Inhibitors of Blood Platelet cAMP Phosphodiesterase. 4. Structural Variation of the Side-Chain Terminus of Water-Soluble 1,3-Dihydro-2*H*-imidazo[4,5-*b*]quinolin-2-one Derivatives[1]

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1-(Cyclohexylmethyl)-4-[4-[(2,3-dihydro-2-oxo-1*H*-imidazo[4,5-*b*]quinolin-7-yl)oxy]-1-oxobutyl]-piperazine (**2**) was previously identified as a potent, water-soluble inhibitor of human blood platelet cAMP phosphodiesterase and of induced aggregation *in vitro* that demonstrated effective antithrombotic activity in animal models of thrombosis. Although **2** exhibited 25% oral bioavailability in rats, pharmacokinetic studies conducted in monkeys revealed that the parent compound was less than 5% bioavailable, the result of extensive first-pass biotransformation in the liver. In an effort to identify potent platelet aggregation inhibitors with enhanced metabolic stability, the side-chain amide moiety of **2** was replaced with chemically more stable urea (**6a–s**), sulfonamide (**13a–m**), sulfone (**19a–r**), and tetrazole (**23a–s**) moieties. Many representatives from each of these structural types effectively combine potent inhibition of ADP-induced human platelet aggregation *in vitro* with excellent aqueous solubility, and several are superior to **2**. Within each series, the *N*-(cyclohexylmethyl)-, *N*-(2-ethylbutyl)-, *N*-benzyl-, and *N*-(4-fluorobenzyl)-substituted derivatives were evaluated for *in vitro* metabolic stability by incubating with the S-9 fraction of monkey liver for 2 h, and the extent of biotransformation was compared with that of the prototype **2**. The sulfone **19e** and the tetrazoles **23e**, **23g**, **23j**, and **23q** were significantly more stable than **2** under these conditions, and **19e** and **23e** were selected for evaluation *in vivo*. Tetrazole **23e** exhibited 72% bioavailability following ip administration to rats compared with 35% bioavailability for **2** and **19e** under the same conditions. However, the oral bioavailability of **19e** and **23e** in the rat was estimated to be only 3%, suggesting that **19e** and **23e** are less readily absorbed from the gastrointestinal tract than **2**.

Introduction

The therapeutic benefit of inhibitors of blood platelet aggregation in a number of pathological conditions that involve thrombotic or thromboembolic components has been established in clinical studies using primarily aspirin but also dipyridamole and, more recently, ticlopidine.[2-13] However, these studies have also demonstrated the inadequacies of the drugs currently available for clinical use and provide an impetus to discover and develop more efficacious agents with a reduced incidence of side effects.[13-15]

For some time, we have been exploring the potential of a series of imidazo[4,5-*b*]quinolin-2-one derivatives as antithrombotic agents.[1,16-21] The prototype of this structural class, **1**, possesses potent intrinsic blood platelet aggregation inhibitory activity that is readily enhanced by introduction of substituents at the 6, 7, 8 and 9 positions.[16] The most potent, broad-spectrum inhibitors of blood platelet function to emerge from this study are compounds appended with functionalized side chains linked to the heterocycle through an oxygen atom at the 7 position of the nucleus.[1,17] The side-chain terminus of this structural type is thought to interact with a secondary binding site in the platelet low K_m, cGMP-inhibited cAMP phosphodiesterase enzyme that appears to be the site of action of these agents.[22] While many representatives of this class of platelet aggregation inhibitor have demonstrated protective effects in animal models of thrombosis,[18,20,21] the compounds studied initially suffered from poor and erratic absorption from the gastrointestinal tract following oral administration. This property was ascribed to the generally highly insoluble nature of this structural type and, in an effort to improve solubility, we synthesized and evaluated a series of imidazo[4,5-*b*]quinolin-2-one derivatives incorporating a basic amino moiety in the side-chain terminus.[1] By providing a second site for salt formation, a series of compounds with enhanced aqueous solubility was identified that retained the potent human blood platelet cAMP PDE inhibitory properties characteristic of this structural class.[1,19] BMY 43351 (**2**) emerged from that study as an effective inhibitor of human blood platelet function that was characterized as the most potent, orally-effective inhibitor of thrombus formation in rabbit and dog models of thrombosis that we have identified from the imidazo[4,5-*b*]quinolin-2-one series of platelet aggregation inhibitors.[20,21] The high potency of **2** following oral administration suggested that the bioavailability of this compound was enhanced compared to earlier studied agents. This observation was confirmed by metabolism and pharmacokinetic studies conducted with **2** in the rat where the oral bioavailability of **2** was estimated to be 25%.[21,23] However, since it was estimated that 43% of the dose of **2** administered to rats was absorbed, amide **2** was apparently susceptible to first-pass metabolic modification. A similar study conducted in the cynomologous monkey using ^{14}C-labeled **2**[24] revealed that although 45%

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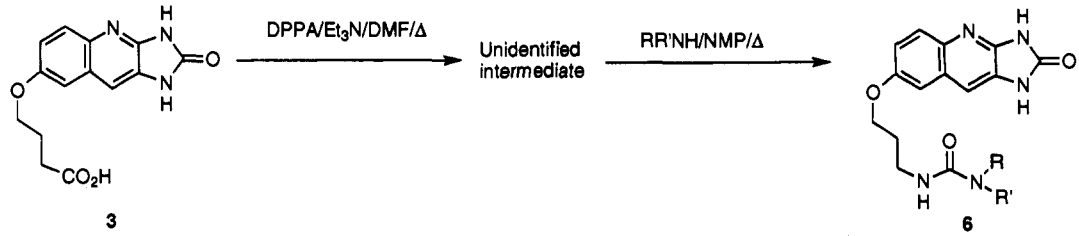
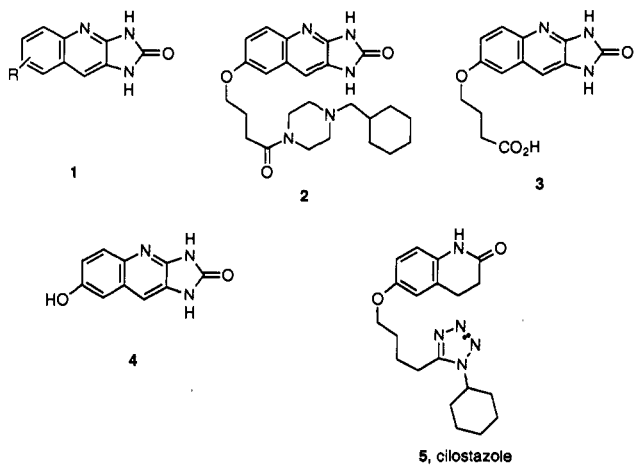
Scheme I

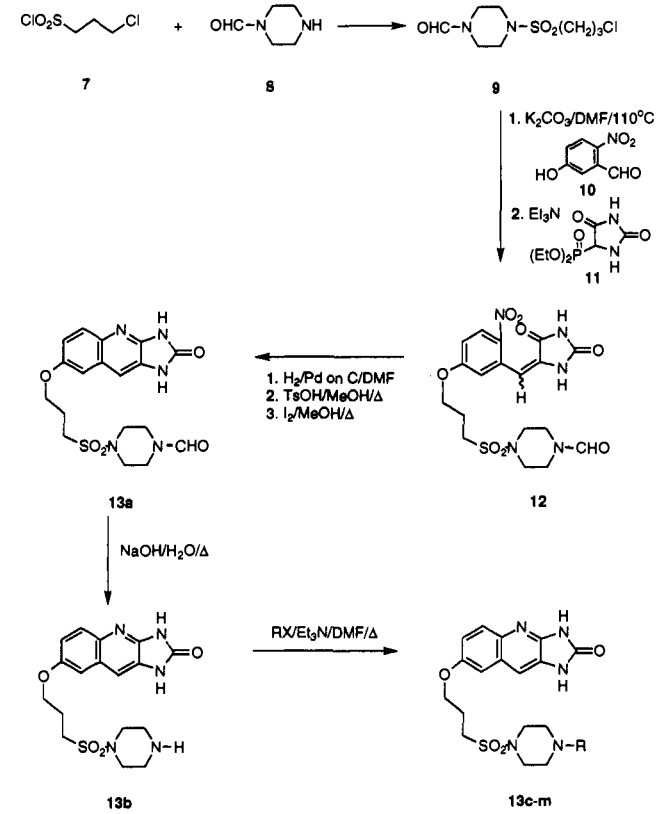


of the radiolabeled material was absorbed, the bioavailability of parent drug was less than 5%, indicative of extensive first-pass biotransformation in this species.[23] Metabolites of **2** that were identified in monkey urine were the carboxylic acid **3** and the phenol **4**, as a mixture of free phenol and glucuronide. Phenol **4** predominanted over acid **3** in urine, and small amounts of the piperazinamide resulting form N-dealkylation were also identified. However, in the bile of bile-cannulated African green monkeys administered **2**, acid **3** was the major metabolite, comprising 30% of the total radioactivity, and substantially smaller amounts of **4** were present. Most of the biotransformation of **2** occurs on first pass through the liver, and *in vitro* studies, in which **2** is incubated with the S-9 fraction of liver homogenates[25] from rat, monkey, and human, have revealed that acid **3** is the primary metabolite.[23]



The carboxylic acid **3** is a potent inhibitor of human platelet cAMP PDE that presents a profile unique within this structural class of platelet aggregation inhibitor.[17] Unlike all other members of this series evaluated for effects on hemodynamic parameters, **3** does not significantly alter either blood pressure, heart rate, or myocardial contractility at doses 100-fold higher than that providing complete protection against experimentally-induced thrombosis in animal models.[26] Although the hemodynamically silent profile of **3** is desirable in a blood platelet aggregation inhibitor, our concerns about this metabolic pathway focused on the fact that the platelet inhibitory properties of **3** are species dependent: the acid **3** is almost 30-fold weaker than **2** as an inhibitor of ADP-induced aggregation of human platelets *in vitro*.[1] The amide bond of **2** is chemically quite labile under acidic conditions, possibly a consequence of some anchimeric assistance by the pendant protonated nitrogen atom of the piperazine ring. The strategy adopted in order to provide metabolically more stable, orally effective antithrombotic agents focused initially upon identifying compounds that would combine potent platelet inhibitory properties with side-chain

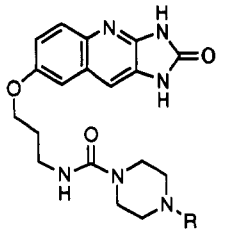
Scheme II

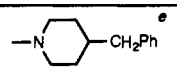
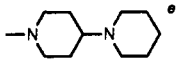
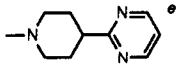
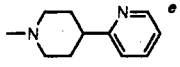


termini expected to offer enhanced chemical and enzymatic stability. Although cleavage of the side chain moiety from the heterocyclic nucleus by way of O-dealkylation remained as a possible alternative site for metabolic transformation, we were encouraged to pursue this strategy by reports that O-dealkylation of the cAMP PDE inhibitor cilostazole (**5**) was not the major mode of metabolic modification in human or dog.[27] However, if O-dealkylation proved to be a significant metabolic pathway for compounds identified by this approach, modification of the ether linkage, either by increasing steric bulk at the adjacent methylene or by replacing the oxygen with a carbon atom,[17] presented possible further structural refinements.

On the basis of previous studies,[17,21] compounds in which the amide functionality of **2** is replaced with urea, sulfonamide, sulfone, and tetrazole moieties were identified as suitable targets with which to explore this strategy. In this report we describe the preparation of a series of compounds based on each of these structural types and examine the effects of these modifications on platelet aggregation inhibitory activity and aqueous solubility. As a means of identifying potential candidates for further development, representatives from each series were evaluated in studies designed to provide insight into metabolic stability and the results compared with **2**.

