Articles

N-Arylpiperazinyl-*N*′-propylamino Derivatives of Heteroaryl Amides as Functional Uroselective α_1-Adrenoceptor Antagonists

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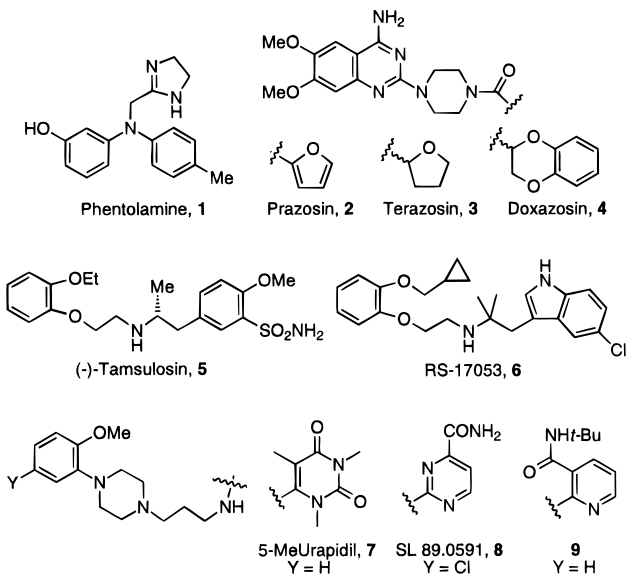
Novel arylpiperazines were identified as α_1-adrenoceptor (AR) subtype-selective antagonists by functional *in vitro* screening. 3-[4-(*ortho*-Substituted phenyl)piperazin-1-yl]propylamines were derivatized with *N*,*N*-dimethyl anthranilamides, nicotinamides, as well as carboxamides of quinoline, 1,8-naphthyridine, pyrazolo[3,4-*b*]pyridine, isoxazolo[3,4-*b*]pyridine, imidazo[4,5-*b*]pyridine, and pyrazolo[1,5-*a*]pyrimidines. Strips of rabbit bladder neck were employed as a predictive assay for antagonism in the human lower tract. Rings of rat aorta were used as a "negative screen" for the test antagonists. Binding to α_1-ARs was relatively sensitive to size and electronic features of the arylpiperazine portion of the antagonists and permissive to these features on the heteroaryl carboxamide side. These structure−affinity findings were exploited to produce nicotinamides (*e.g.* **13ii** and **25x**) and pyrazolo[3,4-*b*]pyridines (*e.g.* **37f** and **37y**) ligands with nanomolar affinity at the α_1-AR subtype prevalent in the human lower urinary tract (pA_2 values: 8.8, 10.7, 9.3, and 9.9, respectively) and displaying 2−3 orders of magnitude selectivity over the α_{1D}-AR.

Introduction and Pharmacology

Benign prostatic hyperplasia (BPH) is present in nearly one in seven men aged 40−49 years, and the occurrence rises to four in nine men aged 60−69. The condition contributes to urethra obstruction and the development of lower urinary tract symptoms (*e.g.* frequency, hesitancy, reduced urine flow rates, large residual volumes).[1] Caine and co-workers reported in 1976 that the administration of the mixed α_1/α_2-adrenoceptor (AR) antagonist phentolamine (**1**, Chart 1) alleviated these symptoms.[2] The clinical study of the selective α_1-AR (over α_2-ARs) antagonist prazosin (**2**) supported the relevance of the blockade of α_1-ARs.[3] Despite evidence for the clinical efficacy of **2** and related agents such as terazosin (**3**)[4] and doxazosin (**4**),[5] as well as tamsulosin (**5**),[6] these drugs antagonize the vascular, CNS, as well as prostatic α_1-ARs. Accordingly, side effects related to depressor and CNS activities have hindered truly efficacious dosing schedules and have underscored the necessity for achieving selective blockade of lower urinary tract α_1-ARs. α_1-AR heterogeneity has been well demonstrated,[7] with three distinct α_1-ARs cloned to date. The subtypes are now pharmacologically classified[7e] as α_{1A}, α_{1B}, and α_{1D}.[7f] Their distribution within the body and which subtype was most relevant to the disease state was not well understood at the outset of this program. Thus we sought a subtype selective antagonist that would effectively relax outlet tissues while sparing subtypes involved principally in cardiovascular and CNS control. A report[8] has recently corroborated our findings that the α_{1a}-AR is significantly expressed in diseased prostatic tissue.

Chart 1



Our initial effort in this area produced potent antagonists (*e.g.* RS-17053, **6**) in a classical α_{1A}-AR preparation, the isolated perfused rat kidney.[7e] These compounds warranted further study in human lower urinary tract tissues. However, a surprisingly low affinity estimated for **6** in the target tissue shifted our attention away from this hybrid class of indoramin and **5** ana-

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Table 1. Validation of *in Vitro* Screen for Uroactive α_1-AR Subtype Antagonists

compound	bovine α_{1a}[a]	human prostate[b]	rabbit bladder neck[c]
phentolamine, **1**	9.1 ± 0.09	NT[d]	8.2 ± 0.02
prazosin, **2**	9.9 ± 0.02	8.7 ± 0.1	8.3 ± 0.1
(±)-terazosin, **3**	8.6 ± 0.03	7.6 ± 0.1	7.7 ± 0.1
(−)-tamsulosin, **5**	9.9[e]	10.4 ± 0.1	9.8 ± 0.1
RS-17053, **6**	9.1 ± 0.32	7.3 ± 0.1	7.3 ± 0.1
5-MeUrapidil, **7**	9.3 ± 0.06	8.2 ± 0.1	8.4 ± 0.1
9	8.8 ± 0.23	8.7 ± 0.3	8.9 ± 0.1

[a] pK_i estimate with [^{3}H]prazosin displacement: Schwinn, D. A.; *et al. J. Biol. Chem.* **1990**, *256*, 8183−8189. [b] pA_2 value *vs* NE according to ref 9. [c] pA_2 value *vs* PE according to ref 9. [d] NT = not tested. [e] pK_i value reported by Foglar, R.; *et al. Eur. J. Pharmacol.* **1995**, *288*, 201−207.

logues.[9] Lower affinity estimates were also obtained in human prostatic tissues for (+)-niguldipine (pA_2 7.5 ± 0.5) than what may be expected for its affinity judged by displacement of [^{3}H]prazosin from the cloned bovine α_{1a}-AR (pK_i 9.2 ± 0.1). Therefore our attention was shifted to *N*-phenylpiperazinyl-containing α_1-AR ligands such as **7**[10] and **8**.[11] This feature will be borne in most of the antagonists described in this report despite their potential interaction with other seven-transmembrane receptors.[12]

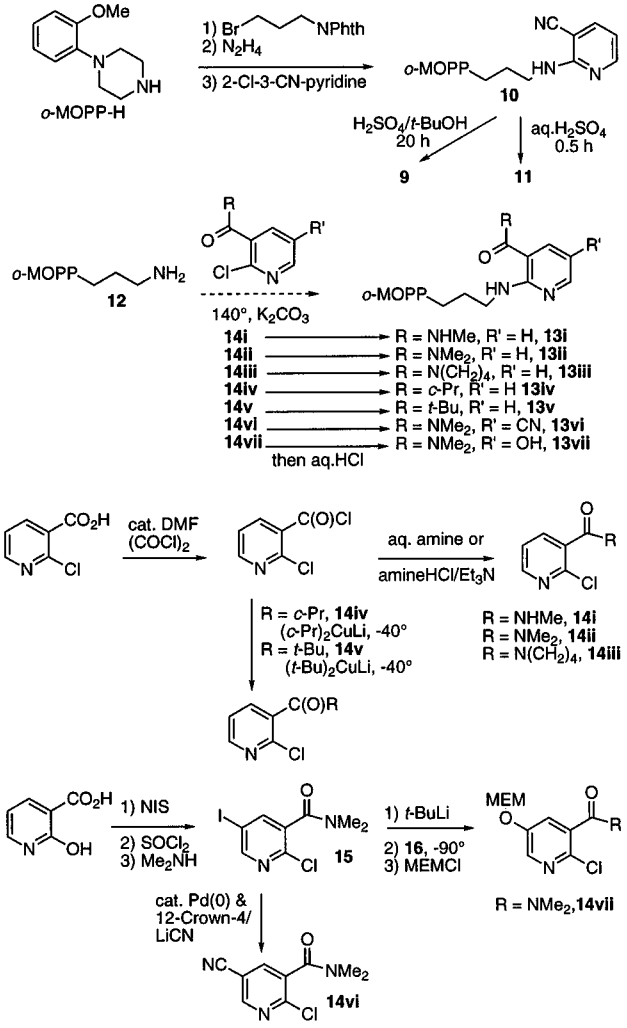
The next requirement was to establish a predictive assay for the α_1-AR subtype(s) of the lower urinary tract smooth muscles from man. In this regard, isolated strips of rabbit bladder neck (RBN)[13] fulfilled the requisite pharmacological profile consistent with the $\alpha_{1A/1L}$-subtype (Table 1). Rat thoracic aortic rings were used as the primary functional screen for the "negative target", with a pharmacological profile reflecting the characteristics of an α_{1D}-AR assay.[14] All compounds described in subsequent tables displayed properties consistent with competitive antagonism, and affinity estimates are reported as pA_2 values.

Chemistry

The initial aryl amides of interest were produced from 2-aminonicotinonitrile **10** by either a Ritter (**9**) or controlled hydrolysis (primary carboxamide, **11**) reactions. As outlined in Scheme 1, 1-(*o*-methoxyphenyl)-piperazine (*o*-MOPP-H) was alkylated with (3-bromopropyl)phthalimide and subjected to hydrazinolysis to give **12**. The primary amine of **12** reacted at the 2-position of **14i**−**vii** to furnish (refluxing xylenes) the nicotinamide family **13**. 2-Chloronicotinoyl chloride was derivatized to the amides **14i**−**iii** in a routine manner, and it also afforded ketones **14iv**,**v** *via* Gilman type reagents.[15] In order to prepare 5-substituted nicotinamides, 2-hydroxynicotinic acid was reacted with NIS to give the 5-iodo intermediate **15**, and palladium(0)-catalyzed cyanation[16] selectively gave **14vi**. Aryl iodide **15** was also treated with *t*-BuLi and immediately with oxaziridine **16**[17] to afford **14vii** after phenolic protection. Antagonists **17**, **18**, **19**, **20**, and **21** were prepared by analogous chemistry from 2-chloro-4,6-dimethylnicotinamide,[18] 4-chloronicotinic acid,[19] nicotinic acid,[20] 6-chloronicotinic acid,[21] and ethyl 4-chloropyrimidine-5-carboxylate,[22] respectively.

