73%), mp 279-280 °C. Anal. ($C_{12}H_7ClO_4$) C, H, Cl.

8-Chloro-2,3-dihydro-4*H*-1,5-naphtho[2,3-*b*]dioxepin-6,11-dione (6c). By the method described above for the preparation of **6b**, Diels-Alder condensation of **9c** (14.0 g, 77.7 mmol) with chloroprene (10.3 g, 116.6 mmol) in acetic acid, followed by aqueous dichromate oxidation, afforded **6c** (13.82 g, 52.2 mmol, 67%), mp 209-210 °C. Anal. ($C_{13}H_9ClO_4$) C, H, Cl.

6-Chloro-2,3-(alkylidenedioxy)-1,4-bis(acyloxy)-naphthalenes (5a-p). Reduction and acylation of **6a-c** by the methods described previously for the synthesis of 1 and analogues[12] gave **5a-p** in 75-90% yields. Physical data are reported in Table I.

Acknowledgment. We acknowledge Richard A. Simpson, Institute of Bio-Organic Chemistry, for preliminary investigations into the synthesis of compounds related to **6**, and we thank Patrick J. Maloney and Karen C. Kappas, Institute of Biological Sciences, for carrying out the arachidonic acid induced mouse ear edema bioassay.

Registry No. 1, 91431-42-4; **5a**, 115943-32-3; **5b**, 115943-33-4; **5c**, 115943-34-5; **5d**, 115943-35-6; **5e**, 115943-36-7; **5f**, 115943-37-8; **5g**, 115943-38-9; **5h**, 115943-39-0; **5i**, 115943-40-3; **5j**, 115943-41-4; **5k**, 115943-42-5; **5l**, 115943-43-6; **5m**, 115943-44-7; **5n**, 115943-45-8; **5o**, 115943-46-9; **5p**, 115943-47-0; **6a**, 115943-48-1; **6b**, 115943-49-2; **6c**, 115943-50-5; **9a**, 86319-72-4; **9b**, 42965-39-9; **9c**, 115943-51-6; 14, 115943-52-7; **15a**, 115943-53-8; **15b**, 82299-37-4; **16**, 115943-54-9; **17**, 86319-80-4; 18, 115943-55-0; chloroprene, 126-99-8.

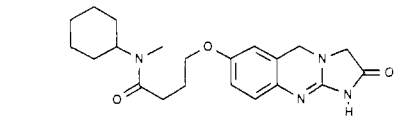
Inhibitors of Cyclic AMP Phosphodiesterase. 3. Synthesis and Biological Evaluation of Pyrido and Imidazolyl Analogues of 1,2,3,5-Tetrahydro-2-oxoimidazo[2,1-*b*]quinazoline[1]

Michael C. Venuti,*[,†,§] Robert A. Stephenson,[†] Robert Alvarez,[‡] John J. Bruno,[‡] and Arthur M. Strosberg[‡]

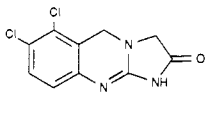
Institutes of Bio-Organic Chemistry and Experimental Pharmacology, Syntex Research, 3401 Hillview Avenue, Palo Alto, California 94304. *Received April 11, 1988*

Hybridization of structural elements of 1,2,3,5-tetrahydro-2-oxoimidazo[2,1-*b*]quinazoline ring system common to the cyclic AMP (cAMP) phosphodiesterase (PDE) inhibitors lixazinone (RS-82856, 1) and anagrelide (3) with complementary features of other PDE inhibitor cardiotonic agents prompted the design and synthesis of the title compounds **7a-d**, 11, 12, and **13a,b**. The necessary features of these compounds were determined within the framework of the proposed active-site models for the high affinity form of cAMP PDE inhibited by cGMP (type IV). Evaluation of these targets, both in vitro as inhibitors of platelet or cardiac type IV PDE or in vivo as inotropic agents in the pentobarbital-anesthetized dog model of congestive heart failure, showed that these structure possessed negligibly enhanced activities over the parent heterocyclic system, and remained significantly inferior to 1 in all respects. This difference is ascribed to the absence of the *N*-cyclohexyl-*N*-methylbutyramidyl-4-oxy side chain of 1. The proposal that the acidic lactam-type functionality, common to the type IV PDE inhibitor inotropic agents such as **4-6** and **8-10**, mimics the polarizable cyclic phosphate moiety of cAMP suggested that the side chain of 1 may function as an effective surrogate for selected characteristics of the adenine portion of cAMP. However, the results of this study show that incorporation of adenine-like hydrogen-bonding functionalities common to other type IV PDE inhibitors into the 1,2,3,5-tetrahydro-2-oxoimidazo[2,1-*b*]quinazoline system did not enhance activity to the levels observed for 1 and analogues. These observations, coupled with the kinetic pattern of inhibition of type IV PDE observed for 1 and analogues, suggest that access to a secondary, lipophilic-tolerant binding site, possibly coincident with the adenine binding domain, and adjacent to the catalytic ribose-phosphate binding site of platelet and cardiac type IV PDE, is responsible for the increased potency of these compounds.

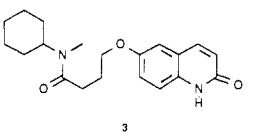
The search for non-glycoside cardiotonic drugs for treating congestive heart failure has, of late, increasingly concentrated on the development of agents that raise myocardial levels of cyclic AMP (cAMP), either by receptor-mediated stimulation of adenylate cyclase or by direct inhibition of cAMP phosphodiesterase (PDE).[2,3] Within this latter class, a number of new agents displaying potent and specific inhibition of the cyclic GMP (cGMP) inhibited form (type IV) of cAMP PDE, the enzyme primarily responsible for cAMP turnover in myocardial tissue, have been examined as potential cardiotonic agents.[4-6] Our attention in this area has focused on lixazinone (RS-82856, 1), a compound combining structural features of two potent inhibitors of type IV PDE, anagrelide (**2**) and cilostamide (**3**). We have previously reported the PDE inhibitory profile of 1 in comparison with its progenitors, and ascribed the observed enhancement of activity to the positionally specific attachment of the lipophilic *N*-cyclohexyl-*N*-methyl-4-oxybutyramide side chain of **3** onto



1



2



3

the 1,2,3,5-tetrahydro-2-oxoimidazo[2,1-*b*]quinazoline heterocycle of **2**.[7-9] The combination of potency and tissue

[†] Institute of Bio-Organic Chemistry.

[‡] Institute of Experimental Pharmacology.

[§] Present address: Medicinal and Biomolecular Chemistry Department, Genentech, Inc., 460 Point San Bruno Blvd., South San Francisco, CA 94080.

(1) Contribution No. 284 from the Institute of Bio-Organic Chemistry. For parts 1 and 2, see ref 8 and 9. Address inquiries to Dr. R. Alvarez.

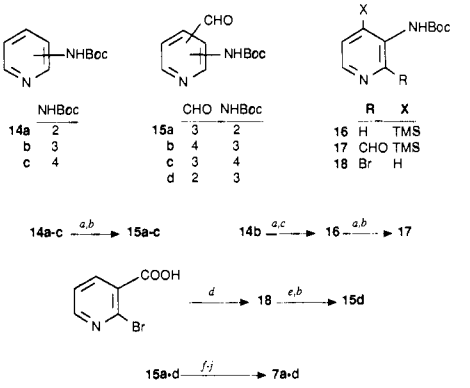
(2) Bristol, J. A.; Chorvat, R. J. *Cardiovascular Drugs*; Bristol, J. A., Ed.; Wiley: New York, 1986; Chapter 6, p 255.
(3) Erhardt, P. W. *J. Med. Chem.* **1987**, *30*, 231.
(4) Weishaar, R. E.; Cain, M. H.; Bristol, J. A. *J. Med. Chem.* **1985**, *28*, 537.
(5) Weishaar, R. E.; Burrows, S. D.; Kobylarz, D. C.; Quade, M. M.; Evans, D. B. *Biochem. Pharmacol.* **1986**, *35*, 787.
(6) Ahn, H. S.; Eardley, D.; Watkins, R.; Prioli, N. *Biochem. Pharmacol.* **1986**, *35*, 1113.

0022-2623/88/1831-2136$01.50/0

specificity observed for 1 as a type IV PDE inhibitor and its activity as a positive inotropic agent with afterload reduction and peripheral vasodilator properties has led us to advance this compound into human clinical trials.

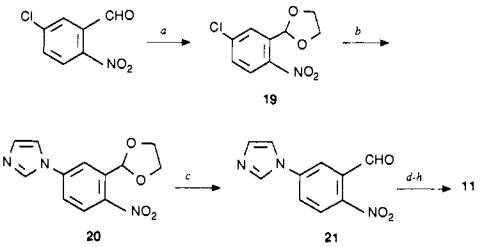
In this paper, we describe the synthesis and biological evaluation of a series of compounds designed to combine the heterocyclic portion of 1 with salient structural features of other cardiotonic agents currently under clinical development, within the framework of the developing model of the PDE binding site[10-12] constructed around the numerous structure–activity relationships for inhibition of type IV PDE.[9,13-16]. Such compounds might be expected to yield an indication of the relative importance of the contribution of the butyramide side chain of 1 as a lipophilic and/or steric pharmacophore in relation to the heterocycle itself. To this end, three types of compounds were prepared: (a) combination of the pyridyl residue common to amrinone (**4**),[17] milrinone (**5**),[18] and piroximone (**6**)[14] with the acidic acyl guanidinium moiety of the heterocycle, to produce the isomeric 1,2,3,5-tetrahydro-2-oxoimidazo[1,2-*a*]pyrido[*d*]pyrimidines **7a–d**; (b) direct attachment of the *N*-imidazolyl residue, common to imazodan (**8**), its 5-methyl analogue, CI-930 (**9**),[15] and CK-2130 (**10**),[16] to the 7-position of the heterocycle, to produce

Scheme I



Reagents: a, *t*-buLi/THF, -78°C→-20°C; b, DMF or NFP; c, TMSCl; d, DPPA/Et_3N/*t*-buOH; e, *n*-buLi/THF, -78°C; f, GlyOEt/NaOAc/EtOH; g, $NaBH_3CN$; h, TFA/CH_2Cl_2; i, BrCN; j, Et_3N.