Table I. Physical Properties and Biological Activity Associated with Urea Derivatives



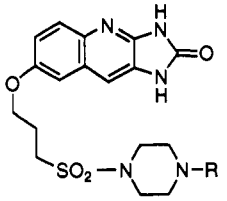
compd no.	R	mp (°C)	yield (%)[a]	anal.[b]	aqueous solubility (mg/mL)	inhibition of human platelet cAMP PDE, IC_{50} (nM) ±SD[c]	IC_{50} vs ADP induced aggregation of human PRP (μM) ± SD[d] 3 min	15 min
6a	 [e]	253–261	53	$C_{26}H_{29}N_5O_3 \cdot HCl \cdot 0.5H_2O$	<0.2		0.16	
6b	CH_2Ph	224–239	82	$C_{25}H_{28}N_6O_3 \cdot 2HCl \cdot 0.5H_2O \cdot EtOH$	>20	1.11	0.31 ± 0.02	0.05
6c	CH_2-*p*-ClC_6H_4	256–268	50	$C_{25}H_{27}ClN_6O_3 \cdot 2HCl \cdot H_2O$	0.2		0.29	
6d	CH_2-*p*-FC_6H_4	240–265	49	$C_{25}H_{27}FN_6O_3 \cdot 2HCl \cdot 0.5H_2O \cdot 0.6EtOH$	>20	2.78 ± 1.10	0.35 ± 0.13	0.05
6e	CH_2-2-C_4H_3S	246–272	31	$C_{23}H_{26}N_6O_3S \cdot 2HCl \cdot 0.3H_2O \cdot 0.6EtOH$	>10		0.16	
6f	CH_2-3-C_4H_3S	273–285	50	$C_{23}H_{26}N_6O_3S \cdot 2HCl \cdot 0.2H_2O$	3		0.28	
6g	$(CH_2)_2Ph$	217–235	44	$C_{26}H_{30}N_6O_3 \cdot 2HCl \cdot 0.9H_2O$	0.25		0.30	
6h	CH_2-c-C_6H_{11}	259–263	69	$C_{25}H_{34}N_6O_3 \cdot 2HCl \cdot 0.5H_2O$[f]	>20	1.13	0.072 ± 0.04	0.018 ± 0.002
6i	CH_2-c-C_7H_{13}	239–285	36	$C_{26}H_{36}N_6O_3 \cdot 2HCl$	2		0.054	
6j	CH_2-c-C_6H_9	241–289	45	$C_{24}H_{32}N_6O_3 \cdot 2HCl \cdot 0.3H_2O$	0.7		0.094	
6k	$(CH_2)_2$-c-C_6H_{11}	255–275	42	$C_{26}H_{36}N_6O_3 \cdot 2HCl \cdot 0.3H_2O$	0.5		0.072	
6l	CH_2-2-THP	222–250	36	$C_{24}H_{32}N_6O_4 \cdot 2HCl \cdot 0.5H_2O \cdot 0.6EtOH$[g]	>20		0.16	
6m	CH_2CHMe_2	234–265	39	$C_{22}H_{30}N_6O_3 \cdot 2HCl \cdot 0.3H_2O$	>20		0.18	
6n	CH_2CHEt_2	230–263	38	$C_{24}H_{34}N_6O_3 \cdot 2HCl$	>20	1.25	0.042	0.007
6o	CH_2CHPr_2	208–240	36	$C_{26}H_{36}N_6O_3 \cdot 2HCl$	0.5		0.13	
6p	H	274–285	48	$C_{16}H_{22}N_6O_3 \cdot 2HCl \cdot 0.5EtOH$	>20		8.15	
6q	 [e]	298–301	48	$C_{24}H_{32}N_6O_3 \cdot 2HCl \cdot 0.1H_2O$	>20		9.86	
6r	 [e]	236–269	22	$C_{22}H_{24}N_8O_3 \cdot 2HCl \cdot 0.5H_2O$	0.1		0.32	
6s	 [e]	256–270	47	$C_{23}H_{25}N_7O_3 \cdot 2HCl \cdot 0.5H_2O \cdot 0.5EtOH$	0.5		0.69	

[a] Yields given reflect the amount of purified hydrochloride salt isolated after heating 2.00 g of the unidentified intermediate with 1.2 equiv of the amine component in NMP at 200 °C. [b] All compounds were purified by recrystallizion from EtOH or precipitation from EtOH by the addition of Et_2O. [c] Data reported are the average of duplicate determinations with variance from the mean of less than 50%. Data that includes standard deviation are the result of triplicate determinations. [d] Data shown are the result of a single determination or the average of duplicates in which variance from the mean was less than 80%. [e] Group shown replaces the substituted piperazine moiety. [f] C: calcd, 54.74; found, 54.10. N: calcd, 15.32; found, 14.84. [g] C: calcd, 53.85; found, 52.31. N: calcd, 14.95; found, 14.52.

Chemistry

The most straightforward access to a series of ureas involved a Curtius-type rearrangement of the readily accessible acid **3**[17] followed by reaction of the resultant isocyanate with an amine derivative, as depicted in Scheme I. However, a major impediment to such an approach appeared to be the severely limited solubility of **3** in common or suitable organic solvents and the presence of potentially reactive functionality in the heterocyclic nucleus. In an effort to simultaneously solve both of these problems, the installation of a number of protecting groups on N-1 and N-3 was explored.[17] Unfortunately, we were unable to identify a protecting moiety that combined ease of introduction and removal with an appropriate degree of stability to the planned synthetic protocols. As a consequence, attempts were made to conduct the Curtius rearrangement on the unprotected acid **3**. Heating a suspension of **3** in DMF containing a 1.5-fold excess of DPPA[28] and Et_3N resulted in solution occurring at about 60 °C followed by the formation of a heavy precipitate as the temperature continued to rise. After 1 h at 120 °C, the mixture was cooled and diluted with water and a gray solid filtered off. The material isolated in this fashion proved to be extremely insoluble and has not been definitively identified. The IR spectrum, recorded as a KBr disk, exhibits no absorption in the 2200–2300-cm^{-1} region, indicating the absence of an isocyanate, and shows a single carbonyl absorption peak at 1750 cm^{-1}. The ^1H NMR spectrum of this material, recorded as a solution in CF_3CO_2H, is complex and not interpretable. Isocyanates are known to dimerize, trimerize, and polymerize in reactions catalyzed by DMF, tertiary amines, or carbonyl-containing compounds.[29] In addition, isocyanates have been demonstrated to react with compounds containing relatively acidic hydrogen atoms, including amides, and react with formamide derivatives.[29] However, despite the possibility of several reaction pathways, mass spectral analysis revealed a clean spectrum with an apparent parent ion at *m/e* 284. This molecular ion corresponds to the isocyanate, or possibly an intramolecular addition product, and would appear to be the result of thermal regeneration of the isocyanate in the mass spectrometer. The material isolated in this fashion may correspond to a polymeric isocyanate species since these have been shown to revert to the isocyanate at high (190 °C) temperatures and have been trapped with amines to afford urea derivatives.[29] Regardless of the exact nature of the intermediate, the apparent thermal regeneration of the isocyanate in the

Table II. Physical Properties and Biological Activity Associated with Sulfonamide Derivatives



compd no.	R	mp (°C)	yield (%)[a]	anal.[b]	aqueous solubility (mg/mL)	inhibition of human platelet cAMP PDE, IC_{50} (nM) ± SD[c]	IC_{50} vs ADP induced aggregation of human PRP (μM) ± SD[d] 3 min	15 min
13a	CHO	315–318	98	$C_{16}H_{21}N_5O_5S\cdot0.5H_2O$	<1		13.05	
13b	H	237–240 (dec)	96	$C_{17}H_{21}N_5O_4S\cdot2HCl$[e]	>20		15.50	
13c	$CH_2C_6H_5$	261–264	80	$C_{24}H_{27}N_5O_4S\cdot2HCl\cdot0.4H_2O$	>20	5.42	0.13 ± 0.04	0.06 ± 0.033
13d	CH_2-*p*-ClC_6H_4	272–275	96	$C_{24}H_{26}ClN_5O_4S\cdot2HCl\cdot0.6H_2O$	>20		0.53	
13e	CH_2-*p*-FC_6H_4	282–285	72	$C_{24}H_{26}FN_5O_4S\cdot2HCl$	>20	4.96	0.28 ± 0.087	0.035
13f	CH_2-*p*-$OMeC_6H_4$	210–213	92	$C_{25}H_{29}N_5O_5S\cdot2HCl$[f]	>20		0.46	
13g	CH_2-*m*-$CF_3C_6H_4$	260–262	82	$C_{25}H_{26}F_3N_5O_4S\cdot2HCl$	~2		0.32	
13h	$(CH_2)_2C_6H_5$	293–295	64	$C_{25}H_{29}N_5O_4S\cdot2HCl\cdot0.5H_2O$	<10		1.04	
13i	CH_2-*c*-C_6H_{13}	287–290	94	$C_{24}H_{33}N_5O_4S\cdot2HCl\cdot0.7H_2O$	>20	2.56	0.11 ± 0.06	0.06 ± 0.016
13j	$(CH_2)_2cC_6H_{13}$	295–298	66	$C_{25}H_{35}N_5O_4S\cdot2HCl\cdot0.8H_2O$	<5		2.04	
13k	CH_2CHEt_2	273–275	68	$C_{23}H_{33}N_5O_4S\cdot2HCl\cdot0.7H_2O$	>10	5.14 ± 1.81	0.16 ± 0.01	0.04
13l	2-benzoxazolyl	348–350 (dec)	93	$C_{24}H_{24}N_6O_5S\cdot2HCl$	>20		2.41	
13m	2-benzthiazolyl	345–348	78	$C_{24}H_{24}N_6O_4S_2\cdot2HCl\cdot0.6H_2O$	~1		4.88	

[a] With the exception of **13a** and **13b**, yields refer to the overall amount of purified hydrochloride salt isolated after alkylation of **13b**. [b] All compounds were purified by recrystallizion from MeOH or precipitation from MeOH by the addition of Et_2O. [c] Data reported are the average of duplicate determinations with variance from the mean of less than 50%. Data that includes standard deviation are the result of triplicate determinations. [d] Data shown are the result of a single determination or the average of duplicates in which variance from the mean was less than 80%. [e] N: calcd, 15.08; found, 14.52. [f] H: calcd, 4.53; found, 5.59.

mass spectrometer prompted a study of the effects of heating this material with (cyclohexylmethyl)piperazine. Heating a concentrated slurry of the solid in DMF (153 °C) or DMSO (189 °C) at reflux with an excess of the piperazine provided a red solution that contained the desired urea product (**6f**) according to TLC analysis along with other products. A cleaner reaction occurred when the substrates were combined with the higher boiling 1-methyl-2-pyrrolidinone (NMP) and the mixture was heated at 200 °C for 30 min. Approximately 2 mL of NMP per gram of imidazoquinoline and 1.2 equiv of the piperazine proved to be satisfactory conditions. Under more dilute conditions yields were poorer and the addition of a greater excess of piperazine did not improve the yields of urea. Two minor side products were apparent by TLC. One was identified as the amide **2** arising from a direct coupling of the amine with acid **3** while the other more polar and insoluble material has not been identified. The urea derivatives prepared by this procedure are presented in Table I along with their characteristic physicochemical properties.

A series of sulfonamides were synthesized by the route depicted in Scheme II. Treatment of commercially available 3-chloropropanesulfonyl chloride[30] (**7**) with 1-piperazinecarboxaldehyde (**8**) gave the sulfonamide **9**. This was heated with phenol **10** in the presence of K_2CO_3, and the resultant aryl ether aldehyde coupled with the Wadsworth–Emmons-type reagent **11**[31] to furnish the unsaturated hydantoin derivative **12**, isolated as a mixture of geometrical isomers. The imidazo[4,5-*b*]quinolin-2-one heterocycle was constructed according to the previously established protocol[16] to provide the formylated piperazine derivative **13a** in 98% overall yield. Alkaline hydrolysis of **13a** afforded the N-H congener **13b**, which was efficiently derivatized by exposure to an alkyl halide in the presence of Et_3N as the acid scavenger.[32] The use of Et_3N as the base proved to be superior to K_2CO_3, and yields for the alkylation step under these conditions were 66–96%. The series of target compounds, **13a–m**, that constitute this study are compiled in Table II.

Compounds incorporating an N-substituted sulfonylpiperidine side chain terminus were prepared by the synthetic sequence outlined in Scheme III. The requisite side-chain moiety was assembled from 1-methyl-4-piperidone (**14**) by treatment with H_2S in *i*-PrOH to afford the corresponding *gem*-dithiol,[33] which was reduced with $NaBH_4$ in *i*-PrOH to give the thiol **15**.[33] Demethylation of **15** was accomplished by heating with ethyl chloroformate, which furnished the doubly protected amino thiol **16**. This was dissolved in EtOH containing a slight excess of NaOEt, and the resultant thiolate was alkylated with an α-chloro-ω-iodoalkane to afford **17**. Oxidation of **17** to the corresponding sulfone was accomplished by exposure to CH_3CO_3H in CH_2Cl_2 and the product coupled with phenol **10** to provide aldehyde **18**. The heterocyclic ring system was constructed in conventional fashion to afford the imidazo[4,5-*b*]quinolin-2-ones **19a** and **19b**, which were saponified to furnish the amines **19c** and **19d**. Derivatization of **19c** and **19d** with a variety of alkylating agents was accomplished under conditions similar to that described for the preparation of sulfonamides **13c–m**. The sulfones **19a–r** prepared by this approach are presented in Table III.

