51 g, 60.0 mmol) and $NaHCO_3$ (8.40 g, 100 mmol) were added thereto, and the solution was refluxed for 2.5 h. The reaction mixture was

poured into water and extracted with EtOAc. The organic layer was washed with water and brine, dried ($MgSO_4$), evaporated, and purified by silica gel column chromatography (EtOAc elution) to give *N*-[3-(2-methylthiazol-4-yl)benzyl]-acetamide **45** (8.24 g, 67%) as a solid: ^{1}H NMR (DMSO-d_6) δ 1.88 (3H, s), 2.72 (3H, s), 4.29 (2H, d, J = 5.9 Hz), 7.21 (1H, d, J = 7.6 Hz), 7.37 (1H, dd, J = 7.6, 7.6 Hz), 7.75−7.88 (2H, m), 7.90 (1H, s), 8.35−8.50 (1H, m); IR (KBr) 3296, 3109, 3068, 2929, 1643, 1551, 1431 cm^{-1}; MS *m*/*z* 247 (MH^+).

To a solution of **45** (8.23 g, 33.4 mmol) in EtOH (100 mL) was added concentrated HCl (13.9 mL), and the mixture was refluxed for 12 h. The mixture was ice cooled, and acetone (100 mL) was added slowly. The resulting precipitate was collected, washed with acetone, and dried to give **5** (5.14 g, 64%) as a solid: ^{1}H NMR (DMSO-d_6) δ 2.73 (3H, s), 4.00−4.15 (2H, m), 7.42−7.52 (2H, m), 7.90−8.00 (1H, m), 7.97 (1H, s), 8.14 (1H, s), 8.57 (3H, br s); IR (KBr) 2840 (br), 2636, 1605, 1576, 1508 cm^{-1}; MS *m*/*z* 205 (MH^+ − HCl).

4-(Pyrid-2-yl)benzyl Bromide (6a). To a mixture of 2-(4-tolyl)pyridine **46a** (3.39 g, 20.0 mmol) and *N*-bromosuccinimide (NBS) (4.27 g, 24.0 mmol) in CCl_4 (100 mL) was added benzoyl peroxide (48 mg, 0.2 mmol), and the mixture was refluxed for 2 h. After the mixture was cooled to room temperature, insoluble materials were filtered off. The filtrate was evaporated and purified by silica gel column chromatography (hexane−EtOAc, 4:1 elution) to give impure **6a** (4.52 g, 91%) as an oil: ^{1}H NMR ($CDCl_3$) δ inter alia 4.55 (2H, s), 7.20−7.33 (1H, m), 7.50 (2H, d, J = 8.4 Hz), 7.65−7.85 (2H, m), 7.98 (2H, d, J = 8.4 Hz), 8.65−8.75 (1H, m); IR (neat) 3051, 3008, 1735, 1585, 1565 cm^{-1}; MS *m*/*z* 248, 250 (MH^+).

4-(Pyrid-3-yl)benzyl Bromide (6b). To a mixture of 3-(4-tolyl)pyridine **46b** (1.79 g, 10.6 mmol) and NBS (1.88 g, 10.6 mmol) in CCl_4 (50 mL) was added benzoyl peroxide (52 mg, 0.2 mmol), and the mixture was refluxed for 6 h. After the mixture was cooled to room temperature, insoluble materials were filtered off. The filtrate was washed with water and brine, dried ($MgSO_4$), and evaporated to give impure **6b** (2.11 g, 80%) as an oil: MS *m*/*z* 248, 250 (MH^+).

4-(1-Trityl-1*H*-pyrazol-4-yl)benzyl Bromide (6c). To a suspension of **26** (11.7 g, 30.0 mmol) and 4-methylphenylboric acid **47** (9.23 g, 45.0 mmol) in toluene (250 mL) were added powdered K_2CO_3 (6.22 g, 45.0 mmol) and $Pd(PPh_3)_4$ (1.73 g, 1.5 mmol), and the mixture was refluxed for 8 h. The reaction mixture was poured into a mixture of EtOAc and ice water. The separated organic layer was washed with water and brine, dried ($MgSO_4$), evaporated, and purified by silica gel column chromatography (hexane−EtOAc, 7:1 elution) to give 4-(4-tolyl)-1-trityl-1*H*-pyrazole **48** (3.75 g, 31%) as a solid: ^{1}H NMR (DMSO-d_6) δ 2.27 (3H, s), 7.00−7.45 (19H, m), 7.73 (1H, s), 8.04 (1H, s); MS *m*/*z* 243 (Ph_3C^+).

