Benzophenone Derivatives: A Novel Series of Potent and Selective Inhibitors of Human Immunodeficiency Virus Type 1 Reverse Transcriptase

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A series of benzophenone derivatives has been synthesized and evaluated as inhibitors of HIV-1 reverse transcriptase (RT) and the growth of HIV-1 in MT-4 cells. Through the use of the structure–activity relationships within this series of compounds and computational chemistry techniques, a binding conformation is proposed. The SAR also indicated that the major interactions of **1h** with the RT enzyme are through hydrogen bonding of the amide and benzophenone carbonyls and π-orbital interactions with the benzophenone nucleus and an aromatic function separated from the benzophenone by a suitable spacer group. The crystal structure of compound **1h** has been determined. A number of compounds with potent inhibitory activity against HIV-1 RT and HIV in cellular assays at levels comparable with AZT and our efforts to identify a metabolically stable analogue are described.

Introduction

Since the identification of the human immunodeficiency virus (HIV) as the causative agent of AIDS,[1,2] the search for safe and effective treatments for HIV infection has become a major focus for drug discovery groups worldwide. Investigations into the molecular biology of HIV[3] have identified a number of viral targets for drug design, such as reverse transcriptase (RT), protease and integrase enzymes, and regulatory proteins (e.g., TAT and REV), as well as virus attachment and fusion. HIV RT, an essential enzyme in the life cycle of HIV, catalyzes the transcription of HIV-encoded single-stranded RNA into double-stranded DNA. The RNA-dependent DNA polymerase function of HIV RT does not have a parallel in mammalian metabolism and thus is a good target for a chemotherapeutic agent. Many nucleoside analogues after conversion to their 5′-triphosphates by cellular enzymes inhibit HIV RT and in consequence inhibit the growth of HIV in cell culture. However, adverse toxicity has limited the progression of many of these compounds into the clinic. Zidovudine[4] (AZT, 3′-azido-3′-deoxythymidine) the first anti-HIV compound to be approved for used in the clinic is beneficial in the treatment of HIV infected patients. However, its clinical usage is compromised by serious side effects which are attributed to inhibition of cellular DNA polymerases, e.g., bone marrow suppression, and by the emergence of AZT resistant strains. Other nucleoside analogues didanosine (DDI, 2′,3′-dideoxyinosine) and zalcitabine (DDC, 2′,3′-dideoxycytosine) now approved for clinical use also suffer from serious side effects.[4]

The toxicity of the nucleoside analogues has stimulated considerable interest into alternative approaches in the search for effective anti-HIV agents. Of particular prominence has been a structurally diverse group of compounds that inhibit the RT of HIV-1 but not HIV-2. Notable examples of such compounds include benzodiazepinones,[5] dipyridodiazepinones,[5] 2-pyridones,[5] bis(heteroaryl)piperazines,[5] 6-substituted pyrimidines,[6] and imidazopyridazines.[7] These compounds are noncompetitive inhibitors of RT, and many bind close to the nucleotide binding site[8] and are potentially devoid of the toxic side effects of the nucleoside analogues.

High-throughput screening at Glaxo against recombinant HIV-1 RT[9] identified benzophenone **1a** as a weak inhibitor of the enzyme with an IC_{50} of 10 μg/mL. In this paper we report the more significant results of the structural requirements of this series of compounds and our efforts to identify a potent, selective, and metabolically stable inhibitor of HIV-1.

Synthetic Chemistry

The benzophenone derivatives **1a–l** (Table 1) were obtained from the 2-hydroxybenzophenones **2a–j**[10] using one of two methods (Schemes 1 and 2). Anilines **4a–e** were obtained from nitrophenols **5a–d** (Scheme 3). Anilides **8a–d** and **10** (Table 2) were obtained from the coupling of acids **7**[11] and **9**[12] with anilines **4b–e** and **4c**, respectively (Scheme 4). Compounds **1m,n** (Table 3) were synthesized by acylation of 4-chlorophenol with the required acid chlorides, followed by a Fries rearrangement to give phenols **2k,l** (Scheme 2). Alkylation of **2k** and **2l** with *N*-phenylbromoacetamide gave anilides **1m,n** (Table 3). Sodium borohydride reduction of **1g** gave the benzhydrol **11** (Table 3).

Acid-catalyzed ketalization of the carbonyl of **2e** (Scheme 5) with ethylene glycol, followed by alkylation using bromoacetonitrile, gave cyanomethyl ether **13**. Reaction of **13** with benzylmagnesium bromide and subsequent treatment with acid gave the keto derivative **14** (Table 4). Carbodiimide-mediated coupling of acid **3e** with cyclohexylamine, 2-methylbenzylamine, or 1,2,3,4-tetrahydroisoquiniline under standard conditions

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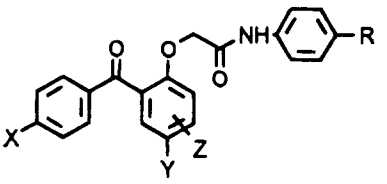
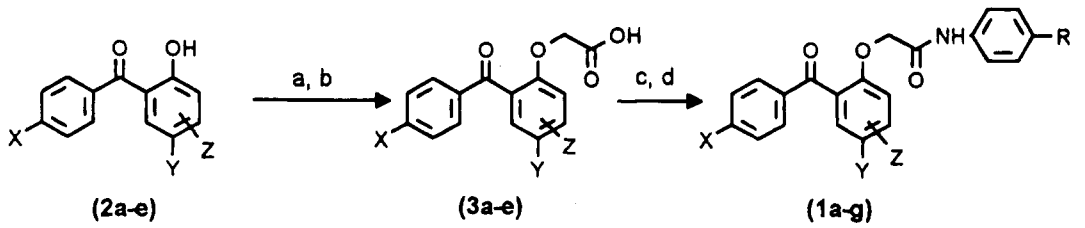
Table 1. Antiviral Activity



no.	X	Y	Z	R	mp, °C	formula	method[a]	RT[b]	MTM[c]	TOX[d]	SYN[e]	p24[f]
1a	OCH_3	H	H	$O(CH_2)_2NEt_2$	136–137	$C_{30}H_{34}N_2O_9$[g]	A	6.8	0.44	5	0.34	0.18
1b	F	H	H	$O(CH_2)_2NEt_2$	141–142	$C_{31}H_{33}FN_2O_8$[h]	A	10	0.75	>0.5	0.016	<0.05
1c	H	H	H	$O(CH_2)_2NEt_2$	oil	$C_{27}H_{30}N_2O_4$	A	2.3	<0.001	>0.5	0.005	0.0015
1d	H	H	4-OCH_3	$O(CH_2)_2NEt_2$	89–90	$C_{28}H_{32}N_2O_5$	A	6.3	<0.01	5	0.05	0.013
1e	H	Cl	H	$O(CH_2)_2NEt_2$	115–116	$C_{27}H_{29}ClN_2O_4$	A	0.45	>10	10	NT	NT
1f	H	Cl	H	$O(CH_2)_3NMe_2$	119–120	$C_{26}H_{27}ClN_2O_4$	A	0.097	<0.01	>0.5	0.0009	<0.0005
1g	H	Cl	H	H	118–119	$C_{21}H_{16}ClNO_3$	A	0.01	0.0004	>0.005	0.0002	0.0012
1h	H	F	H	H	127–129	$C_{21}H_{16}FNO_3$	B	0.003	0.09	10	0.014	0.006
1i	H	*N*-imidazolyl	H	H	amorph	$C_{24}H_{19}N_3O_3$[i]	B	>10	>10	10	NT	NT
1j	H	Cl	3-Cl	H	138–141	$C_{21}H_{15}Cl_2NO_3$[j]	B	>100	NT	NT	NT	NT
1k	H	Cl	4-Cl	H	128–129	$C_{21}H_{15}Cl_2NO_3$[k]	B	0.014	0.023	100	NT	NT
1l	H	Cl	6-Cl	H	123–124	$C_{21}H_{15}Cl_2NO_3$[l]	B	>100	NT	NT	NT	NT