The anthranilamides **22** studied in this program were prepared according to Scheme 2. Substituted 2-nitrobenzoic acids produced anthranilamides **23i**−**iii**, acetylsalicyloyl chloride gave **23iv**, and 2,2′-dithiosalicylic acid gave **23v**. These nucleophiles (**23** or "ArX$^-$") all displaced the mesylate of (3-(mesyloxy)propyl)-*o*-MOPP with K_2CO_3 present. 2-Aminobenzophenone also reacted with the electrophile to give **22vi**. Acylation of **23i** with acryloyl chloride and a subsequent Michael reaction with *o*-MOPP-H furnished **22vii**.

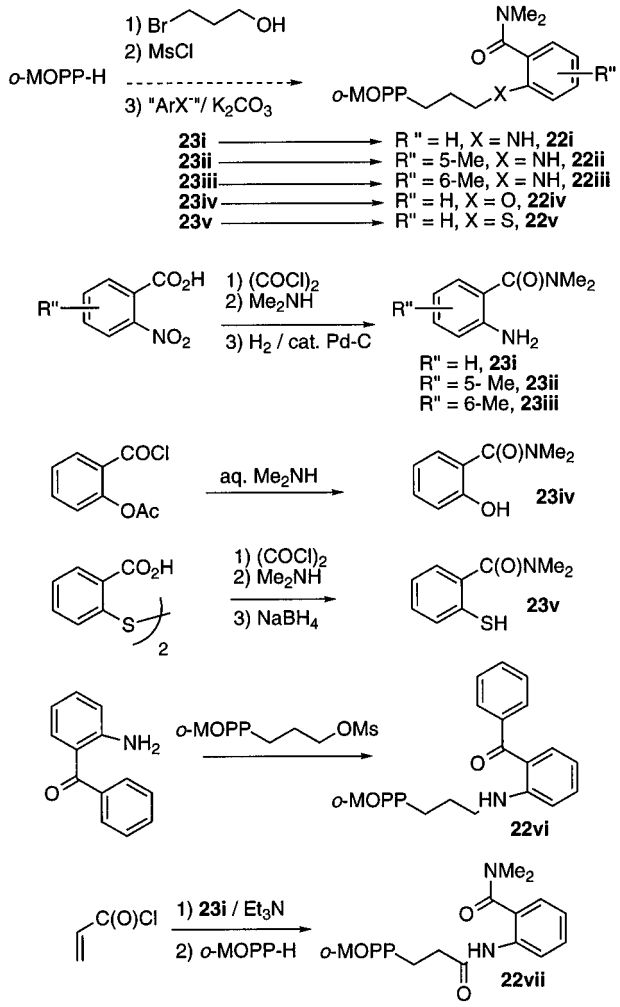
Scheme 1. Preparation of Nicotinamides



Several compounds with a modified arylpiperazine moiety were prepared. Most *N*-phenylpiperazines were obtained by a Prelog procedure[23] (Scheme 3). We employed the method of Poindexter[24] in the case of a substrate with an acid stable substituent to prepare **24q**, so as to avoid the use of bis(2-chloroethyl)amine. Aromatic displacement of halogens accomplished the efficient incorporation of the piperazine ring. *N*-Lithiopiperazine afforded **24j**,**y** by direct *ortho* substitution as modified from the work of Meyers[25] and elaborated by ten Hoeve.[26] *N*-Formylpiperazine displaced chloride from the appropriate aromatics to prepare **24l**,**x**.

The preparation of (aryloxy)ethylamines is outlined in Scheme 4. Ethylene carbonate was pyrolyzed in the presence of catechol, and the resulting phenol was alkylated with 2,2,2-trifluoroethyl tosylate in the presence of K_2CO_3 to produce **27a**. 2-Iodophenol was alkylated, and the pendent ester was hydrolyzed. The homologated aryl iodide was transformed to a presumed boronic ester (NaH, followed by *t*-BuLi, and sequential quench with $(MeO)_3B$ and HOAc), which participated in a Suzuki reaction[27] to give **27b**. By sequential

Scheme 2. Preparation of Anthranilamides

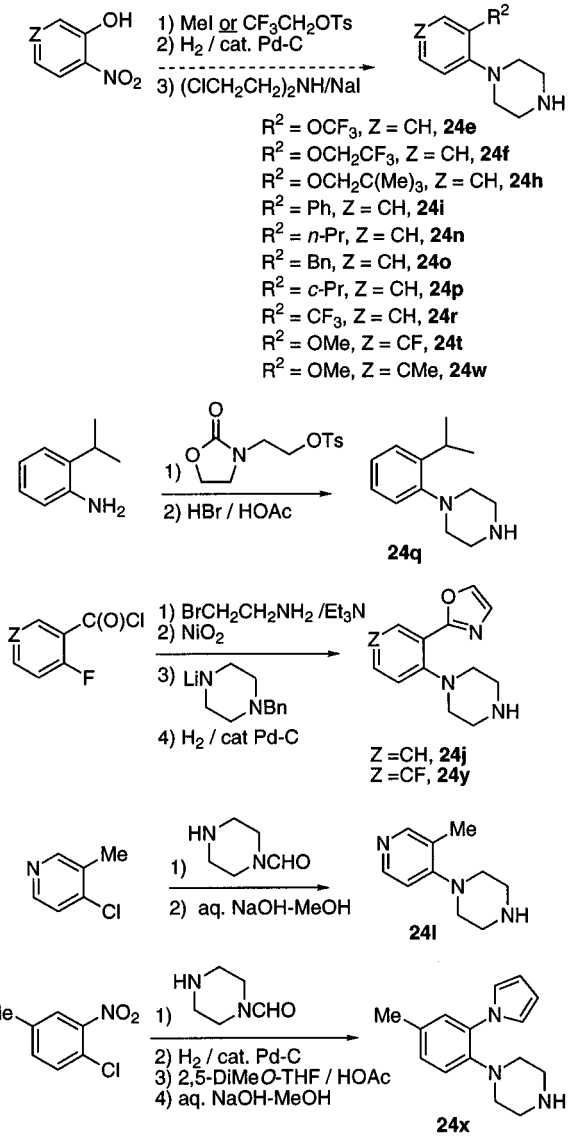


treatment of these alcohols with MsCl, and then 4-amino-1-benzylpiperidine and hydrogenolysis, *N*,*N*-dimethylnicotinamide could be appended to furnish compounds **28a**−**c**.

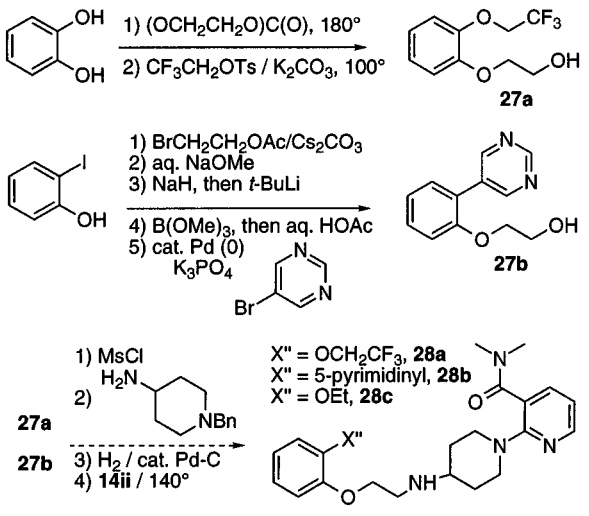
We also designed and prepared some fused heterocyclic *N*,*N*-dimethylamides. Scheme 5 illustrates the annulation chemistry and significant transformations obtained with a variety of heterocycles. *Ortho*-substituted anilines yielded 8-substituted-4-chloroquinoline ethyl carboxylates **30**, **31**, and **32** upon exposure to diethyl ethoxymethylenemalonate and then refluxing phosphoryl chloride. The ester of **31** and **32** was converted to the *N*,*N*-dimethyl carboxamide of **33** and **34** by first careful hydrolysis. 4-Chloro-8-cyanoquinoline **35** was produced from **34** and LiCN in the presence of catalytic amounts of 12-crown-4 and Pd(0).[16] Analogous treatments led to chloroheterocyclic carboxamides **36** through **42**.

The assembly of the target antagonists is shown in Scheme 6, and we employed two strategies. A route that was unsuccessful for the preparation of 2-aminonicotinamides (*i.e.* Scheme 1) was efficient in these cases. Quinoline **30** was reacted with 3-amino-1-propanol, and the pendant primary hydroxyl was activated with MsCl. Arylpiperazine **24f** was then alkylated in the presence of NaI. The antangonist **30f** was produced following ester−amide conversion and **30f′** upon treatment with 1 atm of H_2 and 10% Pd/C. An alternative route was routinely used and is identical to that described in