Scheme II



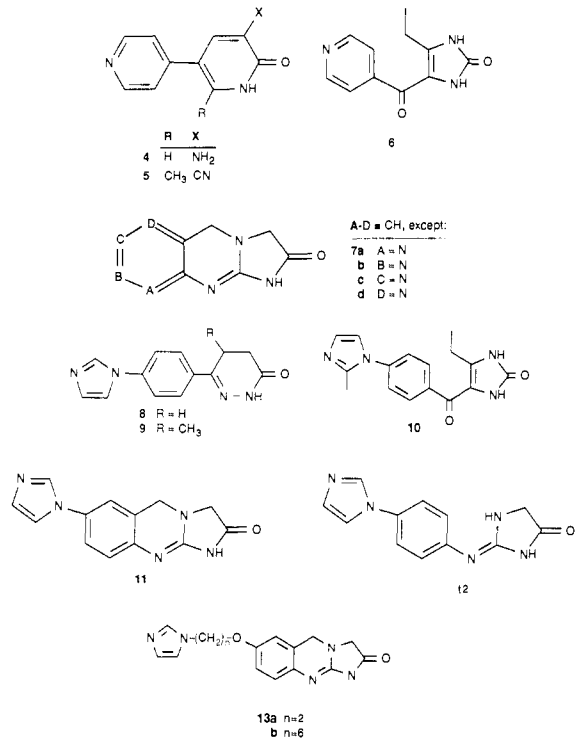
Reagents: a, 2-methoxy-1,3-dioxolane/*p*-TsOH/ethylene glycol; b, imidazole/K_2CO_3/DMF, 100°C; c, aq. $HClO_4$; d, GlyOMe/NaOAc/MeOH; e, $NaBH_3CN$; f, H_2/Pd-C/EtOH; g, BrCN; h, Et_3N.

7-(*N*-imidazolyl)-1,2,3,5-tetrahydro-2-oxoimidazo[2,1-*b*]-quinazoline (**11**) and its ring-opened analogue (**12**); and (c) alkyloxy attachment of imidazole at position 7, to produce the 7-[ω-(*N*-imidazolyl)alkoxy]-1,2,3,5-tetrahydro-2-oxo-imidazo[2,1-*b*]quinazolines (**13a,b**). The first series is unreported in the literature; the second compound is related to a series of 7-heteroaryl-substituted analogues recently disclosed;[19] the third pair bears distant resemblance to a number of imidazole-containing inhibitors of thromboxane synthetase.

Chemistry

The isomeric imidazo[1,2-*a*]pyrido[*d*]pyrimidine derivatives **7a–d** were synthesized by variation of the ring construction sequence previously described for the preparation of **1** and analogues (Scheme I).[8,9] The required isomeric *N-tert*-butyloxycarbonyl (*N*-BOC) aminopyridines (**14a–c**) were prepared either by treatment of the appropriate aminopyridine with di-*tert*-butyl dicarbonate in *tert*-butyl alcohol (**14a**) or in THF (**14c**) or by lead(IV) acetate oxidative rearrangement of the corresponding carboxamide in *tert*-butyl alcohol (**14b**).[20] On the basis of precedents set for the ortho lithiation of BOC-protected anilines,[21] pivaloyl-protected aminopyridines,[22] and (BOC-amino)pyridines themselves,[23,24] lithiation of **14a–c**, followed by formylation with either DMF or *N*-formylpiperidine (NFP),[25] afforded three of the four desired (*N*-

(7) Alvarez, R.; Banerjee, G. L.; Bruno, J. J.; Jones, G. H.; Liittschwager, K.; Strosberg, A. M.; Venuti, M. C. *Mol. Pharmacol.* **1986**, *29*, 554.
(8) Jones, G. H.; Venuti, M. C.; Alvarez, R.; Bruno, J. J.; Berks, A. H.; Prince, A. *J. Med. Chem.* **1987**, *30*, 295.
(9) Venuti, M. C.; Jones, G. H.; Alvarez, R.; Bruno, J. J. *J. Med. Chem.* **1987**, *30*, 303.
(10) Rakhit, S.; Marciniak, G.; Leclerc, G.; Schwartz, J. *Eur. J. Med. Chem.-Chim. Ther.* **1986**, *21*, 511.
(11) Moos, W. H.; Humblet, C. C.; Sircar, I.; Rithner, C.; Weishaar, R. E.; Bristol, J. A.; McPhail, A. T. *J. Med. Chem.* **1987**, *30*, 1963.
(12) Erhardt, P. W.; Hagedorn, A. A., III; Sabio, M. *Mol. Pharmacol.* **1988**, *33*, 1.
(13) Among the many studies not specifically cited below are: Sircar, I.; Bobowski, G.; Bristol, J. A.; Weishaar, R. E.; Evans, D. B. *J. Med. Chem.* **1986**, *29*, 261. Sircar, I.; Duell, B. L.; Cain, M. C.; Bristol, J. A.; Burke, S. E. *J. Med. Chem.* **1986**, *29*, 2142. Sircar, I.; Duell, B. L.; Bristol, J. A.; Weishaar, R. E.; Evans, D. B. *J. Med. Chem.* **1987**, *30*, 1023. Sircar, I.; Weishaar, R. E.; Kobylarz, D.; Moos, W. H.; Bristol, J. A. *J. Med. Chem.* **1987**, *30*, 1955. Leclerc, G.; Marciniak, G.; Decker, N.; Schwartz, J. *J. Med. Chem.* **1986**, *29*, 2427. Leclerc, G.; Marciniak, G.; Decker, N.; Schwartz, J. *J. Med. Chem.* **1986**, *29*, 2433. Robertson, D. W.; Beedle, E. E.; Krushinski, J. H.; Pollock, G. D.; Wilson, H.; Wyss, V. L.; Hayes, J. S. *J. Med. Chem.* **1985**, *28*, 717. Robertson, D. W.; Krushinski, J. H.; Beedle, E. E.; Wyss, V.; Pollock, G. D.; Wilson, H.; Kauffman, R. F.; Hayes, J. S. *J. Med. Chem.* **1986**, *29*, 1832. Robertson, D. W.; Krushinski, J. H.; Beedle, E. E.; Wyss, V.; Pollock, G. D.; Hayes, J. S. *Eur. J. Med. Chem.-Chim. Ther.* **1986**, *21*, 223. Robertson, D. W.; Krushinski, J. H.; Pollock, G. D.; Wilson, H.; Kauffman, R. F.; Hayes, J. S. *J. Med. Chem.* **1987**, *30*, 824. Okushima, H.; Narimatsu, A.; Kobayashi, M.; Furuya, R.; Tsuda, K.; Kitada, Y. *J. Med. Chem.* **1987**, *30*, 1157.
(14) Schnettler, R. A.; Dage, R. C.; Palopoli, F. P. *J. Med. Chem.* **1986**, *29*, 860.
(15) Bristol, J. A.; Sircar, I.; Moos, W. H.; Evans, D. B.; Weishaar, R. E. *J. Med. Chem.* **1984**, *27*, 1099. Sircar, I.; Duell, B. L.; Bobowski, G.; Bristol, J. A.; Evans, D. B. *J. Med. Chem.* **1985**, *28*, 1405.
(16) Hagedorn, A. A., III; Erhardt, P. W.; Lumma, W. C., Jr.; Wohl, R. A.; Cantor, E.; Chou, Y.-L.; Ingebretsen, W. R.; Lampe, J. W.; Peng, D.; Pease, C. A.; Wiggins, J. *J. Med. Chem.* **1987**, *30*, 1342.
(17) Ward, A.; Brogden, R. N.; Heel, R. C.; Speight, T. M.; Avery, G. S. *Drugs* **1983**, *26*, 468.
(18) *Milrinone: Investigation of New Inotropic Therapy for Congestive Heart Failure*; Braunwald, E., Sonnenblick, E. J., Chakrin, L. W., Schwartz, R. P., Eds.; Raven: New York, 1984.
(19) Campbell, S. F.; Roberts, D. A. Eur. Patent Appl. EP 205 280, 17 Dec 1986; *Chem. Abstr.* **1987**, *107*, 23355*m*.
(20) Baumgarten, H. E.; Smith, H. L.; Staklis, A. *J. Org. Chem.* **1975**, *40*, 3554.
(21) Muchowski, J. M.; Venuti, M. C. *J. Org. Chem.* **1980**, *45*, 4798.
(22) Turner, J. A. *J. Org. Chem.* **1983**, *48*, 3401.
(23) Fishwick, C. W. G.; Storr, R. C.; Manley, P. W. *J. Chem. Soc., Chem. Commun.* **1984**, 1304.
(24) Estel, L.; Marsais, F.; Quéguiner, G. *J. Org. Chem.* **1988**, *53*, 2740.

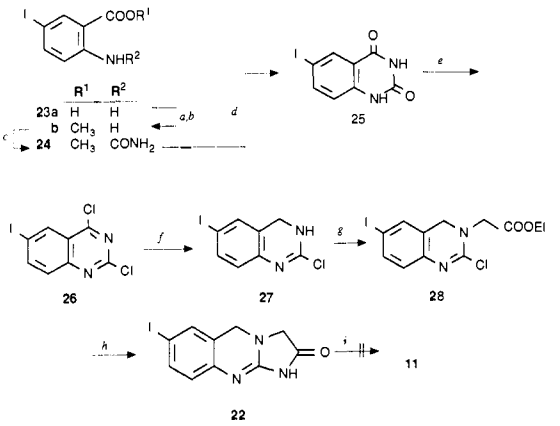


BOC-amino)pyridinecarboxaldehydes (**15a–c**). Attempts to divert ortho-lithiation of **14b** to position 2 by blockade of the favored 4-position with a trimethylsilyl group to afford **16**, followed by a second lithiation, did not give preparatively useful amounts of **17**. However, metal–halogen exchange using 2-bromo-3-(BOC-amino)pyridine (**18**), itself prepared from 2-bromonicotinic acid[26] and diphenyl phosphorazidate (DPPA) in *tert*-butyl alcohol,[27] followed by formylation, gave the remaining aldehyde isomer **15d**. Reductive amination of aldehydes **15a–d** with glycine ethyl ester and sodium cyanoborohydride, followed sequentially by removal of the BOC-protection with TFA and base-mediated cyclization with BrCN, afforded the corresponding isomeric heterocycles **7a–d**.

The preparation of 7-(*N*-imidazolyl)-substituted heterocycle (**11**) proceeded along a similar route (Scheme II). Protection of 5-chloro-2-nitrobenzaldehyde as its ethylene acetal (**19**), followed by nucleophilic displacement of chlorine by imidazole to (**20**) and removal of the acetal, afforded the required benzaldehyde (**21**). Sequential reductive amination, reduction of the nitro group, and cyclization, according to the procedures previously described for the preparation of **1**,[8,9] gave the desired product (**11**). Attempted direct displacement reactions with imidazole on the 7-iodo heterocycle **22**, itself prepared from 5-iodoanthranilic acid (**23a**) in seven steps via **23b–28** (Scheme III),[28,29] failed under a variety of conditions, likely due to the insolubility of **22** in even hot DMF. However, it should be noted that **22** has since been successfully used in similar coupling reactions by use of heteroarylzinc reagents and a palladium catalyst.[19] The corresponding ring-opened 5-nor analogue of 11 (**12**) was prepared by the straightforward condensation of **29** with **30** (Scheme IV).

