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Perspective

The Many Roles for Fluorine in Medicinal Chemistry

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Introduction

Drug candidates with one or more fluorines have become commonplace. The special nature of fluorine imparts a variety of properties to certain medicines, including enhanced binding interactions, metabolic stability, changes in physical properties, and selective reactivities. Advances in fluorine chemistry have presented to the synthetic chemist a wide variety of reagents for the selective introduction of fluorine or fluoroalkyl groups into specific locations in their target molecules. This Perspective will try to provide to the practicing medicinal chemist a guide to some of the effects that the introduction of fluorine can have on potential drug candidates, including recent examples of successful strategies along with a list of leading references to synthetic transformations that may be useful.

The role of fluorine in medicinal chemistry and drug design has been reviewed often in the past few years, and it is impossible to provide even an overview of the tremendous progress that has been reported in the organofluorine arena. Two excellent volumes dedicated to the established and emerging roles that fluorine has played in drug design and discovery are highly recommended. The first is a collection of papers from a symposium entitled "Fluorine in the Life Sciences" held in Switzerland in July 2003 which presented a program focused on the biological activities, structures, and properties of fluoroorganic compounds.[1] In particular, one review focuses on many of the strategies employed by medicinal chemists to optimize desired druglike properties by incorporating fluorine into their molecules.[2] The second volume dedicated to fluoroorganics was edited by Kenneth Kirk from the National Institutes of Health (NIH[a]) and addresses the many issues and opportunities that incorporating fluorine can offer.[3] He also authored an excellent review of more recent examples of fluorinated drugs.[4]

The early successful introductions of fluorinated steroids[5] and fluorouracil[6] were followed by a steady succession fluorinated drugs, usually with the launch of one to three candidates per year until the early 1980s (see Table 1).[2,7] It is interesting to note a rise in the number of fluorinated drugs (red bars) around 1982 which follows the earlier reports[8,9] of selective fluorination chemistry employing (diethylamino)sulfur trifluoride (DAST) in a time frame that it usually takes to develop a drug candidate. On the other hand, the number of fluorine-containing launched drugs as a percentage of the total number of launched drugs has remained relatively constant (green bars). Fluorinated drugs have constituted approximately 5−15% of the total number of launched drugs worldwide over the past 50 years with a noticeable increase in the past 5 years. As of June 2007, there were 44 fluorinated drug candidates under active investigation in phase III clinical trials and 115 in phase II studies.[7] As new fluorinating methodologies and fluorinated commercial intermediates continue to become available, the medicinal chemist will have even broader access to synthetic and design strategies for incorporating fluorine into target molecules. It will be interesting to see if the percentage of fluorinated drugs increases as a result.

The high electronegativity and small size of fluorine as well as its very different chemical reactivity with respect to hydrogen have dominated design considerations. Whereas fluorine is larger than hydrogen, its van der Waals radius is closer to that of oxygen as is its electronegativity (Table 2).[10] Numerous examples can be found where fluorine has effectively replaced either hydrogen or oxygen and retained comparable activities, albeit with different properties. The trifluoromethyl group has generally been described as being "slightly larger" than an isopropyl group. However, depending upon the methods employed to estimate volume, it has been described as having twice the bulk of a methyl group to being the size of a phenyl or *tert*-butyl group.[11,12] Rotational energy studies on o,o′-disubstituted biphenyl derivatives suggest that the trifluoromethyl group supports a volume slightly larger than the volume of isopropyl,[13,14] whereas X-ray crystal data put its volume closer

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[a] Abbreviations: NIH, National Institutes of Health; DAST, (diethylamino)sulfur trifluoride; CNS, central nervous system; PET, positron emission tomography; Pgp, P-glycoprotein; HMGR, 3-hydroxy-3-methylglutaryl-coenzyme A reductase; NBS, *N*-bromosuccinimide; MFSDA, methylfluorosulfonyldifluoroacetate; $TMSCF_3$, trifluoromethyl-trimethylsilane (Ruppert−Prakash reagent); DPP-4, dipeptidyl peptidase 4; CB1R, cannabinoid-1 receptor; COX-2, cyclooxygenase.

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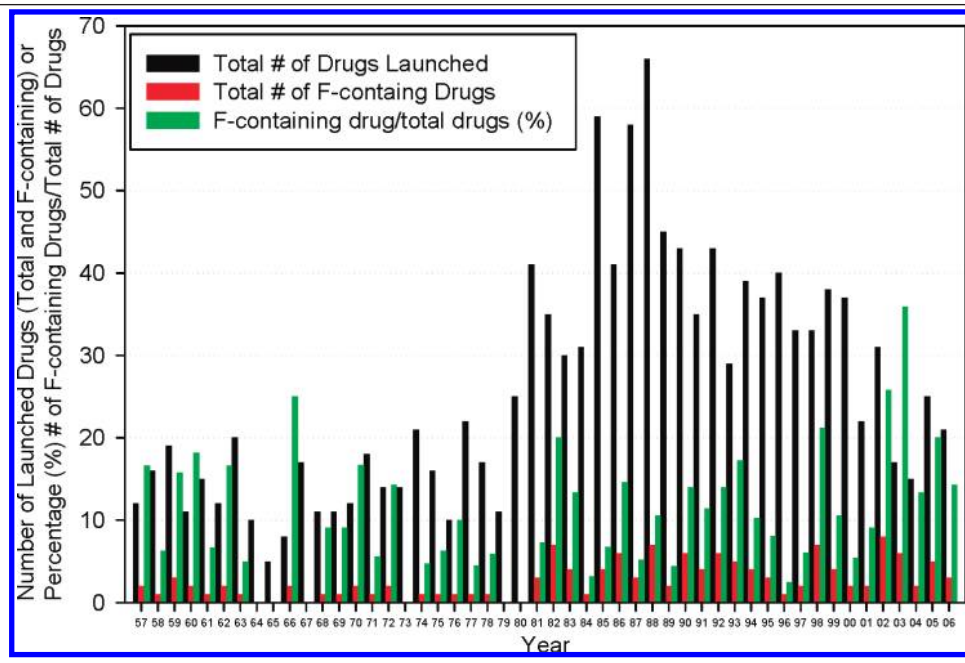
Table 1. Launched Drugs Containing Fluorine 1957−2006[7] [a]



[a] Drugs launched worldwide, excluding biologics, inorganics, reformulations, and agricultural agents.