A series of tetrazoles were prepared as outlined in Scheme IV. Acylation of the commercially-available amine **20**[30] with an ω-chloroacyl chloride gave the amides **21**. These were converted to the corresponding iminoyl chlorides, by treatment with PCl_5, and then exposed *in situ* to $TMSN_3$ to provide the tetrazoles **22**.[17] These side-chain synthons were used to alkylate phenol **10** and the products elaborated into the imidazo[4,5-*b*]quinolin-2-one derivatives **23a** and **23b**. Alkaline hydrolysis of the carbamate moiety of **23a** and **23b** furnished the corresponding piperidines **23c** and **23d** which were derivatized

Scheme III

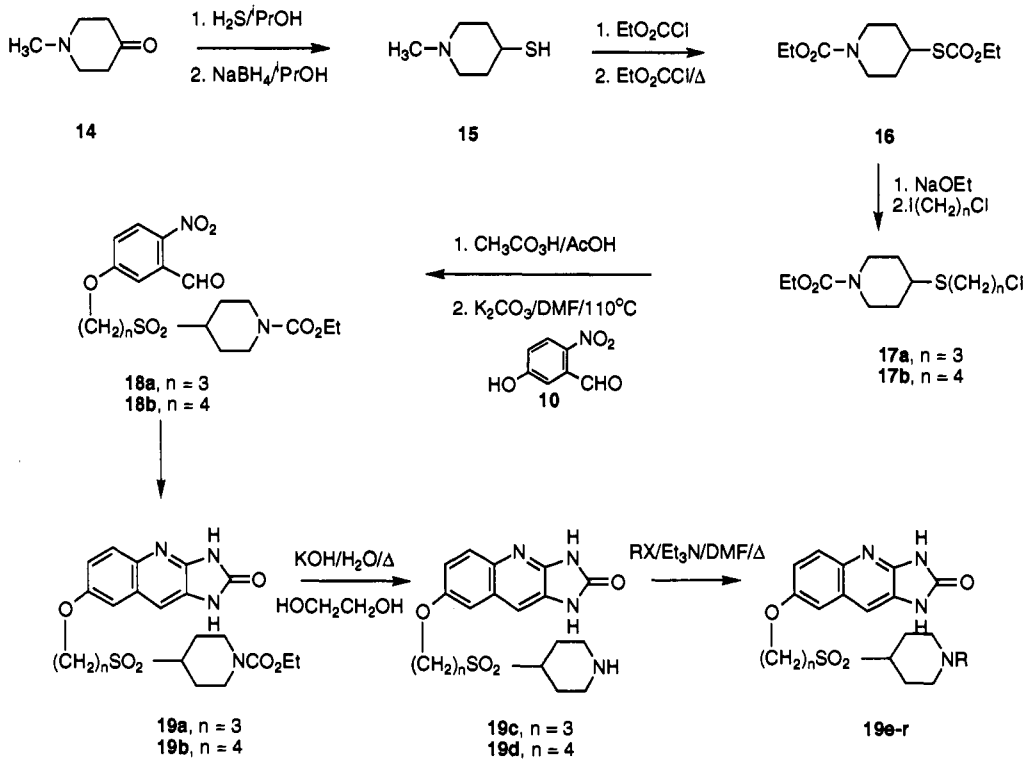
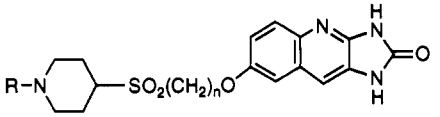


Table III. Physical Properties and Biological Activity Associated with Sulfone Derivatives



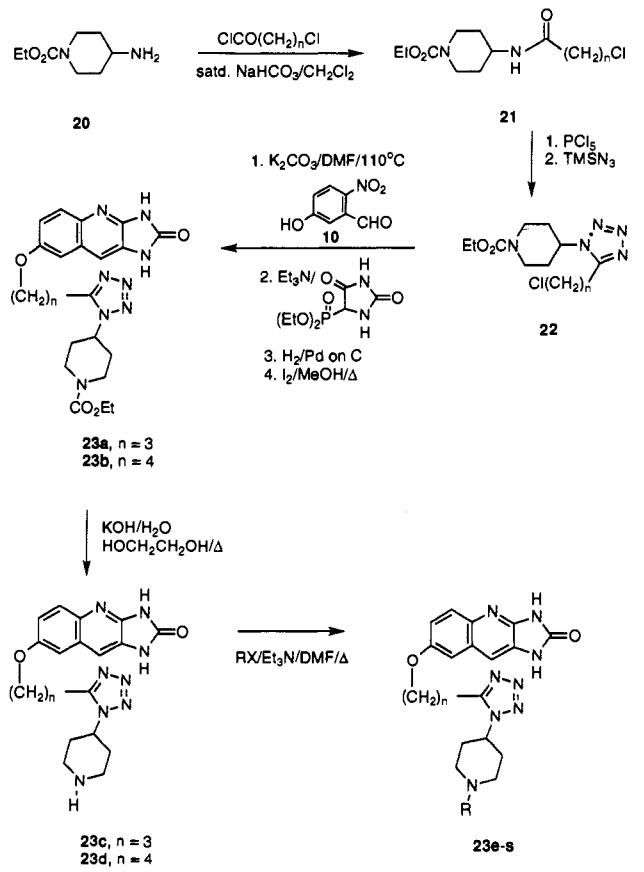
compd no.	*n*	R	mp (°C)	yield (%)[a]	anal.[b]	aqueous solubility (mg/mL)	inhibition of human platelet cAMP PDE, IC_{50} (nM) ± SD[c]	IC_{50} vs ADP induced aggregation of human PRP (μM) ± SD[d] 3 min	15 min
19a	3	CO_2Et	318–321	98	$C_{21}H_{26}N_4O_6S$	<1		0.65	
19b	4	CO_2Et	289–292	95	$C_{22}H_{28}N_4O_6S·0.5H_2O$	<1		0.41	
19c	3	H	340–345	98	$C_{16}H_{22}N_4O_4·2HCl·1.2H_2O$[e]	>10		>66	
19d	4	H	235–237	96	$C_{19}H_{24}N_4O_4S·2HCl·1.3H_2O$[f]	>10		14.78	
19e	3	$CH_2C_6H_5$	282–285	87	$C_{25}H_{28}N_4O_4S·2HCl·0.7H_2O$	>10	0.63 ± 0.32	0.025 ± 0.005	0.0064 ± 0.0002
19f	4	$CH_2C_6H_5$	228–231	85	$C_{26}H_{30}N_4O_4S·2HCl$	~5		0.042	
19g	3	CH_2-*p*-FC_6H_4	308–311	89	$C_{25}H_{27}FN_4O_4S·2HCl·1.3H_2O$	>10	1.00 ± 0.59	0.02 ± 0.002	0.0084 ± 0.004
19h	4	CH_2-*p*-FC_6H_4	207–210	88	$C_{26}H_{29}FN_4O_4S·2HCl·0.5H_2O$	~2		0.067	
19i	3	CH_2-*m*-$CF_3C_6H_4$	283–285	77	$C_{26}H_{27}F_3N_4O_4S·2HCl·H_2O$	<5		0.038	
19j	3	$(CH_2)_2C_6H_5$	305–308	72	$C_{26}H_{30}N_4O_4S·2HCl·0.6H_2O$	<5		0.13	
19k	3	CH_2-c-C_6H_{13}	310–313	76	$C_{25}H_{34}N_4O_4S·2HCl·2H_2O$	>10	1.13	0.03	0.0084
19l	4	CH_2-c-C_6H_{13}	311–314	74	$C_{26}H_{36}N_4O_4S·2HCl·1.5H_2O$[g]	~2		0.03	
19m	3	$(CH_2)_2$-c-C_6H_{13}	314–317	79	$C_{26}H_{36}N_4O_4S·2HCl·0.7H_2O$	<5		0.048	
19n	3	CH_2-2-THP	221–224	85	$C_{24}H_{32}N_4O_5S·2HCl·1.5H_2O$	>10		0.034	
19o	3	$CH_2CH(CH_3)_2$	323–325	69	$C_{22}H_{30}N_4O_4S·2HCl·1.5H_2O$	>10		0.027	
19p	3	CH_2CHEt_2	261–264	74	$C_{24}H_{34}N_4O_4S·2HCl·1.1H_2O$	<10	1.13	0.039 ± 0.009	0.009 ± 0.002
19q	4	CH_2CHEt_2	241–245	70	$C_{25}H_{36}N_4O_4S·2HCl·2H_2O$[h]	~5		0.021	
19r	3	CH_2CHPr_2	249–252	88	$C_{26}H_{36}N_4O_4S·2HCl·2.6H_2O$[i]	~1		0.23	

[a] With the exception of **19a–d**, yields refer to the overall amount of purified hydrochloride salt isolated after alkylation of **19c** or **19d**. [b] All compounds were purified by recrystallizion from MeOH or precipitation from MeOH by the addition of Et_2O. [c] Data reported are the average of duplicate determinations with variance from the mean of less than 50%. Data that includes standard deviation are the result of triplicate determinations. [d] Data shown are the result of a single determination or the average of duplicates in which variance from the mean was less than 80%. [e] N: calcd, 11.55; found, 11.03. [f] H: calcd, 5.76; found, 5.28. [g] H: calcd, 6.88; found, 6.29. [h] H: calcd, 7.08; found, 6.58. [i] H: calcd, 7.32; found 6.56. N: calcd, 9.00; found, 10.00.

with a variety of alkylating agents, in the presence of Et_3N as the acid scavenger,[32] to afford the target compounds **23e–s**. The tetrazole derivatives synthesized and evaluated are listed in Table IV along with pertinent physical properties.

The imidazo[4,5-*b*]quinolin-2-one derivatives prepared as part of this study were generally isolated as their dihydrochloride salts, which frequently proved to be hygroscopic and difficult to crystallize. This hampered purification, and the target compounds were generally isolated as amorphous solids after precipitation from an alcohol solvent by the addition of Et_2O. Aqueous solubility was determined by attempting to dissolve a 10-mg sample in 0.5 mL of H_2O and diluting up to 10 mL or until solution

Scheme IV



occurred. These data are included in Tables I–IV. For purposes of comparison, the dihydrochloride salt of **2** gave a clear solution at a concentration of 20 mg/mL.[1]

Results and Discussion

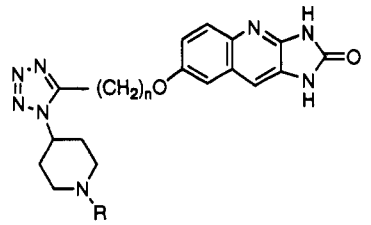
The target compounds were evaluated as inhibitors of human platelet aggregation *in vitro* induced by the addition of 5.86 μM ADP. The standard experimental protocol comprised incubation of platelet-rich plasma (PRP) with drug for 3 min prior to the addition of ADP, but select compounds were incubated with PRP for 15 min before adding ADP. The extent of aggregation in the presence of various concentrations of drug was compared with that in vehicle-treated controls; dose–response curves were obtained and IC_{50}'s values determined. The data presented in Tables I–IV are the result of a single determination or the average of duplicates except where standard deviations are included. The amide **2** was included as a positive control in all experiments and half-maximally inhibited ADP-induced aggregation at concentrations of 0.33 ± 0.16 μM (n = 26) and 0.071 ± 0.032 μM (n = 10) for the 3- and 15-min protocols, respectively.

Select compounds were evaluated as inhibitors of human platelet cAMP PDE according to the previously described protocol[16] with the exception that the [^{3}H]adenosine was resolved using DEAE sephadex.[34] The results presented in Tables I–IV are the means of triplicate or duplicate (deviation always less than 50% of the mean) determinations. Compound **2** was employed as a standard reference agent and under the present conditions displayed an IC_{50} of 1.91 ± 0.6 nM (n = 9).

It is apparent from the data presented in Tables I–IV that imidazo[4,5-*b*]quinoline derivatives substituted with side chains that incorporate urea, sulfone, sulfonamide, or tetrazole moieties in the terminus region are generally potent inhibitors of ADP-induced human blood platelet aggregation *in vitro*. Many of the compounds reported in Tables I–IV very effectively combine potent biological properties with a high degree of aqueous solubility, and several are among the most potent agents yet identified from studies of this class of platelet function inhibitor. Moreover, the structure–activity correlates compiled in Tables I–IV provide further insight into the functional and structural demands of the secondary binding region of the cAMP PDE enzyme that is postulated to accommodate the side-chain terminus of this class of platelet aggregation inhibitor.[1,35,36] Inhibition of human platelet cAMP PDE correlates reasonably well with inhibition of platelet function for those compounds evaluated in both assays. Within each of the four individual chemotypes studied, substituents installed on the side-chain terminus nitrogen atom were selected on the basis of the findings of the previous investigation[1] and were designed to probe not only structure–activity parameters but also to define the substitution patterns that would promote optimal aqueous solubility. In general, larger and more lipophilic substituents tended to provide compounds with reduced aqueous solubility, and the structure–solubility relationships are broadly similar to those recorded for the amide series from which **2** was identified.[1] However, the presence of a substituent on the N atom of the side-chain terminus is clearly important since the unsubstitued amine derivatives in each series (**6p**, **13b**, **19c**, **19d**, **23c**, and **23d**) are associated with weak platelet inhibitory properties.