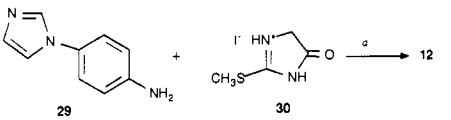
Analogues with the imidazole appended to the terminus of an alkoxy chain attached to the heterocycle at position 7 were prepared by two complementary routes (Scheme

Scheme III



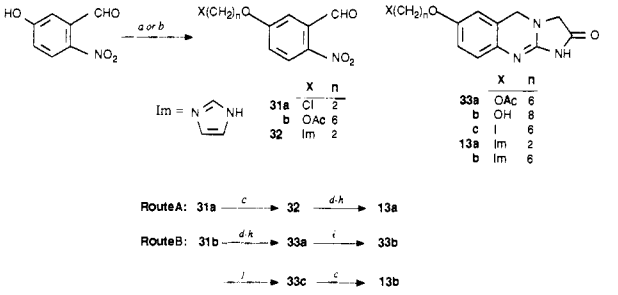
Reagents: a, $COCl_2$/dioxane; b, CH_3OH/DMAP/DMF; c, KNCO/HOAc; d, NaOH/aq. MeOH; e, $POCl_3$; f, $NaBH_4$/$CHCl_3$/EtOH; g, $BrCH_2COOEt/K_2CO_3$/MEK; h, NH_3/ethylene glycol; i, imidazole/K_2CO_3/DMF.

Scheme IV



Reagents: a, KOH/EtOH.

Scheme V



Reagents: a, $Cl(CH_2)_2OTs/K_2CO_3$/DMF; b, $AcO(CH_2)_6Cl/K_2CO_3$/DMF; c, molten imidazole; d, GlyOEt/NaOAc/EtOH; e, $NaBH_3CN$; f, H_2/Pd-C/EtOH; g, BrCN; h, Et_3N; i, NaOH/MeOH; j, $CH_3(PhO)_3PI$/DMF.

Table I. In Vitro Biological Evaluation

compd	IC_{50}, μM: human platelet cAMP PDE	IC_{50}, μM: human platelet aggregation
lixazinone (1)	0.01	0.11
milrinone (5)	0.86	
piroximone (6)	>100[b]	
7a	330	200
7b	26	26
7c	18	46
7d	30	25
CI-930 (9)	0.15	
CK-2130 (10)	37[c]	
11	0.6	6
12	250	inactive
13a	2.0	40
13b	0.7	23

[a] Refer to the Experimental Section for assay methods and statistical interpretation of data. [b] 40% inhibition at 100 μM. [c] Inhibition of dog heart PDE; from ref 16.

(25) Olah, G. A.; Arvanaghi, M. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 878.
(26) Bradlow, H. L.; Vanderwerf, C. A. *J. Org. Chem.* **1949**, *14*, 509.
(27) Ninomiya, K.; Shioiri, T.; Yamada, S. *Tetrahedron* **1974**, *30*, 2151.
(28) Yamaguchi, H.; Ishikawa, F. *J. Heterocycl. Chem.* **1981**, *18*, 67.
(29) This rather lengthy route was pursued in place of one originating from the corresponding nitroaldehyde, in order to avoid hydrogenolytic loss of iodine during reduction of the nitro functionality. Use of the corresponding fluoro derivative, a potential solution for both synthetic problems encountered with **22**, brought to our attention by a referee, was, unfortunately, not pursued as part of the current study.

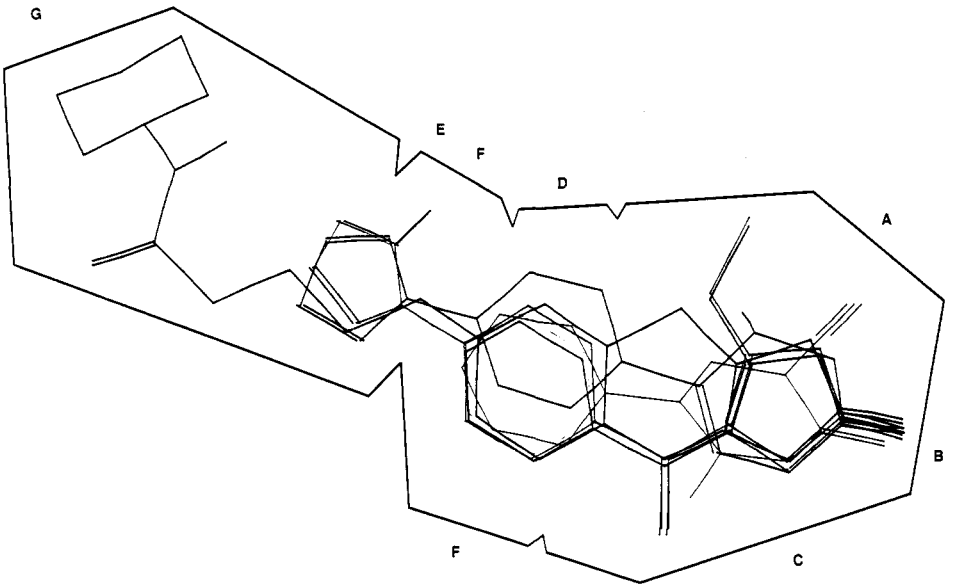


Figure 1. Overlap mapping of structures of lixazinone (1), milrinone (5), piroximone (6), CI-930 (9), and CK-2130 (10), generated by Alchemy molecular modelling program. Structures were subjected to minimization procedure from planarity to the energetically closest local minimum. Hydrogens have been omitted, and the side chain of 1 was left in a staggered, extended form for clarity. Regions of the PDE type IV binding domain shown: (A) planar, sterically limited region; (B) polarizable functionality; (C) acidic lactam functionality; (D) region of aromatic π-electron density; (E) hydrogen-bonding functionality; (F) regiospecific connection requirement; (G) lipophilic, sterically tolerant secondary binding site.

V). 5-Hydroxy-2-nitrobenzaldehyde was alkylated with either 2-chloroethyl *p*-toluenesulfonate or 6-chlorohexanol acetate, with potassium carbonate as base, to afford **31a** or **31b**, respectively. Treatment of **31a** with molten imidazole effected displacement of the chloride to give **32**, which was converted by the standard ring construction sequence used above, to afford the 2-(*N*-imidazolyl)ethoxy analogues **13a** (route A). In an alternative sequence to this generalized structure, nitro aldehyde **31b** was converted to **33a** by the ring construction sequence. Hydrolysis of the acetate, followed by conversion of the alcohol (**33b**) to the corresponding iodide (**33c**), and displacement with imidazole gave the 6-(*N*-imidazolyl)hexyloxy analogue **13b** (route B). The overall yield in this latter route was poorer than by the former, suggesting that early introduction of the imidazole is preferred.

Biological Evaluation

Biological evaluation of both the lead and target compounds was carried out by using the in vitro biological assays for inhibition of platelet cyclic AMP phosphodiesterase and of ADP-induced human platelet aggregation described previously.[8] This assay has proved to be a useful predictor for cAMP inhibitory activity in cardiac tissue, since parallel evaluation of a large series of compounds including 1 and close analogues in both tissue types showed a high degree (0.912 coefficient) of correlation. The results, reported as IC_{50} values, are summarized in Table I. In vivo evaluation of selected compounds as inotropic agents was carried out in anesthetized dogs, by methods identical with those reported by us for the evaluation of 1.[7] These results, with comparative data for standards, are reported in Table II.

Structure–Activity Correlations

The functional divergence generated by replacement of the oxy-linked side chain of 1 by hydrogen-bonding pyridyl or imidazolyl residues found in other PDE inhibitor inotropic agents, in a manner consistent with the proposed models of the PDE type IV active site,[10-12] can be qualitatively appreciated in a simplified overlap procedure utilizing near-planar, energy-minimized structures (Figure 1). This assumption was previously validated by both proposed models of the PDE binding site in which selective PDE type IV (F III) inhibitors mimic the phosphate portion of the anti conformation of cAMP.[11,12] This overlap procedure, using the acidic lactam functionality common to these agents as anchor, demonstrates three important facts: (1) the 1,2,3,5-tetrahydro-2-oxoimidazo-[2,1-*b*]quinazoline ring system effectively mimics the near-planarity of the torsional conformers of the other agents in this class found to be necessary to fit the proposed binding site as predicted;[12] (2), the *N*-cyclohexyl-*N*-methyl-4-oxybutyramide side chain of 1 is unique among these agents in terms of providing a secondary mode of binding to a proposed area of bulk tolerance;[9,11,12] and (3), the oxy side chain–heterocycle linkage, found to be crucial to activity in our previous studies,[9] may effectively substitute for pyridyl or imidazolyl nitrogen as an hydrogen-bonding acceptor at the active site.

Among the compound (**7a–d**) designed to replace the side chain of 1 by pyrido nitrogen, none displayed an advantage over 1. The most potent of these (**7c**), albeit by barely a factor of 2 (Table I), possesses the positioning of

Table II. Inotropic Activity in Instrumented, Anesthetized Dogs[a]

compd	N^b	% max CF response (nmol/kg)[c]	ED_{50},[d] nmol/kg		
			CF	HR	BP
lixazinone (1)	4	71 (75)	20	30	50
milrinone (5)	4	65 (140)	90	190	590
piroximone (6)	1	11 (>4000)	*e*		
7c	1	27 (>5000)	780	>1000	>1000
CI-930 (9)	3	72 (125)	100	100	100
11	2	63 (185)	180	220	640
12	1	*f*			

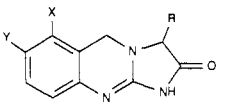
[a] Refer to the Experimental Section for assay methods and statistical interpretation of data. [b] N = number of experiments. [c] Percent of the maximum increase in cardiac force achieved in the same animal with isoproterenol as agonist. [d] Dose at which 50% maximal effect for cardiac force (CF) increase, heart rate (HR) increase, and blood pressure (BP) decrease due to the test compound were observed. [e] Not determined. [f] Inactive at all doses up to 1000 μg/kg.

the pyrido nitrogen atom most favored by the overlap mapping used (Figure 1) to bridge the structural gap between 1 and the other members of this class. This result also correlates with a similar finding made by Robertson et al., within a series of pyridyl analogues of imazodan, in which a marked preference for the 3- versus 4-pyridyl substitution was observed, as measured by inotropic activity.[30] In comparison with the known pyridyl-containing standards milrinone (**5**) and piroximone (**6**), potencies midway between the two were found for three (**7b–d**) of the four members of the series. Inotropic evaluation of the most potent of these (**7c**), however, showed the compound to be relatively weak and nonselective for cardiac force over heart rate and blood pressure effects (Table II).

On the basis of the same overlap model (Figure 1) used above, the *N*-imidazolyl residue common to **9** and **10** was attached to the 1,2,3,5-tetrahydro-2-oxoimidazo[2,1-*b*]-quinazoline heterocycle at position 7. This combination of structural features afforded **11**, found to be modestly potent as an inhibitor of PDE type IV and as an inotropic agent. In sharp contrast, however, the analogue **12**, formally the product of cleavage of the center pyrimidine ring, was much less active as an in vitro PDE inhibitor and inactive as an inotropic agent. Appendage of a terminal *N*-imidazolyl residue onto two different chain lengths of 7-alkoxy heterocycle substitution (**13a,b**) gave no improvement over the direct *N*-imidazolyl/heterocycle attachment used in **11**.