Table 2. van der Waals Radii and Pauling Electronegativities[10]

	van der Waals radius (Å)	Pauling electronegativity
C	1.70	2.55
H	1.20	2.20
F	1.47	3.98
O	1.52	3.44
N	1.55	3.04
Cl	1.75	3.16

to that of an isobutyl group.[15,16] Whatever their isosteric mimicry, fluoro or trifluoromethyl substitutions will generally have a profound effect on the physical and/or biological properties of the targeted molecule.

The strongly electron withdrawing nature of fluorine substitution is especially evident in its effect on the acidity of neighboring functional groups.[17–19] As seen in Table 3, linear and cyclic amines become much less basic with both β- and γ-fluorine substitution. These inductive effects influence pK_a even with δ-substitution. The effects are seen to be additive as each additional fluorine lowers the pK_a by a similar increment. The lower pK_a of trifluoroethyldimethylamine relative to trifluoroethylamine has been attributed to a through space interaction between fluorine and the protonated amine in a conformation induced by the dimethyl substitution.[17] Anilines, pyridines, and quinolines can also exhibit profound lowering of basicity, although the effects are attenuated by the nature of the aromatic ring. Not surprisingly, alcohols, carboxylic acids, heterocycles, and phenols become more acidic with adjacent fluorine substitution.

Changes in pK_a can have effects on a number of different parameters in lead optimization including physicochemical properties (solubility, log D), binding affinities (potency, selectivity), and absorption, distribution, metabolism, excretion (ADME), and safety issues. Among the physicochemical properties important for effective central nervous system (CNS) drugs relative to non-CNS drugs are those properties that favor enhanced membrane penetration, including fewer positive charges and no negative charges (pK_a dependent) and greater lipophilicity (cLogP, cLogD).[20] Fluorine substitution may do double duty by enhancing brain penetration and providing a site for radiolabeling with ^{18}F to produce a positron emission tomography (PET) ligand useful for noninvasive imaging of the CNS.[21] Some of these properties may also have effects on susceptibility to P-glycoprotein (Pgp)-mediated efflux as well.

Beyond the expected inductive effects that fluorine may exert on neighboring functionalities to alter physical properties or chemical reactivities, there is now a greater appreciation for the role that fluorine substitution may play in direct binding interactions. These interactions may occur between fluorine and a protein directly, may be bridged by a sphere of solvation, or may occur by alterations in the conformation of the molecule.[22] The type 2 statins (fluvastatin, cerivastatin, atorvastatin, and rosuvastatin) are all characterized by having an essential fluorophenyl substitution, whereas the type 1 statins contain the compactin scaffold (lovastatin, simvastatin). The X-ray crystal structure of each of these statins bound to the catalytic domain of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGR) was solved.[23] For the fluorine-containing type 2 statins, the guanidinium group of Arg^{590} stacks on top of the fluorophenyl group and a direct polar interaction between the arginine ε nitrogen atoms and the fluorine is proposed. A search of structural databases provided further examples of fluorinated inhibitors cocrystallized with their target proteins (e.g., thrombin, porcine pancreatic elastase, endoglucanase Cel5A, and carbonic anhydrase II), providing evidence for conformational, stacking, edge-on, and direct binding interactions.[22]

Fluorination of target molecules would be expected to have a profound effect on dipolar interactions, and yet, the change in binding potency of a fluorinated species versus its hydrocarbon parent may sometimes be quite small. In those cases, if direct binding interactions are present, especially in aromatic species, a modest effect on overall binding suggests that those interactions are quite weak.[24] Whereas fluorination of alkanes will actually decrease lipophilicity, the addition of fluorine or trifluoromethyl groups on an aryl ring or adjacent to a π-system or heteroatom-containing functional group increases lipophilicity and can strongly polarize the parent molecule.[25] Nonproductive

Table 3. Effect of Fluorine Substitution on pK_a of Various Functions Groups[18,19]

linear amines					
β-substitution					
$CH_3CH_2NH_3^+$	10.7				
$FCH_2CH_2NH_3^+$	9.0				
$F_2CHCH_2NH_3^+$	7.3				
$F_3CCH_2NH_3^+$	5.7				
$CH_3CH_2N(CH_3)_2H^+$	10.2				
$F_3CCH_2N(CH_3)_2H^+$	4.8				
γ-substitution					
$CH_3CH_2CH_2NH_3^+$	10.7				
$FCH_2CH_2CH_2NH_3^+$	9.9				
$F_3CCH_2CH_2NH_3^+$	8.7				
δ-substitution					
$CH_3CH_2CH_2CH_2NH_3^+$	10.7				
$F_3CCH_2CH_2CH_2NH_3^+$	9.7				
piperidineH$^+$	11.1				
3-F-piperidineH$^+$	9.3				
3,3-F_2-piperidineH$^+$	7.4				
4-F-piperidineH$^+$	9.4				
4,4-F_2-piperidineH$^+$	8.5				
anilineH$^+$	2-	3-	4-		
H	4.62				
F	3.20	3.58	4.65		
CF_3		3.49	2.57		
pyridineH+	2-	3-			
H	5.17				
F	−0.44	2.97			
quinolineH$^+$	3-	5-	6-	7-	8-
H	4.85				
F	2.36	3.68	4.00	4.04	3.1
simple alcohols					
CH_3CH_2OH	16.0				
F_3CCH_2OH	12.37				
carboxylic acids					
CH_3CO_2H	4.76				
FCH_2CO_2H	2.66				
F_2CHCO_2H	1.24				
F_3CCO_2H	0.23				
$CH_3CH_2CO_2H$	4.87				
$F_3CCH_2CO_2H$	3.06				
benzoic acids	2-	3-	4-		
H	4.20				
F	3.27	3.87	4.14		
CF_3		3.79			
tetrazole					
5-CH_3	4.9				
5-CF_3	1.7				
phenols	2-	3-	4-		
H	9.99				
F	8.73	9.29	9.89		
CF_3		8.9			

fluorination may have modest effects on affinity because weak repulsive interactions are counterbalanced by increased hydrophobicity. In the end, this apparent weak interaction could be a desirable outcome in that the medicinal chemist can have some confidence that a particularly labile site of metabolic oxidation can be blocked by fluorination without adversely effecting affinity.