The urea **6h** (Table I), in which the length of the alkyl chain is the same as that presented by **2**, is 7-fold more potent than **2** under the standard assay conditions involving a 3-min incubation of drug with PRP prior to the addition of ADP. Increasing the incubation time of **6h** with PRP to 15 min before adding the agonist led to a 4-fold increase in potency, indicating that the inhibitory effect of **6h**, like **2**, develops somewhat slowly. This presumably reflects time-dependent permeation of **6h** across platelet membranes, a phenomenon also observed with the analogues **6b**, **6d**, and **6n**. That the immediate homologue of **2**[1] is of comparable potency to **6h** suggests that the important structural element is the separation between the heterocyclic nucleus and the carbonyl group rather than the nature of the carbonyl moiety. The increased hydrophilicity of the urea moiety of **6h** is, however, associated with increased aqueous solubility compared to **2**. This observation extends to several derivatives of **6** when compared to similarly substituted amide counterparts. A 20 mg/mL solution of the dihydrochloride of **2** in H_2O produced a heavy white precipitate of the highly insoluble monohydrochloride derivative upon standing for a period of 1 h.[37] In contrast, a 20 mg/mL solution of the dihydrochloride of **6h** in H_2O remained as such for at least 3 days, indicative of increased solubility of the monohydrochloride salt of the urea derivative. The structure–activity relationships summarized in Table I demonstrate that the piperazine substituent in this series of ureas influences both potency and aqueous solubility. In general, simple alkyl and cycloalkyl substituents are associated with both enhanced potency and aqueous solubility compared to substituents that incorporate aromatic or heterocyclic ring systems, a finding that provides some contrast with the series of amides from which **2** was discovered.[1]

Table IV. Physical Properties and Biological Activity Associated with Tetrazole Derivatives



compd no.	*n*	R	mp (°C)	yield (%)[a]	anal.[b]	aqueous solubility (mg/mL)	inhibition of human platelet cAMP PDE, IC_{50} (nM)[c]	IC_{50} vs ADP induced aggregation of human PRP (μM) ± SD[d] 3 min	15 min
23a	3	CO_2Et	279–281	84	$C_{22}H_{26}N_8O_4 \cdot 0.3H_2O$	<1		0.42	
23b	4	CO_2Et	233–236	91	$C_{23}H_{28}N_8O_4 \cdot 0.4H_2O$	<1		0.10	
23c	3	H	355–357	95	$C_{19}H_{22}N_8O_2 \cdot 2HCl$	>20		11.55	
23d	4	H	315–318	94	$C_{20}H_{24}N_8O_2 \cdot 2HCl \cdot 0.3H_2O$	~5		5.33	
23e	3	$CH_2C_6H_5$	273–275	82	$C_{28}H_{28}N_8O_2 \cdot 2HCl \cdot 0.5H_2O$	>10	0.84	0.039	0.004
23f	4	$CH_2C_6H_5$	203–207	85	$C_{27}H_{30}N_6O_2 \cdot 2HCl \cdot 1.1H_2O$	>5		0.031	
23g	3	CH_2-*p*-FC_6H_4	250–255	83	$C_{26}H_{27}FN_8O_2 \cdot 2HCl \cdot 1.4H_2O$	>10	1.03	0.032	0.008
23h	4	CH_2-*p*-FC_6H_4	229–232	81	$C_{27}H_{29}FN_8O_2 \cdot 2HCl \cdot 1.3H_2O$	>5		0.051	
23i	3	$(CH_2)_2C_6H_5$	238–241	50	$C_{27}H_{30}N_8O_2 \cdot 2HCl \cdot 0.5H_2O$	<5		0.083	
23j	3	CH_2-*c*-C_6H_{13}	245–250	85	$C_{26}H_{34}N_8O_2 \cdot 2HCl \cdot 0.5H_2O$	>10	0.81	0.016	0.003
23k	4	CH_2-*c*-C_6H_{13}	253–256	87	$C_{27}H_{36}N_8O_2 \cdot 2HCl \cdot 1.1H_2O$	>5		0.02	
23l	3	CH_2-*c*-C_6H_{11}	237–240	63	$C_{25}H_{32}N_8O_2 \cdot 2HCl \cdot H_2O$	~3		0.009	
23m	3	CH_2-*c*-C_7H_{15}	224–228	73	$C_{27}H_{36}N_8O_2 \cdot 2HCl$	~1		0.017	
23n	3	CH_2-2-THP	245–248	74	$C_{25}H_{32}N_8O_3 \cdot 2HCl$	>10		0.071	
23o	3	$CH_2CH(CH_3)_2$	258–261	88	$C_{23}H_{30}N_8O_2 \cdot 2HCl \cdot 0.3H_2O$	>10		0.0094	
23p	4	$CH_2CH(CH_3)_2$	225–228	87	$C_{24}H_{32}N_8O_2 \cdot 2HCl \cdot 1.35H_2O$	>10		0.009	
23q	3	CH_2CHEt_2	253–256	89	$C_{25}H_{34}N_8O_2 \cdot 2HCl \cdot 1.4H_2O$	>10	0.81	0.012 ± 0.002	0.003 ± 0.0006
23r	4	CH_2CHEt_2	239–242	90	$C_{26}H_{36}N_8O_2 \cdot 2HCl \cdot 0.8H_2O$	>5		0.012	
23s	3	CH_2CHPr_2	189–192	71	$C_{27}H_{36}N_8O_2 \cdot 2HCl \cdot 0.4H_2O$	~2		0.082	

[a] With the exception of **23a–d**, yields refer to the overall amount of purified hydrochloride salt isolated after alkylation of **23c** or **23d**. [b] All compounds were purified by recrystallizion from MeOH or precipitation from MeOH by the addition of Et_2O. [c] Data reported are the average of duplicate determinations with variance from the mean of less than 50%. [d] Data shown are the result of a single determination or the average of duplicates in which variance from the mean was less than 75%.

Replacement of the amide moiety of **2** by a sulfonamide gave a compound **13i** (Table II) with enhanced potency under both the 3- and 15-min incubation protocols. Variations of the piperazine substituent were well tolerated with both aromatic and alkyl substituents providing potent inhibitors of platelet function. Where comparisons can be made, the sulfonamides **13** are generally of similar potency to their amide counterparts, demonstrating an isosteric relationship in this setting. As was observed with the amide[1] and urea termini, heterocyclic substituents (**13l**, **13m**) are associated with poor activity in this structural class.

The series of sulfones **19a–r**, summarized in Table III, are potent inhibitors of ADP-induced platelet aggregation that are generally superior to similarly substituted sulfonamide and amide[1] derivatives. Simple phenylsulfonyl derivatives were cursorily explored in the earlier study and provided potent inhibitors of platelet function, although these compounds exhibited only limited solubility in water or dilute acid.[17] Several representatives of the series of sulfones **19** effectively combine good aqueous solubility, as their dihydrochloride salts, with potent platelet inhibitory properties. Those examples evaluated under the 15-min incubation protocol (**19e,g,k,p**) demonstrated enhanced potency compared to the effects after 3-min exposure, and these compounds are among the most potent inhibitors of platelet function that we have identified based on the imidazo[4,5-*b*]quinolin-2-one heterocyclic nucleus. For the benzylpiperazine derivatives **19e–h**, the propyl side-chain tether in **19e** and **19g** provides only a slight advantage over the butyl homologues **19f** and **19h**, respectively. This contrasts with the amide series where homologation of the side chain of **2** and closely related compounds generally led to a 10-fold increase in potency.[1] Comparison of **19k** with **19l** and **19p** with **19q** also suggests that side-chain length is less important in this class of platelet aggregation inhibitor than in the amide series studied earlier, an observation that may reflect the effects of the longer carbon–sulfur bonds in **19** on recognition by the platelet cAMP PDE enzyme.

The tetrazole moiety provides a topologically quite different presentation of the side-chain terminus functionality to the cAMP PDE enzyme than the more linear amides, ureas, sulfonamides, and sulfones described above. Although a cyclohexyl-substituted tetrazole terminus provided a potent but water-insoluble platelet aggregation inhibitor based on the imidazo[4,5-*b*]quinolin-2-one heterocyclic class of cAMP PDE inhibitor, the effects of varying the cyclohexyl moiety were not explored.[17] A tetrazole-containing side chain is the key structural element of cilostazole (**5**), a quinolin-2-one derivative that has been evaluated clinically as a platelet aggregation inhibitor,[38] and SAR for this compound has been explored in some detail.[39] For the case at hand, large substituents on the tetrazole heterocycle are well tolerated, and the tetrazoles **23e**, **23j**, and **23q** are the most potent water-soluble platelet aggregation inhibitors to emerge from our investigation of the imidazo[4,5-*b*]quinoline class of cAMP PDE inhibitor. The cyclohexylmethyl-substituted tetrazole **23j** is over 30-fold more potent than the amide **2** after both a 3- and a 15-min incubation period with PRP prior to the introduction of ADP. However, **23j** is only 2-fold more potent than **2** as an inhibitor of cAMP PDE, suggesting that the origin of the enhanced effects of **23j**

Table V. Metabolic Stability of Select Compounds in Monkey Liver S-9 Homogenate

compd no.	% metabolized after 2 h at 10 μg/mL	stability half-life (min)[a]	% metabolized after 2 h at 1 μg/mL	stability half-life (min)[a]
2	21.7	333	40.6	144
6b	46.8	130		
6d	70.0	65		
6h	23.6	304	58.5	92.5
6n	37.3	161		
13c	21.2	387	67.7	69
13e	18.0	405	29.4	241
13i	49.4	121		
13k	38.8	172		
19e	9.6	990	25.2	290
19g	53.0	120		
19k	15.2	453		
19p	22.4	365	17.0	423
23e			7.2	949
23g			4.9	1474
23j			22.9	308
23q			31.3	202

[a] An estimate of the percent drug remaining at 2 h was determined by dividing the mean peak height at $t = 2$ h by the mean initial peak height, $t = 0$ h. A linear regression of the peak height at each time point was used to estimate the relative metabolic rate of each compound. The stability was expressed as a half-life, which was calculated by dividing ln 2 by the slope of the line obtained from the least-squares linear regression analysis.

on platelet function may be the result of improved membrane permeability. The structure–activity relationships summarized in Table IV demonstrate a ready tolerance for both aromatic- and alkyl-containing piperazine substituents in this pharmacophore, and potency is not greatly affected by variation of the length of the side-chain tether.

The results of this study demonstrate that several different functional groups that offer enhanced chemical stability can very effectively combine potent inhibition of platelet function with reasonable aqueous solubility. However, in order to identify compounds that would provide significant advantage over **2** *in vivo* and thus may be suitable for further development as orally-effective antithrombotic agents, four representatives of each of the four structural classes were selected for evaluation in an assay designed to provide insight into metabolic stability *in vitro*. The *N*-(cyclohexylmethyl), *N*-(2-ethylbutyl), *N*-benzyl-, and *N*-(4-fluorobenzyl)-substituted derivatives of each of the four structural types were identified as suitable candidates for study on the basis of their efficacy as inhibitors of ADP-induced blood platelet aggregation and the fact that these substituents provide some structural diversity. To assess their metabolic stability, samples of each of these compounds were incubated with the S-9 fraction[25] prepared from monkey liver, and the disappearance of parent drug was monitored by HPLC analysis. The percent of parent drug remaining after 2 h of incubation was determined, and a rate of biotransformation was estimated. The results of these experiments are summarized in Table V, which includes comparative data for the amide derivative **2**.

It is apparent from these data that in the family of urea derivatives examined, **6h**, which incorporates the same N substituent as **2**, is the most stable representative with less than 25% metabolized over the 2-h incubation period at a concentration of 10 μg/mL. The other alkyl-substituted compound, **6n**, is somewhat less stable than **6h**, but the 2-benzylated derivatives **6b** and **6d** are quite rapidly degraded. However, **6h** provides no significant advantage over **2**, at concentrations of both 1 and 10 μg/mL, which suggests that in this series even though the labile amide bond of **2** has been modified, metabolic modification is readily occurring at alternative sites of the molecule. O-Dealkylation of the side chain moiety is one possibility, and this appears to be the case for **6d** since a major component of the mixture after incubation of this compound was identified as phenol **4**.[23]

The series of four sulfonamides evaluated are also quite susceptible to biotransformation when incubated with the monkey liver S-9 fraction, although in this series the benzyl-substituted compounds **13c** and **13e** appear to be more stable than the alkyl derivatives **13i** and **13k**. Within the series of sulfones, the *N*-benzyl compound **19e** is more stable than amide **2**, at concentrations of both 1 and 10 μg/mL. The metabolic stability of the 4-fluoro-substituted derivative, **19g**, is less than that of **19e**, and the cyclohexylmethyl derivative, **19k**, appears to be less stable than the similarly substituted amide **2**.