[a] For methods, see the Experimental Section. [b] IC_{50} *versus* RT of HIV-1 (μg/mL), AZT triphosphate control = 0.02 ± 0.005 μM. [c] IC_{50} *versus* HIV-1 (strain RF)-infected MT-4 cells (μg/mL), AZT = 0.002–0.02 μM. [d] IC_{50} *versus* uninfected MT-4 cells (mg/mL). [e] IC_{50} *versus* syncytia formation in infected C8166-cells (μg/mL), AZT = 0.002–0.02 μM. [f] IC_{50} *versus* p24 antigen formation in infected C8166-cells (μg/mL), AZT = 0.001–0.01 μM. [g] oxalate salt + 0.25H_2O. [h] Fumarate salt. [i] 0.75H_2O. [j] 0.5H_2O. [k] C: calcd, 63.02; found, 63.83. [l] 0.25H_2O.

Scheme 1. (Method A)[a]



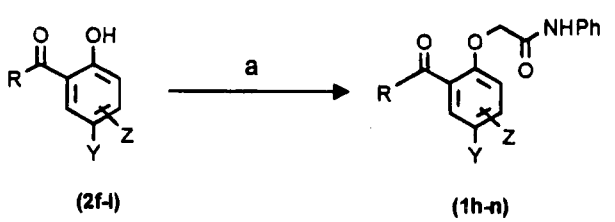
(2a-e) (3a-e) (1a-g)

	X	Y	Z
2a, 3a	OMe	H	H
2b, 3b	F	H	H
2c, 3c	H	H	H
2d, 3d	H	H	4-OMe
2e, 3e	H	Cl	H

	X	Y	Z	R
1a	OMe	H	H	$O(CH_2)_2NEt_2$
1b	F	H	H	$O(CH_2)_2NEt_2$
1c	H	H	H	$O(CH_2)_2NEt_2$
1d	H	H	4-OMe	$O(CH_2)_2NEt_2$
1e	H	Cl	H	$O(CH_2)_2NEt_2$
1f	H	Cl	H	$O(CH_2)_3NMe_2$
1g	H	Cl	H	H

[a] (a) NaH, $BrCH_2CO_2Et$, DMF; (b) NaOH, EtOH, H_2O; (c) $SOCl_2$; (d) **4a–e**, NEt_3, PhH.

Scheme 2. (Method B)[a]



(2f-l) (1h-n)

	R	Y	Z
2f, 1h	Ph	F	H
2g, 1i	Ph	N-imidazole	H
2h, 1j	Ph	Cl	3-Cl
2i, 1k	Ph	Cl	4-Cl
2j, 1l	Ph	Cl	6-Cl
2k, 1m	3-pyridyl	Cl	H
2l, 1n	cyclopentyl	Cl	H

[a] (a) $BrCH_2CONHPh$, K_2CO_3, DMF.

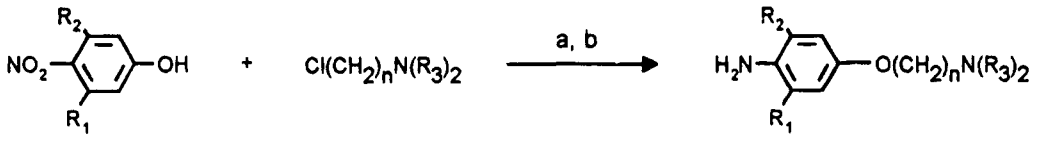
gave the amides **16**, **17**, and **18**, respectively (Table 4). The methods to compounds **12**, **15**, **21**, and **23** (Table 4) are outlined in Scheme 5.

Biological Methods

The benzophenone derivatives described were initially tested for their ability to inhibit the poly(rA)·oligo-$(dT)_{12-18}$-directed RT activity of HIV-1. Selected compounds were then progressed to a primary assay against HIV-1 (strain RF) in MT-4 cells and additional screens designed to measure the formation of syncytia (SYN) and p24 antigen (p24) in C8166 cells infected with HIV-1 (strain RF).[7]

The resistance study on compound **8b** was carried out using the following procedure. C8166 cells (1×10^6 cells/mL) in RPMI 1640 growth medium were infected

Scheme 3[a]



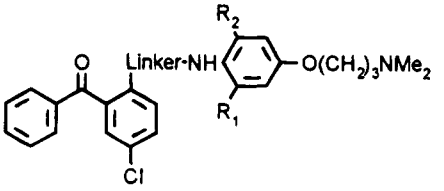
	R_1	R_2
5a	H	H
5b	H	Me
5c	H	Et
5d	Me	Me

	R_3
6a	Me
6b	Et

	R_1	R_2	R_3	n
4a	H	H	Et	2
4b	H	H	Me	3
4c	Me	H	Me	3
4d	Et	H	Me	3
4e	Me	Me	Me	3

[a] (a) K_2CO_3, DMF; (b) 10% Pd/C, EtOH.

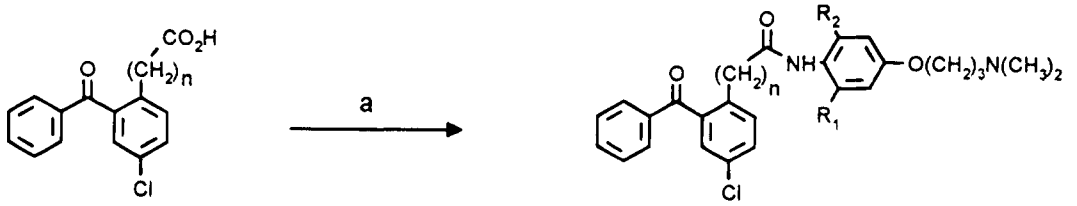
Table 2. Antiviral Activity



no.	linker	R_1	R_2	mp, °C	formula[a]	RT[a]	MTM[a]	TOX[a]	SYN[a]	p24[a]
8a	$-CH_2CO-$	H	H	oil	$C_{26}H_{27}ClN_2O_3$[b]	0.2	0.21	10	NT	NT
8b	$-CH_2CO-$	CH_3	H	144–145	$C_{27}H_{29}ClN_2O_3$[c]	0.35	0.0044	>0.5	0.016	0.0029
8c	$-CH_2CO-$	Et	H	123–124	$C_{28}H_{31}ClN_2O_3$	2.5	0.21	10	NT	NT
8d	$-CH_2CO-$	CH_3	CH_3	117–118	$C_{28}H_{31}ClN_2O_3$[d]	>50	NT	NT	NT	NT
10	$-CO-$	CH_3	H	129–130	$C_{26}H_{27}ClN_2O_3$[e]	>100	NT	NT	NT	NT

[a] For definitions, see Table 1. [b] $1.0H_2O$. [c] C: calcd, 69.73; found, 69.13. [d] $0.25H_2O$. [e] $0.75H_2O$, N; calcd, 6.03; found, 5.53.