Scheme 3. Preparation of *N*-Arylpiperazines

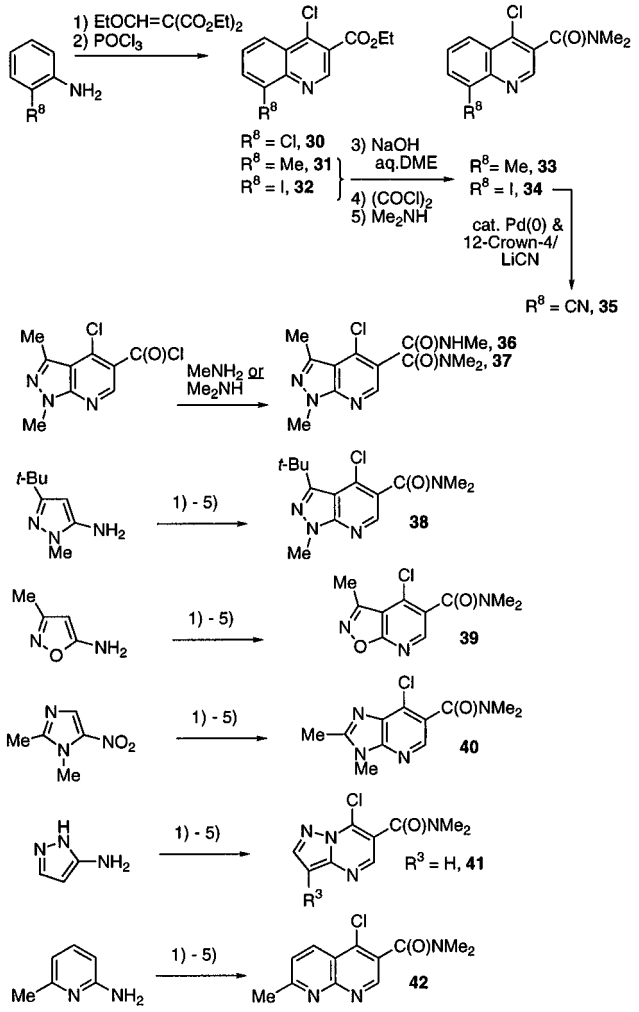


Scheme 4. Preparation of (Aryloxy)ethylamines

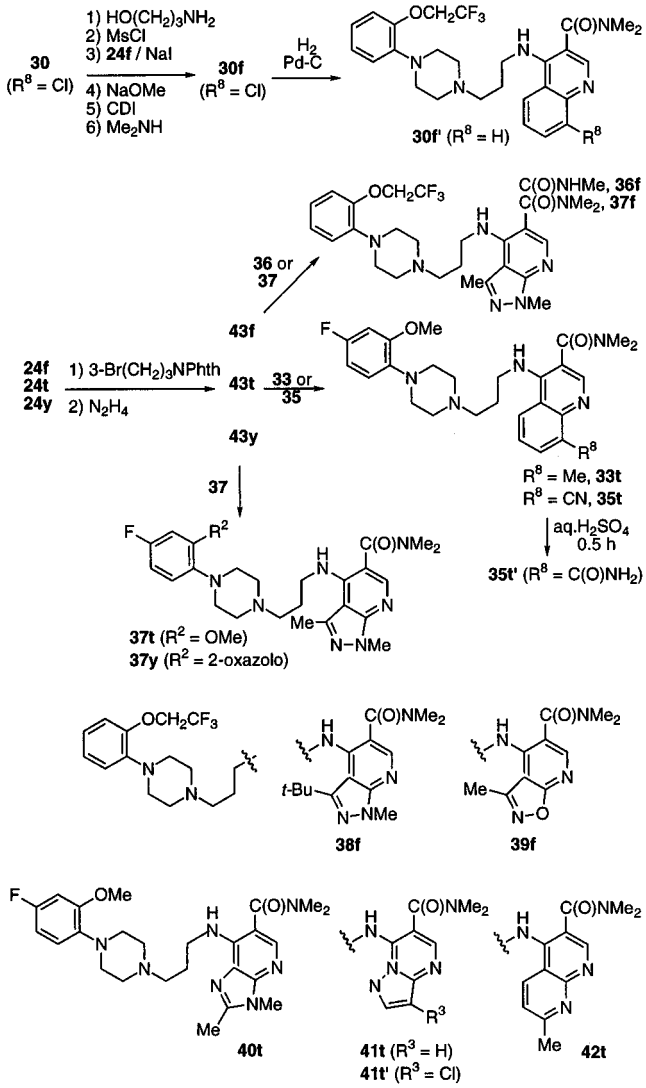


Scheme 1. Arylpiperazines **24f**, **24t**, and **24y** were homologated to 3-propylamines **43f**, **43t**, and **43y**, respectively. Amine **43f** was subjected to substitution conditions with **36** and **37** (as described for Scheme 1) to produce antagonists **36f** and **37f**. The quinolines **33**

Scheme 5. Preparation of Quinoline-, 1,8-Naphthyridine-, Pyrazolo[3,4-*b*]pyridine-, Isoxazolo[4,5-*b*]pyridine-, Imidazo[4,5-*b*]pyridine-, and Pyrazolo[1,5-*a*]pyrimidinecarboxamides



Scheme 6. Preparation of Bicyclic Carboxamide Antagonists



and **35** were smoothly converted to antagonists **33t** and **35t**. 8-Carboxamide **35t′** was obtained by hydrolysis of **35t**. Additional targets prepared by the later approach were **37t** and **37y** that were prepared from piperazines **24t** and **24y**, respectively. Chlorohetereocycles **38**, **39**, **40**,[29] **41**,[30] and **42** produced antagonists **38f**, **39f**, **40t**, **41t**, and **42t** respectively. Antagonist **41t** was chlorinated at the 3-position of the pyrazolo[1,5-*a*]pyrimidine[30] to produce **41t′**.

Results and Discussion

The primary screens employed in this program were functional assays: RBN and rat aorta for affinity estimates representative of the $\alpha_{1A/1L}$- and α_{1D}-ARs, respectively. These numbers were usually corroborated by displacement of [^{3}H]prazosin by test antagonists at all three cloned subtypes. However, the functional data derived from the RBN were of greater predictive value for the human target tissue compared with homogenate binding at the recombinant α_{1a}-AR (*vide supra*, Table 1). The next criteria were to identify novel and selective ligands. To the former, patents by Byk-Gulden[31] and Synthelabo,[11] had described primary carboxamides of pyridine and pyrimidine (*e.g.* **8**). The data summarized in Table 2 suggested that dialkylamides gave subtype selectivity. *N*-Monomethylnicotinamide **13i** and *N*,*N*-dimethylnicotinamide **13ii** possessed roughly the same affinity in the RBN assay. But, **13ii** displayed lower affinity in the rat aorta assay, and hence selective. No significant improvement was realized with pyrrolidinoamide **13iii**, nor ketones **13iv**,**v**. 4-Aminonicotinamide **18**, attachment isomer of **13ii**, and phenol **13vii** demonstrated the same decreased selectivity. Isomer **20** (of **13ii**) showed *no* subtype selectivity thus defining an optimal *ortho* relationship of amino attachment and the carboxamide. The more potent antagonist is amino-linked. The nitrogen analog **22i** is 2−3-fold more selective than its oxygen (**22iv**) and sulfur (**22v**) counterparts. Bis-amide **22vii** shows a 4-fold loss of affinity relative to **22i**, indicating a significance of electron donation.

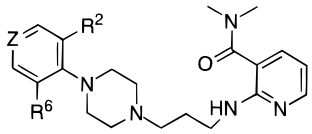
Diminished affinity at the α_{1D}-AR was revealed by the out-of-plane substituents (with respect to the π-carbonyl-aromatic overlap) of the carbonyls of **13i** (pA_2 value: 8.5, methylamide), **9** (8.0, *tert*-butylamide), **13ii** (7.7, dimethylamide), **13iv** (8.7, cyclopropyl ketone), and **13v** (8.2, *tert*-butyl ketone). The effect is substantiated in comparing **22i** (7.8) and benzophenone **22vi** (8.0) and may be explained by the likely capacity of **13i** and **22vi** to form an *intra*molecular H-bond. To resolve whether this intolerance of the α_{1D}-AR is due to an unfavorable H-bond acceptor presented by the carbonyl oxygen *or*

Table 2. Structure−Selectivity Relationships of Ketones and Amides of Benzene, Pyridine, and Pyrimidine

compound	scheme	RBN, pA_2 (α_{1a})[a]	rat aorta, pA_2
9	1	8.9 ± 0.1 (8.8 ± 0.2)	8.0 ± 0.2
11	1	NT[b] (9.9 ± 0.3)	8.0 ± 0.2
13i	1	9.0 ± 0.05	8.5 ± 0.1
13ii	1	8.8 ± 0.1 (9.1 ± 0.2)	7.7 ± 0.01
13iii	1	NT (9.1 ± 0.1)	7.7 ± 0.3
13iv	1	9.3 ± 0.03	8.7 ± 0.1
13v	1	NT (9.4 ± 0.3)	8.2 ± 0.2
13vi	1	9.1 ± 0.2	7.7 ± 0.1
13vii	1	8.7 ± 0.1	8.0 ± 0.1
o-MOPP(CH_2)$_3$NH-2-(4,6-dimethylnicotinamide), **17**	1	8.0 ± 0.1 (8.8 ± 0.2)	7.4 ± 0.03
o-MOPP(CH_2)$_3$NH-4-(*N*,*N*-dimethylnicotinamide), **18**	1	7.9 ± 0.1 (9.1 ± 0.2)	7.3 ± 0.2
o-MOPP(CH_2)$_3$NH-4-(*N*,*N*-diisopropylnicotinamide), **19**	1	NT (8.8 ± 0.2)	6.6 ± 0.2
o-MOPP(CH_2)$_3$NH-6-(*N*,*N*-dimethylnicotinamide), **20**	1	7.6 ± 0.1	7.5 ± 0.1
o-MOPP(CH_2)$_3$NH-4-(5-pyrimidine-*N*,*N*-dimethylcarboxamide), **21**	1	8.4 ± 0.1	7.3 ± 0.1
22i	2	9.0 ± 0.1 (9.4 ± 0.2)	7.8 ± 0.1
22ii	2	9.3 ± 0.1	7.7 ± 0.2
22iii	2	8.5 ± 0.1	7.2 ± 0.3
22iv	2	8.4 ± 0.1	7.5 ± 0.1
22v	2	8.7 ± 0.1	7.9 ± 0.1
22vi	2	7.5 ± 0.04	8.0 ± 0.2
22vii	2	NT (8.8 ± 0.04)	7.2 ± 0.1

[a] See ref *a* of Table 1. [b] NT = not tested.