All of the tetrazoles evaluated demonstrated enhanced metabolic stability when compared with the amide **2** as well as ureas **6**, sulfonamides **13**, and sulfones **19**, suggesting that the identity of the side-chain terminus can influence metabolic stability. However, within this series, the rate of biotransformation appears to be dependent upon the identity of the piperidine substituent, and the two benzyl-substituted compounds, **23e** and **23g**, are the more stable compounds. Both **23e** and **23g** are metabolized only slowly over the 2-h time period with over 90% of parent drug remaining at the end of the experiment, and these tetrazole derivatives are significantly more stable than amide **2**, for which approximately 60% of parent drug remained under these conditions. The piperidino-*N*-alkyl-substituted-tetrazole derivatives **23j** and **23q** appear to be less stable than the benzyl analogues **23e** and **23g**, but both are metabolized less readily than **2**. Hydroxylation of the piperazine substituents of **23j** and **23q** may represent a metabolic pathway for these compounds based on studies of the biotransformation of cilostazole (**5**).[27]

The increased metabolic stability associated with the tetrazole series compared to the other structural classes **6**, **13**, and **19** may be a consequence of the markedly different topology associated with this side-chain moiety. The vicinal substitution pattern of the tetrazole ring of **23** presents a conformationally distorted side-chain topography when compared to the more linear arrangement associated with the ureas **6**, sulfonamides **13**, and sulfones **19**. On the basis of the identification of **4** as a metabolite of **2** *in vivo* and the *in vitro* data presented above, O-dealkylation of the side chain may be an important metabolic pathway for **6**, **13**, and **19**. If this is indeed the case, then the tetrazoles **23** would appear to be less susceptible to this mode of biotransformation. The unique topography associated with the tetrazole-containing side chain may interfere with the ability of the liver enzymes to efficiently bind this structural class of platelet aggregation inhibitor and effect O-dealkylation. Consistent with this contention, O-dealkylation does not appear to be a major metabolic pathway for cilostazole (**5**) in humans or dogs.[27]

Representatives of the ureas **6** and sulfonamides **13** that were evaluated in the monkey liver S-9 fraction offer no significant advantage over amide **2**, and it is apparent that further structural modification is required in order to provide compounds based on these side-chain termini with

enhanced metabolic stability. However, the sulfone **19e** and, in particular, the tetrazoles **23e**, **23g**, and **23j** are compounds with markedly improved metabolic stability *in vitro*, compared to amide **2**, and provided the level enhancement that we felt would be of value if it translated to the *in vivo* situation. From these compounds, sulfone **19e** and tetrazole **23e** were selected as candidates suitable for further study. To confirm that only unchanged drug was present in the HPLC peak corresponding to sulfone **19e** and tetrazole **23e**, aliquots of the 2-h sample extracts from the monkey liver S-9 experiments were chromatographed and the peak corresponding to the retention time of the parent drug was collected. The mobile phase was evaporated, and the residues were analyzed by negative-ion LC/MS. The analysis revealed that each peak had a retention time identical to that of an authentic sample, and mass spectral data indicated the presence of only parent drug.

Having established the stability of sulfone **19e** and sulfone **23e** *in vitro*, the pharmacokinetic profiles of these agents were determined in rats in order to establish comparison with amide **2**, which was employed as a control in these studies, and to identify compounds for evaluation in the monkey. Because of our previous experience with the unpredictable absorption properties of this class of compound, particular attention was focused on determining the amount of drug absorbed after oral administration in addition to evaluating the extent of first-pass metabolism in this species. Assuming that no biotransformation occurs in the gut, the differences between ip and iv administration (iv administered drug is defined as 100% bioavailable) reflect the extent of first-pass metabolism of the drug as it passes through the liver.[40] Tetrazole **23e**, when given intraperitoneally, was estimated to exhibit 72% bioavailability while, in contrast, the ip bioavailability of both **19e** and **2** was estimated to be only 35%. These results demonstrate that **23e** is less susceptible to first-pass metabolism in the rat when compared to **19e** and **2**. Furthermore, the data demonstrate a reasonably good correlation with the stability of these compounds determined in the monkey S-9 liver preparation although **19e** is somewhat less metabolically stable than predicted by the *in vitro* studies. However, oral administration of these compounds to rats provided a quite different perspective of bioavailability and **2**, with an estimated bioavailability of 23%, was clearly superior to **19e** and **23e**, both of which were estimated to be only 3% bioavailable. Thus, **19e** and **23e** appear to be significantly less readily absorbed from the gastrointestinal tract of rats than **2**. The unique physicochemical properties of **2** that are responsible for its enhanced oral absorption compared to either **19e** and **23e** are not immediately apparent. Although the increased aqueous solubility of **2**, when compared to earlier studied compounds, appeared to contribute to increased oral absorption,[1,21] the observations reported herein for **19e** and **23e** suggest that other factors must play a significant role. Indeed, studies of cAMP PDE inhibitors of a different structural class have revealed that relatively minor structural changes can exert a significant impact on oral bioavailability.[41] Taken together with our previous experience of erratic and varied absorption properties of the imidazo[4,5-*b*]quinolin-2-one class of compound in several species, these data suggest that individual series may be associated with unique problems. Although the increased metabolic stability associated with tetrazole **23e** fulfilled our criteria, the poor oral absorption of this compound was not compatible with our objective of identifying orally-effective antithrombotic agents, and further development of this series of blood platelet aggregation inhibitor was not pursued.

In summary, we have described the synthesis and SAR of four series of imidazo[4,5-*b*]quinolin-2-ones structurally related to BMY 43351 (**2**) that incorporate chemically stable side-chain termini. In general, these compounds are highly potent inhibitors of platelet function *in vitro*, and several representatives combine this property with excellent aqueous solubility. The results presented in Tables I–IV extend the scope of side-chain terminus functionality that can be effectively accommodated by the secondary binding region of the cAMP PDE enzyme. The results of *in vitro* metabolism studies conducted with representatives of the four structural types revealed that sulfone **19e** and tetrazoles **23e**, **23g**, and **23j** offered enhanced metabolic stability when compared to the prototype **2**. *In vivo* pharmacokinetic studies conducted in rats confirmed that **23e** demonstrated increased metabolic stability *in vivo* compared to **2**. These observations demonstrate the value of *in vitro* studies using the liver S-9 fraction as a means of identifying compounds with enhanced metabolic stability *in vivo*. However, the poor and unpredictable oral absorption associated with this class of platelet aggregation inhibitor and other cAMP PDE inhibitors[41,42] presents a serious impediment to their development as orally effective antithrombotic agents.

Experimental Section

Melting points were recorded on a Thomas-Hoover capillary apparatus and are uncorrected. Magnetic resonance (NMR) spectra were recorded on a Bruker AM FT instrument operating at 300 MHz for proton (^{1}H) and 75 MHz for carbon (^{13}C) or a Varian Gemini 300. All spectra were recorded using tetramethylsilane as an internal standard, and signal multiplicity was designated according to the following abbreviations: s = single, d = doublet, t = triplet, q = quartet, m = multiplet, bs = broad singlet. Infrared (IR) spectra were obtained using a Nicolet MX1 FT spectrometer, scanning from 4000 to 400 cm^{-1}, and calibrated to the 1601-cm^{-1} absorption of a polystyrene film. Mass spectral data were obtained on a Finnigan Model 4500 GC/MS using chemical ionization (isobutane) procedures. Fast atom bombardment (FAB) mass spectra were obtained on a Kratos MS 25 spectrometer using *m*-nitrobenzyl alcohol (NOBA) as the matrix. Analytical samples were dried *in vacuo* at 78 °C or in the presence of P_2O_5 at room temperature for at least 12 h. Elemental analyses were provided by Bristol-Myers Squibb's Analytical Chemistry Department, and C, H, and N values are within ±0.4 of calculated values.

***N*-[3-[(2,3-Dihydro-2-oxo-1*H*-imidazo[4,5-*b*]quinolin-7-yl)oxy]propyl]-4-(2-ethylbutyl)-1-piperazinecarboxamide Dihydrochloride (6n).** A mixture of **3** (11.70 g, 38 mmol), Et_3N (5.37 g, 7.36 mL, 53 mmol), DPPA (14.58 g, 11.50 mL, 53 mmol), and DMF (225 mL) was heated to 130 °C with stirring. At approximately 50–60 °C, solution occurred followed by the formation of a gray precipitate as the temperature rose through 100 °C. After 2 h, the suspension was cooled and diluted with H_2O, and a gray solid was filtered off and washed with H_2O, MeOH, and Et_2O to leave 10.65 g.

A slury of 2 g of this material, 2-(ethylbutyl)-1-piperazine (2.40 g, 14 mmol) and NMP (4 mL) was heated at 200 °C for 30 min. The cooled reaction mixture was filtered, the solid washed with DMF (75 mL), and the filtrate concentrated *in vacuo* to ca. 30 mL. The solution was diluted with H_2O (45 mL) and the precipitate filtered off and dried in air. The solid material was dissolved in EtOH by the addition of excess of a 10% solution of HCl in EtOH, and the mixture was heated at reflux for 30 min and cooled to room temperature. Filtration provided a solid (2.32 g, 72%) which was stirred with aqueous Na_2CO_3 solution

and filtered, and the solid was dissolved in hot DMF, filtered, and diluted with H_2O. The precipitated solid was dissolved in EtOH containing an excess of dry HCl gas and diluted with Et_2O to give **6n**: mp 230–263 °C; IR (KBr) 1750, 1640, 1540 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 0.76 (6H, t, J = 7 Hz, $(CH_3)_2$), 1.33 (4H, nontuplet, J = 7 Hz, $(CH_2CH_3)_2$), 1.67 (1H, m, $NCH_2CH(Et)_2$), 1.90 (2H, bs, OCH_2CH_2), 2.89 (4H, bs, NCH_2), 3.19 (2H, t, J = 6 Hz, $CONHCH_2$), 3.40 (4H, m, NCH_2 + axial $CONCH_2$), 4.04 (4H, bs, OCH_2 + equatorial $CONCH_2$), 7.14 (1H, dd, J = 9 Hz, J' = 2 Hz, aryl H ortho to O), 7.41 (1H, d, J = 2 Hz, aryl H ortho to O), 7.74 (1H, s, aryl H ortho to CONH), 7.84 (1H, d, J = 9 Hz, aryl H meta to O), 10.74 (1H, bs, NH), 11.64 (1H, bs, NH); MS m/z 455 (MH$^+$). Anal. ($C_{24}H_{34}N_6O_3$·2HCl) C, H, N.

4-[(3-Chloropropyl)sulfonyl]piperazine-1-carboxaldehyde (9). A solution of **8** (21.50 g, 0.19 mol) in CH_2Cl_2 (50 mL) was added dropwise over 20 min to a vigorously stirred biphasic mixture of **7** (27.70 g, 0.16 mol) in CH_2Cl_2 (150 mL) and saturated $NaHCO_3$ solution (20 g in 200 mL H_2O) at room temperature. After the mixture was stirred for 4 h, the organic phase was separated, the aqueous layer was extracted with CH_2Cl_2, and the combined extracts were washed consecutively with 1 N HCl (100 mL), 10% Na_2CO_3 solution, H_2O, and brine. After the extracts were dried over $MgSO_4$, the solvent was evaporated to give **9** (33.70 g, 84%) as a white solid. Recrystallization from EtOAc/hexane gave analytically pure **9** (30.50 g, 76%): mp 84–85 °C; IR (KBr) 1680, 1340, 1155 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.24 (2H, m), 3.05 (2H, t, J = 7.5 Hz), 3.24 (2H, t, J = 5 Hz), 3.29 (2H, m), 3.44 (2H, t, J = 5 Hz), 3.62 (4H, m), 8.02 (1H, s); MS m/z 255 (MH$^+$). Anal. ($C_8H_{15}ClN_2O_3S$) C, H, N.