Scheme 4[a]



7 n = 1
9 n = 0

	n	R_1	R_2
8a	1	H	H
8b	1	Me	H
8c	1	Et	H
8d	1	Me	Me
10	0	Me	H

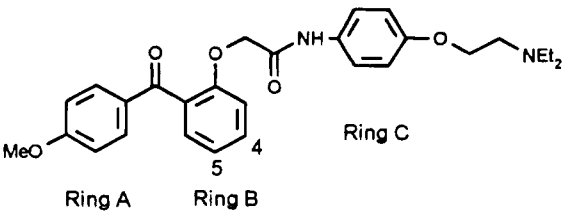
[a] (a) **4b–e**, HOBT, DCC, DMF.

with HIV-1 RF strain at a moi of 1 infectious dose/cell. The virus was adsorbed at room temperature for 3 h, after which cells were washed in RPMI 1640 growth medium to remove unabsorbed virus. **8b** was initially added to the culture at 0.02 μM. The culture was incubated until a cytopathic effect was detectable (3–4 days). Following a cycle of infection, supernatant fluids were titrated in fresh C8166 cells at a doubled concentration of **8b**. The culture at the highest dilution of virus showing a cytopathic effect was harvested and passaged further in an increased **8b** concentration as described above. Levels of HIV-1 infection were monitored regularly by analysis of p24 antigen in the culture supernatant using a commercial ELISA kit. Approximately after eight passages, **8b**-resistant virus stock was prepared by passaging three times in 2 μM **8b**. These virus stocks were then titrated, and drug sensitivity of the **8b**-resistant variant was determined in a MT-4 assay.[7]

The compound stability studies carried out in mouse serum and mouse S9 liver preparations were based on methods described by Gillette[13] and Mazel.[14]

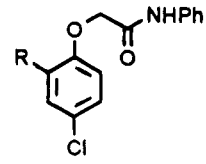
Discussion

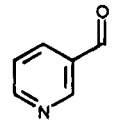
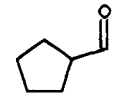
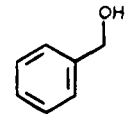
Further screening of closely related structures to the initial lead (**1a**) available in the Glaxo compound library gave useful structure–activity information.



(**1a**)

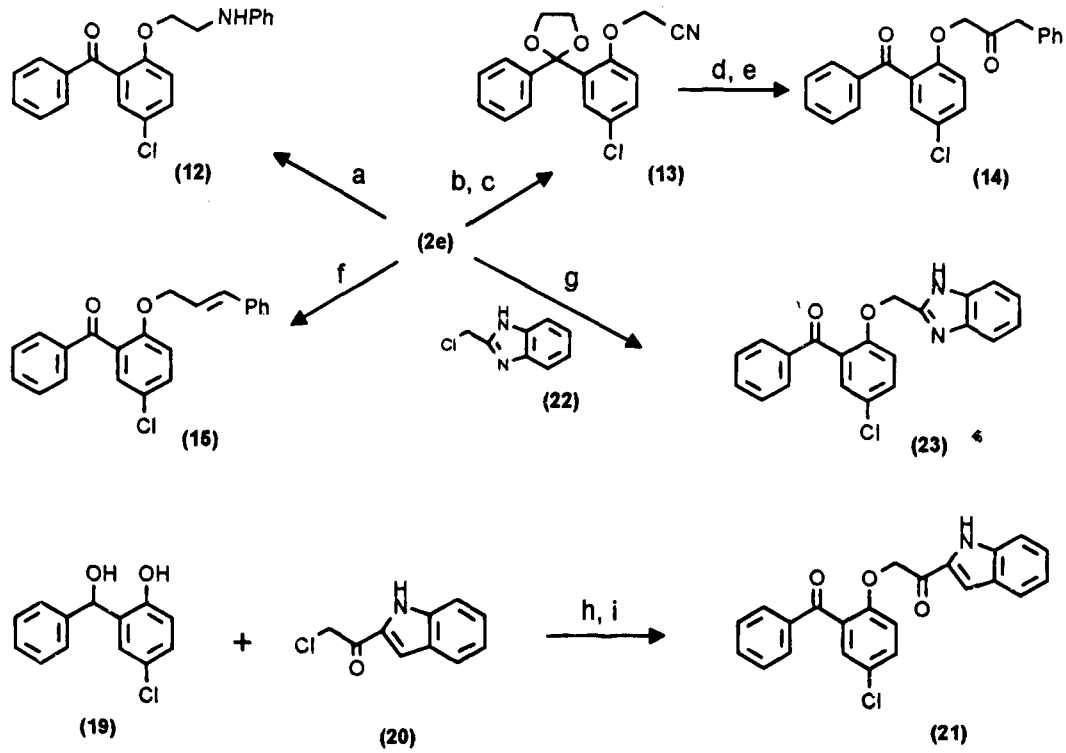
Table 3. Antiviral Activity



no.	R	mp, °C	formula	RT[a]	MTM[a]	TOX[a]	SYN[a]	p24[a]
1m		169-170	$C_{20}H_{15}ClN_2O_3$	0.16	<0.01	10	NT	NT
1n		137-138	$C_{20}H_{20}ClNO_3$	1.8	0.22	>100	NT	NT
11		147-148	$C_{21}H_{18}ClNO_3$	> 100	NT	NT	NT	NT

[a] For definitions, see Table 1.

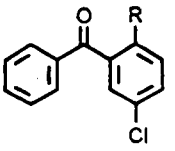
Scheme 5[a]

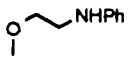
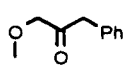
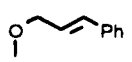
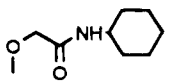
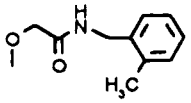
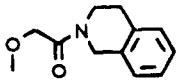
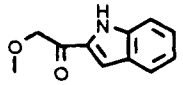
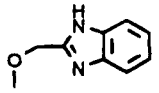


[a] (a) $PhNHCH_2CH_2Cl$, K_2CO_3, DMF; (b) $HOCH_2CH_2OH$, $TsOH{\cdot}H_2O$, PhH; (c) $BrCH_2CN$, K_2CO_3, DMF; (d) $PhCH_2MgBr$, THF, −78 °C; (e) 1 N HCl, THF; (f) (*E*)-$BrCH_2CH{=}CHPh$, K_2CO_3, DMF; (g) NaH, DMF; (h) K_2CO_3, DMF; (i) PCC, CH_2Cl_2.