Table 3. Selectivity Effects of Arylpiperazine Substitution on α_1-AR Subtype Antagonists



compound	Z	R^2	van der Waals radii (Å)[a]	R^6	scheme	RBN, pA_2 (α_{1a})[b]	rat aorta, pA_2
25a	CH	H	1.2	H	1	8.2 ± 0.1 (8.7 ± 0.2)	7.8 ± 0.2
25b	CH	CN	1.51	H	1	8.7 ± 0.05	8.0 ± 0.1
25c	CH	OH	1.53	H	1[c]	8.3 ± 0.1	7.2 ± 0.02
13ii	CH	OMe	1.52	H	1	8.8 ± 0.1 (9.1 ± 0.2)	7.7 ± 0.01
25d	CH	OEt	1.52+	H	1	9.3 ± 0.2	8.1 ± 0.04
25e	CH	OCF_3		H	1 (*via* **24e**)	8.5 ± 0.3	7.0 ± 0.1
25f	CH	OCH_2CF_3		H	1 (*via* **24f**)	10.0 ± 0.2	7.8 ± 0.2
25g	CH	OCH_2c-Pr	1.52+	H	1[d]	9.8 ± 0.2 (10.1 ± 0.3)	8.0 ± 0.3
25h	CH	OCH_2*t*-Bu	1.52+	H	1 (*via* **24h**)	NT[e] (9.1 ± 0.2)	7.3 ± 0.03
25i	CH	Ph	1.62	H	1 (*via* **24i**)	8.9 ± 0.2	7.2 ± 0.02
25j	CH	2-oxazolo		H	1 (*via* **24j**)	9.5 ± 0.1	7.6 ± 0.1
25k	CH	Me	1.80	H	1	8.7 ± 0.04 (9.1 ± 0.04)	8.0 ± 0.1
25l	N	Me	1.80	H	1 (*via* **24l**)	6.7 ± 0.2	NT
25m	CH	SMe	1.82	H	1	9.2 ± 0.03	7.5 ± 0.2
25n	CH	*n*-Pr	1.80+	H	1 (*via* **24n**)	9.7 ± 0.1	7.5 ± 0.04
25o	CH	Bn	1.80+	H	1 (*via* **24o**)	8.2 ± 0.1	7.1 ± 0.3
25p	CH	c-Pr	1.80+	H	1 (*via* **24p**)	9.2 ± 0.2	7.2 ± 0.1
25q	CH	*i*-Pr	2.2	H	1 (*via* **24q**)	9.4 ± 0.3	7.2 ± 0.2
25r	CH	CF_3	2.2	H	1 (*via* **24r**)	7.9 ± 0.1	6.5 ± 0.1
25s	CH	Me	1.80++	Me	1	NT (8.1 ± 0.1)	NT
25t	CF	OMe	1.52	H	1 (*via* **24t**)	8.8 ± 0.03	7.2 ± 0.1
25u	COH	OMe	1.52	H	1[f]	7.9 ± 0.05	7.1 ± 0.1
25v	COMe	OMe	1.52	H	1	7.5 ± 0.02	6.0 ± 0.2
25w	CMe	OMe	1.52	H	1 (*via* **24w**)	9.1 ± 0.1	7.4 ± 0.1
25x	CMe	1-pyrrolo		H	1 (*via* **24x**)	10.7 ± 0.3	7.9 ± 0.2

[a] See ref 32 of text. [b] See ref *a* of Table 1. [c] Prepared from the free base of **13ii** by the action of NaCN in boiling DMSO. [d] Prepared from **25c** with (bromomethyl)cyclopropane and cesium carbonate. [e] NT = not tested. [f] See Experimental Section.

an interaction of the substituent born on the carbonyl carbon, ligands **19** (7.3, dimethylamide) and **20** (6.6, diisopropylamide) appear to support the latter. 5-Methylanthranilamide **22ii** displayed higher affinity at the target tissue over its unsubstituted parent **22i** and its 6-methyl isomer **22iii**. The trend of affinity increase, in both assays, tracks with decreasing polarity of the aryl amide: Benzamide **22i** (pA_2 in the RBN, 9.0) > pyridinamide **13ii** (8.8) > pyrimidinamide **21** (8.4). Lower affinity was also observed with more polar amides such as pyridol **13vii** and nicotinamide **19**. These suggestions of a hydrophobic pocket were explored with the study of bicyclic compounds summarized in Table 4.

The α_1-ARs topologies were next examined by retaining the *N*,*N*-dimethyl-2-(*n*-propylamino)nicotinamide subunit and studying the substitution of the arylpiperazine. The data summarized in Table 3 suggests an additional selectivity feature(s) of the antagonists. The greater the size[32] of a *single ortho* moiety the greater the affinity **and** selectivity of the antagonist. The 2-methyl-substituted **25k** has 3-fold higher affinity than the unsubstituted parent **25a** and 10-fold greater than

Table 4. Uroselective Bicyclic Amide Antagonists

compound	scheme	RBN, pA_2 (α_{1a})[a]	rat aorta, pA_2
28a	4	8.8 ± 0.1 (8.8 ± 0.2)	7.2 ± 0.2
28b	4	7.7 ± 0.1	5.6 ± 0.2
28c	4	NT[b] (8.5 ± 0.05)	7.8 ± 0.01
30f	6	9.1 ± 0.2	6.9 ± 0.1
30f′	6	8.4 ± 0.2	7.0 ± 0.1
33t	6	8.1 ± 0.3	6.5 ± 0.1
35t	6	8.9 ± 0.03	6.4 ± 0.1
35t′	6	9.3 ± 0.1	6.8 ± 0.2
36f	6	10.0 ± 0.1	8.4 ± 0.1
37f	6	9.3 ± 0.2	6.9 ± 0.2
37t	6	8.9 ± 0.1	6.5 ± 0.1
37y	6	9.9 ± 0.1	6.7 ± 0.02
38f	6	8.6 ± 0.4	7.2 ± 0.1
39f	6	8.8 ± 0.1	7.1 ± 0.1
40t	6	9.2 ± 0.1	7.1 ± 0.1
41t	6	9.2 ± 0.1	7.0 ± 0.05
41t′	6	9.1 ± 0.02	6.8 ± 0.2
42t	6	8.9 ± 0.1	6.2 ± 0.1

[a] See Table 1, ref *a*. [b] NT = not tested.

the 2,6-dimethyl **25s**. However, the optimum substitutents are small alkyl, alkyloxy, or heterocyclic. The following antagonists **25d** (R^2 = OEt), **25q** (R^2 = *i*-Pr), **25g** (R^2 = OCH_2*c*-Pr), and **25f** (R^2 = OCH_2CF_3) displayed increasing affinity and selectivity. This trend is echoed by the small *o*-aryl-bearing targets **25i** (R^2 = Ph), **25j** (R^2 = 2-oxazolo), **25x** (R^2 = 1-pyrrolo). The following antagonists suggest a size restriction as what the $\alpha_{1A/1L}$-AR may tolerate. The neopentyloxy-substituted ligand **25h** displayed significantly lower affinity than (cyclopropylmethyl)oxy **25g** and benzyl **25o** was less affine than phenyl **25i**. The size sensitivity is also realized at a receptor contact area from the *para* position (relative to piperazine attachment). Antagonists **25t** (Z = CF) and **25w** (Z = CMe) share indistinguishable pharmacological properties and have higher affinity than phenol **25u** (Z = COH) which is a tighter binder than its methyl ether **25v** (Z = COMe). An additional feature was identified. The presence of electron-withdrawing substituents, regardless of size, led to loss of affinity: **25f** (R^2 = OCH_2CF_3) > **25e** (R^2 = OCF_3) > **25r** (R^2 = CF_3) with the exception of **25b**. The electron poor 4-pyridylpiperazine **25l** possessed almost micromolar affinity, a dramatic loss of activity to its carbacyclic comparator **25k**.

(Aryloxy)ethylamines are a known class of α-AR antagonists,[33] and we prepared some related nicotinamides for evaluation of α_1-AR subtype selectivity. The three (aryloxy)ethylamine ligands **28a**−**c** displayed lower affinity than their arylpiperazine counterparts but reveal some noteworthy points (Table 4). These ligands are incapable of *intra*molecular H-bonding, and subtype selectivity is retained with the *N*,*N*-dimethyl-2-(4-aminopiperidinyl)nicotinamide component, thus lending further support to the notion of out-of-plane carbonyl requirement of the ligand to interact with the $\alpha_{1A/1L}$-AR and reduce interaction with the α_{1D}-AR. *Ortho* substitution of the (aryloxy)ethylamine led to desired antagonist properties (*i.e.* **28a** is 8-fold more selective than **28c**) as also realized in the arylpiperazine series. The π-poor *ortho* substituent of **28b** provided a relatively low affinity ligand but is still subtype selective by *2 orders* of magnitude. Further outlined in Table 4, the first quinoline-3-carboxamides **30f** and **30f′** were derived from [*o*-(trifluoroethoxy)phenyl]piperazine **24f** and displayed significant subtype selectivity *if* the 8-position is substituted. The compounds in Scheme 6 were prepared to probe the tolerance of the ARs to peri and distal substitution as well as polarity of antagonists. Ligands **36f** (methylamide) and **37f** (dimethylamide) conferred increased affinities, with 40- and 250-fold subtype selectivity, respectively, and thus all successors would bear dimethylamide. Quinolines **33t**, **35t**, and **35t′** displayed remarkably similar properties, despite the changes from R^8 = Me, CN, to C(O)NH_2, respectively. Oxazole-bearing **37y** gave greater than 1000-fold subtype selectivity, furnishing additive selectivity elements in both arylpiperazine and heteroarylamide moieties. 3-*tert*-Butylpyrazolopyridine **38f** revealed lower affinity and selectivity compared to 3-methyl **37f**, thus demonstrating that a bulky peri substituent unfavorably restrains the aminopropane linker over the carboxamide. The best comparators for removal of this feature are quinoline **33t** and imidazopyridine **40t**. Antagonist **40t**, which bears no peri substituent, displays subnanomolar affinity at the target receptor and 100-fold selective while **33t** bears a peri-H and has 10-fold lower affinity. The selective pharmacological properties of **40t** are present even with increased polarity of the ligand. The latter was noted earlier (*i.e.* compare affinities of **22i**, **13ii**, and **21**) as a feature leading to diminished affinity. Removal of the distal substituent of **37f** provides **39f**, which is less potent and less selective. This effect mirrors that observed with quinolines **30f** and **30f′**, but is less pronounced in the more polar ligands pyrazolopyrimidines **41t** (R^3 = H) and **41t′** (R^3 = Cl).