The necessity of electron-donating functionality capable of participating in hydrogen-bond formation regiospecifically at position 7 of the 1,2,3,5-tetrahydro-2-oxoimidazo[2,1-*b*]quinazoline heterocycle was proposed as one requirement of our original model of the PDE type IV binding domain, based on the marked potency advantage of **1** over its 6-, 8-, or 9-oxybutyramide isomers, both in vitro and in vivo, and the diminished activity of analogues lacking the ether oxygen.[9,31] This feature of the overall structure–activity relationship governing the PDE type IV binding domain was examined with the set of hybrids described in this study, which varied the common positioning of electron-donating functionality, provided either by alkyl–aryl ether oxygen or by pyridyl or imidazolyl nitrogen around C-7. The overlap model used to examine these functional characteristics evolved from a qualitatively simple active analogue picture of the PDE type IV binding domain, made increasingly simpler by the sheer number of compounds that have been demonstrated to be potent inotropic and peripheral vasodilatory agents operating by this mechanism. The relative positioning of acidic lactam, intervening aromatic π-electron density, and hydrogen-bonding functionalities common to most of the type IV PDE inhibitors effectively mimics the anti conformation of cAMP bound to the active site. This conformationally available spatial arrangement of relatively strong bonding interactions must stabilize the accommodation of such a divergent group of compounds within the *anti*-cAMP binding site of type IV PDE. The presence of three such stabilizing interactions must be even more important for compounds such as **5**, **6**, **9**, or **10**, where rotational mobility must be restricted to attain near-planarity for optimal binding. This spatial arrangement also suggested that the *N*-cyclohexyl-*N*-methylbutyramidyl-4-oxy side chain of **1** might be functioning as an adenine substitute in binding at the active site.

Table III. Comparison of Substituted 1,2,3,5-Tetrahydro-2-oxoimidazo[2,1-*b*]quinazolines as Inhibitors of Human Platelet PDE Type IV



compd[a]	R	X	Y	human platelet cAMP PDE,[b] IC_{50}, μM
34	H	H	H	8.8
Ro 13-6438 (**35**)	(*R*)-CH_3	Cl	H	0.24
Ro 15-2041 (**36**)	(±)-CH_3	CH_3	Br	0.07[c]
37	H	H	Cl	1.5
22	H	H	I	0.52
anagrelide (**2**)	H	Cl	Cl	0.08
7c	H	H	*d*	18
11	H	H	NCH=NCH=CH	0.6
DN-9693 (**38**)	H	H	$N(CH_2)_4CH_2$	0.15[e]
39	H	H	OH	3.3
40	H	H	OCH_3	1.5
41	H	H	OCH_2Ph	0.56
42	H	H	O-*n*-C_6H_{13}	0.29
lixazinone (**1**)	H	H	$O(CH_2)_4CON(CH_3)C_6H_{11}$	0.01

[a] Compound preparation and references are included in the Experimental Section. [b] Data determined experimentally according to assay methods and statistical interpretation used in Table I, unless otherwise noted. [c] Data from ref 33. [d] Not applicable. [e] Data from ref 34.

The 1,2,3,5-tetrahydro-2-oxoimidazo[2,1-*b*]quinazoline heterocyclic system itself incorporates two of the three features favorable to activity at the PDE type IV binding domain. The amphoteric acylguanidine moiety functions as well as the cyclic phosphate mimic (pK_{a1} = 3.5, pK_{a2} = 11.3),[32] while molecular modelling calculations demonstrate the near-planarity of the tricyclic system (N-4 approximately 17–22° out of the plane), providing the aromatic π-electron density as fused benzo rather than phenyl. These characteristics account for the in vitro activity observed for **34** and close analogues such as anagrelide (**2**) and Ro 13-6438 (**35**), which lack C-7 hydrogen-bonding functionality (Table III). Addition of such functionality by inclusion of pyridyl nitrogen, *N*-imidazolyl nitrogen or alkoxide oxygen maintains this general range of activity but does not bring it to the level of **1**.

Conclusions

The functional groups incorporated into the hybrid compounds of this study are proposed by the modelling studies to mimic some portion of the adenine residue of cAMP. The contribution to binding stability derived from hydrogen-bonding interactions seems to offer something less, or different from, that imparted by the lixazinone side chain. The attachment of the *N*-cyclohexyl-*N*-methylbutyramidyl-4-oxy side chain maximally augments the intrinsic activity observed within this heterocyclic series (Table III). In addition to containing an electron-donating

(30) Robertson, D. W.; Krushinski, J. H.; Pollock, G. D.; Hayes, J. S. *J. Med. Chem.* **1988**, *31*, 461
(31) Alvarez, R.; Venuti, M. C.; Strosberg, A. M.; Johnson, L., unpublished results.
(32) Gu, L.; Hunyh, O.; Becker, A.; Peters, S.; Nguyen, H.; Chu, N. *Drug Dev. Ind. Pharm.* **1987**, *13*, 437.
(33) Muggli, R.; Tschopp, T. B.; Mittelholzer, E.; Baumgartner, H. R. *J. Pharmacol. Exp. Ther.* **1985**, *235*, 212.
(34) Sakuma, K.; Ashida, S. *Thromb. Haemostas.* **1985**, *54*, 134 (abstr. P795).

functionality contributing potential hydrogen bonding capability, the side chain of 1 must have access to a secondary, lipophilic binding site capable of enhancing the stability of the enzyme–inhibitor complex. The previously reported kinetics of inhibition of PDE type IV by 1 indicate that 1 is not perceived by the binding domain to be solely a substrate mimic, but that 1 might actually bind at an additional, noncatalytic site that either presents 1 to or stabilizes the binding of 1 at the catalytic site. This does not, however, eliminate the possibility that the side chain occupies some portion of the adenine binding domain but functions in a fundamentally different manner from adenine itself while resident therein. The fact that the side chain positional isomers of 1, essentially isolipophilic with 1, demonstrated dramatically different IC_{50} values for both PDE inhibition[9] and inotropic activity[31] points to the existence of a distinct secondary, lipophilic-tolerant site, independent of the ribose phosphate catalytic binding site, regiospecifically oriented and sterically controlled as a secondary point of interaction for compounds of this class.

Experimental Section

Melting points were obtained on a Thomas-Hoover melting point apparatus and are uncorrected. ^1H NMR spectra were obtained on either an EM-390 (90 MHz) or a Bruker WM 300 (300 MHz) instrument. Infrared spectra were recorded as KBr pellets with a Perkin-Elmer 237 grating spectrometer. Mass spectra were determined on an Atlas CH-7 instrument. All compounds exhibited NMR, IR, and mass spectral data consistent with the proposed structures. Elemental analyses were performed by either Atlantic Microlabs, Atlanta, GA, or by the Analytical and Environmental Research Department, Syntex Research, on samples dried 24 h at ambient temperature and high vacuum. Results were within 0.4% of theoretical values, unless otherwise stated. Lead(IV) acetate (Fluka puriss.) was dried over concentrated sulfuric acid at high vacuum for 48 h prior to use. *tert*-Butyl alcohol (Fluka puriss.) was used as received. Tetrahydrofuran (THF) for metalation reactions was freshly distilled from sodium benzophenone ketyl immediately prior to use. *N,N*-Dimethylformamide (DMF) and *N*-formylpiperidine (NFP) were distilled from calcium hydride. All organic extracts were dried over sodium sulfate prior to evaporation.

Molecular modelling (energy minimization and overlap fit) was carried out by using Alchemy molecular modelling software (Tripos Associates–Evans and Sutherland, Inc., 6548 Clayton Road, St. Louis, MO 63117), using an IBM-AT personal computer equipped with an Intel 80287 math coprocessor and an HP7475A 6-color pen plotter.

2-[*N*-(*tert*-Butyloxycarbonyl)amino]pyridine (14a). 2-Aminopyridine (18.8 g, 200 mmol) was added to a solution of di-*tert*-butyl dicarbonate (48 g, 220 mmol) in dry *tert*-butyl alcohol (1.6 L). After the mixture was stirred overnight at room temperature, the solvent was removed by evaporation. The residue was filtered through silica gel with dichloromethane as eluant to afford **14a** (33.6 g, 173 mmol, 87%), mp 92–93 °C (lit.[27] mp 96–97 °C). With tetrahydrofuran as solvent in the preceding reaction, the major product isolated upon workup was *N,N'*-bis(2-pyridyl)urea, mp 175–176 °C (lit.[35] mp 172 °C).

3-[*N*-(*tert*-Butyloxycarbonyl)amino]pyridine (14b). A suspension of nicotinamide (122 g, 1 mol) in dry *tert*-butyl alcohol (2.5 L) was treated with dried lead(IV) acetate (444 g, 1 mol) under nitrogen. The resulting mixture was heated at reflux for 2 h and then cooled and filtered through Celite. The filtrate was evaporated, and the residue was dissolved in diethyl ether (500 mL). The solution was washed with saturated aqueous sodium bicarbonate (4 × 500 mL) and with brine (2 × 500 mL) and then dried, filtered, and evaporated. Recrystallization of the residue from diethyl ether–pentane afforded **14b** (101 g, 520 mmol, 52%), mp 116–117 °C (lit.[20] mp 117–118 °C). It should be noted that 3-aminopyridine was resistant to reaction with di-*tert*-butyl dicarbonate, even under forcing conditions used for the preparation of either **14a** or **14c**.

4-[*N*-(*tert*-Butyloxycarbonyl)amino]pyridine (14c). 4-Aminopyridine (28.2 g, 300 mmol) was added in portions to a solution of di-*tert*-butyl dicarbonate (72 g, 330 mmol) in dry THF (300 mL). After the mixture was stirred at room temperature for 1 h, the solvent was removed by evaporation, and the residue was crystallized from diethyl ether to yield **14c** (43.4 g, 223 mmol, 75%), mp 144–145 °C. Anal. ($C_{10}H_{14}N_2O_2$) C, H, N.[36]

4-[*N*-(*tert*-Butyloxycarbonyl)amino]-3-pyridinecarboxaldehyde (15c). A solution of **14c** (19.4 g, 100 mmol) in dry THF (350 mL) was cooled to −78 °C and was treated dropwise with *tert*-butyllithium (120 mL, 2 M in pentane, 240 mmol) at a rate such that the temperature did not exceed −65 °C. Upon completion of the addition, the reaction was stirred at −78 °C for an additional 15 min and then at −20 °C (dry ice–CCl_4 bath) for 1.5 h. Dry DMF (50 mL, excess) was added while the temperature was maintained below −15° C, and then the mixture was allowed to stir at room temperature overnight. The solution was cooled to 0 °C and was quenched by the addition of 1 M HCl to bring the pH to 2. Solid Na_2CO_3 was then added to adjust the pH to 7. The solution was extracted with ethyl acetate (3 × 250 mL), and the combined organic laers were washed with water (3 × 500 mL) and brine (2 × 500 mL). After drying, filtration, and evaporation, the residue was chromatographed over silica gel, with 10% ethyl acetate in dichloromethane as eluant, to afford **15c** (14.9 g, 67 mmol, 67%), mp 68–69 °C. Anal. ($C_{11}H_{14}N_2O_3$) C, H, N.