To a mixture of **48** (3.74 g, 9.34 mmol) and NBS (1.66 g, 9.34 mmol) in CCl_4 (100 mL) was added benzoyl peroxide (45 mg, 0.19 mmol), and the mixture was refluxed for 6 h. After being cooled to room temperature, the reaction mixture was poured into water and extracted with CH_2Cl_2. The organic layer was washed with water and brine, dried ($MgSO_4$), and evaporated to give impure **6c** (3.36 g, 75%) as a solid: ^{1}H NMR (DMSO-d_6) δ inter alia 4.77 (2H, s), 7.00−8.10 (21H, m).

Typical Procedure for Method A. *N*-Benzyl-3-(pyrazol-3-yl)benzylamine (7v). A mixture of 3-(pyrazol-3-yl)-benzaldehyde **4r** (56.0 g, 0.33 mol) and benzylamine (42.6 mL, 0.39 mol) in toluene (560 mL) was refluxed for 5 h. The mixture was cooled to room temperature and evaporated. The residue was suspended in EtOH (840 mL), and $NaBH_4$ (12.3 g, 0.33 mol) was added carefully with ice cooling. The mixture was then stirred at 50 °C for 1 h. After additional stirring at room temperature for 2 h, the reaction mixture was evaporated. To the residue was added water (300 mL), and the mixture was extracted with CH_2Cl_2. The organic layer was washed with water and brine, dried ($MgSO_4$), evaporated, and purified by silica gel column chromatography (CH_2Cl_2−MeOH, 10:1 elution) to give **7v** (71.8 g, 84%) as a solid: ^{1}H NMR (DMSO-d_6) δ 3.71 (2H, s), 3.72 (2H, s), 6.68 (1H, d, J = 2.1 Hz), 7.15−7.42 (7H, m), 7.50−7.90 (3H, m), 12.85, 13.22 (total 1H, each br); IR (KBr) 3310−2290 (br), 1606, 1543, 1441, 1354 cm^{-1}; MS *m*/*z* 264 (MH^+).

***N*-[4-(Dimethylamino)benzyl]-3-(pyrazol-3-yl)benzylamine (7w).** A mixture of 3-(pyrazol-3-yl)benzaldehyde **4r** (1.20 g, 6.98 mmol), 4-(dimethylamino)benzylamine dihydrochloride (1.87 g, 8.37 mmol), and Et_3N (11.7 mL, 83.7 mmol) in toluene (30 mL) was refluxed for 5 h. Insoluble materials were removed by filtration, and the filtrate was evaporated. The residue was dissolved in EtOH (18 mL), $NaBH_4$ (264 mg, 6.98 mmol) was added carefully, and the mixture was stirred at ambient temperature for 2 h. The reaction mixture was poured into water and extracted with CH_2Cl_2. The organic layer was washed with water and brine, dried ($MgSO_4$), evaporated, and purified by silica gel column chromatography (CH_2Cl_2−MeOH, 8:1 elution) to give **7w** (1.68 g, 79%) as an oil: ^{1}H NMR ($CDCl_3$) δ 2.93 (6H, s), 3.75 (2H, s), 3.84 (2H, s), 6.59 (1H, d, J = 2.2 Hz), 6.65−6.75 (2H, m), 7.15−7.40 (4H, m), 7.55−7.66 (2H, m), 7.76 (1H, s); IR (neat) 3700−2330 (br), 1614, 1524, 1446, 1350, 804, 766 cm^{-1}; MS *m*/*z* 440 ($M + Me_2NC_6H_4CH_2^+$).