Table 5. Binding Affinities of Selected Antagonists[a]

compound	α_{2B}[b]	D_2[c]	5-HT_{1A}[d]	human prostate[e]
13ii	ND[f]	7.4 ± 0.1	7.6 ± 0.1	8.5 ± 0.1
22ii	6.5 ± 0.1	7.3 ± 0.05	8.0 ± 0.04	9.0 ± 0.1
25t	6.5 ± 0.2	6.7 ± 0.3	6.7 ± 0.1 (1.5)	8.5 ± 0.1
25i	7.1 ± 0.2	6.9 ± 0.2 (ND)	ND	ND
37f[g]	8.6 ± 0.2 (0.6)	8.1 ± 0.1	7.5 ± 0.2 (1.3)	9.0 ± 0.1
37t	ND	6.4 ± 0.3 (0.6)	6.5 ± 0.1	9.3 ± 0.1

[a] Mean pK_i values with a minimum of three determinations and mean Hill coefficients ranging from 0.8 to 1.1 except where noted in parentheses. [b] [^{3}H]Rauwolscine (New England Nuclear) displacement from rat kidney homogenate in the presence of 10 μM phentolamine. [c] pK_i estimate: Theodorou, A. E.; *et al. J. Pharm. Pharmacol.* **1980**, *32*, 441. [d] Michel, A. D.; Whiting, R. L. *Br. J. Pharmacol.* **1984**, *83*, 460p. [e] See ref 9 and Experimental Section for pA_2 determinations. [f] ND = not determined. [g] pK_i value <5 in $GABA_A$-benzodiazepine (rat brain) binding.

Conclusions

Table 5 summarizes select data of novel α_1-AR subtype selective antagonists at other 7-TM receptors, as well as their affinities at the target tissue. Nicotinamides **25t** and **25i** as well anthranilamide **22ii** show low (micromolar) affinities at the α_{2B}-AR. Furthermore, the possibility of depressor action *via* CNS 5-HT receptor activation[10] would appear, as well as metabolic considerations that will be presented in subsequent reports, to have excluded **22ii** from further evaluation. Pyrazolopyridines **37f** and **37t**, having displayed selective lower urinary tract blockade *in vivo*,[34] were evaluated in the dog for pharmacokinetics and **37f** produced emesis. This latter effect could be suppressed by coadminitration with the D_2-antagonist domperidone; therefore **37f** was removed from clinical consideration.

The data produced from studying isolated prostatic (human) tissue suggested that data gathered from the displacement of [^{3}H]prazosin (bovine-cloned α_{1a}) over-

estimated affinity values of test antagonists. Affinity estimates obtained from strips of rabbit bladder neck served predictive as a primary screen for the progression of drug discovery for the treatment of BPH. The predominantly expressed adrenoceptor in the human lower tract is the α_{1a}. However, it bears functional pharmacological distinction and hence was termed $\alpha_{1A/1L}$. The novel heteroarylamide antagonists described in this article point to a common mode of interaction at the $\alpha_{1A/1L}$- and α_{1D}-ARs despite the differences in size or conformational restriction. Antagonist **13ii** (RS-97078) has been studied in healthy volunteer men (ages 18−70 years) following oral administration of single doses ranging from 2.5 to 30 mg. A clinically efficacious dose is expected to be in the range of 5−15 mg/80 kg man for an agent of this affinity. These findings may be reported by the clinical investigators in due course.

Experimental Section

Pharmacology. Estimates of affinity for antagonists were obtained as described elsewhere.[9] In the case of rabbit bladder neck (RBN), strips of smooth muscle tissue approximately 8−10 mm long and 2−3 mm wide were taken in a longitudinal manner from the area of urothelium denuded bladder between trigone and the first 3−4 mm of proximal urethra. RBN tissues were then used as described elsewhere for human lower urinary tract tissues. All assays employed cumulative concentration−effect curves using norepinephrine (NE; rat aorta and human LUT) or phenylephrine (PE; RBN). Affinity determinations for several antagonists were calculated by full Schild regression analysis. For many novel compounds, affinity estimates were calculated from data with two antagonist concentrations by assuming a competitive, reversible interaction at a singular subtype according to the following equation: apparent $pA_2 = -\log[B] + \log(r - 1)$, where [B] is concentration of test compound and r is the ratio of concentrations of agonist required to generate 50% maximal response in presence and absence of test compound. Mean pA_2 values are reported for a minimum of three determinations on tissues obtained from at the least two animals where in all cases standard errors of the mean were less than 0.3.

Chemistry. General: ^{1}H (300 MHz) and ^{13}C NMR spectra are reported in ppm (δ) with tetramethylsilane at 0.0 ppm using $CDCl_3$ for free bases and DMSO-d_6 for salts. The following abbreviations are used: CDI = 1,1′-carbonyldiimdazole, DMF = dimethylformamide, THF = tetrahydrofuran (distilled from sodium benzophenone ketyl), NIS = *N*-iodosuccinimide, NMP = 1-methyl-2-pyrrolidinone, DCE = 1,2-dichloroethane, SGC = silica gel chromatography, TFA = trifluoroacetic acid, rt = room or ambient temperature, and brine refers to an aqueous saturated solution of NaCl. The following piperazines were purchased (registry numbers supplied by author): 1-phenyl- [Reg. No. 92-54-6], (2-cyano)phenyl- [Reg. No. 111373-03-6], (2-methoxy)phenyl- (*o*-MOPP-H) [Reg. No. 5464-78-8], (2-ethoxy)phenyl- [Reg. No. 83081-75-8], (2-mercaptomethyl)phenyl- [Reg. No. 1013-24-7], (2-methyl)phenyl- [Reg. No. 39512-51-1], (2,6-dimethyl)phenyl- [Reg. No. 1012-91-5], and (2,4-dimethoxy)phenyl- [Reg. No. 16015-75-1].

Compounds Described in Scheme 1. *N,N*-Dimethyl 2-Chloronicotinamide (14ii). 2-Chloronicotinic acid (19.55 g, 124 mmol) was suspended in CH_2Cl_2 (200 mL) and cooled to 0 °C, and $(COCl)_2$ (16 mL, 186 mmol) was added slowly. A few drops of DMF were added, and the mixture was heated to reflux for 4 h. Upon cooling, the solvent was evaporated to give a crude oil. The crude material was dissolved in THF (200 mL), cooled to 0 °C, and treated with aqueous Me_2NH (40 mL). The mixture was stirred at rt for 3 h, solvent was removed *in vacuo*, the residue was extracted with Et_2O (3 × 100 mL), and the crude oil was crystallized from hexanes/*i*-Pr_2O/acetone to give a white solid (18.55 g, 83%): mp 69−70 °C (lit.[35] bp 142−145° (4.1 mmHg)); ^{1}H NMR δ 2.90 (s, 3 H), 3.15 (s, 3 H), 7.31 (dd, 1 H, J = 4.8 and 7.5 Hz), 7.67 (dd, 1 H, J = 1.8 and 7.5 Hz), 8.43 (dd, 1 H, J = 1.8 and 4.5 Hz); ^{13}C NMR δ 34.66, 37.98, 122.64, 132.59, 136.83, 146.91, 149.89, 166.44.

Representative Procedure for Test Compounds Prepared by Scheme 1 (and in Table 3). *N,N*-Dimethyl 2-[[3-[4-(2-Methoxyphenyl)piperazin-1-yl]propyl]amino]nicotinamide Hydrochloride (13ii). 1-(2-Methoxyphenyl)-piperazine (5.03 g, 26.2 mmol), *N*-(3-bromopropyl)phthalimide (7.01 g, 26.2 mmol), and K_2CO_3 (3.62 g, 26.2 mmol) were suspended in DMF (60 mL) and heated to 90 °C for 4 h. The mixture was partitioned between H_2O and Et_2O (100 mL, 4×). The combined organic fractions were washed with brine and dried over $MgSO_4$, and solvent was evaporated. The crude material was purified by SGC (hexanes/EtOAc, 3:2, tr. Et_3N) to give a clear oil (8.60 g, 82%): ^{1}H NMR δ 1.91 (quin, 2 H, J = 6.9 Hz), 2.49 (t, 2 H, J = 6.9 Hz), 2.57 (broad s, 4 H), 2.92 (broad s, 4 H), 3.79 (t, 2 H, J = 6.9 Hz), 3.83 (s, 3 H), 6.79−7.01 (m, 4 H), 7.65−7.72 (m, 2 H), 7.83−7.89 (m, 2 H). To a solution of the phthalimide (8.60 g, 21.66 mmol) in absolute EtOH (60 mL) was added $N_2H_4 \cdot H_2O$ (2.1 mL, 43.2 mmol). The mixture was heated to reflux for 3 h, cooled to rt, triturated with Et_2O, filtered, diluted with H_2O (70 mL) and 1 N NaOH (70 mL), and extracted with Et_2O (150 mL, 2×). The combined organic fractions were washed with brine and dried over $MgSO_4$, and the solvent was evaporated to give a clear oil. The crude oil (3.62 g, 13.5 mmol), **14ii** (2.50 g, 13.5 mmol), and K_2CO_3 (1.86 g, 13.5 mmol) were suspended in anhydrous xylenes (50 mL) and heated to reflux for 20 h. After cooling to rt, the title compound was obtained following extraction [EtOAc (100 mL, 3×) and H_2O], drying (brine wash and $MgSO_4$), concentration, and SGC (CH_2Cl_2/MeOH, 96:4, tr. Et_3N) to give a clear oil, **13ii** (2.6 g, 48%). A salt was obtained from a HCl/EtOH solution: mp 203.8−204.4 °C; ^{1}H NMR δ 1.95−2.10 (m, 2 H), 2.94 (broad s, 6 H), 3.12 (t, 2 H, J = 7.2 Hz), 3.18−3.50 (m, 10 H), 3.79 (s, 3 H), 6.40 (s, broad, 1 H), 6.58 (dd, 1 H, J = 4.8, 7.2 Hz), 6.88−7.05 (m, 4 H), 7.37 (dd, 1 H, J = 1.8, 7.2 Hz), 8.08 (dd, 1 H, J = 1.8, 4.9 Hz); ^{13}C NMR δ 23.5 (t), 37.9 (t), 46.9 (t), 51.1 (t), 53.6 (t), 55.4 (q), 111.1 (d), 111.9 (d), 115.9 (s), 118.2 (d), 120.8 (d), 123.4 (d), 135.7 (d), 139.5 (s), 148.3 (d), 151.8 (s), 154.4 (s), 167.9 (s); MS *m/z* 397 (M^+), 382 (M^+ loss of Me), 192. Anal. ($C_{22}H_{31}N_5O_2 \cdot$HCl) C, H, N.

2-[[3-[4-(2-Methoxyphenyl)piperazin-1-yl]propyl]amino]nicotinonitrile hydrochloride (10): (39%) mp 190−192 °C. Anal. ($C_{20}H_{25}N_5O \cdot (HCl)_2$) C, H, N.