2-[*N*-(*tert*-Butyloxycarbonyl)amino]-3-pyridinecarboxaldehyde (15a). Metalation and formylation of **14a** according to the above method, but using 3 equiv of NFP[25] in place of excess DMF, afforded **15a** in 58% yield, mp 109–111 °C. Anal. ($C_{11}H_{14}N_2O_3$) C, H, N.

3-[*N*-(*tert*-Butyloxycarbonyl)amino]-4-pyridinecarboxaldehyde (15b). Metalation and formylation of **14b** according to the method used for **14a** afforded **15b** in 63% yield, mp 52–53 °C. Anal. ($C_{11}H_{14}N_2O_3$) C, H, N.

3-[*N*-(*tert*-Butyloxycarbonyl)amino]-4-(trimethylsilyl)-pyridine (16). Metalation of **14b** according to the method described above, followed by quenching the anion with 1.0 equiv of chlorotrimethylsilane and aqueous workup, afforded **16** in 72% yield, mp 96–97 °C. Anal. ($C_{13}H_{22}N_2O_2Si$) C, H, N. Attempts to metalate **16** under a variety of conditions gave only poor yields of impure **17** as an unstable oil.

2-Bromo-3-[*N*-(*tert*-Butyloxycarbonyl)amino]pyridine (18). Diphenyl phosphorazidate (Aldrich, 56 mL, 260 mmol) was added to a solution of 2-bromonicotinic acid[26] (53.5 g, 250 mmol) and triethylamine (35 mL, 275 mmol) in dry *tert*-butyl alcohol (500 mL). The resulting mixture was brought to reflux for 2 h and then was cooled and evaporated. The residue was dissolved in ethyl acetate (500 mL), and the organic extract was washed with water (3 × 250 mL), saturated aqueous sodium bicarbonate (3 × 250 mL), and brine (2 × 250 mL). The solution was dried, filtered, and evaporated, and the residue was recrystallized from diethyl ether to yield **18** (62 g, 227 mmol, 91%), mp 81–82 °C. Anal. ($C_{10}H_{13}N_2O_2Br$) C, H, N.

3-[*N*-(*tert*-Butyloxycarbonyl)amino]-2-pyridinecarboxaldehyde (15d). A solution of **18** (41 g, 150 mmol) in dry THF (200 mL) was cooled to −78 °C and was treated dropwise with *n*-butyllithium (188 mL of 1.6 M solution in hexane) such that the temperature never exceeded −65 °C, and the resulting mixture was stirred at −78 °C for an additional hour. After dropwise addition of NFP (18.3 mL, 165 mmol), the reaction mixture was allowed to warm to 0 °C, maintained there for 1 h, and then quenched by the addition of 1.5 M HCl (400 mL). The pH was adjusted to 7 by the addition of solid Na_2CO_3, and the resulting mixture was extracted with ethyl acetate (3 × 250 mL). The combined organic layers were washed with water (3 × 500 mL) and brine (2 × 500 mL). After drying, filtration, and evaporation, the residue was filtered through silica gel, with dichloromethane as eluant, to afford **15d** (30 g, 135 mmol, 90%), mp 77–78 °C. Anal. ($C_{11}H_{14}N_2O_3 \cdot 0.25H_2O$) C, H, N.

(35) Franz, R. A.; Appelgath, F.; Morriss, F. V.; Baiocchi, F.; Bolze, C. *J. Org. Chem.* **1961**, *26*, 3309.

(36) This compound is noted as an intermediate in ref 23, but no data are reported.

1,2,3,5-Tetrahydro-2-oxoimidazo[1,2-*a*]pyrido[3,2-*d*]pyrimidine (7d). Sodium acetate (8.2 g, 100 mmol) was added to a clear solution of glycine ethyl ester hydrochloride (16.75 g, 120 mmol) in warm ethanol (150 mL). After the mixture returned to ambient temperature, aldehyde **15d** (11.1 g, 50 mmol) was added, and the resulting mixture was stirred for 30 min. Sodium cyanoborohydride (1.89 g, 30 mmol) was then added, and the reaction was stirred overnight. Upon evaporation of the solvent, the residue was partioned between ethyl acetate and water (500 mL each). The organic extract was washed with water (4 × 200 mL), saturated aqueous sodium bicarbonate (2 × 200 mL), and brine (2 × 200 mL) and then was dried, filtered, and evaporated. The residue was chromatographed over silica gel (20% ethyl acetate in dichloromethane as eluant) to afford ethyl *N*-[[3-(BOC-amino)-2-pyridyl]methyl]glycinate (14.1 g, 45.5 mmol, 91%) as a syrup.

Trifluoroacetic acid (30 mL) was added dropwise to a solution of the above BOC-amino compound (13.9 g, 45 mmol) in dichloromethane (80 mL), and the resulting solution was stirred overnight at room temperature. The solution was evaporated to a syrup and then was reevaporated from toluene twice to remove final traces of trifluoroacetic acid. The syrupy ethyl (3-amino-2-pyridyl)-*N*-methylglycinate tris(trifluoroacetate) was crystallized under high vacuum into a waxy semisolid and used directly in the final step.

Triethylamine (12.6 mL, 90 mmol) was added to a solution of the above salt (16.5 g, 30 mmol) in ethanol (100 mL), and the mixture was then treated dropwise with a solution of BrCN (3.18 g, 30 mmol) in ethanol (50 mL). After the mixture was stirred overnight at room temperature, additional triethylamine (8.4 mL, 60 mmol) was added, and the solution was brought to reflux for 3 h. Upon cooling, concentration by evaporation, and dilution with water, the deposited precipitate was collected by filtration and drying to yield **7d** (2.4 g, 12.75 mmol, 42.5%), mp >300 °C. Anal. ($C_9H_8N_4O \cdot 0.5H_2O$) C, H, N.

The preparation of the title compound **7d** is exemplary of the procedure used for isomers **7a–c**.

1,2,3,5-Tetrahydro-2-oxoimidazo[1,2-*a*]pyrido[2,3-*d*]pyrimidine (7a): yield 21.8% on a 15-mmol scale, mp >300 °C. Anal. ($C_9H_8N_4O \cdot 0.33H_2O$) C, H, N.

1,2,3,5-Tetrahydro-2-oxoimidazo[1,2-*a*]pyrido[3,4-*d*]pyrimidine (7b): yield 9.4% on a 9-mmol scale, mp >300 °C. Anal. ($C_9H_8N_4O \cdot 0.1H_2O$) C, H, N.

1,2,3,5-Tetrahydro-2-oxoimidazo[1,2-*a*]pyrido[4,3-*d*]pyrimidine (7c): yield 66% on a 3.2-mmol scale, mp 290 °C dec. Anal. ($C_9H_8N_4O$) C, H, N.

5-Chloro-2-nitrobenzaldehyde Ethylene Acetal (19). A mixture of 5-chloro-2-nitrobenzaldehyde (Aldrich; 139 g, 750 mmol), 2-methoxy-1,3-dioxolane (Aldrich; 90 mL, 940 mmol), and *p*-toluenesulfonic acid monohydrate (6 g) in ethylene glycol (100 mL) was heated to 100 °C for 30 min. Upon cooling, the mixture was diluted with chloroform (200 mL) and was washed with water (3 × 100 mL), saturated aqueous sodium bicarbonate (2 × 100 mL), and brine (2 × 100 mL). The organic layer was dried, filtered, and evaporated to a thick oil (160 g), which was Kugelrohr distilled to afford **19** (139 g, 603 mmol, 81%), bp 125–130 °C (0.2 Torr). Anal. ($C_8H_8NO_4Cl$) C, H, N, Cl.

5-(*N*-Imidazolyl)-2-nitrobenzaldehyde Ethylene Acetal (20). A mixture of **19** (75 g, 325 mmol), imidazole (24 g, 358 mmol), and potassium carbonate (49 g, 358 mmol) in DMF (250 mL) was heated under nitrogen at 100 °C overnight. The mixture was cooled, identical amounts of imidazole and potassium carbonate were added, and the mixture was again heated for 8 h. The reaction was cooled and poured into water (500 mL), and the resulting mixture was extracted with ethyl acetate (3 × 500 mL). The combined organic extracts were washed with water (6 × 300 mL) and brine (2 × 500 mL) and then were dried, filtered, and evaporated. Trituration of the resulting slurry with diethyl ether and filtration yielded **20** (57.5 g, 220 mmol, 68%), mp 142–143 °C. Anal. ($C_{12}H_{11}N_3O_4$) C, H, N.

5-(*N*-Imidazolyl)-2-nitrobenzaldehyde (21). Acetal **20** (26.1 g, 100 mmol) was added to a solution prepared from concentrated perchloric acid (150 mL) and water (100 mL), resulting in a mildly exothermic reaction (40 °C). After stirring at ambient temperature overnight, the reaction mixture was diluted with water (250 mL), overlayered with ethyl acetate (250 mL), and carefully quenched with solid sodium carbonate to bring the pH to 9. The layers were separated, and the aqueous solution was extracted with additional ethyl acetate (4 × 200 mL). The organic extracts were combined and washed with saturated aqueous sodium bicarbonate (2 × 200 mL) and brine (3 × 200 mL) and then were dried, filtered, and evaporated to afford the title aldehyde **21** (22.0 g, 100 mmol, 100%), mp 124–125 °C. Anal. ($C_{10}H_7N_3O_3$) C, H, N.

7-(*N*-Imidazolyl)-1,2,3,5-tetrahydro-2-oxoimidazo[2,1-*b*]quinazoline (11). Aldehyde **21** (22.0 g, 100 mmol) was added to a solution prepared from glycine ethyl ester hydrochloride (30 g, 240 mmol) and anhydrous sodium acetate (8.2 g, 100 mmol) in methanol (800 mL). Within moments, a thick precipitate had formed. After the mixture was stirred for 15 min, sodium cyanoborohydride (3.8 g, 60 mmol) was added, resulting in dissolution of the precipitate (presumably the intermediate imine) within 5 min. After an additional hour, the solvent was evaporated, and the residue was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate (500 mL each). The resulting aqueous solution was extracted with ethyl acetate (4 × 200 mL), and the combined organic layers were washed with saturated aqueous sodium bicarbonate (3 × 300 mL) and brine (2 × 300 mL) and then were dried, filtered, and evaporated. Chromatography of the residue on silica gel (1–2.5% methanol in dichloromethane) afforded methyl *N*-[[4-(*N*-imidazolyl)-2-nitrophenyl]methyl]glycinate (19.4 g, 66.8 mmol, 67%), mp 87–88 °C. Anal. ($C_{13}H_{14}N_4O_4$) C, H, N.