Recent Progress in Synthetic Methods of Organofluorine Chemistry

Synthetic methods in organofluorine chemistry have made enormous progress since the first reports of Borodine in 1863 of fluoride displacement of halogens[26] and of Swarts in 1892 of the fluorination of polychloroalkenes with antimony trifluoride or zinc and mercury fluorides.[27] Fluorination reactions to form organofluorine compounds utilize nucleophilic, electrophilic, and radical forms of fluorine in reagents that no longer require specialized laboratory equipment, vessels, or lines. These reagents are readily prepared or are commercially available. Many books, monographs, and reviews have been published that detail the broad array of reactions available for the preparation of unique and useful fluorinated organic compounds.[28,29] It should be understood that most chemists will generally utilize commercially available intermediates or building blocks that already contain fluorine or fluoroalkyl substituents in a desired position. That said, not every conceivable substitution pattern will be available, so a working knowledge of organofluorine synthesis is desirable. A few synthetic transformations that may be of interest to the medicinal chemist are highlighted here along with some more recent reports of asymmetric fluorination reactions.

Various nucleophilic fluorine reagents are available, and some representative reactions are shown in Table 4.[30,31] As mentioned above, the first reports of DAST ((diethylamido)sulfur trifluoride) had an effect on the selective introduction of fluorine into drug candidates. Ketones and aldehydes **1** react with DAST to form difluoroalkyl compounds **2**.[32] Alcohols will also react to form monofluoroalkyls. Tetralkylammonium fluorides will react with alkenes **3** in the presence of an electrophilic halogenating reagent, such as *N*-bromosuccinimide (NBS), to afford the *trans*-1-fluoro-2-bromoalkane **4** in good yield.[33] The reaction works well with cyclic and trisubstituted acyclic alkenes. In a process referred to as oxidative desulfurization−fluorination, thioesters **5**, derived from ortho-directed metalation and reaction with carbon disulfide, will react initially with a strong halogenating agent followed by a nucleophilic tetraalkylammonium fluoride reagent to yield a trifluoromethylbenzene **6** in good yield.[34] Difluoroalkyl derivatives may also be prepared. In an analogous reaction, the thioester **7** will react with bromine trifluoride followed by aqueous acid treatment to yield the β-trifluoromethyl ester **8**.[35] Bromine trifluoride is commercially available and represents nonsolvated fluoride coupled with highly electrophilic bromine.

Electrophilic fluorine reagents, employing an "F^+" moiety, are also available and usually contain a nitrogen−fluorine species. These N−F reagents can deliver fluorine to carbanions generated from carbonyl compounds **9** to afford the α-fluoroketones, aldehydes, and esters **10**[36] and to ortho-lithiated aryls **11** to yield the fluorinated aryls **12** (Table 5).[37] Among the more efficient reagents for delivery of a fluorine cation is 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate (Selectfluor, which is a trademark of Air Products and Chemicals, Inc.). This reagent has been especially useful for the preparation of fluorinated heterocycles, illustrated by the reaction of 3-stannylindole **13** with Selectfluor to afford the 3-fluoroindole **14**.[38] The 2-fluoroindole can be prepared in an analogous manner. This reagent will also react with 3-substituted indoles **15** to give the 3-fluorooxindole derivatives **16** in good yields.[39] The reaction is nearly quantitative in the presence of an ionic liquid cosolvent.

Occasionally, a monofluorinated derivative with a specific configuration is desired, such as was explored for a class of 3-fluoropyrrolidine dipeptidyl peptidase-4 (DPP-4) inhibitors.[40] Methodologies to introduce fluorine enantioselectively are emerging, some with very impressive yields and selectivities (Table 6).[41] The progress in this area is all the more impressive when considering the rapid enolization of α-fluoroketones, aldehydes, and esters that had to be overcome. Mild reaction and workup conditions to minimize loss of chirality characterize the more successful methodologies. Utililization of anions generated from chiral auxiliaries, such as Evan's oxazolidinones **17**, with an electrophilic fluorinating reagent afforded a chiral