4-[[3-(3-Formyl-4-nitrophenoxy)propyl]sulfonyl]-1-piperazinecarboxaldehyde. A mixture of **10** (17.10 g, 0.102 mol), **9** (26.00 g, 0.102 mol), pulverized anhydrous K_2CO_3 (17.00 g, 0.12 mol), KI (3.40 g, 0.02 mol), and anhydrous DMF (100 mL) was heated at 105 °C under N_2 for 1.25 h. The bulk of the DMF was removed at reduced pressure, and the residual slurry was diluted with H_2O and extracted with CH_2Cl_2 to give a solid which was triturated with a mixutre of CH_2Cl_2 and Et_2O to afford the title compound (36.70 g, 93%): mp 108–110 °C; IR (KBr) 1678, 1502, 1340, 1328, 1236, 1146, 825 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.15 (2H, m), 3.16 (2H, t, J = 5 Hz), 3.25 (4H, m), 3.44 (4H, m), 4.26 (2H, t, J = 6 Hz), 7.25 (1H, d, J = 3 Hz), 7.36 (1H, dd, J = 9 Hz, J' = 3 Hz), 8.04 (1H, s), 8.18 (1H, d, J = 9 Hz), 10.27 (1H, s); MS m/z 386 (MH$^+$). Anal. ($C_{15}H_{19}N_3O_7S$) C, H, N.

(*E*)- and (*Z*)-4-[[3-[3-[(2,5-Dioxo-4-imidazolidinylidene)methyl]-4-nitrophenoxy]propyl]sulfonyl]-1-piperazinecarboxaldehyde (12). A solution of 4-[[3-(3-formyl-4-nitrophenoxy)propyl]sulfonyl]-1-piperazinecarboxaldehyde (35.00 g, 0.91 mol) in CH_3CN (100 mL) was added dropwise over 30 min to a stirred solution of **11** (25.70 g, 0.11 mol) and Et_3N (20 mL, 0.14 mol) in CH_3CN (100 mL). The mixture was stirred for 4.5 h and concentrated, and the residual syrup was diluted with 1 N HCl solution to give a solid which was filtered off and dried in air to furnish **12** (41.80 g, 98%): IR (KBr) 1770, 1730, 1654, 1510, 1370, 1338, 1260, 1144, 835 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.15 (2H, quintuplet, J = 6 Hz, OCH_2CH_2), 3.10–3.55 (10H, m, NCH_2 + CH_2SO_2), 4.18 (0.3H, t, J = 6 Hz, OCH_2 of Z isomer), 4.26 (1.7H, t, J = 6 Hz, OCH_2 of E isomer), 6.56 (0.15H, s, olefinic H of E isomer), 6.59 (0.85H, s, olefinic H of Z isomer), 7.00–7.10 (1.85H, m, aromatic H), 7.32 (0.15H, d, J = 2 Hz, aromatic H ortho to O of E isomer), 8.03 (1H, s, NCHO), 8.08 (0.15H, d, J = 9 Hz, aromatic H ortho to NO_2 of E isomer), 8.15 (0.85H, d, J = 9 Hz, aromatic H ortho to NO_2 of Z isomer), 10.44 (0.15 H, s, NH), 10.67 (0.85H, s, NH), 11.10 (0.15H, s, NH), 11.33 (0.85H, s, NH); MS m/e 468 (MH$^+$). Anal. ($C_{18}H_{21}N_5O_6S$) C, H, N.

4-[[3-[4-Amino-3-[(2,5-dioxo-4-imidazolidinyl)methyl]phenoxy]propyl]sulfonyl]-1-piperazinecarboxaldehyde. A solution of **12** (41.00 g, 0.88 mol) in DMF (800 mL) was hydrogenated over 10% Pd on C (4.00 g) at 60 psi in a Parr apparatus. After 19 h, 10% Pd on C (2.00 g) was added, and hydrogenation continued for an additional 24 h. After H_2 uptake ceased, the mixture was filtered through Celite and concentrated to give a solid which was triturated with MeOH to give the title compound (38.50 g, 99%): mp 200–203 °C dec; IR (KBr) 3500–2700, 1766, 1724, 1640, 1326, 1260, 1144, 815 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.03 (2H, m), 2.71 (1H, dd, J = 13 Hz, J' = 5 Hz), 2.85 (1H, dd, J = 13 Hz, J' = 5 Hz), 3.16 (4H, m), 3.20 (2H, t, J = 6 Hz), 3.33 (1H, s), 3.43 (4H, m), 3.89 (2H, t, J = 6 Hz), 4.32 (1H, t, J = 5 Hz), 4.42 (1H, s), 6.57 (3H, s), 7.76 (1H, s), 8.02 (1H, s), 10.55 (1H, s); MS m/z 440 (MH$^+$). Anal. ($C_{18}H_{25}N_5O_6S$) C, H, N.

4-[[3-[(2,3,9,9a-Tetrahydro-2-oxo-1*H*-imidazo[4,5-*b*]quinolin-7-yl)oxy]propyl]sulfonyl]-1-piperazinecarboxaldehyde. A stirred suspension of 4-[[3-[4-amino-3-[(2,5-dioxo-4-imidazolidinyl)methyl]phenoxy]propyl]sulfonyl]-1-piperazinecarboxaldehyde (38.00 g, 86 mmol) and *p*-TsOH (1.00 g) in anhydrous MeOH (500 mL) was heated at reflux under N_2 for 6 h. The mixture was cooled, filtered, and dried *in vacuo* to provide the title compound (35.40 g, 97%): mp 285–288 °C; IR (KBr) 3600–3100, 1674, 1644, 1340, 1278, 1148 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.07 (2H, m), 2.61 (1H, t, J = 15 Hz), 2.95 (1H, dd, J = 15 Hz, J' = 7 Hz), 3.19 (6H, m), 3.43 (4H, m), 4.00 (2H, t, J = 6 Hz), 4.19 (1H, dd, J = 15 Hz, J' = 9 Hz), 6.77 (1H, dd, J = 9 Hz, J' = 2.5 Hz), 6.83 (1H, d, J = 2.5 Hz), 6.91 (1H, d, J = 9 Hz), 7.65 (1H, s), 8.03 (1H, s), 10.57 (1H, s); MS m/z 422 (MH$^+$). Anal. ($C_{18}H_{23}N_5O_5S$) C, H, N.

4-[[3-[(2,3-Dihydro-2-oxo-1*H*-imidazo[4,5-*b*]quinolin-7-yl)oxy]propyl]sulfonyl]-1-piperazinecarboxaldehyde (13a). I_2 (20.70 g, 82 mmol) was added portionwise to a stirred mixture of 4-[[3-[(2,3,9,9a-tetrahydro-2-oxo-1*H*-imidazo[4,5-*b*]quinolin-7-yl)oxy]propyl]sulfonyl]-1-piperazinecarboxaldehyde (32.80 g, 78 mmol) in anhydrous DMF (950 mL) maintained at 100 °C under N_2. The mixture was stirred at 100–110 °C for 1 h and cooled, and the DMF was evaporated at reduced pressure. The residue was diluted with saturated $NaHCO_3$ (100 mL) and 10% $Na_2S_2O_3$ solution (400 mL) and filtered, and the solid was washed with H_2O and dried in air. Trituration with boiling MeOH provided **13a** (32.10 g, 98%): mp 315–318 °C; IR (KBr) 3600–2200, 1706, 1670, 1320, 1234, 1146 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.15 (2H, m), 3.22 (6H, m), 3.43 (4H, m), 4.13 (2H, t, J = 6 Hz), 7.14 (1H, dd, J = 9 Hz, J' = 2.5 Hz), 7.30 (1H, d, J = 2.5 Hz), 7.49 (1H, s), 7.66 (1H, d, J = 9 Hz), 8.02 (1H, s), 10.95 (1H, s), 11.36 (1H, s); MS m/z 420 (MH$^+$). Anal. ($C_{18}H_{21}N_5O_5S$·0.53H_2O) C, H, N.

1-[[3-[(2,3-Dihydro-2-oxo-1*H*-imidazo[4,5-*b*]quinolin-7-yl)oxy]propyl]sulfonyl]piperazine (13b). A mixture of **13a** (30.00 g, 72 mmol), MeOH (400 mL), and 1 N NaOH solution (160 mL) was heated at reflux for 23 h to give a solution. The mixture was cooled and concentrated, and the residue was acidified with 3 N HCl (60 mL) with cooling as necessary. Saturated $NaHCO_3$ solution was added until pH = 8, and the precipitate was filtered off, washed with H_2O and triturated with boiling MeOH to afford **13b** (26.90 g, 96%): mp 293–295 °C; IR (KBr) 3600–2300, 1718, 1358, 1154, 1250, 830 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.15 (2H, m), 2.71 (4H, m), 3.07 (4H, m), 3.19 (2H, t, J = 6 Hz), 3.31 (1H, s), 4.14 (2H, t, J = 6 Hz), 7.16 (1H, dd, J = 9 Hz, J' = 3 Hz), 7.31 (1H, d, J = 3 Hz), 7.50 (1H, s), 7.67 (1H, d, J = 9 Hz), 10.95 (1H, s), 11.28 (1H, s); MS m/z 392. Anal. ($C_{17}H_{21}N_5O_4S$·0.5H_2O) C, H, N. A sample was converted to the hydrochloride salt: mp 237–240 °C; IR (KBr) 3600–2300, 1758, 1328, 1232, 1148, 830 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.16 (2H, m), 3.14 (4H, m), 3.34 (2H, t, J = 8 Hz), 3.48 (4H, m), 4.16 (2H, t, J = 6 Hz), 7.22 (1H, dd, J = 9 Hz, J' = 3 Hz), 7.40 (1H, d, J = 3 Hz), 7.64 (1H, s), 7.77 (1H, d, J = 9 Hz), 9.20 (1H, bs), 9.69 (2H, s), 11.29 (1H, s); MS m/z 392 (MH$^+$). Anal. ($C_{17}H_{21}N_5O_4S$·2HCl) C, H, N.

General Procedure for the N-Alkylation of 13b. A stirred suspension of **13b** (1 mmol), Et_3N (2–4 mmol), and the alkylating agent (2–4 mmol) in anhydrous DMF was maintained at room temperature or heated to 60–100 °C as necessary, dependent on the identity of the alkylating agent. When the reaction was complete according to TLC analysis, the mixture was cooled and diluted with H_2O, and the pH was adjusted to between 7 and 8 with saturated $NaHCO_3$ solution. The precipitate was filtered off, washed with H_2O, and dried in air before being triturated with boiling MeOH. The material was dissolved in MeOH saturated with anhydrous HCl gas with warming, and the mixture was cooled and diluted with Et_2O to precipitate the dihydrochloride salt.

13c had mp 261–264 °C; IR (KBr) 3600–2200, 1750, 1638, 1346, 1232, 1148, 700, 756 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.15 (2H, m), 3.08 (2H, m), 3.33 (4H, m), 3.44 (2H, t, J = 12 Hz), 3.74 (2 H, m), 4.15 (2H, t, J = 6 Hz, OCH_2), 4.33 (2H, s, NCH_2), 7.20 (1H, d, J = 9 Hz), 7.42 (4H, m), 7.61 (3H, m), 7.74 (1H, d, J = 9 Hz), 7.50

(2H, bs), 11.21 (1H, s, NH), 11.88 (1H, bs, NH); MS *m/e* 482 (MH^+). Anal. ($C_{24}H_{27}N_5O_4S \cdot 2HCl \cdot 0.4H_2O$) C, H, N.

1-Methyl-4-mercaptopiperidine (15). H_2S was bubbled vigorously through a solution of freshly distilled 14 (80.00 g, 0.71 mol) in *i*-PrOH (200 mL) maintained at 0–5 °C. After 1 h, the mixture was filtered to give 18.50 g of the *gem*-dithiol. The filtrate was treated with H_2S gas for 2 h to give an additional 26.00 g of the *gem*-dithiol. The filtrate from this crop was treated with H_2S for 2–3 h at −5 to 0 °C, the gas source was removed, and the mixture was stirred overnight. Filtration gave a further 21.50 g of *gem*-dithiol and brought the combined yield to 66.00 g (51%) which was dried over P_2O_5 *in vacuo* in the dark.

The *gem*-dithiol (44.00 g, 0.243 mol) was added in small portions to a stirred suspension of $NaBH_4$ (11.00 g, 0.29 mol) in *i*-PrOH (100 mL) maintained at 0–5 °C under N_2. After the addition was complete, the mixture was stirred at 0–5 °C for 0.5 h, warmed to room temperature, and stirred overnight. The mixture was heated at 80 °C for 2 h, cooled, and concentrated *in vacuo* to leave a white pasty residue which was diluted with H_2O and Et_2O. The ethereal layer was separated, the aqueous layer was extracted with Et_2O, and the combined extracts were washed with brine and dried over Na_2SO_4. The solvent was removed and the residual oil distilled under reduced pressure to afford 15 (25.80 g, 81%): bp 30–35 °C (0.04–0.05 Torr); IR (film) 3000–2800, 2678, 1446, 1376 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.42 (1H, d, J = 7 Hz), 1.53 (2H, m), 1.89 (4H, m), 2.13 (3H, s), 2.66 (3H, m); MS *m/z* 132 (MH^+). Anal. ($C_6H_{13}NS$) C, H, N.