The nitrobenzylamine (18.9 g, 65 mmol) was dissolved in ethanol (200 mL) and was reduced at 60 psi over 10% Pd–C (2.0 g) overnight. The catalyst was removed by filtration, and the filtrate was treated dropwise with a solution of BrCN (7.6 g, 71.5 mmol) in ethanol (50 mL). After the mixture was stirred overnight, triethylamine (11 mL, 78 mmol) was added, resulting in a fine precipitate after 24 h. The mixture was concentrated and diluted with water, and the solid was isolated by centrifugation. After three additional washes in this manner, the solid was triturated with ethanol–ether and then was collected by filtration. Resuspension in DMF, followed by stirring overnight and filtration, afforded **11** (8.0 g, 31.6 mmol, 48%), mp >300 °C. Anal. ($C_{13}H_{11}N_5O \cdot 0.5H_2O$) C, H, N.

Methyl 5-Iodoanthranilate (23b). Condensed phosgene (80 mL) was added to a solution of 5-iodoanthranilic acid (100 g, 380 mmol) in dry dioxane (500 mL), and the resulting mixture was stirred overnight at 60 °C overnight. Upon cooling and filtration, the corresponding 6-iodoisatoic anhydride (101.2 g, 350 mmol, 92%) was obtained.

A suspension of the above isatoic anhydride in dry DMF was treated with methanol (25 mL) and 4-(dimethylamino)pyridine (4.0 g), and the resulting mixture was stirred at 60 °C for 3 h.[37] After cooling and evaporation of solvent, the residue was dissolved in ethyl acetate (500 mL) and was washed with water (2 × 300 mL) and brine (2 × 300 mL). The organic layer was dried, filtered, and evaporated to give an oil which solidified at high vacuum to yield **23b** (94 g, 339 mmol, 97%), mp 83–84 °C (lit.[38] mp 83–85 °C).

***N*-[4-Iodo-2-(methoxycarbonyl)phenyl]urea (24).** A solution of **23b** (94 g, 339 mmol) in acetic acid (275 mL) was treated with a solution of KNCO (37.5 g, 441 mmol) in water (50 mL). After brief heating on the steam bath, the resulting precipitate was collected by filtration and dried to yield **24** (76 g, 238 mmol, 70%), mp 280–282 °C. Anal. ($C_6H_9IN_2O_3$) C, H, N, I.

6-Iodoquinazoline-2,4(1*H*,3*H*)-dione (25). A solution of NaOH (11.25 g, 281 mmol) in water (150 mL) was added to a mechanically stirred suspension of **24** (72 g) in methanol (750 mL). After 1 h at reflux, the mixture was cooled and diluted with water (500 mL), and the pH was adjusted to 3 with 6 M HCl. The precipitate was collected by filtration, air-dried and dried at high vacuum over P_2O_5 to give a white solid (60.5 g, 210 mmol), mp >300 °C. Anal. ($C_8H_5IN_2O_2$) C, H, N, I.

2,4-Dichloro-6-iodoquinazoline (26). A suspension of **25** (57.6 g, 200 mmol) in $POCl_3$ (300 mL) was treated with *N,N*-dimethylaniline (51 mL, 400 mmol), and the resulting mixture was

(37) Venuti, M. C. *Synthesis* **1982**, 266.
(38) Petyunin, P. A.; Konshin, M. E. *Zh. Obshch. Khim.* **1957**, *27*, 475; *Chem. Abstr.* **1957**, *51*, 15523a.

heated in a 150 °C oil bath. After 2 h, the solution was evaporated. Trituration of the residue with dichloromethane–ether afforded **26** (58 g, 178 mmol, 89%), mp 164–165 °C. Anal. ($C_8H_3Cl_2IN_2$) C, H, N, Cl, I.

2-Chloro-6-iodo-3,4-dihydroquinazoline (27). A solution of **26** (58 g, 178 mmol) in chloroform (470 mL) and ethanol (180 mL) cooled to 0 °C was treated portionwise with solid $NaBH_4$ (27 g, 714 mmol). After the mixture was stirred at ambient temperature for 1 h, the resulting precipitate was collected by filtration and was resuspended in water. After the mixture was stirred for 10 min, the solid was collected by filtration and dried at high vacuum over P_2O_5 to give **27** (50 g, 170 mmol, 96%). The analytical sample was recrystallized from acetone, mp 196–197 °C. Anal. ($C_8H_6ClIN_2$) C, H, N, Cl, I.

Ethyl (2-Chloro-6-iodo-3,4-dihydroquinazolin-3-yl)acetate (28). A mechanically stirred suspension containing **27** (50 g, 170 mmol), finely powdered potassium carbonate (77.4 g, 561 mmol), and ethyl bromoacetate (20.7 mL, 187 mmol) in 2-butanone (650 mL) was heated at reflux overnight. Addition of powdered potassium carbonate (20 g) completed the reaction. The mixture was then cooled, filtered to remove salts, and concentrated to give a crystalline mass, collected by filtration, washed with diethyl ether, and air-dried to yield **28** (54 g, 143 mmol, 84%), mp 157–158 °C. Anal. ($C_{12}H_{12}ClIN_2O_2$) C, H, N, Cl, I.

7-Iodo-1,2,3,5-tetrahydro-2-oxoimidazo[2,1-*b*]quinazoline (22). Ethylene glycol (500 mL) cooled to 0 °C was saturated with ammonia, and to the solution was added **28** (53 g, 140 mmol) with stirring. The mixture was heated in an oil bath to 140 °C and then was allowed to cool. Filtration and ethanol wash afforded **22** (35.5 g, 113 mmol, 81%), mp >300 °C (lit.[19] mp 323–324 °C). Anal. ($C_{10}H_8N_3OI$) C, H, N, I.

4-(*N*-Imidazolyl)aniline (29). A mixture of *p*-iodoaniline (Aldrich; 100 g, 456 mmol), imidazole (37.3 g, 550 mmol), potassium carbonate (82 g, 593 mmol), and copper(I) iodide (22 g, 114 mmol) in dry, degassed DMF (500 mL) was heated at 100 °C overnight. Identical additional amounts of imidazole, potassium carbonate, and copper(I) iodide were added, and the mixture was heated an additional 72 h. The mixture was cooled, the DMF was decanted off and evaporated, and the residue was partitioned between ethyl acetate (500 mL) and 0.5 M ammonium hydroxide (300 mL). The pot residue was washed with ethyl acetate and combined with the organic extract. The organic layer was washed with 0.5 M ammonium hydroxide (4 × 300 mL) and brine (2 × 300 mL) and then was dried, filtered, and evaporated to give **29** (27 g, 170 mmol, 37%), mp 145–146 °C (lit.[39] mp 143–145 °C).

2-[[4-(*N*-Imidazolyl)phenyl]amino]-2-imidazolin-4-one (12). A mixture of **29** (0.8 g, 5 mmol) and **30** (1.42 g, 5.5 mmol)[40] was added to a solution of potassium hydroxide (0.31 g, 5.5 mmol) in ethanol (50 mL). After the mixture was heated at reflux for 4 h, the resulting precipitate was collected by filtration to yield **12** (1.08 g, 4.5 mmol, 90%), mp 280–282 °C. Anal. ($C_{12}H_{11}N_5O{\cdot}1.75H_2O$) C, H, N.

5-(2-Chloroethoxy)-2-nitrobenzaldehyde (31a). A solution of 5-hydroxy-2-nitrobenzaldehyde (Aldrich; 50.1 g, 300 mmol) and 2-chloroethyl *p*-toluenesulfonate (Aldrich; 77.4 g, 330 mmol) in DMF (750 mL) was treated with potassium carbonate (51.9 g, 375 mmol), and the resulting suspension was heated overnight at 80 °C under nitrogen. After cooling, the mixture was evaporated, and the residue was partitioned between ethyl acetate (500 mL) and water (500 mL). The organic extract was washed with saturated sodium carbonate (3 × 300 mL) and brine (2 × 300 mL) and then was dried, filtered, and evaporated. The residue was triturated with diethyl ether, and the small amount of brown precipitate was removed by filtration and discarded. The filtrate was evaporated, and the residue was triturated with petroleum ether to afford **31a** (64 g, 278 mmol, 93%), mp 59–60 °C, upon filtration and drying. Anal. ($C_9H_8ClNO_4$) C, H, N, Cl.

5-[2-(*N*-Imidazolyl)ethoxy]-2-nitrobenzaldehyde (32). A mixture of **31a** (11.5 g, 50 mmol) and imidazole (34 g, 500 mmol) and heated under nitrogen at 100 °C for 2 h. The molten reaction mixture was cooled slightly and then was poured into ethyl acetate (300 mL). The solution was washed with water (6 × 100 mL) and brine (2 × 200 mL) and then was dried, filtered, and evaporated. Chromatography of the residue over silica gel (0–4% gradient of methanol in dichloromethane as eluant) and evaporation of the appropriate fractions afforded **32** (8.25 g, 31.6 mmol, 63%), mp 89–90 °C. Anal. ($C_{12}H_{11}N_3O_4$) C, H, N.

7-[2-(*N*-Imidazolyl)ethoxy]-1,2,3,5-tetrahydro-2-oxoimidazo[2,1-*b*]quinazoline (13a). Ring construction using **32** (7.84 g, 30 mmol) according to the procedure used for **11** afforded **13a** (2.40 g, 8.07 mmol, 27%), mp 207–208 °C. Anal. ($C_{15}H_{15}N_5O_2{\cdot}1.5H_2O$) C, H, N.

5-[(6-Acetoxyhexyl)oxy]-2-nitrobenzaldehyde (31b). Alkylation of 5-hydroxy-2-nitrobenzaldehyde (50 g, 300 mmol) with 6-chlorohexanol acetate[41] (59 g, 330 mmol) was carried out according to the procedure used for the preparation of **31a**. Kugelrohr distillation of the crude product afforded **31b** as a yellow syrup which crystallized upon trituration with petroleum ether (81.5 g, 263 mmol, 88%), mp 42–43 °C. Anal. ($C_{15}H_{19}NO_6$) C, H, N.

7-[(6-Acetoxyhexyl)oxy]-1,2,3,5-tetrahydro-2-oxoimidazo-[2,1-*b*]quinazoline (33a). Ring construction using **31b** (30.90 g, 100 mmol) according to the procedure used for **11** afforded **33a** (15.8 g, 45.7 mmol, 46%), mp 192–193 °C. Anal. ($C_{18}H_{23}N_3O_4$) C, H, N.

7-[(6-Hydroxyhexyl)oxy]-1,2,3,5-tetrahydro-2-oxoimidazo[2,1-*b*]quinazoline (33b). A suspension of **33a** (13.9 g, 40 mmol) in methanol (100 mL) was treated with 2.5 M NaOH (20 mL) in one portion. The solution cleared momentarily, and then a precipitate was deposited. After 1 h at ambient temperature, the solid was collected by filtration, triturated with acetone, refiltered, and then dried to yield **33b** (11.5 g, 37.9 mmol, 95%), mp 236–237 °C. Anal. ($C_{16}H_{21}N_3O_3$) C, H, N.