Table 4. Examples of Nucleophilic Fluorine Reactions

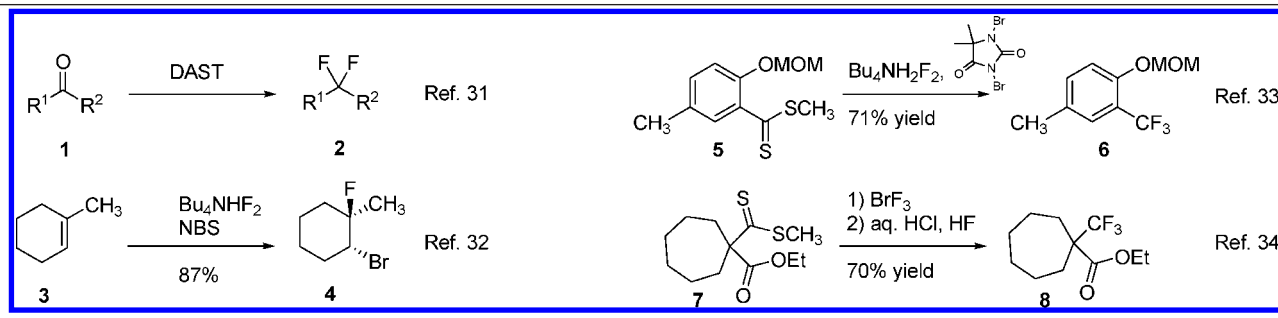


Table 5. Examples of Electrophilic Fluorine Reactions

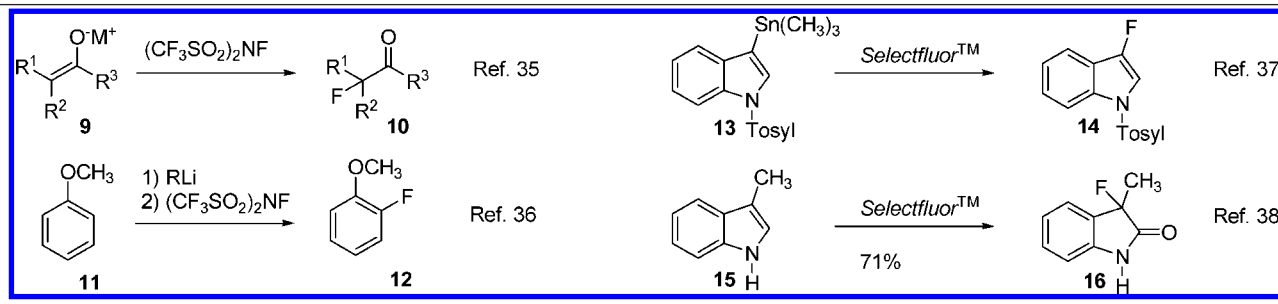
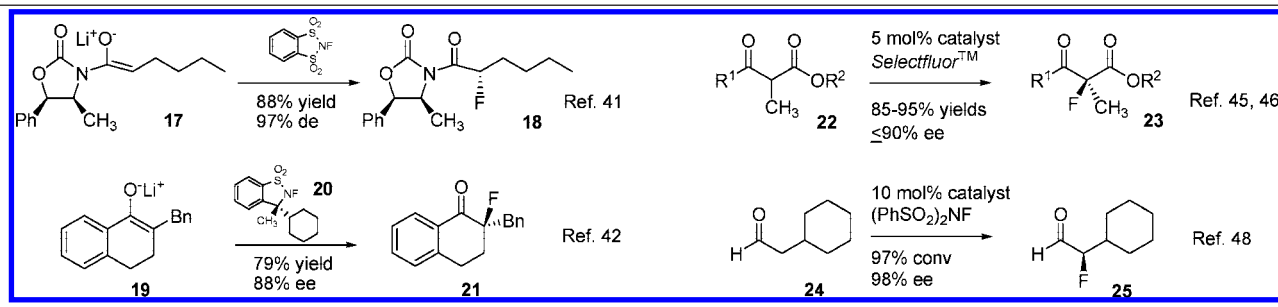


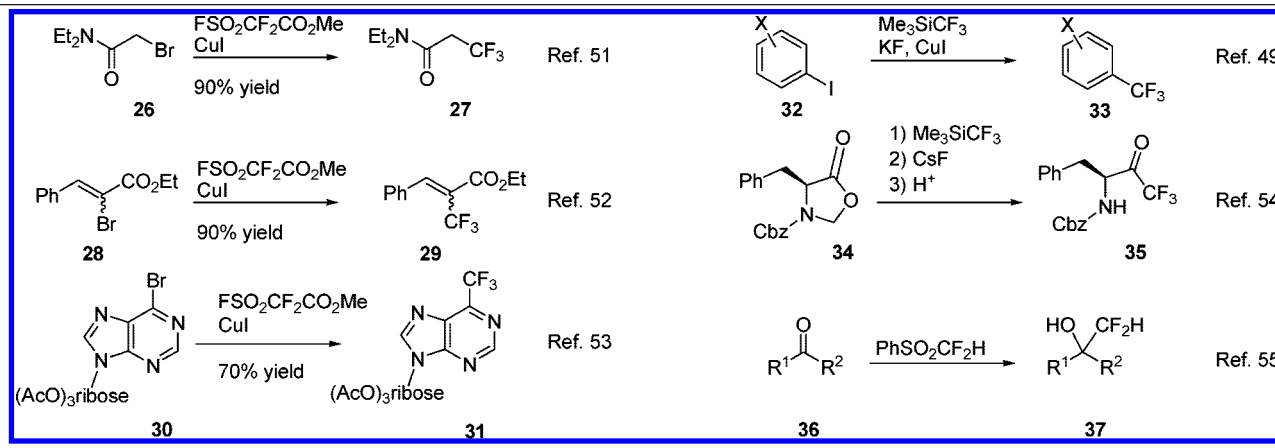
Table 6. Enantioselective Introduction of Fluorine



α-fluorocarbonyl derivative **18** in excellent yield and selectivity.[42] Alternatively, chiral fluorinating agents have been explored with mixed results. The best results to date utilize a chiral N−F sulfonamide **20** reacting with enolates, such as **19**, to yield the tetralone **21** in good yield and enantiomeric excess.[43] Further improvements in yields and enantioselectivity have been reported with N−F fluorinating agents derived from cinchona alkaloids.[44,45] The first enantioselective transition metal catalyzed reaction of Selectfluor and a β-keto ester **22** was reported by Togni.[46,47] These titanium catalysts afforded good yields (≤80%) and high enantioselectivity (60−90% ee) of the chiral α-fluoro-β-keto-esters **23**. More recently, MacMillan reported the use of a commercially available imidazolidinone that catalyzed the reaction between aldehydes **24** and *N*-fluorobenzenesulfonimide to afford the chiral α-fluoroaldehydes **25** in good yields (50−100%) and excellent enantioselectivity (91−99% ee).[48] These reactions are characterized by their mild conditions and ease of operation.

Among the very useful reactions is the introduction of polyfluoroalkyl groups, such as a trifluoromethyl, onto a specific position.[49] Trifluoromethyliodide (a gas) reacts with zinc and aryl (and vinyl and allyl) iodides in a palladium-catalyzed cross-coupling reaction in the presence of ultrasonic irradiation to form the corresponding trifluoromethylaryls in good yields.[50] Methyl fluorosulphonyl difluoroacetate (MFSDA, a liquid) is more convenient to handle than trifluoromethyl iodide. Again, a variety of aryl, vinyl, benzyl, and allyl halides reacts with MFSDA in the presence of copper(I) iodide in dimethylformamide (DMF) to form the corresponding trifluoromethyl aryl, vinyl, benzyl, and allyl derivatives in good yield.[51] The α-bromoamide **26** reacts with MFSDA in the presence of copper iodide to afford the β-trifluoropropanamide **27** in excellent yield (Table 7). Likewise, the α-bromocinnamate **28** will react similarly to yield the α-trifluoromethyl cinnamate **29**. Heterocyclic halides, such as a 6-bromopurine derivative **30**, have also been reported to react with MFSDA to give the 6-trifluoromethylpurine **31**.[53] The Ruppert−Prakash reagent, trifluoromethyltrimethylsilane ($TMSCF_3$), is very useful for generating a nucleophilic trifluoromethyl anion species that readily adds to a variety of carbonyl compounds to form carbon−trifluoromethyl bonds.[54] Subsequent transformations can afford a wide variety of fluoroalkyl intermediates. Highly nucleophilic trifluoromethyl (CF_3^-) and difluoromethyl (CF_2^-) anions are also generated from a variety of sulfur-based fluoroalkylating reagents and shown to react with numerous electrophiles to generate trifluoromethyl and difluoromethyl (and difluoromethylene) species.[55] Substituted iodobenzenes **32** react with $TMSCF_3$ in the presence of potassium fluoride and copper iodide to yield the trifluo-