Replacement of the methoxy group of ring A of **1a** (Table 1) with fluorine (**1b**) resulted in little change in activity, whereas removal of the substitution (**1c**) resulted in a modest increase in the inhibition of RT. Introduction of a methoxy group (**1d**) at the 4-position of ring B resulted in a slight loss of RT inhibition; however, introduction of a chlorine atom at the 5-position (**1e**) gave a 10-fold increase in activity in the RT assay but resulted in a toxic compound in the whole cell assay. A number of compounds with various (*N,N*-dialkylamino)alkoxy substituents on ring C were tested (data not shown), and the most active was the (*N,N*-dimethylamino)propoxy derivative **1f**. Compound **1f** was found to be rapidly metabolized in both mouse serum and S9 mouse liver preparations (Table 5). Shortening of the amide linker to give **8a** (Table 2) resulted in a loss of activity in both the enzyme and whole cell assays. The 2-(methylphenyl) amide **8b** (Table 2) was synthesized to increase the steric crowding around the amide linker of **8a** to add stability toward

Table 4. Antiviral Activity



no.	R	mp, °C	formula	RT[a]	MTM[a]	TOX[a]	SYN[a]	p24[a]
12		131-132	$C_{21}H_{18}ClNO_2$[b]	>100	NT	NT	NT	NT
14		oil	$C_{22}H_{17}ClO_3$	12	>100	>100	NT	NT
15		89-90	$C_{22}H_{17}ClO_2$	>100	NT	NT	NT	NT
16		119-120	$C_{21}H_{22}ClNO_3$	14.5	NT	NT	NT	NT
17		84-85	$C_{23}H_{20}ClNO_3$	2.5	0.028	10	0.05	0.032
18		101-102	$C_{24}H_{20}ClNO_3$	0.006	0.014	>0.5	0.011	0.016
21		125-126	$C_{23}H_{16}ClNO_3$	0.063	0.7	10	>50	>5
23		144-145	$C_{21}H_{15}ClN_2O_2$[c]	0.51	0.31	>0.5	0.052	0.032

[a] For definitions, see Table 1. [b] HCl salt. [c] $0.25H_2O$.

Table 5. Metabolic Stability of Benzophenone Derivatives

	half-life, h	
no.	mouse serum[a]	mouse S9 liver[b]
1f	<0.25	>2
1g	<0.25	<0.25
8b	4.75	1.8
17	2.8	>6
18	1.2	2.8
21	<0.25	3.5
23	>6	>6

[a] Stability of compound in mouse serum preparation; for method, see ref 13. [b] Stability of compounds in mouse S9 liver preparation; for method, see ref 14.

amidases. Compound **8b** proved to be more active than **8a** and was moderately stable in both metabolism tests (Table 5). Replacement of the methyl group with ethyl (**8c**) resulted in a reduction in activity. Inclusion of two *o*-methyl substituents (**8d**) or further reduction in the amide linker chain length (**10**) resulted in a total loss of activity (Table 2). The removal of the ring C aminoalkoxy group of **1f**, to provide **1g**, showed that this substituent was not essential for potent activity. Therefore, further analogues related to **1g** were prepared. Replacement of the ring A with the more polar pyridyl ring (**1m**) or the saturated cyclopentyl ring (**1n**) (Table 3) resulted in a significant loss of activity. Reduction of the benzophenone carbonyl to afford the benzhydrol **11** (Table 3) resulted in a total loss of activity. The hydrogen-bonding acceptor capabilities of carbonyl and hydroxy groups are reported to be similar,[15] and therefore, the change in conformation of ring A relative to ring B, rather than a reduction of hydrogen bonding capability, is probably the reason for the loss of activity of **11**.

We next investigated the effect of substitution of ring B (Table 1, compounds **1g–l**). Replacement of the 5-chloro substituent of ring B (**1g**) with fluorine (**1h**) resulted in little change in activity. Replacement of chlorine with a polar imidazole group (**1i**) resulted in a significant loss of activity. The dichloro-substituted compounds **1j–l** gave significant SAR information. The 4,5-dichloro-substituted **1k** retained the activity of the monosubstituted **1g**, whereas the 3,5- and 5,6-dichloro derivatives **1j,l** were devoid of activity. The activity of **1k** seems to suggest there is room to accommodate the two chlorines in the binding site and that the loss of activity of **1j,l** was due to effects on the allowable conformations of the compounds.

The structure–activity data identified compound **1g** (Table 1) as a lead compound. However, compound **1g** was rapidly metabolised in mouse serum and S9 mouse liver preparations (Table 5). For a compound to be a suitable candidate for progression we required it to be metabolically stable (half-life > 6 h) in these tests. Thus we sought a derivative with comparable activity to **1g** but with greater metabolic stability.

To investigate whether the amide of **1g**, a likely site of metabolism, was required for activity, we synthesized the corresponding amine **12**, ketone **14**, and *trans*-vinyl **15** derivatives (Table 4). The loss of activity associated

with these modifications against HIV-1 RT suggests that the hydrogen-bonding capabilities of the amide is a major determinant of the activity of **1g**.

Although the amide of **1g** appeared to be required for potent activity, amide cleavage to release potentially toxic anilines was considered a possibility, and therefore, alternative amides were investigated. The significant loss of activity of the *N*-cyclohexylamide **16** (Table 4) indicated the anilino aromatic ring of **1g** was essential for potent activity. The 2-methylbenzyl amide derivative **17** (Table 4) was synthesized to incorporate the amide linker of **1g** and a phenyl ring, both required for potent activity, together with the *o*-methyl substituent of **8b** found to increase metabolic stability. Compound **17** was less active than **1g** in enzyme and cellular assays but was significantly more metabolically stable (Table 5). The bicyclic amide **18** (Table 4) synthesized as a constrained version of **17** proved to be a potent inhibitor of the enzyme and exhibited good activity in antiviral assays but was less metabolically stable than **17** (Table 5).

The potent activity of **18** suggests the amide hydrogen is not involved in hydrogen bonding to the enzyme and the major interaction is through the amide carbonyl. Therefore, compounds were synthesized that satisfied the requirements for both a hydrogen bond acceptor and aromatic residue but did not contain the potentially metabolically unstable amide linkage. The acylindole group of **21** (Table 4) was shown by molecular modelling to closely resemble the *trans*-*N*-phenylamide moiety of **1g**. Indeed, **21** exhibited potent inhibition of HIV-1 RT; however, this level of activity was not translated into activity in antiviral assays. In the metabolism tests **21** (Table 5) proved to be surprisingly unstable; however, the major site of metabolism was not determined. The benzimidazole derivative **23** (Table 4) capable of acting as a hydrogen bond acceptor through an imidazole ring nitrogen exhibited moderate activity in both the enzyme and whole cell assays. This compound proved to be stable in both metabolism test systems (Table 5).