1-Methyl-4-[(ethoxycarbonyl)thio]piperidine. EtO_2CCl (23.20 g, 0.21 mol) was added dropwise to a stirred solution of 15 (25.00 g, 0.19 mol) in anhydrous acetone (200 mL) maintained at 15–20 °C. The mixture was stirred at room temperature under N_2 for 2 h and filtered, and the filtrate was concentrated and diluted with Et_2O to precipitate additional hydrochloride salt. The solids were combined and dried *in vacuo* to leave 44.20 g, 97%. This material was suspended in Et_2O (150 mL) and H_2O followed by the addition of NH_4OH solution. The ethereal layer was separated and the aqueous layer extracted with Et_2O to give a colorless oil which was distilled *in vacuo* to afford the title compound (33.70 g, 87%): bp 60–62 °C (0.01 Torr); IR (film) 3000–2800, 1704, 1144, 1378 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.21 (3H, t, J = 7 Hz), 1.63 (2H, m), 1.94 (2H, m), 2.06 (2H, m), 2.17 (3H, s), 2.64 (2H, m), 3.23 (1H, m), 4.17 (2H, q, J = 7 Hz); MS *m/z* 204 (MH^+). Anal. ($C_{19}H_{17}NO_2S$) C, H, N.

1-(Ethoxycarbonyl)-4-[(ethoxycarbonyl)thio]piperidine (16). EtO_2CCl (35.20 g, 0.32 mol) was added dropwise over 30 min to a stirred solution of 1-methyl-4-[(ethoxycarbonyl)thio]piperidine (33.00 g, 0.16 mol) in dry toluene (35 mL) maintained at 90 °C. The mixture was heated at 110 °C for 2 h, additional EtO_2CCl (12 mL) was added dropwise, and the mixture was heated at 110 °C for 3 h before being stirred overnight at room temperature. The mixture was filtered and concentrated, and the residual oil was distilled *in vacuo* to give 16 (37.00 g, 87%): bp 116–118 °C (0.01 Torr); IR (film) 1702, 1252, 1144, 1388 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.18 (3H, t, J = 7 Hz), 1.23 (3H, t, J = 7 Hz), 1.52 (2H, m), 1.95 (2H, m), 3.02 (2H, m), 3.40 (1H, m), 3.90 (2H, m), 4.03 (2H, q, J = 7 Hz), 4.19 (2H, *q*, J = 7 Hz); MS *m/z* 262 (MH^+). Anal. ($C_{11}H_{19}NO_4S$) C, H, N.

1-(Ethoxycarbonyl)-4-[(3-chloropropyl)thio]piperidine (17, *n* = 3). A solution of Na (2.90 g, 0.126 g atom) in EtOH (200 mL) was added dropwise over 15 min to a stirred solution of 16 (30.00 g, 0.115 mol) in EtOH (50 mL) maintained in an ice bath. The mixture was stirred at room temperature for 3 h and cooled to 0 °C, and 1-chloro-3-iodopropane (25.80 g, 0.126 mol) was added over 15 min. The mixture was warmed to room temperature and stirred for 22 h before being diluted with Et_2O (200 mL) and 50% saturated brine (100 mL). The layers were separated, and the aqueous layer was extracted with Et_2O to give an oil which was chromatographed on a column of silica gel using a mixture of hexane and EtOAc (3:2) as eluent to give 17, n = 3 (30.30 g, 99%): IR (film) 1700, 1470, 1432, 1250, 1114 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (3H, t, J = 7 Hz), 1.46 (2H, m), 1.89 (2H, m), 1.99 (2H, m), 2.65 (2H, t, J = 7 Hz), 2.76 (1H, m), 2.92 (2H, m), 3.60 (2H, t, J = 6 Hz), 3.96 (2H, m), 4.07 (2H, q, J = 7 Hz); MS *m/z* 266. Anal. ($C_{11}H_{20}ClNO_2S$) C, H, N.

1-(Ethoxycarbonyl)-4-[(3-chloropropyl)sulfonyl]piperidine. A solution of CH_3CO_3H in AcOH (32% wt, 57.00 g, 50.5 mL, 0.24 mol) was added dropwise over 30 min to a stirred solution of 17, n = 3 (29.00 g, 0.11 mol) in CH_2Cl_2 (500 mL) maintained at −20 °C. The mixture was warmed to room temperature and stirred for 5 h before cooling in an ice bath and then quenching with 10% Na_2SO_3 solution (200 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 to give a viscous oil which crystallized on standing to afford the title compound (32.60 g, 100%): mp 49–51 °C; IR (KBr) 1696, 1300, 1254, 1126 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.19 (3H, t, J = 7 Hz), 1.69 (2H, m), 2.07 (2H, m), 2.27 (2H, m), 2.75 (2H, m), 2.97 (1H, m), 3.05 (2H, t, J = 7.5 Hz), 3.64 (2H, t, J = 6 Hz), 4.07 (2H, q, J = 7 Hz), 4.28 (2H, m); MS *m/z* 298 (MH^+). Anal. ($C_{11}H_{20}ClNO_4S$) C, H, N.

Ethyl 4-[[3-(3-Formyl-4-nitrophenoxy)propyl]sulfonyl]-1-piperidinecarboxylate (18, *n* = 3). A mixture of 10 (18.00 g, 0.017 mol), 1-(ethoxycarbonyl)-4-[(3-chloropropyl)sulfonyl]-piperidine (32.00 g, 0.017 mol) pulverized anhydrous K_2CO_3 (17.80 g, 0.129 mol), KI (3.60 g, 0.02 mol), and anhydrous DMF (120 mL) was stirred at 110 °C under N_2 for 1.25 h. The mixture was cooled and concentrated *in vacuo*, and the residue was diluted with H_2O and extracted with CH_2Cl_2 to give an oil which was triturated with Et_2O and filtered to furnish the title compound (41.80 g, 91%): mp 101–103 °C; IR (KBr) 1696, 1508, 1344, 1310, 1264, 1256, 1134, 848 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (3H, t, J = 7 Hz), 1.75 (2H, m), 2.11 (2H, m), 2.41 (2H, m), 2.79 (2H, m), 3.05 (1H, m), 3.13 (2H, t, J = 7 Hz), 4.11 (2H, q, J = 7 Hz), 4.26 (2H, t, J = 6 Hz), 4.33 (2H, m), 7.13 (1H, dd, J = 9 Hz, J' = 3 Hz), 7.28 (1H, d, J = 3 Hz), 8.13 (1H, d, J = 9 Hz), 10.43 (1H, s); MS *m/z* 429 (MH^+). Anal. ($C_{18}H_{24}N_2O_8S$) C, H, N.

Ethyl 4-[[3-[(2,3-Dihydro-2-oxo-1*H*-imidazo[4,5-*b*]quinolin-7-yl)oxy]propyl]sulfonyl]-1-piperidinecarboxylate (19a). A solution of ethyl 4-[[3-(3-formyl-4-nitrophenoxy)propyl]sulfonyl]-1-piperidinecarboxylate (37.00 g, 86 mmol) in CH_3CN (250 mL) was added dropwise over 30 min to a stirred mixture of 11 (24.50 g, 0.103 mol) and Et_3N (19 mL) in CH_3CN (125 mL). The mixture was stirred at room temperature for 5 h and concentrated, and the residue was diluted with 0.05 N HCl to afford a solid (45.70 g).

This material was dissolved in DMF (750 mL) and hydrogenated at 60 psi over 10% Pd on C (2.25 g) in a Parr hydrogenation apparatus. After 19 and 32 h, additional 10% Pd on C (2.25 g) was added, and hydrogenation continued until uptake ceased. The mixture was filtered through Celite and concentrated *in vacuo* to afford a viscous oil which was suspended in MeOH (1 L). *p*-TsOH (2.00 g) was added, and the mixture was heated at reflux for 20 h and filtered to give ethyl 4-[[3-[(2,3,9,9a-tetrahydro-2-oxo-1*H*-imidazo[4,5-*b*]quinolin-7-yl)oxy]propyl]sulfonyl]-1-piperidinecarboxylate (36.60 g, 89%).

This material was suspended in hot (105 °C) DMF (900 mL), and I_2 (20.50 g, 81 mmol) was added in small portions. After the addition was complete, the mixture was heated at 105 °C for 1.25 h, cooled, and concentrated *in vacuo*. The residue was diluted with saturated $NaHCO_3$ solution until pH = 7, a 10% $Na_2S_2O_3$ solution (300 mL) was added, and a solid was filtered off and dried in air. Trituration with boiling MeOH gave **19a** (35.20 g, 98%): mp 318–321 °C; IR (KBr) 1720, 1696, 1388, 1366, 1260, 1220, 1130, 824 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.15 (3H, t, J = 7 Hz), 1.46 (2H, m), 2.01 (2H, m), 2.18 (2H, m), 2.81 (2H, m), 3.27 (2H, t, J = 7.5 Hz), 3.42 (2H, m), 4.01 (2H, q, J = 7 Hz), 4.07 (1H, m), 4.16 (2H, t, J = 6 Hz), 7.15 (1H, dd, J = 9 Hz, J' = 3 Hz), 7.31 (1H, d, J = 3 Hz), 7.50 (1H, s), 7.67 (1H, d, J = 9 Hz), 10.96 (1H, s), 11.37 (1H, s); MS *m/z* 463 (NH^+). Anal. ($C_{21}H_{26}N_4O_6S$) C, H, N.

4-[[3-[(2,3-Dihydro-2-oxo-1*H*-imidazo[4,5-*b*]quinolin-7-yl)oxy]propyl]sulfonyl]piperidine Dihydrochloride (19c). A mixture of **19a** (34.00 g, 0.07 mol), ethylene glycol (200 mL), and 3 N KOH solution (100 mL) was stirred at 110 °C under N_2 for 46 h. The mixture was cooled, acidified with 3 N HCl to pH = 3, and then adjusted to pH = 7 by adding saturated $NaHCO_3$ solution. The precipitate was filtered, washed with H_2O, and dried in air before being triturated with boiling MeOH to give **19c** (28.20 g, 98%). A small sample was converted to the dihydrochloride salt of **19c** by treating with anhydrous HCl gas in MeOH and had mp 340–345 °C: IR (KBr) 3600–2300, 1744, 1298, 1236, 1130, 824 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.89 (2H, m), 2.17 (4H, m), 2.89 (2H, m), 3.33 (4H, m), 3.53 (1H, m), 4.18 (2H, t, J = 6 Hz), 7.20 (1H, dd, J = 9 Hz, J' = 3 Hz), 7.38 (1H, d, J

= 3 Hz), 7.61 (1H, s), 7.76 (1H, d, J = 9 Hz), 8.00 (1H, bs), 9.13 (1H, bs), 9.49 (1H, bs) 11.23 (1H, s); MS m/z 391 (MH^+). Anal. ($C_{18}H_{22}N_4O_4S \cdot 2HCl \cdot 1.2H_2O$) C, H, N.

4-[[3-[(2,3-Dihydro-2-oxo-1*H*-imidazo[4,5-*b*]quinolin-7-yl)oxy]propyl]sulfonyl]-1-(phenylmethyl)piperidine Dihydrochloride (19e). A sample of **19c** was alkylated with benzyl bromide according to the general procedure described for the preparation of **13c** and converted to the dihydrochloride salt. **19e**: mp 282–285 °C; IR (KBr) 3600–2200, 1724, 1294, 1240, 1130, 825, 746, 700 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.19 (6H, m), 2.93 (2H, m), 3.31 (2H, t, J = 6 Hz), 3.45 (3H, m), 4.16 (2H, t, J = 6 Hz), 4.27 (2H, m), 7.16 (1H, dd, J = 9 Hz, J' = 3 Hz), 7.34 (1H, d, J = 3 Hz), 7.44 (3H, m), 7.54 (1H, s), 7.60 (2H, m), 7.70 (1H, d, J = 9 Hz), 11.09 (1H, s), 11.23 (1H, bs), 11.52 (1H, bs); MS m/z 481 (MH^+). Anal. ($C_{25}H_{28}N_4O_4S \cdot 2HCl \cdot 0.7H_2O$) C, H, N.