General Procedure for Method B. *N*-Cycloheptyl-3-(2-methylthiazol-4-yl)benzylamine (7aw). To a solution of 3-(2-methylthiazol-4-yl)benzylamine hydrochloride **5** (2.41 g, 10.0 mmol) in CH_2Cl_2−water (3:1, 40 mL) was added 5 N NaOH solution to adjust the pH to 9−10. The separated organic layer was washed with water and brine, dried ($MgSO_4$), and evaporated. To the residue was added cycloheptanone (1.77 mL, 15.0 mmol), and the mixture was stirred at 120 °C for 5 h. After being cooled to room temperature, the mixture was dissolved in EtOH (30 mL). To the solution was added carefully $NaBH_4$ (378 mg, 10.0 mmol), and the mixture was stirred at ambient temperature for 2.5 h. The mixture was poured into water and extracted with CH_2Cl_2. The organic layer was washed with water and brine, dried ($MgSO_4$), evaporated, and purified by silica gel column chromatography (CH_2Cl_2−MeOH, 20:1 elution) to give **7aw** (2.07 g, 69%) as an oil: ^{1}H NMR ($CDCl_3$) δ 1.25−2.00 (12H, m), 2.62−2.82 (1H, m), 2.78 (3H, s), 3.82 (2H, s), 7.32 (1H, s), 7.25−7.42 (2H, m), 7.70−7.88 (2H, m); IR (neat) 3381, 2916, 2854, 1497, 1458 cm^{-1}; MS *m*/*z* 301 (MH^+).

General Procedure for Method C. *N*-Cycloheptyl-4-(pyridin-2-yl)benzylamine (7ax). A mixture of impure 4-(pyrid-2-yl)benzyl bromide **6a** (2.56 g, 10.3 mmol) and cycloheptylamine (3.94 mL, 30.9 mmol) was stirred at 120 °C for 3 h. After the mixture was cooled to room temperature, a mixture of CH_2Cl_2 and water was added, and the separated organic layer was washed with water and brine, dried ($MgSO_4$), evaporated, and purified by silica gel column chromatography (CH_2Cl_2−MeOH, 10:1 elution) to give **7ax** (1.33 g, 46%) as an oil: ^{1}H NMR (DMSO-d_6) δ 1.15−2.15 (12H, m), 2.50−2.70 (1H, m), 3.74 (2H, s), 7.25−7.35 (1H, m), 7.44 (2H, d, J = 8.2 Hz), 7.80−8.00 (2H, m), 8.02 (2H, d, J = 8.2 Hz), 8.58−8.72 (1H, m); IR (neat) 2920, 2852, 1587, 1560, 1466, 1435 cm^{-1}; MS *m*/*z* 281 (MH^+).

General Procedure for Method D. *N*-Cycloheptyl-*N*-[3-(pyrazol-3-yl)benzyl]-*N*′-(2,4,6-trimethylphenyl)urea (3m). To a solution of *N*-cycloheptyl-3-(pyrazol-3-yl)benzylamine **7s** (730 mg, 2.71 mmol) in CH_2Cl_2 (15 mL) was added 2,4,6-trimethylphenyl isocyanate (437 mg, 2.71 mmol), and the mixture was stirred at room temperature for 2 h. After evaporation, the residue was purified by silica gel column chromatography (iPE−EtOAc, 1:1 elution) to give **3m** (755 mg, 65%) as a solid: mp 180−181 °C; ^{1}H NMR (DMSO-d_6) δ 1.30−1.90 (12H, m), 2.08 (6H, s), 2.20 (3H, s), 4.10−4.25 (1H, m), 4.54 (2H, s), 6.62 (1H, br s), 6.82 (2H, s), 7.18−7.82 (6H, m), 12.86, 13.30 (total 1H, each br s); IR (KBr) 3406, 3209, 2924, 2856, 1639, 1498, 1242, 1209 cm^{-1}; MS *m*/*z* 431 (MH^+). Anal. ($C_{27}H_{34}N_4O$) C, H, N.

General Procedure for Method E. *N*-Cycloheptyl-*N*-[4-(2-thienyl)benzyl]-*N*′-(2,4,6-trifluorophenyl)urea (3a). To a solution of 2,4,6-trifluoroaniline (441 mg, 3.0 mmol) and triphosgene (297 mg, 1.0 mmol) in CH_2Cl_2 (15 mL) was added Et_3N (0.42 mL, 3.0 mmol) at 5 °C, and the mixture was refluxed for 1.5 h. The mixture was cooled to room temper-