7-[6-(*N*-Imidazolyl)hexyloxy]-1,2,3,5-tetrahydro-2-oxoimidazo[2,1-*b*]quinazoline (13b). A suspension of **33b** (6.10 g, 20 mmol) in DMF (150 mL) was treated with methyltriphenoxyphosphonium iodide (Fluka; 9.05 g, 40 mmol), and the resulting mixture was heated 1 h at 110 °C to effect dissolution. The reaction was then cooled, diluted with water (150 mL), and made basic by the addition of saturated aqueous sodium carbonate. The resulting solution was extracted with ethyl acetate (3 × 300 mL), and the organic extract was washed with brine (2 × 300 mL), dried, filtered, and evaporated to give an oily residue which crystallized upon trituration with diethyl ether to yield **33c** (6.7 g, 16.2 mmol, 81%), mp 90–91 °C.

Solid **33c** (4.13 g, 10 mmol) was slowly added to molten imidazole (125 °C internal temperature) over 1.5 h. After cooling, the dark mixture was dissolved in chloroform (200 mL) and was washed with 10% ammonium hydroxide (3 × 100 mL) and brine (2 × 200 mL) and then was dried, filtered, and evaporated. Chromatography of the residue over silica gel (2.5–5% methanol gradient in 0.5% ammonium hydroxide–chloroform) and evaporation of the appropriate fractions afforded **13b** (650 mg, 1.84 mmol, 18%), mp 188–189 °C. Anal. ($C_{19}H_{23}N_5O_2$) C, H, N.

Substituted 1,2,3,5-Tetrahydro-2-oxoimidazo[2,1-*b*]-quinazolines (Table III). Compounds **34**,[42] **35**,[43] **37**,[42] and **38**[44] were prepared by literature procedures. Convenient preparations of compounds **40** and **42** were previously reported by us.[8] Compound **41** was prepared by the general route of Yamaguchi and Ishikawa,[42] previously used for the preparation of **40**,[8] which parallels that used for the preparation of **22** (vide supra).

5-(Benzyloxy)-2-nitrobenzoic Acid. A method using in situ generation of tetra-*n*-butylammonium permanganate[45] was developed for this large-scale reaction: A solution of 5-(benzyloxy)-2-nitrobenzaldehyde[46] (469 g, 1.825 mol) and tetra-*n*-buty-

(39) Bouchet, P.; Coquelet, C.; Elguero, J. *J. Chem. Soc., Perkin Trans. 2* **1974**, 449.
(40) Lempert, K.; Doleschall, G. *Acta Chim. Acad. Sci. Hung.* **1963**, *37*, 457; *Experientia* **1962**, *18*, 401.
(41) Bennett, G. M.; Mosses, A. N. *J. Chem. Soc.* **1931**, 1697.
(42) Yamaguchi, H.; Ishikawa, F. *J. Heterocycl. Chem.* **1981**, *18*, 67.
(43) Kienzle, F.; Kaiser, A.; Chodnekar, M. S. *Eug. J. Chem.-Chim. Ther.* **1982**, *17*, 547.
(44) Ishikawa, F.; Saegusa, J.; Inamura, K.; Sakuma, K.; Achida, S. *J. Med. Chem.* **1985**, *28*, 1387.
(45) Sala, T.; Sargent, M. V. *J. Chem. Soc., Chem. Commun.* **1978**, 253.
(46) Skiles, J. W.; Cava, M. C. *J. Org. Chem.* **1979**, *44*, 409.

lammonium hydrogen sulfate (Aldrich; 62 g, 0.183 mol) in acetone (2 L) was cautiously treated in portions with $KMnO_4$ (2 16.5 g, 1.37 mol) at a rate (over 4–5 h) such that the temperature never exceeded 40 °C. Upon completion of the addition, the mixture was stirred an additional 4 h and then was evaporated. The residue was partitioned between ethyl acetate–ether (1:1, 2 L) and 1 M HCl (1 L) and was treated with solid $NaHSO_3$ to disproportionate the residual MnO_2. The resulting clear organic layer was washed with additional 1 M HCl (3 × 500 mL) and brine (2 × 500 mL) and then was dried, filtered, and evaporated. The residual oil was triturated with hexane to yield 5-(benzyloxy)-2-nitrobenzoic acid (447 g, 1.637 mol, 90%), mp 143–144 °C (lit.[47] mp 143–144 °C).

Methyl 5-(Benzyloxy)-2-nitrobenzoate. A suspension of the above benzoic acid (136.5 g, 500 mmol) in benzene (500 mL) and DMF (0.5 mL) was treated with oxalyl chloride (65.5 mL, 750 mmol) dropwise at room temperature. When the acid had completely dissolved, the mixture was thoroughly evaporated, and the residue was dissolved in methanol (500 mL) and heated 30 min on the steam bath. Upon cooling, the mixture crystallized to yield methyl 5-(benzyloxy)-2-nitrobenzoate (123 g, 429 mmol, 86%), mp 79–80 °C. Anal. ($C_{15}H_{13}NO_5$) C, H, N.

Methyl 5-(Benzyloxy)anthranilate. A variation of the method of Nose and Kudo[48] was used. An ice-cooled solution of the above ester (122 g, 425 mmol) and $NiCl_2 \cdot 6H_2O$ (202 g, 850 mmol) in methanol (2 L) was treated portionwise (5 g) with $NaBH_4$ (64.3 g, 1.7 mol maximum) at a rate such that the temperature remained below 30 °C. When TLC (dichloromethane) showed complete consumption of starting material, the addition was halted, and the mixture was stirred at room temperature for 1 h. The metallic gray solution was evaporated to give a black residue, which was dissolved in water (2.5 L) and then was acidified to pH 1 (concentrated HCl) to consume precipitated Ni. The mixture was then made basic (pH 10) with concentrated ammonium hydroxide and was thoroughly extracted with diethyl ether (5 × 500 mL). The combined organic layers were washed with water (2 × 500 mL) and brine (2 × 500 mL). The solution was dried, filtered, and evaporated to give methyl 5-(benzyloxy)anthranilate (85 g, 331 mmol, 78%), mp 70–71 °C. Anal. ($C_{15}H_{15}NO_3$) C, H, N.

Methyl 5-(Benzyloxy)-2-ureidobenzoate. A solution of the above compound (77 g, 300 mmol) in acetic acid (300 mL) was treated in one portion with a solution of KNCO (31.6 g, 390 mmol) in water (50 mL). Within moments, a thick precipitate formed, which was collected by filtration, air-dried, and recrystallized from methanol to yield methyl 5-(benzyloxy)-2-ureidobenzoate (73 g, 243 mmol, 81%), mp 185–186 °C. Anal. ($C_{16}H_{16}N_2O_4$) C, H, N.

6-(Benzyloxy)-2,4-dichloroquinazoline. Aqueous NaOH (10 g in 200 mL) was added to a refluxing suspension of methyl 5-(benzyloxy)-2-ureidobenzoate (60 g, 200 mmol) in methanol (1 L). The mixture momentarily cleared and then deposited a thick precipitate. The mixture was neutralized with concentrated HCl and then was cooled and filtered. After air-drying, the crude solid (51 g) was suspended in a mixture of $POCl_3$ (300 mL) and *N,N*-dimethylaniline (50 mL, 400 mmol). The resulting suspension was heated to 140 °C to give a pink-violet solution after 2 h. The mixture was then cooled, and excess $POCl_3$ was removed by evaporation. The residue was cautiously quenched by addition to crushed ice to yield a gummy solid after removal of the water by decantation. The residue was recrystallized from ether–ethyl acetate to yield 6-(benzyloxy)-2,4-dichloroquinazoline (51.6 g, 169 mmol, 85%), mp 138–139 °C. Anal. ($C_{15}H_{10}Cl_2N_2O$) C, H, N, Cl.

6-(Benzyloxy)-2-chloro-3,4-dihydroquinazoline. Reduction of the above dichloroquinazoline (22.8 g, 75 mmol) with $NaBH_4$ (14 g, 375 mmol) in chloroform–ethanol (5:2, 175 mL) at 0 °C, according to literature procedure,[42] afforded the title compound (18.8 g, 68.9 mmol, 92%), mp 158–160 °C. Anal. ($C_{15}H_{13}ClN_2O \cdot 0.25H_2O$) C, H, N, Cl.

Ethyl [6-(Benzyloxy)-2-chloro-3,4-dihydroquinazolin-3-yl]acetate. Alkylation of the above compound (21.8 g, 80 mmol) with ethyl bromoacetate (9.8 mL, 88 mmol) and K_2CO_3 (36.4 g, 264 mmol) in methyl ethyl ketone (250 mL) according to literature procedure[42] gave the title compound (19.4 g, 54.1 mmol, 68%), mp 121–122 °C. Anal. ($C_{19}H_{19}ClN_2O_3$) C, H, N, Cl.

7-(Benzyloxy)-1,2,3,5-tetrahydro-2-oxoimidazo[2,1-*b*]quinazoline (41). Ring closure of the above compound in a saturated ammonia solution of ethylene glycol at 70–80 °C afforded **41** in 72–95% yields, depending on scale, mp 246–248 °C. Anal. ($C_{17}H_{15}N_3O_2 \cdot 0.25H_2O$) C, H, N.

7-Hydroxy-1,2,3,5-tetrahydro-2-oxoimidazo[2,1-*b*]quinazoline Hydrochloride (39). Hydrogenation of **41** (2.96 g, 10 mmol) in DMF (50 mL), methanol (50 mL), and HCl-saturated methanol (5 mL) at 60 psi over 10% Pd–C (1 g) for 1 h gave a thick precipitate, which was collected by filtration and recrystallized from hot DMF (with filtration to remove the catalyst) and ether to yield **39** as its HCl salt (1.50 g, 6.25 mmol, 63%), mp >300 °C (lit.[49] mp 300 °C). Anal. ($C_{10}H_9N_3O_2 \cdot HCl \cdot H_2O$) C, H, N, Cl.

Cyclic AMP Phosphodiesterase Assay. In vitro evaluation of test compounds as inhibitors of type IV (F III) PDE present in human platelets was carried out according to methods described by us in ref 8. Assays were performed in triplicate at five different inhibitor concentrations, the mean of the determinations (n = 3) at each concentration was plotted, and the IC_{50} values reported in Tables I and III were determined graphically. Standard deviations from mean values in each experiment were generally less than ±5%. IC_{50} values presented are from representative experiments, were highly reproducible, and varied by less than a factor of 0.5–2 times of the initial determination.

Inotropic Studies. Cardiovascular evaluation of test compounds was carried out in instrumented, anesthetized dogs according to methods described by us in ref 7. ED_{50} values (SE 10%) were determined graphically from plots of the cardiac force, heart rate, and blood pressure response curves. In experiments with $n > 1$, the mean of the determinations at each dose level administered was plotted and used for the graphical determination of the ED_{50} values. Standard deviation from mean values in each experiment were generally less than ±10%.