***N-tert*-Butyl 2-[[3-[4-(2-methoxyphenyl)piperazin-1-yl]-propyl]amino]nicotinamide Oxalate (9).** Compound **10** (380 mg, 0.89 mmol) was dissolved in a mixture of H_2SO_4 (0.75 mL) and *t*-BuOH (1.0 mL) and stirred at rt for 14 h. The reaction mixture was cooled to 0 °C, made basic with a 50% aqueous NaOH solution, and extracted with Et_2O (75 mL, 3×). The desired compound was obtained following drying ($MgSO_4$), concentration, and SGC (CH_2Cl_2/MeOH, 95:5, trace Et_3N) to give an oil which was converted into an oxalate salt **9** (400 mg, 83%): mp 89.0−91.0 °C. Anal. ($C_{24}H_{35}N_5O_2(C_2H_2O_4)_{1.5}$) C, H, N.

2-[[3-[4-(2-Methoxyphenyl)piperazin-1-yl]propyl]amino]nicotinamide Hydrochloride (11). Compound **10** (400 mg, 0.94 mmol) was dissolved in an aqueous 90% solution of H_2SO_4 (15 mL) and stirred at 90 °C for 0.5 h. The reaction was cooled to 0 °C, made basic with a 50% aqueous NaOH solution, and extracted with CH_2Cl_2 (50 mL, 3×). The combined organic fractions were acidified with a HCl/EtOH solution and solvent removed to give a white solid **13** (227 mg, 51%): mp 240−242 °C. Anal. ($C_{20}H_{27}N_5O_2 \cdot (HCl)_3$) C, H, N.

***N*-Methyl-2-[[3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl]amino]nicotinamide hydrochloride (13i):** from *N*-methyl-2-chloronicotinamide (**14i**: mp 110.1−111.8 °C; lit.[35] mp 90−92 °C) in 75% yield; mp 160.8−161.8 °C. Anal. ($C_{21}H_{29}N_5O_2 \cdot (HCl)_3 \cdot (EtOH)_{0.65}$) C, H, N.

Pyrrolidino-2-[[3-[4-(2-methoxyphenyl)piperazin-1-yl]-propyl]amino]nicotinamide hydrochloride (13iii): from **14iii** in 48% yield; mp 223.1−223.9 °C. Anal. ($C_{24}H_{33}N_5O_2 \cdot$HCl) C, H, N.

3-(2-Chloropyridyl) Cyclopropyl Ketone (14iv). Cyclopropyltributyltin[36] (3.2 g, 9.6 mmol) in THF (20 mL) at −78

°C was treated with *n*-BuLi (3.8 mL, 2.5 M, 9.5 mmol) and stirred at 0 °C for 0.5 h. The resulting solution was transferred to a −40 °C suspension of CuI (914 mg, 4.8 mmol) in THF (15 mL) and stirred for 45 min. 2-Chloronicotinyl chloride (793 mg, 4.5 mmol) was added in 10 mL of THF, and stirring was continued at −40 °C for an additional 1.5 h. Upon warming to rt, the reaction was quenched with aqueous NH_4Cl, stirred with CH_2Cl_2 (100 mL), and filtered, and the organic layer was separated. It was dried (Na_2SO_4), evaporated, and subjected to SGC, eluting with 9:1 hexanes:EtOAc. Ketone **14iv** was obtained as an oil (451 mg, 2.5 mmol, 55%): IR (neat) 3011, 1682 cm^{-1}; ^1H NMR δ 1.14−1.20 (m, 2 H), 1.36 (quin, 2 H, J = 3.8 Hz), 2.51−2.59 (m, 1 H), 7.33 (dd, 1 H, J = 4.5, 7.8 Hz), 7.83 (dd, 1 H, J = 1.8, 4.8 Hz); MS *m/z* 183 (M^+ with ^{37}Cl), 181 (M^+ with ^{35}Cl), 140 (M^+ loss of Pr).

Cyclopropyl2-[[3-[4-(2-methoxyphenyl)piperazin-1-yl]-propyl]amino]pyrid-3-yl ketone maleate (13iv): 47% yield; mp 159.4−161.3 °C. Anal. ($C_{23}H_{30}N_4O_2 \cdot C_4H_4O_4$) C, H, N.

***tert*-Butyl 3-(2-chloropyridyl) ketone (14v):** 77% yield prepared from 2-chloronicotinoyl chloride prepared as **14iv** was prepared: IR (neat) 2972, 1705 cm^{-1}; ^1H NMR δ 1.29 (s, 9 H), 7.27 (dd, 1 H, J = 1.8, 4.8 Hz), 7.50 (dd, 1 H, J = 2.4, 7.5 Hz), 8.43 (dd, 1 H, J = 1.8, 4.8 Hz); MS *m/z* 199 (M^+ with ^{37}Cl), 197 (M^+ with ^{35}Cl), 142 (M^+ loss of Bu with ^{37}Cl), 140 (M^+ loss of Bu with ^{35}Cl).

***tert*-Butyl 2-[[3-[4-(2-methoxyphenyl)piperazin-1-yl]-propyl]amino]pyrid-3-yl ketone maleate (16v):** 41% yield; mp 122.3−126.0 °C. Anal. ($C_{24}H_{34}N_4O_2 \cdot (C_4H_4O_4)_{1.0} \cdot (H_2O)_{0.4}$) C, H, N.

***N,N*-Dimethyl-2-chloro-5-iodonicotinamide (15).** A DMF (200 mL) solution of 2-hydroxynicotinic acid (13.3 g, 95.7 mmol) and NIS (33.6 g, 149 mmol) was stirred in an Al foil wrapped flask at rt for 4 days then heated to 50 °C for 15 h. A short-path distillation head was attached, and the volatiles were removed at reduced pressure while the pot temperature was increased to 75 °C. Upon cooling, the pot residue was partitioned between H_2O and EtOAc. Solids were collected and dried *in vacuo* at 80 °C, providing 21.3 g of a gray powder. The 5-iodo acid [*ca.* 70% pure by ^1H NMR δ 7.71 (d, 1 H, J = 2.7 Hz), 8.03 (d, 1 H, J = 2.7 Hz); MS *m/z* 265 (M^+), 221 (M^+ loss of CO_2); 9.1 g, *ca.* 24 mmol] was suspended in $SOCl_2$ (35 mL) and 3 drops of DMF and heated to reflux for 3 h. A short-path still head was attached, and the excess $SOCl_2$ was removed under 1 atm of N_2 and chased with 10−20 mL of DCE. Upon cooling and dilution with DCE (50 mL), the suspension was cooled to 0 °C and treated with Et_3N (8.5 mL, 61 mmol) and Me_2NH (13 mL, 2 M THF, 26 mmol). After 15 min at 0 °C, the dark solution was partitioned between aqueous $NaHCO_3$ and CH_2Cl_2 (3 × 50 mL). The combined extracts were dried (Na_2SO_4), and the volatiles were removed and subjected to SGC (elute with 5:1 hexanes:acetone). The desired compound was obtained as a pale yellow solid (3.5 g, 11.3 mmol): mp 130.0−131.4 °C; IR 3040, 1628 cm^{-1}; ^1H NMR δ 2.92 (s, 3 H), 3.13 (s, 3 H), 7.94 (d, 1 H, J = 2.4 Hz), 8.63 (d, 1 H, J = 2.4 Hz); MS *m/z* 311 (M^+ with ^{37}Cl), 309 (M^+ with ^{35}Cl), 266 (M^+ loss Me_2N with ^{35}Cl).

***N,N*-Dimethyl-2-chloro-5-cyanonicotinamide (14vi).** A DMF solution of LiCN (20 mL, 0.5 M, 10 mmol) was evaporated to dryness and treated with the following: benzene (50 mL), 12-crown-4 (0.20 mL, 1.25 mmol), $[Ph_3P]_4Pd$ (2.2 g, 1.9 mmol),[16] and **15** (1.54 g, 5.0 mmol). The resulting suspension was stirred at 50 °C for 1 week, partitioned between pH 10 buffer and EtOAc (3 × 50 mL), dried (Na_2SO_4), and subjected to SGC (elute with 5:1 hexanes:acetone). Amide **14vi** was obtained as a solid (570 mg, 2.7 mmol, 54%): mp 148.0−152.5 °C; IR 3063, 2238, 1647 cm^{-1}; ^1H NMR δ 2.92 (s, 3 H), 3.17 (s, 3 H), 7.92 (d, 1 H, J = 2.4 Hz), 8.69 (d, 1 H, J = 2.4 Hz); MS *m/z* 211 (M^+ with ^{37}Cl), 209 (M^+ with ^{35}Cl), 167 (M^+ loss Me_2N with ^{37}Cl), 165 (M^+ loss Me_2N with ^{35}Cl).

***N,N*-Dimethyl-5-cyano-2-[[3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl]amino]nicotinamide oxalate (13vi):** mp 126.0−128.5 °C. Anal. ($C_{23}H_{30}N_6O_2 \cdot (C_2H_2O_4)_{1.5}$) C, H, N.

***N,N*-Dimethyl-2-chloro-5-[[(2-methoxyethoxy)methyl]-oxy]nicotinamide (13vii).** A THF (80 mL) solution of **15** (2.18 g, 7.0 mmol) was cooled to −90 °C and treated with *t*-BuLi (9.8 mL, 1.5 M, 14.8 mmol) dropwise and stirred 10 min. A THF (30 mL) solution of (−)-(10-camphorsulfonyl)-oxaziridine **16** (1.76 g, 7.7 mmol) was added rapidly *via* syringe, and stirring was continued for an additional 10 min. The desired phenol was obtained following aqueous NH_4Cl/EtOAc (4 × 50 mL) extraction, drying (Na_2SO_4), and SGC (elute with 2:1 hexanes:acetone) as a powder (478 mg, 34%): ^1H NMR δ 2.95 (s, 3 H), 3.17 (s, 3 H), 7.09 (d, 1 H, J = 2.7 Hz), 7.97 (d, 1 H, J = 3.0 Hz), 9.2 (broad s, 1 H); MS *m/z* 202 (M^+ with ^{37}Cl), 200 (M^+ with ^{35}Cl), 158 (M^+ loss Me_2N with ^{37}Cl), 156 (M^+ loss Me_2N with ^{35}Cl). The phenol (410 mg, 2.05 mmol) was dissolved in CH_2Cl_2 (20 mL) and (*i*-Pr)$_2$NEt (0.43 mL, 2.4 mmol) at 0 °C and treated with MEMCl (0.25 mL, 2.1 mmol). After 14 h at rt, the desired ether was obtained following extraction with aqueous NH_4Cl/CH_2Cl_2 (4 × 20 mL), drying (Na_2SO_4), and filtration through a pad of SiO_2, as an oil (472 mg, 78%): ^1H NMR δ 2.92 (s, 3 H), 3.14 (s, 3 H), 3.36 (s, 3 H), 3.53−3.56 (m, 2 H). 3.81−3.84 (m, 2 H), 5.29 (s, 2 H), 7.40 (d, 1 H, J = 3.0 Hz), 8.22 (d, 1 H, J = 3.0 Hz).