Table 7. Introduction of Fluoroalkyl Groups



romethylbenzenes **33** in good yield. An interesting use for this reagent is its reaction with oxazolidinones **34** followed by reaction with cesium fluoride and then acidic resin to afford the trifluoromethylketone of a protected α-amino acid **35**.[54] Other nucleophilic fluorinating agents generated from fluorinated organosulfur compounds have proved to be useful in preparing tri-, di-, and monofluorinated compounds. For example, ketones or aldehydes **36** will react with (phenylsulfonyl)difluoromethane in the presence of base to afford the difluoromethyl alcohol **37** in good yield.[55] Other sulfinyl and sulfidyl reagents facilitate the preparation of difluoromethylene and monofluoromethyl derivatives.

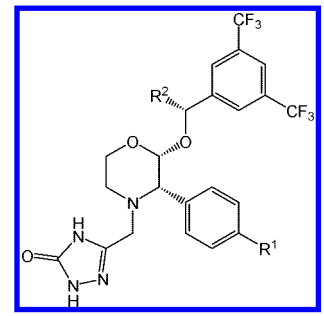
Improved Drug Properties Resulting from the Introduction of Fluorine

There are many examples of the use of fluorine to alter the physical properties, binding characteristics, and metabolic disposition of developing drug leads. The reader is directed to the examples cited in the many reviews of fluorination in medicinal chemistry. A few recent examples are described here where selective placement of fluorine substitution played a key role in the identification of novel drug candidates.

Aprepitant: Improved Duration of Action

The morpholine acetal NK1 receptor antagonist **38** was reported to be very potent in binding (NK1 IC_{50} = 0.09 nM) and effective in preclinical models of emesis (ID_{90} at 24 h, 5.4 mg/kg po).[56,57] Further efforts to improve its metabolic stability focused on stabilizing the benzylic position by methylation[58] and the phenyl group by fluorination.[59] As seen in Table 8, methylation and fluorination had little effect on NK-1 potency. Although no pharmacokinetic data were available for comparison, both modifications had the desired effect of improving pharmacodynamic properties. In a model of peripheral NK-1 activity, fluorination of **38** gave **39**, which exhibited a 2-fold improvement in potency when measured 24 h postdose. Likewise in a model of NK-1 agonist mediated CNS activity (gerbil foot tapping), **39** was also 2-fold more potent than **38** at 24 h postdose. Methylation of the benyzlic ether gave a similar improvement in both animal models **40**. Incorporation of both changes were additive in **41**, which was successfully developed as aprepitant for the treatment of chemotherapy induced nausea and vomiting. It is interesting to note that many reported NK-1 antagonists contain a bis-trifluoromethylphenyl group that appears to enhance CNS penetration.[60]

Table 8. Fluorine Substitution Improves in Vivo Potency of NK-1 Antagonists[a]



compd	R^1	R^2	NK-1 IC_{50} (nM)[a]	SYVAL[b] ID_{90} at 24 h (mg/kg po)	NK-1 agonist-induced foot-tapping[c] ID_{50} at 24 h (mg/kg iv)
38	H	H	0.09	5.4	2.88
39	F	H	0.07	2.3	1.24
40	H	CH_3	0.09	2.3	1.11
41	F	CH_3	0.09	1.8	0.33

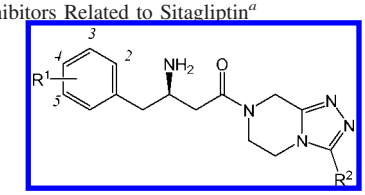
[a] References 57 and 58. [b] Dose required to elicit 90% inhibition of resiniferatoxin-induced systemic vascular leakage in guinea pigs 24 h after oral dose. [c] Dose required to elicit 50% inhibition of foot tapping in gerbils induced by the NK-1 agonist GR73632 (δ-aminovaleryl-L-Phe-L-Phe-L-Pro-L-(*N*-Me)Leu-L-Met-NH_2) (icv) 24 h after iv dose.

Sitagliptin: Enhanced Potency

Fluorophenyl substitution proved to be very important for improvements in potency and pharmacokinetics in the triazolopiperazine class of dipeptidyl peptidase-4 inhibitors.[61,62] The 2,5-difluorophenyl analogue **43** was nearly 5-fold more potent versus DPP-4 than the isomeric 3,4-difluorophenyl **42**. Addition of a fluorine to the 4-position gave the 2,4,5-trifluorophenyl derivative **44**, which gave a modest enhancement of enzyme inhibition. All three analogues are characterized by moderate to high clearance in the rat with similar plasma half-lives. However, **44** exhibited significantly improved oral bioavailability and maximal exposure. Other patterns of trifluorophenyl substitution (**45**−**47**) were considerably less potent versus DPP-4.[63] So by optimization of fluorophenyl substitution, both potency and oral bioavailability were enhanced in **44**, which was rapidly developed as sitagliptin, the first marketed DPP-4 inhibitor for the treatment of type 2 diabetes.

The triazolopiperazines in Table 9 illustrate a couple of characteristics of organofluorine substitution in medicinal

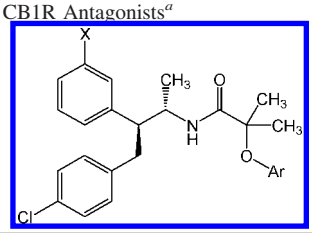
Table 9. Effect of Fluorine Substitution on DPP-4 Inhibitors Related to Sitagliptin[a]



				rat pharmacokinetics[b]			
compd	R^1	R^2	DPP-4 IC_{50} (nM)	Cl_p ((mL/min)/kg)	$T_{1/2}$ (h)	C_{max} (μM)	F (%)
42	3,4-F_2	CF_3	128	51	1.8	0.14	44
43	2,5-F	CF_3	27	43	1.6	0.19	51
44	2,4,5-F_3	CF_3	18	60	1.7	0.33	76
45	2,3,5-F_3	CF_3	805				
46	2,3,6-F_3	CF_3	151				
47	2,4,6-F_3	CF_3	87				
48	2,4,5-F_3	H	68	40	1.0	0.03	3
49	2,4,5-F_3	C_2H_5	37	70	1.7	nd	2
50	2,4,5-F_3	C_2F_5	71	58	2.3	0.16	61

[a] References 60–62. [b] Cl_p = rate of compound clearance from plasma; $T_{1/2}$ = half-life of compound circulating in plasma; C_{max} = maximum concentration of compound achieved after an oral dose of 2 mg/kg; F = oral bioavailability.