The generated SAR for this series identified the major interactions with the enzyme to be hydrogen bonding of the amide and benzophenone carbonyls and π-orbital interactions of the benzophenone nucleus and an aromatic function separated from the benzophenone by a suitable spacer group.

X-ray Crystallography and Discussion of the Binding Conformation

Crystals suitable for X-ray crystallography were obtained from the fluoro derivative **1h** (Figure 1). The full crystal coordinate data for **1h** are available as supplementary material. The conformation shown includes an internal hydrogen bond between the amide and the benzophenone carbonyl which is unlikely to occur in solution or during binding to the enzyme. In order to identify possible enzyme binding conformations of **1g**, systematic searches were performed on **1g** (IC_{50} vs HIV-1 RT = 0.01 μg/mL) and the inactive dichloro derivatives **1j** and **1l**. A 15-deg step was used in SYBYL,[16] with a 4-dimensional distance map calculated using the following distances: amide carbonyl−benzophenone carbonyl; amide carbonyl−centroid of ring B; amide carbonyl−centroid of ring A; amide linker oxygen−benzophenone carbonyl. A proposed "active" distance map was produced by removing those conformations present in the map for **1j** or **1l** and present in **1g**. This proposed 608 conformations within 5 kcal/mol of the lowest van der Waals energy for **1g**. The conformations were clustered using the atomic RMS similarity tool within MACROMODEL.[17] A representative of each set was minimised using MM2* forcefield and GB/SA solvent term. Of the low-energy conformations, the one shown in Figure 2 was felt to best match the SAR. This model was used for the design of further compounds such as indole **21**. A proposed overlay of this conformation with nevirapine is shown (Figure 3). The comparison indicates that the benzophenones can make similar interactions with RT as those made by nevirapine, suggesting the two compounds bind at the same site. Consideration of this information together with comparisons with other non-nucleoside RT inhibi-

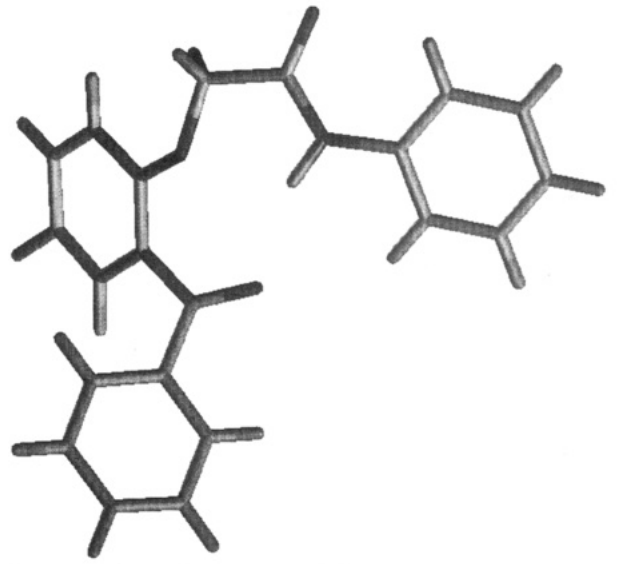


Figure 1. Crystal structure of **1h**.

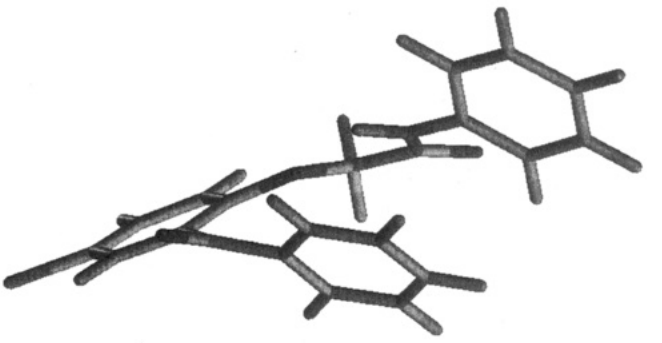


Figure 2. Proposed binding conformation of **1g**.

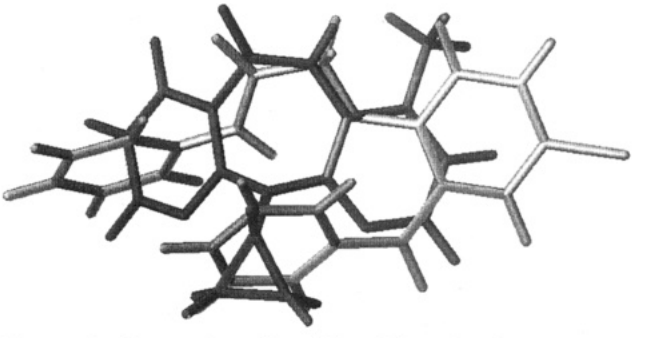


Figure 3. Proposed overlay of **1g** with nevirapine.

Table 6. Antiviral Activity

compound	HIV-1 RF (wild-type)		HIV-1 (**8b**-resistant)	
	IC_{50}[a]	TOX[b]	IC_{50}[a]	TOX[b]
8b	0.026	10	0.48	>10
AZT	0.0024	>1	0.0065	>1
3TC	0.043	>100	0.048	>100
Ro 31-8959	0.028	>1	0.0038	>1
TIBO R-82150	0.005	10	0.32	10
nevirapine	0.010	>10	0.22	>10
imidazopyridazine	0.004	>1	0.5	>1
L-697,661	0.0017	100	0.0023	100

[a] IC_{50} *versus* HIV-1 (strain RF)-infected MT-4 cells (μg/mL), AZT = 0.002–0.02 μM. [b] IC_{50} *versus* uninfected MT-4 cells (μg/mL).

tors could aid the design of compounds with potent activity against resistant HIV strains.

Selection of Resistant Virus

The rapid emergence of resistant strains has proved to be a problem with non-nucleoside anti-HIV agents progressed to clinical trials,[18] and therefore it was important to ascertain whether this series of compounds selected for resistant virus. The selection of resistant virus was investigated using the benzophenone derivatives **8b** (Table 2) (see Biological Methods). After eight passages of virus in the presence of increasing concentrations of **8b**, a resistant strain was isolated that was 10-fold less sensitive to **8b**. A number of known inhibitors of HIV-1 were tested against this virus strain in parallel with the wild-type strain to determine whether cross resistance occurred (Table 6). The nucleoside analogues AZT[4] and 3TC[19] and the protease inhibitor Ro 31-8959[20] were not cross resistant with the **8b**-resistant strain. The non-nucleoside inhibitors, TIBO,[5] nevirapine,[5] and the imidazopyridazine[7] proved to be cross resistant to the virus strain, also exhibiting a 10-fold loss of potency. In contrast, the non-nucleoside inhibitor L-697,661[5] was not cross resistant and was equally potent against both the wild-type virus and **8b**-resistant strain. However, **8b** was inactive in a similar test using the HIV-1 strain A17 (supplied by Merck Sharp and Dohme Research Laboratories, West Point, PA) that was resistant to L-697,661. The A17 strain includes the mutation of the tyrosine-181 residue to cysteine, frequently associated with resistance to non-nucleotide RT inhibitors. This data shows the mutation in the **8b**-resistant strain is not the commonly found tyrosine-181 to cysteine change but occurs in a region of the RT important for binding of TIBO, nevirapine, and the imidazopyridazine but not L-697,661.