ature and a solution of *N*-cycloheptyl-4-(2-thienyl)benzylamine **7g** (570 mg, 2.0 mmol) in CH_2Cl_2 (6 mL) added thereto. After 2 h of stirring, the reaction mixture was poured into water. The separated organic layer was washed with water and brine, dried ($MgSO_4$), evaporated, and purified by silica gel column chromatography (hexane−EtOAc, 4:1 elution) to give **3a** (736 mg, 80%) as a solid: mp 136−137 °C; ^{1}H NMR ($CDCl_3$) δ 1.38−2.08 (12H, m), 4.25−4.45 (1H, m), 4.55 (2H, s), 5.57 (1H, s), 6.55−6.72 (2H, m), 7.09 (1H, dd, J = 5.1, 3.6 Hz), 7.22−7.42 (4H, m), 7.64 (2H, d, J = 8.3 Hz); IR (KBr) 3300, 2927, 1635, 1520, 1444, 1120, 1041 cm^{-1}; MS *m/z* 459 (MH^+). Anal. ($C_{25}H_{25}F_3N_2OS$) C, H, N.

Typical Procedure for Method F. *N*-Benzyl-*N*-[3-(pyrazol-3-yl)benzyl]-*N′*-[2,4-bis(methylthio)-6-methylpyridin-3-yl]urea (3aq, FR186054). To a solution of *N*-benzyl-3-(pyrazol-3-yl)benzylamine **7v** (54.0 g, 0.21 mol) and Et_3N (143 mL, 1.03 mol) in toluene (1.35 L) was added phenyl *N*-[2,4-bis(methylthio)-6-methylpyridin-3-yl]carbamate[13] (62.4 g, 0.20 mmol) at room temperature, and the mixture was stirred for 24 h. The resulting precipitate was collected and recrystallized from CH_2Cl_2−MeOH−hexane to give **3aq** (74.4 g, 78%) as a solid: mp 209−210 °C; ^{1}H NMR (DMSO-d_6) δ 2.42 (6H, s), 2.46 (3H, s), 4.49 (4H, s), 6.67 (1H, br s), 6.90 (1H, s), 7.18−7.90 (10H, m), 8.29 (1H, s), 12.88, 13.30 (total 1H, each br s); IR (KBr) 3390, 3246, 2920, 1651, 1562, 1489, 1228 cm^{-1}; MS *m/z* 490 (MH^+). Anal. ($C_{26}H_{27}N_5OS_2$) C, H, N.

Procedures for Deprotection of Protected Trisubstituted Ureas. *N*-Cycloheptyl-*N*-[3-(1*H*-tetrazol-5-yl)benzyl]-*N′*-(2,4,6-trimethylphenyl)urea (3ae). To a suspension of *N*-cycloheptyl-*N*-[3-(2-trityl-2*H*-tetrazol-5-yl)benzyl]-*N′*-(2,4,6-trimethylphenyl)urea (1.46 g, 2.17 mmol) in MeOH (14 mL) was added concentrated HCl (0.72 mL, 8.7 mmol), and the mixture was stirred at room temperature for 1 h. The insoluble white solid was collected and washed with MeOH and water to give **3ae** (0.79 g, 84%) as a solid: mp 204−206 °C; ^{1}H NMR (DMSO-d_6) δ 1.35−1.90 (12H, m), 2.06 (6H, s), 2.20 (3H, s), 4.14−4.34 (1H, m), 4.59 (2H, s), 6.82 (2H, s), 7.46−7.66 (2H, m), 7.80−7.90 (1H, m), 8.04 (1H, s); IR (KBr) 3359, 3300−2400 (br), 1595, 1512, 1456, 1257 cm^{-1}; MS *m/z* 433 (MH^+). Anal. ($C_{25}H_{32}N_6O$) C, H, N.