***N,N*-Dimethyl-5-hydroxy-2-[[3-[4-(2-methoxyphenyl)-piperazin-1-yl]propyl]amino]nicotinamide hydrobromide (13vii):** mp 197.7−199.3 °C. Anal. ($C_{22}H_{31}N_5O_3 \cdot (HBr) \cdot (H_2O)_{0.3}$) C, H, N.

4,6-Dimethyl-2-[[3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl]amino]nicotinamide hydrochloride (17): 44% yield from **12** and 2-chloro-4,6-dimethylnicotinamide;[18] mp 260.0−261.0 °C. Anal. ($C_{22}H_{31}N_5O_2 \cdot (HCl)_3$) C, H, N.

***N,N*-Dimethyl-4-[[3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl]amino]nicotinamide hydrochloride (18):** 80% yield from *N,N*-dimethyl-4-chloronicotinamide; mp 169.5−172.0 °C. Anal. ($C_{22}H_{31}N_5O_2 \cdot (HCl)_3 \cdot (H_2O)_{1.6}$) C, H, N.

***N,N*-Diisopropyl-4-[[3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl]amino]nicotinamide hydrochloride (19):** 30% yield from *N,N*-diisopropyl-4-bromonicotinamide;[20] mp 128−136 °C. Anal. ($C_{26}H_{39}N_5O_2 \cdot (HCl)_{2.5}$) C, H, N.

***N,N*-Dimethyl-6-[[3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl]amino]nicotinamide hydrobromide (20):** 16% yield from *N,N*-dimethyl-6-chloronicotinamide; mp 188−192 °C. Anal. ($C_{22}H_{31}N_5O_2 \cdot (HBr)_{1.2}$) C, H, N.

***N,N*-Dimethyl-4-[[3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl]amino]pyrimidine-5-carboxamide oxalate (21):** 19% yield from *N,N*-dimethyl-4-chloropyrimidine-5-carboxamide; mp 103−112 °C. Anal. ($C_{21}H_{30}N_6O_2 \cdot (C_2H_2O_4)_{2.2}$) C, H, N.

Compounds Prepared According to Scheme 2. 3-[4-(2-Methoxyphenyl)piperazin-1-yl]-1-propanol. A mixture of 3-bromopropanol (10.5 mL, 116 mmol), 1-(2-methoxyphenyl)-piperazine (21 g, 109.2 mmol), sodium iodide (16.4 g, 109 mmol), and K_2CO_3 (38 g, 275 mol) in 300 mL of acetonitrile was heated at reflux for 3 h. The mixture was cooled and filtered. The filtrate was washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by SGC, eluting with 5% MeOH/CH_2Cl_2. The title compound was obtained as a powder (24.5 g, 97.86 mmol): mp 88−89 °C; ^1H NMR δ 1.78 (m, 2 H, $CH_2CH_2CH_2$), 2.71 (t, 2 H, J = 5.9 Hz, NCH_2), 2.76 (m, 4 H, piperazine *H*), 3.10 (m, 4 H, piperazine *H*), 3.82 (t, 2 H, J = 5.2 Hz, CH_2OH), 3.86 (s, 3 H, OMe), 6.85−7.07 (m, 4 H, aromatic); ^{13}C NMR δ 24.9 (t), 50.5 (t), 53.5 (t), 55.4 (q), 58.6 (t), 64.3 (t), 111.2 (d), 118.3 (d), 121.2 (d), 124.0 (d), 141.0 (s), 152.2 (s); HRMS calcd for $C_{14}H_{22}N_2O_2$ 250.1681, found 250.1677.

2-Amino-*N,N*,5-trimethylbenzamide (23ii). A mixture of 5-methyl-2-nitrobenzoic acid (10 g, 55.2 mmol) and $(COCl)_2$ (6 mL, 68.8 mmol) in 100 mL of CH_2Cl_2 was stirred under Ar at rt for 2 h. The mixture was concentrated, and the residue was evaporated twice with toluene. The residue was dissolved in 60 mL of dioxane, and the solution was added dropwise to a mixture of aqueous Me_2NH (8.2 g, 40% w/w, 72.7 mmol) and NaOH (2.2 g, 55 mmol) in 20 mL of dioxane at 10 °C. The mixture was stirred at rt for 1 h and then poured into water. The mixture was extracted with EtOAc (2 × 150 mL), dried (Na_2SO_4), filtered, and concentrated to give 11 g. This product and 5% Pd/C (1 g) in EtOH (100 mL) was stirred under H_2 for 18 h. Additional 5% Pd/C (1 g) was added, and the mixture was stirred for approximately 8 h. The mixture was filtered, and the filtrate was concentrated. **23ii** was purified by SGC, eluting with 4% EtOH/CH_2Cl_2 (8 g, 44.9 mmol): mp 98−99

°C; ^{1}H NMR δ 2.22 (s, 3 H, ArCH_3), 3.05 (s, 6 H, N(CH_3)$_2$), 6.63 (d, 1 H, J = 8.1 Hz, H-3), 6.90 (d, 1 H, J = 1.5 Hz, H-6), 6.96 (dd, 1 H, J = 1.5, 8.1 Hz, H-4); ^{13}C NMR δ 20.3 (q, *C*H$_3$-Ar), 38.0 (q, N(*C*H$_3$)$_2$), 116 (d, *C*-3), 120.7 (s, *C*-2), 126.7 (s, *C*-5), 128.1 (d, *C*-6), 131.1 (d, *C*-4), 142.8 (s, *C*-1), 171.2 (s, *C*(O)N); MS *m*/*z* 178 (M$^+$). Anal. ($C_{10}H_{14}N_2O\cdot(H_2O)_{0.25}$) C, H, N.

Representative Procedure for Targets Prepared According to Scheme 2. 2-[[3-[4-(2-Methoxyphenyl)piperazin-1-yl]propyl]amino]-*N*,*N*,5-trimethylbenzamide Hydrochloride (22ii). 3-[4-(2-Methoxyphenyl)piperazin-1-yl]-1-propanol (24 g, 95.87 mmol) dissolved in Et_3N (25 mL, 180 mmol) and CH_2Cl_2 (300 mL) was cooled to 0 °C, and then MsCl (8.8 mL, 114 mmol) was added dropwise. The mixture was stirred at 0 °C for 1 h and then at rt for 0.5 h. The mixture was poured into saturated Na_2CO_3 and stirred for 15 min. The organic phase was separated, washed with saturated Na_2CO_3 (2 × 150 mL), dried ($MgSO_4$), and concentrated to give 3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl methanesulfonate (21 g, 63.6 mmol). This product (656.8 mg, 2.0 mmol), **23ii** (356.0 mg, 2.0 mmol), and K_2CO_3 (560.1 mg, 4.05 mmol) in CH_3CN (25 mL) were heated at reflux for 25 h. The mixture was poured into water and extracted with EtOAc (3 × 50 mL). **22ii** (400 mg, 0.97 mmol, 48%) was obtained following drying (K_2CO_3), concentration, and SGC (eluant 6% MeOH/CH_2Cl_2), which formed a precipitate from 0.9 mL of 1 M HCl in MeOH and Et_2O: mp 85 °C dec; ^{1}H NMR δ 1.80−1.90 (m, 2 H), 2.22 (s, 3 H), 2.53 (t, 2 H, J = 7.0 Hz), 2.67 (broad s, 4 H), 3.04 (s, 6 H), 3.12 (broad s, 4 H), 3.17 (t, 2 H, J = 7.0 Hz), 3.86 (s, 3 H), 4.94 (broad s, 1 H), 6.63 (d, 1 H, J = 8.4 Hz), 6.84−7.05 (m, 6 H); ^{13}C NMR δ 20.1 (q), 26.3 (t), 42.2 (t), 50.3 (t), 53.41 (t), 55.3 (q), 56.3 (t), 111.1 (d), 111.6 (d), 118.2 (d), 120.1 (s), 120.9 (d), 122.8 (d), 124.8 (s), 128.2 (d), 131.1 (d), 141.2 (s), 144.3 (s), 152.2 (s), 171.4 (s); MS *m*/*z* 410 (M$^+$). Anal. ($C_{24}H_{34}N_4O_2\cdot HCl\cdot(H_2O)_{1.5}$) C, H, N.

***N*,*N*-Dimethyl-2-[[3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl]amino]benzamide hydrochloride (22i):** 66% yield from *N*,*N*-dimethyl-2-aminobenzamide, **23i**;[37] mp 74−79 °C. Anal. ($C_{23}H_{33}N_4O_2\cdot HCl\cdot(H_2O)_{0.5}$) C, H, N.

***N*,*N*-Dimethyl-2-[[3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl]amino]-6-methylbenzamide hydrochloride (22iii):** 31% yield from **23iii**; mp 66−70.5 °C. Anal. ($C_{24}H_{34}N_4O_2\cdot(HCl)_2\cdot H_2O$) C, H, N.

***N*,*N*-Dimethyl-2-[[3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl]oxy]benzamide hydrochloride (22iv):** 13% yield from **23iv**; mp 160−162 °C. Anal. ($C_{23}H_{31}N_3O_3\cdot(HCl)_2$) C, H, N.

***N*,*N*-Dimethyl-2-[[3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl]thio]benzamide hydrochloride (22v):** 27% yield from **23v**; mp 174−177 °C. Anal. ($C_{23}H_{32}N_3O_2S\cdot HCl\cdot H_2O$) C, H, N.

2-[[3-[4-(2-Methoxyphenyl)piperazin-1-yl]propyl]amino]benzophenone hydrochloride (22vi): 21% yield from 2-aminobenzophenone; mp 96−165 °C. Anal. ($C_{27}H_{32}N_3O_2\cdot HCl\cdot H_2O$) C, H, N.