***N*-[1-(Ethoxycarbonyl)piperidin-4-yl]-4-chlorobutyramide (21).** A solution of **20** (23.20 g, 0.135 mol) in CH_2Cl_2 (50 mL) was added rapidly to a stirred biphasic mixture of 4-chlorobutyryl chloride (22.80 g, 0.162 mol) in CH_2Cl_2 (200 mL) and $NaHCO_3$ (17.00 g) in H_2O (200 mL). The mixture was stirred at room temperature for 3 h, the layers were separated, and the organic phase was washed consecutively with 1 N HCl (100 mL), saturated $NaHCO_3$ (100 mL), H_2O (200 mL), and saturated brine (100 mL). After drying, the solvent was evaporated to leave the title compound as a white solid which was recrystallized from EtOAc/hexanes to give 35.60 g (95%): mp 115–116 °C; IR (KBr) 3279, 1700, 1644, 1548, 1437, 1229, 1143 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.21 (3H, t, J = 7 Hz), 1.27 (2H, m), 1.86 (2H, m), 2.06 (2H, m), 2.30 (2H, t, J = 7 Hz), 2.85 (2H, t, J = 12 Hz), 3.55 (2H, t, J = 6 Hz), 3.89 (1H, m), 4.03 (2H, m), 4.07 (2H, q, J = 7 Hz), 5.85 (1H, d, J = 8 Hz); MS m/z 277 (MH^+). Anal. ($C_{12}H_{21}ClN_2O_3$) C, H, N.

Ethyl 4-[5-(3-Chloropropyl)-1*H*-tetrazol-1-yl]-1-piperidinecarboxylate (22, n = 3). PCl_5 (20.80 g, 0.1 mol) was added in one portion to a stirred solution of **21**, n = 3 (25.0 g, 90 mmol), in anhydrous CH_2Cl_2 (300 mL) maintained at 5 °C under N_2. The mixture was stirred at room temperature for 2 h and cooled to −5 °C, and $TMSN_3$ (20.80 g, 0.18 mol) was added dropwise. The mixture was warmed to room temperature and stirred overnight before carefully neutralizing with saturated $NaHCO_3$ solution (300 mL). The layers were separated; the organic phase was washed with H_2O and brine, dried ($MgSO_4$), and concentrated to give **22**, n = 3 (28.20 g, 100%), as a colorless oil which was used without further purification. An analytical sample was purified by chromatography on a silica gel column using $CHCl_3$ and MeOH (19:1) as eluent: IR (KBr) 1696, 1514, 1482, 1474, 1386, 1238 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (3H, t, J = 7 Hz), 1.96 (2H, m), 2.13 (2H, m), 2.31 (2H, m), 2.95 (2H, m), 2.97 (2H, t, J = 7 Hz), 3.62 (2H, t, J = 6 Hz), 4.10 (2H, q, J = 7 Hz), 4.28 (2H, m), 4.35 (1H, m); MS m/z 302 (MH^+).

2-Nitro-5-[[3-[1-[1-(ethoxycarbonyl)piperidin-4-yl]-1*H*-tetrazol-5-yl]prop-3-yl]oxy]benzaldehyde. A suspension of **10** (14.95 g, 89 mmol), **22**, n = 3 (27.00 g, 89 mmol), anhydrous K_2CO_3 (14.8 g, 107 mmol), and KI (2.95 g, 18 mmol) in anhydrous DMF (110 mL) was stirred at 110 °C under N_2 for 1.25 h. The mixture was cooled and concentrated *in vacuo*, and the residue was diluted with H_2O and extracted with CH_2Cl_2 to give a brown syrup which crystallized on standing. This material was dissolved in CH_2Cl_2 and diluted with hexane to give (34.10 g, 91%) of the title compound: mp 99–101 °C; IR (KBr) 1700, 1594, 1520, 1332, 1284, 1238, 852 cm^{-1}; ^1H-NMR (DMSO-d_6) δ 1.20 (3H, t, J = 7 Hz), 1.86 (2H, m), 2.01 (2H, m), 2.27 (2H, m), 3.04 (2H, m), 3.13 (2H, t, J = 7.5 Hz), 4.06 (2H, q, J = 7 Hz), 4.10 (2H, m), 4.29 (2H, t, J = 6 Hz), 4.72 (1H, m), 7.25 (1H, d, J = 3 Hz), 7.35 (1H, dd, J = 9 Hz, J' = 3 Hz), 8.19 (1H, d, J = 9 Hz), 10.29 (1H, s); MS m/z 433 (MH^+). Anal. ($C_{18}H_{34}N_6O_6$) C, H, N.

Ethyl 4-[5-[3-[(2,3-Dihydro-2-oxo-1*H*-imidazo[4,5-*b*]quinolin-7-yl)oxy]propyl]-1*H*-tetrazol-1-yl]-1-piperidinecarboxylate (23a). A solution of 2-nitro-5-[[3-[1-[1-(ethoxycarbonyl)-piperidin-4-yl]-1*H*-tetrazol-5-yl]prop-3-yl]oxy]benzaldehyde (30.00 g, 69 mmol) in CH_3CN (200 mL) was added dropwise over 30 min to a stirred mixture of **11** (19.60 g, 83 mmol) and Et_3N (11.20 g, 15.5 mL, 0.11 mol) in CH_3CN (100 mL). The mixture was stirred at room temperature under N_2 for 4.5 h and concentrated, and the residue was diluted with 0.05 N HCl solution (200 mL). A solid was filtered off and recrystallized from CH_2Cl_2/MeOH/hexanes to give 4-[5-[3-[3-[(2,4-dioxo-5-imidazolidinylidene)-methyl]-4-nitrophenoxy]propyl]-1*H*-tetrazolyl]-1-piperidinecarboxylic acid ethyl ester (34.10 g, 96%) as 9:2 mixture of geometric isomers: IR (KBr) 3600–2600, 1740, 1708, 1674, 1604, 1588, 1506, 1386, 1326, 1266, 1238, 838 cm^{-1}; MS m/z 515 (MH^+).

A sample of this material (28.00 g, 54.4 mmol) in dry DMF (400 mL) was hydrogenated over 10% Pd on C (1.4 g) at 60 psi in a Parr hydrogenation apparatus. After 7 and 31 h, additional 10% Pd on C (1.4 g) was added, and hydrogenation continued until H_2 uptake ceased. The mixture was filtered through Celite and concentrated to give a viscous oil which was suspended in MeOH (800 mL). *p*-TsOH (2.80 g) was added, and the mixture was heated at reflux for 5 h before solid $NaHCO_3$ (2.00 g) was added in small portions. I_2 (15.20 g, 60 mmol) was added portionwise, and the mixture was heated at reflux for 15 h before concentrating. The residue was neutralized with saturated $NaHCO_3$ solution (50 mL), and 10% $Na_2S_2O_3$ solution (200 mL) was added to give a precipitate which was filtered and suspended in boiling MeOH. Filtration gave **23a** (21.30 g, 84%): mp 279–281 °C; IR (KBr) 3600–2600, 1728, 1692, 1454, 1242, 824 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.17, (3H, t, J = 7 Hz), 1.83 (2H, m), 1.97 (2H, m), 2.25 (2H, m), 2.95 (2H, m), 3.13 (2H, t, J = 7.5 Hz), 4.03 (4H, m), 4.13 (2H, t, J = 6 Hz), 4.69 (1H, m), 7.12 (1H, dd, J = 9 Hz, J' = 3 Hz), 7.31 (1H, d, J = 3 Hz), 7.49 (1H, s), 7.67 (1H, d, J = 9 Hz), 10.94 (1H, s), 11.35 (1H, s); MS m/z 467 (MH^+). Anal. ($C_{22}H_{26}N_8O_4 \cdot 0.3H_2O$) C, H, N.

4-[5-[3-[(2,3-Dihydro-2-oxo-1*H*-imidazo[4,5-*b*]quinolin-7-yl)oxy]propyl]-1*H*-tetrazol-1-yl]piperidine Dihydrochloride (23c). A mixture of **23a** (19.00 g, 41 mmol), ethylene glycol (100 mL), and 3 N KOH (50 mL) was heated at 120 °C for 15 h under N_2. The mixture was cooled and acidified with 3 N HCl to pH = 2, and the pH was adjusted to approximately 8 by adding saturated $NaHCO_3$ solution. The precipitate was filtered, washed with H_2O, dried in air, and triturated with boiling MeOH to give **23c** (15.30 g, 95%) as the free base. A small sample (0.50 g) was converted to dihydrochloride salt by treating with anhydrous HCl in MeOH and had mp 355–357 °C: IR (KBr) 3600–2200, 1764, 1686, 1228, 832 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.15 (2H, m), 2.25 (4H, m), 3.05 (2H, m), 3.13 (2H, t, J = 7.5 Hz), 3.36 (2H, m), 4.15 (2H, t, J = 6 Hz), 4.90 (1H, m), 7.17 (1H, dd, J = 9 Hz, J' = 3 Hz), 7.39 (1H, d, J = 3 Hz), 7.64 (1H, s), 7.77 (1H, d, J = 9 Hz), 9.20 (1H, bs), 9.32 (1H, bs), 9.53 (1H, bs), 11.33 (1H, s); MS m/z 395 (MH^+). Anal. ($C_{19}H_{22}N_8O_2 \cdot 2HCl$) C, H, N.

4-[5-[3-[(2,3-Dihydro-2-oxo-1*H*-imidazo[4,5-*b*]quinolin-7-yl)oxy]propyl]-1*H*-tetrazol-1-yl]-1-(phenylmethyl)piperidine Dihydrochloride (23e). Alkylation of a sample of **23c** (0.40 g, 1 mmol) according to the general protocol provided **23e** (0.40 g, 82%): mp 273–275 °C; IR (KBr) 3600–2400, 1720, 1624, 1242, 824, 750, 702 cm^{-1}; ^1H-NMR (DMSO-d_6) δ 2.22 (4H, m), 2.45 (2H, m), 3.09 (4H, m), 3.47 (2H, m), 4.13 (2H, t, J = 6 Hz), 4.30 (2H, m), 4.80 (1H, m), 7.11 (1H, dd, J = 9 Hz, J' = 3 Hz), 7.32 (1H, d, J = 3 Hz), 7.45 (3H, m), 7.52 (1H, s), 7.60 (2H, m), 7.69 (1H, d, J = 9 Hz), 11.06 (1H, s), 11.08 (1H, bs), 11.40 (1H, bs); MS m/z 485 (MH^+). Anal. ($C_{26}H_{26}N_8O_2 \cdot 2HCl \cdot 0.5H_2O$) C, H, N.

***In Vitro* Metabolism Studies.** For each compound evaluated, approximately 1 g of monkey liver was homogenized at 0 °C in 3 volumes of phosphate-buffered (0.05 M, pH = 7.4) isotonic KCl. The homogenate was centrifuged at 9000*g* for 30 min at 0 °C, and the supernatant was removed and stored on ice until used. A cofactor solution was prepared by adding D-glucose-6-phosphate, monosodium salt (6 mg), α-nicotinamide adenine dinucleotide phosphate, sodium salt (3.4 mg), 0.1 mL of 0.6 M nicotinamide, and 0.2 mL of 0.1 M $MgCl_2$ to 0.7 mL of 0.05 M (pH = 7.4) phosphate buffer. For each compound studied, an incubation mixture (prepared in triplicate) consisting of 1 mL of cofactor solution, 3 mL of pH = 7.4 (0.05 M) phosphate buffer, 1 mL of the monkey S-9 preparation, and 1 mL of substrate solution at either 6 or 60 μg/mL was incubated at 37 °C for 2 h on a shaking water bath. The final drug concentration in the incubation media was 1 or 10 μg/mL. A 0.5-mL aliquot of the incubation mixture was withdrawn after 0 (preincubation), 15, 30, 60, 90, and 120 min. Each aliquot was diluted with 1.5 mL of MeOH to precipitate proteins and then centrifuged at 2500*g* for 10 min. To determine the concentration of unchanged drug, the supernatant (50 μL) was subjected to HPLC chromatography.

Samples were injected onto a 250-mm × 4.6-mm-i.d. Zorbax RX-C18 HPLC column. The solvent system used consisted of mixtures of MeOH/CH_3CN/0.01 M *i*-Pr_2NH·HCl (1:1:1) (solvent A) and 0.01 M *i*-Pr_2NH·HCl (solvent B), typically 75–80% of A in B. The flow rate was adjusted to 1.2 mL/min. The analytes were detected using a Perkin-Elmer 650-10S fluorescence spectrophotometer with emission set at 378 nM and excitation set at 226 nM. An estimate of the percent drug remaining at 2 h was determined by dividing the mean peak height at t = 2 h by the mean initial peak height, t = 0 h. A linear regression of the peak height at each time point was used to estimate the relative metabolic rate of each compound. The stability was expressed as a half-life, which was calculated by dividing ln 2 by the slope of the line obtained from the least-square linear regression analysis, and as a percent of the drug metabolized, calculated as 100% minus the percent of drug remaining after 2 h.

***In Vivo* Metabolism of 19e and 23e.** For **19e** or **23e**, three groups of nine rats were each given either a single iv (1 mg/kg), ip (5 mg/kg), or po (5 mg/kg) dose of drug. Following administration of the drug, serial blood samples were collected from three rats at time points out to 4 h postdose. The plasma was separated and stored at −10 °C until analyzed by a validated fluorescence HPLC assay for either **19e** or **23e**. The lower limit of quantitation for each compound was 1 ng/mL.

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