Table 10. Covalent Binding and Rat Pharmacokinetics of CB1R Antagonists[a]



					rat pharmacokinetics[b]			
compd	Ar	X	CB1 IC_{50} (nM)	covalent binding	Cl_p ((mL/min)/kg)	$T_{1/2}$ (h)	C_{max} (μM)	F (%)
51	Ph	H	2.03	3900	33	2.8	0.18	9
52	3,5-F_2-Ph	H	1.47	1700	35	2.4	0.30	19
53	2-pyr	H	1.80	910	25	2.2	0.44	29
54	5-CF_3-pyr	H	0.54	88	35	2.2	1.2	100
55	5-CF_3-pyr	CN	0.29	27	33	2.7	0.49	74

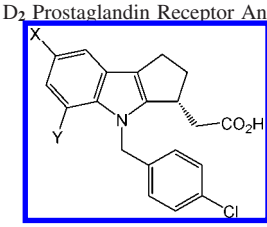
[a] References 66 and 67. [b] Cl_p = rate of compound clearance from plasma; $T_{1/2}$ = half-life of compound circulating in plasma; C_{max} = maximum concentration of compound achieved after an oral dose of 2 mg/kg; F = oral bioavailability.

chemistry. The X-ray structure of sitagliptin **44** bound to DPP-4 shows the amide moiety is aligned in the opposite orientation of that reported for α-amino acid derived DPP-4 inhibitors and docked substrates. The amine portions of the molecules do overlap but the fluorine at the 2-position of the benzyl group appears to overlap well with the carbonyl group of the amide in α-amino acid derived inhibitors. Fluorine at this position gives up to a 10-fold improvement in binding over the unsubstituted benzyl.[62] The trifluoromethyl group on the triazolopiperazine is in a position for an enhanced binding interaction with the side chains of Ser209 and Arg358.[61] One would expect that the trifluoromethyl substitution in **44** would have a dramatic effect on the nature of the dipole of the heterocycle relative to **48** as well as the changing of the overall hydrophobicity of the molecule. It may well do so, but the effects on enzyme inhibition are relatively minor. Replacement of the trifluoromethyl group with ethyl (**49**) or pentafluoroethyl (**50**) also resulted in small decreases in potency relative to **44**. This lack of dramatic change supports the notion that some fluorine substitution may offer only weak interactions with the target protein, whereas other substitution (**45** vs **44**) may be critical. The ability to "freely" substitute at a particular position offers greater flexibility to change other properties of the molecule. In the DPP-4 example, the unsubstituted or alkyl substituted triazolopiperazines **48** and **49** have poor oral bioavailability whereas the fluoroalkyl substituents in **44** and **50** afforded improved oral bioavailability. Since clearance rates and plasma half-lives for all four compounds were similar, these differences were more likely a function of improved absorption resulting from a change in physical properties.

Taranabant: Reduced Potential for Covalent Protein Binding

Idiosyncratic allergic reactions to a therapeutic agent can arise at any time during the course of a drug development program, including in the wider postlaunch market.[64] As the term implies, the appearance of an allergic reaction may not be predicted and can have dire consequences for patients and manufacturer. The covalent modification of proteins by a drug and subsequent immunological responses have been implicated as a causative event in the development of allergic reactions to drugs. Minimizing the formation of reactive intermediates resulting from oxidative metabolism has been proposed as one strategy to lower the potential for these allergic reactions.[65,66] The triphenylamide **51** was an early analogue in a series of potent cannabinoid-1 receptor (CB1R) inverse agonists (Table 10).[67] It displayed poor oral bioavailability and a high level of covalent protein binding.[68] The electron rich phenoxy ring was identified by mass spectrometric analysis as the target for oxidative metabolism and the formation of reactive intermediates, presumably arene oxides. The addition of two fluorines to the phenoxy ring in **52** modestly attenuated covalent protein binding about 2-fold while improving oral bioavailability by the same amount. Replacement of the phenoxy ring with a 2-pyridyloxy (**53**) further reduced covalent binding and improved oral bioavailability. Substitution at the 5-position of the pyridyloxy group

Table 11. Rat Pharmacokinetics and Metabolic Stability of D_2 Prostaglandin Receptor Antagonists[a]



				rat pharmacokinetics[b]				compound stability testing		
compd	X	Y	DP K_i (nM)	Cl_p ((mL/min)/kg)	$T_{1/2}$ (h)	C_{max} (μM)	F (%)	stability (% remaining)[c]	rat biliary concn[d] (μM)	HLM[e]
56	CH_3SO_2	CH_3CO	2.6	14	1.4	21	100	93	1100	18
57	F	CH_3CO	1.1	1.9	4	21	52	35	81	46
58	F	CH_3SO_2	0.57	2.4	7	39	79	32	103	16

[a] Reference 72. [b] Cl_p = rate of compound clearance from plasma; $T_{1/2}$ = half-life of compound circulating in plasma; C_{max} = maximum concentration of compound achieved after an oral dose of 10 mg/kg; F = oral bioavailability. [c] Metabolic stability in rat hepatocytes (% parent remaining at 2 h). [d] Biliary concentration of parent in duct cannulated rats dosed at 5 mg/kg iv. [e] Human liver microsome incubations to assess covalent protein binding ((pmol equiv/mg protein)/h).

with the strongly electron withdrawing trifluoromethyl (**54**) greatly reduced covalent binding, improved oral bioavailability, and had the added benefit of improving CB1R binding. The residual covalent binding in **54** was nearly eliminated by addition of a 3-cyano group on the distal phenyl ring (**55**, taranabant), which is in late stage clinical trials as a treatment for obesity.[69] In this example, a fluoroalkyl group was appended to a heterocycle for its strongly deactivating properties to minimize the formation of reactive intermediates formed by oxidative metabolism. This modification had the added benefit of improving oral bioavailability and CB1R binding without adversely effecting selectivity or CNS penetration.