Acknowledgment. We thank Prof. Victor Snieckus, University of Waterloo, Ontario, Canada, and Dr. Joseph M. Muchowski, Institute of Organic Chemistry, Syntex Research, for helpful comments regarding the pyridine ortho lithiation chemistry. We thank Dr. Robert Wilhelm, Institute of Bio-Organic Chemistry, for providing the sample of **34**. We also gratefully acknowledge Kurt Liittschwager, Linda Osborne, Louise Drinkwater, and Katie Chang for carrying out the in vitro bioassays, and Lowell Johnson, Institute of Experimental Pharmacology, for conducting the in vivo inotropic evaluations.

Registry No. **5**, 78415-72-2; **6**, 84490-12-0; **7a**, 116027-04-4; **7b**, 116027-05-5; **7c**, 116027-06-6; **7d**, 116027-00-0; **9**, 86798-59-6; **10**, 101184-07-0; **11**, 116027-09-9; **12**, 116027-14-6; **13a**, 103786-45-4; **13b**, 103786-39-6; **14a**, 38427-94-0; **14b**, 56700-70-0; **14c**, 98400-69-2; **15a**, 116026-94-9; **15b**, 116026-95-0; **15c**, 116026-93-8; **15d**, 116026-99-4; **16**, 116026-96-1; **17**, 116026-97-2; 18, 116026-98-3; **19**, 26908-35-0; **20**, 116027-24-8; **21**, 116027-07-7; **22**, 108857-18-7; **23b**, 77317-55-6; **24**, 116027-11-3; **25**, 16353-27-8; **26**, 74173-76-5; **27**, 116027-12-4; **28**, 116027-13-5; **29**, 2221-00-3; **30**, 54855-80-0; **31a**, 116005-59-5; **31b**, 103786-38-5; **32**, 116027-15-7; **33a**, 103787-40-2; **33b**, 103787-39-9; **33c**, 103786-40-9; **34**, 50608-24-7; **35**, 70018-51-8; **37**, 58579-16-1; **39**, 50608-87-2; **40**, 61835-03-8; **41**, 116027-23-7; **42**, 105763-71-1; cyclic AMP phosphodiesterase, 9036-21-9; 2-aminopyridine, 504-29-0; *N,N'*-bis(2-pyridyl)urea, 6268-43-5; nicotinamide, 98-92-0; 3-aminopyridine, 462-08-8; 4-aminopyridine, 504-24-5; 2-bromonicotinic acid, 35905-85-2; glycine ethyl ester hydrochloride, 623-33-6; ethyl *N*-[[3-(BOC-amino)-2-pyridyl]methyl]glycinate, 116027-01-1; ethyl (3-amino-2-pyridyl)-*N*-methylglycinate tris(trifluoroacetate), 116027-03-3; 5-chloro-2-nitrobenzaldehyde, 6628-86-0; 2-methoxy-1,3-dioxolane, 19693-75-5; imidazole, 288-32-4; methyl *N*-[[4-(*N*-imidazolyl)-2-nitrophenyl]methyl]glycinate, 116027-08-8; 5-iodoanthranilic acid,

(47) Giovanni, E.; Portmann, P. *Helv. Chim. Acta* **1948**, *31*, 1381.
(48) Nose, A.; Kudo, T. *Chem. Pharm. Bull.* **1981**, *29*, 1159.
(49) Beverung, W. N.; Partyka, R. U.S. Patent 3932407; *Chem. Abstr.* **1976**, *84*, 105646c.

5326-47-6; 6-iodoisatoic anhydride, 116027-10-2; ethyl bromoacetate, 105-36-2; *p*-iodoaniline, 540-37-4; 5-hydroxy-2-nitrobenzaldehyde, 42454-06-8; 2-chloroethyl *p*-toluenesulfonate, 80-41-1; 6-chlorohexanol acetate, 40200-18-8; 5-(benzyloxy)-2-nitrobenzoic acid, 61340-15-6; 5-(benzyloxy)-2-nitrobenzaldehyde, 58662-54-7; methyl 5-(benzyloxy)-2-nitrobenzoate, 116027-16-8; methyl 5-(benzyloxy)anthranilate, 116027-17-9; methyl 5-(benzyloxy)-2-ureidobenzoate, 116027-18-0; 6-(benzyloxy)-2,4-dichloroquinazoline, 116027-19-1; 6-(benzyloxy)quinazoline-2,4-(1*H*,3*H*)-dione, 116027-20-4; 6-(benzyloxy)-2-chloro-3,4-dihydroquinazoline, 116027-21-5; ethyl [6-(benzyloxy)-2-chloro-3,4-dihydroquinazolin-3-yl]acetate, 116027-22-6.

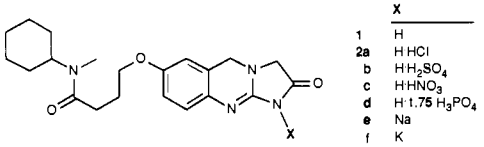
Inhibitors of Cyclic AMP Phosphodiesterase. 4. Synthesis and Evaluation of Potential Prodrugs of Lixazinone (*N*-Cyclohexyl-*N*-methyl-4-[(1,2,3,5-tetrahydro-2-oxoimidazo[2,1-*b*]quinazolin-7-yl)-oxy]butyramide, RS-82856)[1]

Michael C. Venuti,*[†,#] Robert Alvarez,[‡] John J. Bruno,[‡] Arthur M. Strosberg,[‡] Leo Gu,[§] Hi-Shi Chiang,[§] Ian J. Massey,[∥] Nancy Chu,[∥] and John H. Fried[⊥]

Institutes of Bio-Organic Chemistry, Experimental Pharmacology, Pharmaceutical Sciences, and Bioanalytical and Metabolic Research, Syntex Research, 3401 Hillview Avenue, Palo Alto, California 94304. *Received April 11, 1988*

The cyclic AMP phosphodiesterase (cAMP PDE) inhibitor and cardiotonic agent lixazinone (*N*-cyclohexyl-*N*-methyl-4-[(1,2,3,5-tetrahydro-2-oxoimidazo[2,1-*b*]quinazolin-7-yl)oxy]butyramide, RS-82856, **1**) and its acid and base addition salts were found to be insufficiently soluble in formulations suitable for intravenous administration. These results prompted an investigation into potential prodrugs with enhanced aqueous solubility designed to deliver **1** by three distinct mechanisms: (1) decarboxylation of α-carboxamides; (2) hydrolytic loss of a solubilizing N-1-(acyloxy)methyl or (*N*,*N*-dialkylamino)methyl moiety; or (3) intramolecular closure of a guanidino ester or amide. The target compounds were evaluated as delivery systems for **1** by three criteria: (1) chemical conversion rate to **1** under physiological conditions; (2) inhibition of type IV cAMP PDE at a fixed time point; and (3) in vivo inotropic activity in anesthetized dogs by both intravenous and oral administration. Release of **1** from **4a** (series 1) was found to be too slow to be of value as a prodrug of **1**, since decarboxylation could be induced only by strong acid, conditions under which hydrolytic ring opening was found to severely compete. Conversely, **1** was released too readily on exposure of (*N*,*N*-dialkylamino)methyl derivatives such as **8d** (series 2) to physiological conditions, although no large increase in aqueous solubility was realized. Finally, both the physicochemical and in vitro studies indicated that ring closure of the guanidinium esters and amides **17a–k** (series 3) to **1** was quantitative and pH- and time-dependent, suggesting the possibility of delivery of the open, water-soluble prodrug form, followed by closure to **1** in plasma. Detailed examination of these agents in vivo, however, demonstrated that only those compounds that rapidly cyclized to **1**, as measured by plasma levels of **1**, exhibited inotropic activity, indicating that the open prodrug form was not efficiently absorbed upon oral administration.

Selective inhibition of the high-affinity, cyclic AMP specific form (type IV) of phosphodiesterase (cAMP PDE) present in myocardial tissue is generally recognized to be the mechanism of action of a new generation of cardiotonic agents that exhibit a combination of positive inotropic, peripheral vasodilatory, and afterload reducing properties.[2-6] Recent papers have described the development of a generalized model of the active site of the type IV PDE that both accommodates this class of inhibitors and discriminates between cAMP and cGMP.[7-10] One demand of this active-site model made on potential inhibitors is the presence of an acidic hydrogen directly adjacent to a polarizable functionality, a structural requirement met by all representative members of this class. While this functional attribute is no doubt necessary for activity, it simultaneously creates a polar molecule capable of intermolecular hydrogen bonding, most often physically manifested by a high melting point and extreme insolubility, especially in physiologically relevant media.



We have previously described both the biochemical profile of one member of this class, *N*-cyclohexyl-*N*-methyl-4-[(1,2,3,5-tetrahydro-2-oxoimidazo[2,1-*b*]-

[†] Institute of Bio-Organic Chemistry.
[‡] Institute of Experimental Pharmacology.
[§] Institute of Pharmaceutical Sciences.
[∥] Bioanalytical and Metabolic Research.
[⊥] President, Syntex Research.
[#] Present address: Medicinal and Biomolecular Chemistry Department, Genentech, Inc., 460 Point San Bruno Blvd., South San Francisco, CA 94080.

(1) Contribution No. 285 from the Institute of Bio-Organic Chemistry. For part 3, see ref 21. Address inquiries to Dr. R. Alvarez.
(2) Bristol, J. A.; Chorvat, R. J. *Cardiovascular Drugs*; Bristol, J. A., Ed.; Wiley: New York, 1986; Chapter 6, p 255.
(3) Erhardt, P. W. *J. Med. Chem.* **1987**, *30*, 231.
(4) Weishaar, R. E.; Cain, M. H.; Bristol, J. A. *J. Med. Chem.* **1985**, *28*, 537.
(5) Weishaar, R. E.; Burrows, S. D.; Kobylarz, D. C.; Quade, M. M.; Evans, D. B. *Biochem Pharmacol.* **1986**, *35*, 787.
(6) Ahn, H. S.; Eardley, D.; Watkins, R.; Prioli, N. *Biochem. Pharmacol.* **1986**, *35*, 1113.
(7) Bristol, J. A.; Sircar, I.; Moos, W. H.; Evans, D. B.; Weishaar, R. E. *J. Med. Chem.* **1984**, *27*, 1099.
(8) Rakhit, S.; Marciniak, G.; Leclerc, G.; Schwartz, J. *Eur. J. Med. Chem.-Chim. Ther.* **1986**, *21*, 511.
(9) Erhardt, P. W.; Hagedorn, A. A., III; Sabio, M. *Mol. Pharmacol.* **1988**, *33*, 1.
(10) Moos, W. H.; Humblet, C. C.; Sircar, I.; Rithner, C.; Weishaar, R. E.; Bristol, J. A.; McPhail, A. T. *J. Med. Chem.* **1987**, *30*, 1963.

0022-2623/88/1831-2145$01.50/0