***N*-Cycloheptyl-*N*-[4-(pyrazol-4-yl)benzyl]-*N′*-(2,4,6-trimethylphenyl)urea (3n).** A mixture of *N*-cycloheptyl-*N*-[4-(1-trityl-1*H*-pyrazol-4-yl)benzyl]-*N′*-(2,4,6-trimethylphenyl)-urea (1.05 g, 1.56 mmol), anisole (2 mL), and TFA (6 mL) was stirred at 80 °C for 3 h. The reaction mixture was evaporated and the residue poured into water, adjusted to pH 9 with 1 N NaOH solution, and extracted with EtOAc. The separated organic layer was washed with water and brine, dried ($MgSO_4$), evaporated, and purified by silica gel column chromatography (iPE−EtOAc, 1:1 elution) to give **3n** (210 mg, 31%) as an amorphous solid: ^{1}H NMR (DMSO-d_6) δ 1.30−1.85 (12H, m), 2.09 (6H, s), 2.21 (3H, s), 4.05−4.25 (1H, m), 4.48 (2H, s), 6.83 (2H, s), 7.28 (2H, d, J = 8.2 Hz), 7.50 (1H, br s), 7.56 (2H, d, J = 8.2 Hz), 7.87 (2H, s); IR (KBr) 3195, 2926, 2856, 1630, 1605, 1510 cm^{-1}; MS *m/z* 431 (MH^+). Anal. ($C_{27}H_{34}N_4O\cdot 0.25H_2O$) C, H, N.

The following compound was prepared in a similar manner from *N*-cycloheptyl-*N*-[3-(1-trityl-1*H*-pyrazol-4-yl)benzyl]-*N′*-(2,4,6-trimethylphenyl)urea (800 mg).

***N*-Cycloheptyl-*N*-[3-(pyrazol-4-yl)benzyl]-*N′*-(2,4,6-trimethylphenyl)urea (3o):** yield 102 mg (20%); ^{1}H NMR (DMSO-d_6) δ 1.30−1.90 (12H, m), 2.08 (6H, s), 2.20 (3H, s), 4.10−4.30 (1H, m), 4.51 (2H, s), 6.83 (2H, s), 7.13 (1H, d, J = 7.5 Hz), 7.30 (1H, dd, J = 7.5, 7.5 Hz), 7.44 (1H, d, J = 7.5 Hz), 7.51 (2H, br s), 7.84 (1H, br s), 8.11 (1H, br s), 12.95 (1H, br s); IR (KBr) 3400, 3207, 2926, 2856, 1635, 1608, 1510 cm^{-1}; MS *m/z* 431 (MH^+). Anal. ($C_{27}H_{34}N_4O\cdot 0.3H_2O$) C, H, N.

Biological Methods. Effect on Cholesteryl Ester Accumulation in Macrophages. Peritoneal macrophages were harvested from nonstimulated mice by peritoneal lavage with phosphate-buffered saline (PBS) and pooled. They were centrifuged at 400*g* for 10 min and washed with Dulbecco's modified Eagle medium (DMEM). The cells were resuspended in DMEM supplemented with 10% (v/v) fetal bovine serum (FBS), 100 units/mL penicillin, and 100 μg/mL streptomycin (10% FBS−DMEM) at a final concentration of 2×10^6 cells/mL. Each plastic dish (16 mm diameter) was seeded with 0.5 mL of the cell suspension and incubated for 2 h at 37 °C in humidified air containing 5% CO_2. The monolayers formed were washed with DMEM to remove nonadherent cells, then incubated in 10% FBS−DMEM for a further 18 h at 37 °C and used for the experiment.

The macrophages were incubated in 0.5 mL of 10% FBS−DMEM containing 0.2 mmol/L [1-^{14}C]oleate−fatty acid free bovine serum albumin (BSA) complex, 30 μg/mL acetylated human LDL, and test compound dissolved in DMSO for 4 h at 37 °C in humidified air containing 5% CO_2. The concentration of DMSO was adjusted to 0.1%. Control was incubated without test compound, and blank was incubated without acetylated LDL and test compound. After incubation, the cells were washed with PBS, and cellular lipids were then extracted with 0.25 mL of hexane−isopropyl alcohol (3:2, v/v) for 30 min at room temperature. The extracts were dried under nitrogen, dissolved in 50 μL of chloroform−methanol (2:1, v/v), and spotted on TLC plates which were then developed with hexane−ether−acetic acid (73:25:2, v/v/v) as a solvent system. The radioactivity of the fraction containing cholesteryl [1-^{14}C]-oleate was measured as the cellular cholesteryl ester accumulation. The cells, remaining after the lipid extraction, were dissolved in 0.5 N NaOH solution (0.2 mL) for 30 min at room temperature and then neutralized with 1 N HCl (0.1 mL). A 150-μL aliquot was assayed for protein utilizing a Bio-Rad protein assay system (Bio-Rad).

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