Conclusions

A novel series of benzophenone derivatives have been synthesized, and a number are potent inhibitors of HIV-1 RT and HIV-1 in cellular assays. The benzophenone nucleus appears to be important for potent activity together with an aromatic function positioned by a suitable spacer group that contains a hydrogen bond acceptor function. In common with other non-nucleoside HIV-1 RT inhibitors, a member of this series of compounds (**8b**) rapidly induced resistant virus during passage of HIV-1 in the presence of the compound. Interestingly, the observed mutation was not the commonly observed tyrosine-181 to cysteine mutation, even though **8b** was inactive against the A17 strain that contains this mutation. This result together with the rapid onset of resistance during clinical use of other non-nucleoside HIV-1 RT inhibitors led to the cessation of work on this series of benzophenone derivatives.

Experimental Section

Methods and Materials. The ^1H NMR spectra for all compounds were recorded on a Bruker AM250 instrument, and the chemical shifts are reported as part per million (ppm) relative to internal tetramethylsilane (TMS). During workup, organic solutions were dried over $MgSO_4$ and evaporated on a Büchi rotatory evaporator with a bath temperature of 40 °C or below. Thin-layer chromatography was performed on silica plates (Merck Art. No. 5719), and flash column chromatography was carried out on silica (Merck Art. No. 9385). All dried solvents were purchased from the Aldrich Chemical Co. (Sureseal).

Method A: (2-Benzoylphenoxy)acetic Acid (3c). A solution of **2c**[21] (25.0 g, 126 mmol) in DMF (100 mL) was added dropwise to a stirred suspension of sodium hydride (80% dispersion in mineral oil; 3.8 g, 126 mmol) in DMF (100 mL). Stirring was continued for 1 h, and ethyl bromoacetate (14.0 mL, 126 mmol) was added. The mixture was heated at 70 °C for 16 h and then evaporated *in vacuo*. The residue was partitioned between water and EtOAc. The organic portion was washed with dilute aqueous NaOH and water, dried, and evaporated to give an oil (32.5 g). This was dissolved in EtOH (200 mL) and the solution treated with a solution of NaOH (7.0 g, 175 mmol) in water (50 mL). The mixture was heated under reflux for 1 h, cooled, and acidified with 1 N HCl. The oily precipitate was extracted with CH_2Cl_2 and the solution washed with water, dried, and evaporated to give an oil which crystallized from hexane to afford **3c** (24.0 g, 74.3%) as white prisms: mp 109 °C; ^1H NMR (d_6-DMSO) δ 4.63 (s, 2H), 7.0–7.8 (m, 9H). Anal. ($C_{15}H_{12}O_4$) C, H.

2-(2-Benzoylphenoxy)-*N*-[4-[2-(diethylamino)ethoxy]-phenyl]acetamide (1c). A mixture of **3c** (2.56 g, 10.0 mmol) and thionyl chloride (20 mL) was heated at reflux for 30 min and then evaporated. The residue was dissolved in benzene and re-evaporated to give an oil. This was dissolved in benzene (20 mL) and added dropwise to a stirred solution of **4a**[22] (2.08 g, 10.0 mmol) and triethylamine (2.0 mL, 15.0 mmol) in benzene (80 mL). The mixture was heated at 70 °C for 16 h. The cooled solution was washed with dilute aqueous NaOH and water, dried, and evaporated to give an oil. This was purified by chromatography on silica gel using CH_2Cl_2–MeOH (9:1) to give **1c** (1.70 g, 47%) as a colorless oil. Anal. ($C_{27}H_{30}N_2O_4$) C, H, N. A portion of this material (400 mg, 0.89 mmol) was heated in 2-propanol (10 mL) with fumaric acid (110 mg, 0.95 mmol). Upon cooling, **1c** fumarate salt (450 mg, 90%) was deposited as white prisms: mp 144 °C; ^1H NMR (d_6-DMSO) δ 1.02 (t, J = 7.5 Hz, 6H), 2.70 (q, J = 7.5 Hz, 4H), 2.92 (t, J = 7.5 Hz, 2H), 4.04 (t, J = 7.5 Hz, 2H), 4.69 (s, 2H), 6.57 (s, 2H), 6.90 (d, J = 9 Hz, 2H), 7.07 (m, 2H), 7.35–7.70 (m, 7H), 7.80 (d, J = 9 Hz, 2H), 9.60 (s, 1H).

Method B: 2-(2-Benzoyl-4-fluorophenoxy)-*N*-phenylacetamide (1h). A mixture of **2f**[23] (1.08 g, 5.0 mmol), K_2CO_3 (0.69 g, 5.0 mmol), and 2-bromo-*N*-phenylacetamide[24] (1.07 g, 5.0 mmol) in DMF (10 mL) was stirred under a nitrogen atmosphere for 4 h and then evaporated. The residue was partitioned between water and EtOAc. The organic portion was successively washed with water, 1 N HCl, and brine, dried, and evaporated to give an off-white solid (1.52 g) which crystallized from diisopropyl ether to give **1h** (1.17 g, 67%) as white prisms: mp 127–129 °C; ^1H NMR (d_6-DMSO) δ 4.69 (s, 2H), 7.08 (t, J = 7.5 Hz, 1H), 7.22 (dd, J = 4, 9 Hz, 1H), 7.26–7.36 (m, 3H), 7.42 (dt, J = 2.5, 9 Hz, 1H), 7.52 (d, J = 7.5 Hz, 4H), 7.65 (d, J = 7.5 Hz, 1H), 7.82 (d, J = 7.5 Hz, 2H), 9.72 (br s, 1H). Anal. ($C_{21}H_{16}FNO_3$) C, H, F, N.

***N*-[3-(4-Amino-3-methylphenoxy)propyl]dimethylamine (4c).** A mixture of **5b**[21] (20.0 g, 146 mmol) and K_2CO_3 (19.8 g, 143 mmol) in DMF (250 mL) was stirred for 15 min. A solution of *N*-(3-chloropropyl)dimethylamine[21] (31.7 g, 261 mmol) in DMF (50 mL) was added dropwise and the mixture heated at 80 °C for 3 h. The mixture was evaporated and the residue treated with water and extracted with CH_2-

Cl_2. The organic extract was washed with 1 N NaOH, dried, and evaporated to give an oil (27 g). This was dissolved in EtOH (300 mL) and hydrogenated in the presence of 10% palladium on charcoal (2.7 g). The reaction mixture was filtered and the filtrate evaporated to give **4c** as an oil. (23.0 g, 76%): ^{1}H NMR ($CDCl_3$) signals at δ 2.0 (m, 2H), 2.2 (s, 6H), 2.3 (t, 2H), 2.55 (s, 3H), 4.0 (t, 2H). This material was used in the next step, the preparation of **8b**, without further purification.