Laropiprant: Attenuation of Biliary Clearance

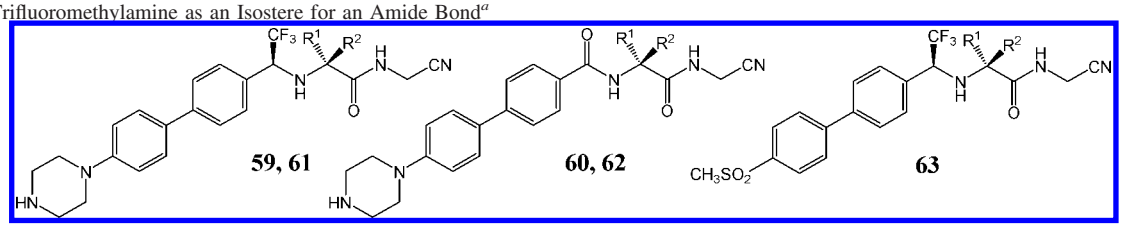
Numerous mechanisms are available for the clearance of xenobiotics, including drugs, from systemic circulation. Phase I (oxidation, hydrolysis) and phase II (conjugation) metabolic pathways have evolved to make unwanted molecules more polar, more soluble, and better substrates for active and passive elimination routes. Multiple active transporters are present in the hepatic-biliary system and have a high capacity and broad specificity for the elimination of metabolized, and sometimes unmetabolized, drugs.[70–72] Such was the case of the prostaglandin D_2 receptor antagonist **56** (Table 11).[73] This compound was found to have good oral bioavailability with moderate plasma clearance and half-life. Interestingly, **56** was found to be reasonably stable in liver microsome incubations but displayed high levels of unmetabolized parent in the bile from bile duct cannulated rats (biliary C_{max} = 1100 μM at 5 mg/kg iv). This result suggested a role for active transport of parent from plasma circulation into the bile. Replacement of the 7-methylsulfone with fluorine gave **57**, which was less stable metabolically, as measured by liver microsome incubations, but displayed much less biliary clearance of parent (biliary C_{max} = 81 μM at 5 mg/kg iv). In rat pharmacokinetics, **57** had lower plasma clearance and a longer plasma half-life than did the more stable **56**. The improvement noted in the pharmacokinetic profile in the change from methylsulfone in **56** to fluorine in **57** cannot be attributed to any metabolic changes. Reduced hepatic clearance into the bile did result in improved pharmacokinetics. This improvement may be attributed to changes in substrate binding to active transporters or changes in plasma protein affinities, although both compounds have similar distribution properties. Further investigation of these differences is ongoing. Replacement of the methylketone in **57** with a methylsulfone improved selectivity versus other prostanoid receptors and further reduced covalent protein binding to afford **58** (laropiprant), which reduces the facial flushing associated with treatment with niacin for lipid control.

Trifluoroethylamines: Amide Isosteres in Cathepsin K Inhibitors

Isosteric replacement of amide bonds have a long history in medicinal chemistry.[74] There are numerous examples that retain the geometry of the amide bond found in the parent structure or present hydrogen bond accepting properties in an appropriate geometry. There are fewer examples of amide bond isosteres that preserve the geometry and basicity of hydrogen bond donation of the amide NH bond. The issue is to identify a suitable NH donor that avoids protonation to form the NH_2^+ species. Such a charged species would not be expected to be accommodated by the same binding interaction of the neutral amide bond and target protein. Various strategies for peptide backbone modification with trifluoromethyl substitution have been reviewed.[75] The fine-tuning of nitrogen pK_a is clearly laid out in the examples listed in Table 3. In addition, amide bond replacement would be expected to enhance metabolic stability by circumventing proteolysis and may offer better pharmacokinetic properties.

Cathepsin K is a cysteine proteinase proposed to be involved in collagen degradation during bone resorption. There are numerous reports of potent peptidyl inhibitors, many of which contain a nitrile group that acts as an electrophile for the active site cysteine.[76] The P_2-P_3 amide bond in the prototypic inhibitor is proposed to form a hydrogen bond to a backbone carbonyl, whereas the carbonyl of the amide is projecting away from the protein. Replacement of the P_2-P_3 amide in **60** with a trifluoroethyl group gave a more potent and selective cathepsin K inhibitor **59** (Table 12).[77] Molecular modeling of a related trifluoroethylamine into the active site of cathepsin K supports the formation of a crucial, and possibly enhanced, hydrogen bond interaction with a backbone carbonyl of the enzyme. The trifluoromethyl group is oriented out toward solvent, analogous to the original P_2-P_3 amide carbonyl. Substituents around the amide bond do influence the orientation of the amide bond and can make the trifluoroethylamine replacement unproductive. The cyclohexyl group in **62** was added to stabilize the P_1-P_2 amide bond. In this case, replacing the amide bond with trifluoroethylamine resulted in a less potent compound (**61**). Optimization of the 4-piperazinylphenyl with 4-methylsulfonylphenyl gave **63**, which afforded good pharmacokinetics across three species and demonstrated efficacy after oral dosing in an ovariectomized rhesus monkey model of bone resorption.[78] Chemical methodology for the synthesis of chiral trifluoromethyl derivatives via

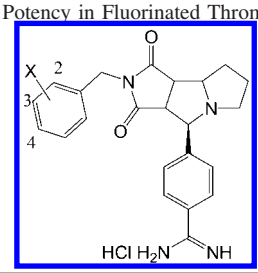
Table 12. Trifluoromethylamine as an Isostere for an Amide Bond[a]



compd	R^1, R^2	cathepsin K (IC_{50}, nM)
59	H, *i*-C_4H_9	≤0.005
60	H, *i*-C_4H_9	0.015
61	−$(CH_2)_5$−	5.0
62	−$(CH_2)_5$−	0.4
63	H, *i*-C_4H_9	0.2

[a] References 76 and 77.

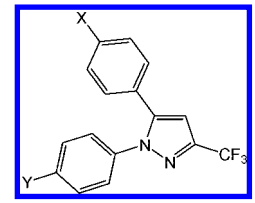
Table 13. Improved Potency in Fluorinated Thrombin Inhibitors[a]



compd	X	thrombin (K_i, μM)	selectivity vs trypsin
64	H	0.31	15
65	2-F	0.50	9.8
66	3-F	0.36	26
67	4-F	0.057	67

[a] References 22 and 79.