2-(2-Benzoyl-4-chlorophenyl)-*N*-[4-[3-(dimethylamino)propoxy]-2-methylphenyl]acetamide (8b). A mixture of **7**[11] (2.0 g, 7.2 mmol) and 1-hydroxybenzotriazole hydrate (0.98 g, 7.2 mmol) in DMF (50 mL) was stirred for 10 min. A solution of **4c** (1.52 g, 7.3 mmol) in DMF (50 mL) followed by *N,N'*-dicyclohexylcarbodiimide (1.5 g, 7.3 mmol) was added, and the mixture was stirred at 21 °C for 16 h and then filtered. The filtrate was evaporated and the residue treated with dilute aqueous NaOH and extracted several times with CH_2Cl_2. The combined extracts were evaporated to give an oil which was chromatographed on silica using CH_2Cl_2–MeOH (9:1) to give a solid which was crystallized from 2-propanol to afford **8b** (1.30 g, 39%) as white prisms: mp 144–145 °C; ^{1}H NMR (d_6-DMSO) δ 1.79 (m, 2H), 1.99 (s, 3H), 2.12 (s, 6H), 2.30 (m, 2H), 3.82 (s, 2H), 3.90 (m, 2H), 6.61 (dd, J = 3, 9 Hz, 1H), 6.69 (d, J = 3 Hz, 1H), 6.98 (d, J = 9 Hz, 1H), 7.46 (d, J = 3 Hz, 1H), 7.5–7.8 (m, 7H), 9.27 (s, 1H). Anal. ($C_{27}H_{29}ClN_2O_3$) H, N; C: calcd, 69.7; found, 69.1.

2-[4-Chloro-2-(pyrid-3-ylcarbonyl)phenoxy]-*N*-phenylacetamide (1m). A mixture of **2k** (280 mg, 1.2 mmol), 2-bromo-*N*-phenylacetamide (250 mg, 1.2 mmol), and K_2CO_3 (180 mg, 1.3 mmol) in DMF (5 mL) was stirred for 21 h and then diluted with EtOAc (50 mL). The solution was washed with water and saturated brine, dried, and evaporated to give a brown glass (428 mg). Crystallization from 2-propanol afforded **1m** (245 mg, 56%) as yellow prisms: mp 169–170 °C; ^{1}H NMR (d_6-DMSO) δ 4.74 (s, 2H), 7.06 (t, J = 9 Hz, 1H), 7.21 (d, J = 9 Hz, 1H), 7.29 (t, J = 9 Hz, 2H), 7.36–7.57 (m, 4H), 7.66 (dd, J = 3, 9 Hz, 1H), 8.18 (dt, J = 2, 9 Hz, 1H), 8.77 (dd, J = 2, 6 Hz, 1H), 8.95 (d, J = 2 Hz, 1H), 9.88 (s, 1H). Anal. ($C_{20}H_{15}ClN_2O_8$) C, H, Cl, N.

2-[4-Chloro-2-(hydroxyphenylmethyl)phenoxy]-*N*-phenylacetamide (11). Sodium borohydride (200 mg, 5.3 mmol) was added to a solution of **1g** (1.83 g, 5.0 mmol) in THF (50 mL) at 0 °C. The mixture was stirred for 4.5 h, during which time it was allowed to warm to 21 °C. Cold 2 N HCl was added, and the solution was concentrated. The residual oil was dissolved in EtOAc and the solution washed with 2 N HCl and brine. The dried solution was evaporated to an oil which crystallized from cyclohexane–EtOAc (5:1) to give **11** (1.31 g, 71%) as white prisms: mp 147–148°C; ^{1}H NMR (d_6-DMSO) δ 4.70 (AB q, J = 14, 20 Hz, 2H), 6.06 (d, J = 5 Hz, 1H), 6.10 (d, J = 5 Hz, 1H), 6.96 (d, J = 9 Hz, 1H), 7.10 (t, J = 9 Hz, 1H), 7.15–7.5 (m, 9H), 7.61 (d, J = 9 Hz, 2H), 10.07 (s, 1H). Anal. ($C_{21}H_{18}ClNO_3$) C, H, Cl, N.

[2-[2-(Phenylamino)ethoxy]-5-chlorophenyl]phenylmethanone (12). A mixture of **2e** (0.80 g, 3.4 mmol), K_2CO_3 (0.50 g, 3.8 mmol), and *N*-(2-chloroethyl)aniline[25] (0.53 g, 3.4 mmol) in DMF (20 mL) was heated at 100 °C under a nitrogen atmosphere for 1 h, cooled, and evaporated. The residue was dissolved in CH_2Cl_2, washed with 2 N K_2CO_3 and water, dried, and evaporated. The residue was purified by flash chromatography on silica gel using cyclohexane–EtOAc (9:1) to give an oil (0.6 g). A portion of the oil was dissolved in Et_2O and treated with HCl in Et_2O to afford **12**·HCl salt: mp 131–132 °C; ^{1}H NMR (CD_3OD) δ 3.55 (t, J = 5 Hz, 2H), 4.30 (t, J = 5 Hz, 2H), 7.25 (m, 3H), 7.45–7.65 (m, 7H), 7.75 (m, 1H), 7.85 (m, 2H). Anal. ($C_{21}H_{19}Cl_2NO_2$) C, H, Cl, N.

[4-Chloro-2-(2-phenyl[1,3]dioxolan-2-yl)phenoxy]acetonitrile (13). A mixture of **2e** (5.0 g, 21.5 mmol), ethylene glycol (25 mL), toluene-4-sulfonic acid monohydrate (250 mg), and toluene (120 mL) was heated at reflux in a Dean–Stark apparatus for 24 h. The mixture was cooled, successively washed with saturated aqueous $NaHCO_3$, water, and brine, dried, and evaporated to give a yellow oil (5.65 g). A portion of this material (1.10 g), K_2CO_3 (0.59 g, 4.3 mmol), and bromoacetonitrile (0.30 mL, 4.3 mmol) in DMF (10 mL) was stirred for 4.5 h. The mixture was diluted with EtOAc (100 mL) and successively washed with 2 N HCl, water, and brine. The dried solution was evaporated to give a dark oil (1.3 g) which was purified by flash chromatography on silica gel using cyclohexane–EtOAc (2:1; containing 0.1% NEt_3) to give **13** (1.03 g, 78%) as a white crystalline solid: mp 86–88 °C; ^{1}H NMR (d_6-DMSO) δ 4.00 (m, 4H), 4.95 (s, 2H), 7.13 (d, J = 8 Hz, 1H), 7.25–7.75 (m, 7H). Anal. ($C_{17}H_{14}ClNO_3$) C, H, Cl, N.