Table 14. Plasma Half-Lives of COX-2 Inhibitors Related to Celecoxib[a]



compd	X	Y	rat plasma half-life $t_{1/2}$ (h)
68	F	CH_3SO_2	221
69	Cl	H_2NSO_2	117
70	CH_3	H_2NSO_2	3.5

[a] Reference 80.

reductive aminations of aryl trifluoromethyl ketones and α-amino esters has been described.[79]

Fluorine Scan: Evidence for Fluorine−Protein Interactions in Thrombin Inhibitors

Structural evidence for a variety of direct fluorine−protein binding interactions resulted from a thorough exploration of fluorine substitution, termed a fluorine scan, in a series of thrombin inhibitors.[22] For example, tricyclic inhibitor **64** had a K_i of 0.31 μM vs human thrombin and was 15-fold selective over trypsin (Table 13).[80] The 2- and 3-fluorobenzyl analogues **65** and **66** offered little improvement in potency or selectivity. The 4-fluorobenzyl **67** afforded a 5.4-fold improvement in thrombin binding and a 4.5-fold improvement in selectivity. Subsequent X-ray structural determination of **67** bound in the active site of thrombin revealed a proximity of the fluorine at the 4-position to the backbone H−$C_α$−C═O of Asn^{98}. These close distances represented both a potential, albeit weak, hydrogen bond interaction (d[C−F···H−$C_α$] = 2.1Å) and an orthogonal dipole interaction with the backbone carbonyl (d[C−F···C═O) = 3.5 Å). The angle of the F···C═O interaction is out of plane of the carbonyl along a psuedotrigonal axis of 96°. A search of structural databases with fluorinated ligands bound to proteins provided further examples of fluorines binding to carbonyls in what the authors describe as orthogonal multipolar interactions between the intrinsically polar C−F and C═O units. These results suggest that a virtual fluorine scan in a structure based drug design effort may prove useful in identifying potentially productive fluorine−protein interactions.

Fluorinated Pharmaceuticals: Too Stable to Metabolism?

Mammalian metabolic processes have evolved to rapidly clear and excrete non-nutritive, potentially toxic xenobiotics. Phase I oxidative, reductive, and hydrolytic pathways and an array of active transport systems can clear unwanted species even before they enter systemic circulation. The products of phase I metabolism are often more polar and can be substrates for phase II conjugation and subsequent clearance. Along with barriers to efficient absorption and distribution, medicinal chemists are all too familiar with optimizing, or at least balancing, ADME properties along with other target or off-target issues. There are many examples in lead optimization where one of the objectives was to increase oral bioavailability, lengthen plasma half-life, or block unwanted metabolic processes, including those examples cited herein. There are fewer reported examples where a particular lead structure had a plasma half-life that was considered too long and the objective was to soften the molecule to metabolism. Such was the case in the discovery of the cyclooxygenase-2 (COX-2) inhibitor, celecoxib.

An early lead in the COX-2 program was the fluorophenylpyrazole **68**. It demonstrated good efficacy in models of inflammation but had an unacceptably long plasma half-life in rats (Table 14).[81] The sulfone moiety was not considered to be a major contributor because the 4-chlorophenylsulfonamide **69** was also long-lived and the trifluoromethyl group on the pyrazole was required. Further investigation of the SAR resulted in replacement of the 4-fluorophenyl with a 4-methylphenyl to afford **70**, which retained all the properties desired in a COX-2 inhibitor along with a more manageable half-life. This compound entered development and became celecoxib, which has a very reasonable human plasma half-life of 11.2 h and is suitable for q.d. and b.i.d. administration.

In most lead optimization programs, the medicinal chemist is faced not with introducing a metabolic soft spot but with stabilizing a lead to a variety of metabolic processes. Making a molecule fully stable to all metabolism may present issues as noted above with the COX-2 inhibitor, **68**, but may also present a more diffuse and insidious problem that is getting much recent

attention. Potent human and animal pharmaceuticals that are not metabolized efficiently and are cleared intact are finding their way into our environment.[82,83] Waste water treatment processes are not always capable of eliminating these products from the waste stream, and natural elimination processes, such as photodegradation and microbial oxidation, cannot handle some of these highly stabilized molecules. As a result, a cocktail of drugs can be detected in aquatic environments by increasingly sensitive analytical methods.[84] Fluorinated pharmaceuticals are singled out for their potential to endure in the environment.[83] In this age of green chemistry, the medicinal chemist is challenged to produce not only a pharmaceutical to exacting biological specifications but also one that benignly disappears when its work is done.

Summary

One cannot overestimate the profound influence that organofluorine chemistry has had on drug discovery. The ever increasing array of commercially available fluorinated starting materials coupled with novel and imaginative synthetic methodologies offers to the medicinal chemist broad opportunities to positively influence the direction and timelines in a drug discovery program. Medicinal chemists should approach the various structure−activity relationships that may need to be addressed with a keen understanding of the potential that selective fluorination may afford. That potential may be realized in solving issues as different as changes in solubility, CNS penetration, metabolic stability, or improvements in potency. A greater appreciation of the role(s) that fluorine substitution can have on the physicochemical properties in a molecule gives the medicinal chemist more strategies to solve some of their challenges in a drug discovery program. Hopefully, this Perspective and the few cited examples will provide incentives to further explore the opportunities in organofluorine chemistry as it relates to medicinal chemistry and drug discovery.

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Biography

William K. Hagmann received his B.S. degree in Chemistry from Hobart and William Smith Colleges (NY) in 1973 and his Ph.D. in Organic Chemistry from Cornell University (NY) in 1978 under Professor Arthur G. Schultz. Following an NIH postdoctoral fellowship in natural products synthesis under Professor Sidney M. Hecht at the Massachusetts Institute of Technology (MA), he joined the Merck Research Laboratories (NJ) in 1980 where he is currently Distinguished Senior Investigator in Medicinal Chemistry. His interests include heterocyclic synthesis, drugs of inflammatory, metabolic, and endocrine disorders, and chemical library design. He has authored 109 publications and is a coinventor on 60 issued U.S. patents.

Note Added after ASAP Publication. This manuscript was released ASAP on June 21, 2008 with an incorrect version of Table 1. The correct version was posted on June 27, 2008.

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