1-(2-Benzoyl-4-chlorophenoxy)-3-phenylpropan-2-one (14). A solution of **13** (936 mg, 3.0 mmol) in anhydrous THF (15 mL) was stirred at −78 °C under an atmosphere of N_2. Benzylmagnesium bromide (2 M) in THF (1.5 mL, 3.0 mmol) was added, and the solution was stirred for 5 h. Additional 2 M benzylmagnesium bromide in THF (0.5 mL, 1.0 mmol) was added, and stirring was continued for 2.5 h. The solution was diluted with EtOAc, washed with aqueous NH_4Cl and brine, dried, and evaporated to give a foam (1.12 g). This was purified by flash chromatography on silica gel using cyclohexane–EtOAc (5:1; containing 0.2% NEt_3) to give an oil (152 mg). The bulk of this material (128 mg) was dissolved in THF (6 mL), and 1 N HCl (6 mL) was added. The mixture was heated at 70 °C for 3 h and then stirred at room temperature for 16 h. The mixture was extracted with ether and the organic extract washed with brine and dried. Evaporation gave a gummy solid (118 mg) which was purified by flash chromatography on silica gel using cyclohexane–EtOAc (5:1) to give **14** (65 mg, 7.0%) as an oil: ^{1}H NMR ($CDCl_3$) δ 3.45 (s, 2H), 4.47 (s, 2H), 6.70 (d, J = 8 Hz, 1H), 7.00–7.65 (m, 8H), 7.86 (d, J = 4 Hz, 1H); MS (TOF) m/z 365.3 (MH^+) (calcd for $C_{22}H_{17}ClO_3$ 364.83).

[2-(3-Phenyl-2(*E*)-propenoxy)-5-chlorophenyl]phenylmethanone (15). A mixture of **2e** (1.00 g, 4.30 mmol), K_2CO_3 (0.71g, 5.16 mmol), and *trans*-cinnamyl bromide (0.85 g, 4.3 mmol) in DMF (50 mL) was heated at 60 °C for 2 h, cooled, and evaporated. The residue was dissolved in CH_2Cl_2, washed with dilute NaOH and water, dried, and evaporated. The residue was purified by flash chromatography on silica gel using cyclohexane–EtOAc (85:15) to give an oil which was crystallized from diisopropyl ether to afford **15** (0.73 g, 49%) as white prisms: mp 89–90 °C; ^{1}H NMR ($CDCl_3$) δ 4.60 (d, J = 5 Hz, 2H), 6.00 (td, J = 5, 16 Hz, 1H), 6.26 (d, J = 16 Hz, 2H), 6.96 (m, 1H), 7.25 (m, 5H), 7.44 (m, 4H), 7.55 (m, 1H), 7.82 (m, 2H). Anal. ($C_{22}H_{17}ClO_2$) C, H, Cl.

2-(2-Benzoyl-4-chlorophenoxy)-1-(3,4-dihydro-1*H*-isoquinolin-2-yl)ethanone (18). Triethylamine (0.35 mL, 2.5 mmol) and 1,2,3,4-tetrahydroisoquinoline[21] (0.32 mL, 2.5 mmol) were added to stirred solution of **3e** (581 mg, 2.0 mmol), 1-hydroxybenzotriazole hydrate (270 mg, 2.0 mmol), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (480 mg, 2.5 mmol) in THF (25 mL). The mixture was stirred for 19 h, diluted with EtOAc, and washed sequentially with water, saturated aqueous $NaHCO_3$, water, 2N HCl, water, and brine. The dried solution was evaporated to give **18** (772 mg, 95.1%) as a white foam. A portion of this material was crystallized from ether to give white prisms: mp 101–102 °C; ^{1}H NMR (d_6-DMSO) δ 2.76 (m, 2H), 3.51 (t, J = 6 Hz, 2H), 3.59 (t, J = 6 Hz, 2H) 4.52 (d, J = 7 Hz, 2H), 4.95 (s, 2H), 7.10 (d, J = 9 Hz, 1H), 7.17 (s, 2H), 7.35–7.70 (m, 5H), 7.81 (d, J = 7 Hz, 2H). Anal. ($C_{24}H_{20}NClO_3$) C, H, Cl, N.

2-(2-Benzoyl-4-chlorophenoxy)-1-(1*H*-indol-2-yl)ethanone (21). A solution of phenol **19**[26] (1.10 g, 4.67 mmol) and K_2CO_3 (645 mg, 4.67 mmol) in DMF (50 mL) was stirred at room temperature for 30 min. Indole **20**[27] (904 mg, 4.67 mmol) was then added, and the solution stirred for 5 h. The reaction was evaporated to afford an oil which was partitioned between EtOAc (50 mL) and brine (50 mL). The organic phase was washed with brine, dried, and evaporated to a brown oil. Flash chromatography on silica gel using $CHCl_3$–MeOH (100:1) afforded a brown oil which was crystallized from cyclohexane–Me_2CO to afford a solid (726 mg). A portion of this material (600 mg) in CH_2Cl_2 (5 mL) was treated with pyridinium chlorochromate (363 mg, 1.68 mmol), and the mixture was stirred for 1 h. Diethyl ether (100 mL) was then added, and the resulting suspension was filtered through Celite. The filter bed was washed with EtOAc, and the combined filtrates were

evaporated to afford a brown oil. Purification by flash chromatography on silica gel using cyclohexane–EtOAc (5:1) gave **21** (284 mg, 48%) as a white crystalline solid: mp 125–126 °C; ^{1}H NMR (d_6-DMSO) δ 5.50 (s, 2H), 7.04–7.90 (m, 13H), 11.85 (br s, 1H). Anal. ($C_{23}H_{16}ClNO_3$) C, H, Cl, N.

[2-(1*H*-Benzimidazol-2-ylmethoxy)-5-chlorophenyl]phenylmethanone (23). A solution of **2e** (0.5 g, 2.15 mmol) in DMF (5 mL) was added dropwise to a stirred suspension of sodium hydride (60% suspension in mineral oil; 95 mg, 2.37 mmol) in DMF (10 mL). The mixture was stirred for 10 min, and a solution of **22**[21] (0.36 g, 2.16 mmol) in DMF (10 mL) was added dropwise. The mixture was heated at 80 °C for 16 h and then evaporated. The residue was partitioned between water and CH_2Cl_2. The organic phase was dried and evaporated to give an oil. Purification by chromatography using CH_2Cl_2–MeOH (19:1) gave an oil which crystallized from 2-propanol to afford **23** (0.18 g, 23%) as pale yellow prisms: mp 144–145 °C; ^{1}H NMR (d_6-DMSO) δ 5.31 (s, 2H), 7.18 (m, 2H), 7.41–7.77 (m, 10H), 12.40 (br s, 1H). Anal. ($C_{21}H_{15}ClN_2O_2 \cdot 0.5H_2O$) H, Cl, N; C: calcd, 67.8; found, 68.5.

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Supplementary Material Available: Atomic coordinates, bond lengths, bond angles, anisotropic displacement coefficients, and hydrogen coordinates for compound **1h** (5 pages); structure factor listings for compound **1h** (9 pages). Ordering information is given on any current masthead page.

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