***N*,*N*-Dimethyl-2-[*N*-[4-(2-methoxyphenyl)piperazin-1-yl]propanamido]benzamide Hydrochloride (22vii). 23i**[37] (1.75 g, 10.6 mmol) was dissolved in Et_3N (1.5 mL, 10.8 mmol) and CH_2Cl_2 (30 mL), cooled to 0 °C, treated with acryloyl chloride (1.0 mL, 12.3 mmol) dropwise, and then stirred at rt for 3 h. The bis-amide was obtained by filtration through a pad of Na_2SO_4 and concentrated to give 2.19 g as an oil, which was partially characterized: ^{1}H NMR δ 3.02−3.19 (m, 6 H), 5.75 (dd, 1 H, J = 1.5, 9.9 Hz), 6.25 (dd, 1 H, J = 9.9, 17.2 Hz), 6.39 (dd, 1 H, J = 1.5, 17.0 Hz), 7.11 (dt, 1 H, J = 1.2, 6.6 Hz), 7.26 (dd, 1 H, J = 1.6, 6.6 Hz), 7.42 (dt, 1 H, J = 1.5, 6.9 Hz), 8.35 (d, 1 H, J = 8.4 Hz), 9.36 (broad s, 1 H). The crude acrylamide was dissolved in THF (20 mL) and treated with *o*-MOPP-H (961 mg, 4.99 mmol), stirred at rt for 20 h, and heated to 45 °C for 6 h. The title compound **22vii** was purified by SGC (1.1 g, 2.68 mmol, 56%; eluent 8% MeOH/CH_2Cl_2) and formed a solid from 1 M HCl/MeOH: mp 120 °C dec. Anal. ($C_{23}H_{30}N_4O_3\cdot(HCl)_2$) C, H, N.

Representative (Modified Prelog) Procedure for *N*-Phenylpiperazine Synthesis in Scheme 3. 1-[2-(2,2,2-Trifluoroethoxy)phenyl]piperazine Hydrochoride (24f). A suspension of 2-nitrophenol (18.8 g, 135 mmol), 2,2,2-trifluoroethyl tosylate (34.5 g, 135 mmol), and K_2CO_3 (18.7 g, 135 mmol) in DMF (200 mL) was heated to 140 °C for 15 h. The mixture was allowed to cool, poured into water (1 L) and extracted with 1:1 Et_2O:hexanes (4 × 200 mL). The combined organic phases were washed with water and then brine, dried (K_2CO_3), and concentrated. The crude ether (27 g) was partially characterized: ^{1}H NMR δ 4.49 (q, 2 H, J = 7.8 Hz), 7.13 (dd, 1 H, J = 0.9, 8.1 Hz), 7.22 (dt, 1 H, J = 1.2, 7.5 Hz), 7.57 (dt, 1 H, J = 1.5, 7.5 Hz), 7.89 (dd, 1 H, J = 1.8, 8.1 Hz); MS *m*/*z* 221 (M$^+$). The ether (13 g, *ca*. 60 mmol) was treated with 10% Pd/C (750 mg) in absolute EtOH and stirred under 1 atm H_2 for 16 h. Upon filtration through Florisil and concentration, the dark oil residue was immediately subjected to bis(2-chloroethyl)amine hydrochloride[23] (10.3 g, 57.6 mmol), NaI (2.2 g, 14.5 mmol), and K_2CO_3 (7.95 g, 57.6 mmol) in diglyme (30 mL), was slowly heated to reflux over 1 h, and then was held there for an additional 2.5 h. The mixture was allowed to cool, poured into pH 10 buffer (80 mL), and extracted with EtOAc (3 × 60 mL). The combined organic phases were washed with 10% aqueous $Na_2S_2O_3$ and then brine, dried (Na_2SO_4), and concentrated, and **24f** was obtained following SGC (8.07 g, 54%, eluent gradient 2−6%MeOH/CH_2Cl_2, tr. Et_3N) as an oil: ^{1}H NMR δ 2.45 (broad s, 1 H), 3.09 (s, 8 H), 4.41 (q, 2 H, J = 8.4 Hz), 6.89−7.08 (m, 4 H); ^{19}F NMR δ −72.5 (t, J = 30.5 Hz); MS *m*/*z* 260 (M$^+$), 218 (M$^+$ loss of CH_2CH_2NH). The free base was treated with 2 M HCl/EtOH and EtOAc: mp 172.3−173.3 °C. Anal. ($C_{12}H_{15}F_3N_2O\cdot HCl\cdot(H_2O)_{0.8}$) C, H, N.

1-[2-(Trifluoromethoxy)phenyl]piperazine (24e) was obtained as a paste (31% from 2-(trifluoromethoxy)aniline): ^{1}H NMR δ 2.05 (broad s, 1 H), 3.04 (m, 8 H), 6.97−7.01 (m, 2 H), 7.16−7.23 (m, 2 H); MS *m*/*z* 246 (M$^+$), 204 (M$^+$ loss of CH_2-CH_2NH).

1-[2-[(2,2-Dimethylpropyl)oxy]phenyl]piperazine (24h) was obtained from 2-nitrophenol (*via* a Mitsunobo reaction with neopentyl alcohol and then Prelog chemistry as above) as an oil: ^{1}H NMR δ 1.08 (s, 9 H), 2.1 (broad s, 1 H), 3.08 (m, 8 H), 3.64 (s, 2 H), 6.82−6.97 (m, 4 H); MS *m*/*z* 248 (M$^+$), 206 (M$^+$ loss of CH_2CH_2NH).

1-(2-Biphenylyl)piperazine (24i) was obtained as an oil (75% from 2-aminobiphenyl): ^{1}H NMR δ 2.33 (broad s, 1 H), 2.72−2.87 (m, 8 H), 7.00−7.09 (m, 1 H), 7.18 (d, 1 H, J = 7.2 Hz), 7.21−7.44 (m, 6 H), 7.65 (td, 1 H, J = 1.5, 6.9 Hz); MS *m*/*z* 238 (M$^+$), 196 (M$^+$ loss of CH_2CH_2NH).

1-(2-Cyclopropylphenyl)piperazine (24p) (41% yield from 2-cyclopropylnitrobenzene): mp 87.9−91.5 °C; ^{1}H NMR δ 0.68−0.74 (m, 2 H), 0.95−1.01 (m, 2 H), 2.02 (broad s, 1 H), 2.25−2.38 (m, 1 H), 2.96−3.10 (m, 8 H), 6.77 (dd, 1 H, J = 1.5, 7.8 Hz), 6.97−7.04 (m, 2 H), 7.12 (dt, 1 H, J = 1.5, 6.9 Hz); MS *m*/*z* 202 (M$^+$), 160 (M$^+$ loss of CH_2CH_2NH).

1-[2-(Trifluoromethyl)phenyl]piperazine (24r) was obtained as an oil (15% from 2-aminobenzotrifluoride): ^{1}H NMR 1.88 (broad s, 1 H), 2.88−3.03 (m, 8 H), 7.21 (t, 1 H, J = 7.5 Hz), 7.37 (d, 1 H, J = 8.1 Hz), 7.49 (t, 1 H, J = 7.5 Hz), 7.62 (d, 1 H, J = 7.8 Hz).

1-(4-Fluoro-2-methoxyphenyl)piperazine hydrochloride (24t) (43% from 5-fluoro-2-nitrophenol): mp 202.3−204.0 °C (Et_2O/EtOH); ^{1}H NMR δ 3.21−3.36 (m, 8 H), 3.85 (s, 3 H), 6.20 (broad s, 2 H), 6.59−6.64 (m, 2 H), 6.82−6.89 (m, 1 H); ^{19}F NMR δ −121.3 (q, J = 0.1 Hz); MS *m*/*z* 210 (M$^+$), 168 (M$^+$ loss of CH_2CH_2NH). Anal. ($C_{11}H_{15}FN_2O\cdot(HCl)_2\cdot(H_2O)_{0.5}$) C, H, N.

1-(2-Methoxy-4-methylphenyl)piperazine (24w) was obtained as an oil (47% yield from 5-methyl-2-nitrophenol): ^{1}H NMR δ 1.62 (broad s, 1 H), 2.31 (s, 3 H), 2.96−3.10 (m, 8 H), 3.85 (s, 3 H), 6.66−73 (m, 2 H), 6.83 (d, 1 H, J = 8.1 Hz); MS *m*/*z* 206 (M$^+$), 164 (M$^+$ loss of CH_2CH_2NH).

1-(2-Isopropylphenyl)piperazine hydrobromide (24q) was prepared according to Poindexter *et al.*[24] (36% yield from 2-isopropylaniline): mp 240.0−241.3 °C; ^{1}H NMR δ 1.16 (d, 6 H, J = 6.9 Hz), 2.98 (t, 4 H, J = 4.8 Hz), 3.23 (t, 4 H, J = 4.5 Hz), 3.41 (sept, 1 H, J = 6.9 Hz), 7.10−7.22 (m, 4 H); MS *m*/*z* 204 (M$^+$), 162 (M$^+$ loss of CH_2CH_2NH). Anal. ($C_{13}H_{20}N_2\cdot HBr\cdot(H_2O)_{0.3}$) C, H, N.

1-[2-(Oxazol-2-yl)phenyl]piperazine (24j). 2-Fluorobenzoyl chloride (4.50 g, 28.5 mmol), Et_3N (15.8 mL, 114 mmol), and 2-bromoethylamine hydrobromide (5.52 g, 27.0 mmol) were added to CH_2Cl_2 and heated to reflux for 24 h. The reaction mixture was cooled to rt, quenched with water, and then extracted with CH_2Cl_2 (150 mL, 3×). The combined organic fractions were washed with brine, dried ($MgSO_4$), and concentrated. The crude oil was purified by SGC (hexanes/acetone, 4:1) to give 2-(2-fluorophenyl)oxazoline (3.94 g, 84%) as an oil: ^{1}H NMR δ 4.04−4.15 (m, 2 H), 4.31−4.41 (m, 2 H), 7.09−7.22 (m, 2 H), 7.38−7.48 (m, 1 H), 7.86 (dt, 1 H, J = 1.4, 8.1 Hz); ^{13}C NMR δ 55.16, 67.01, 116.37, 116.67, 123.81, 130.92, 132.64, 161.07 (d, J = 257 Hz), 161.10 (d, J = 5.99 Hz); EIMS m/z 165 (M^+), 135, 123, 95, 75. Anal. (C_9H_8FNO) C, H, N. The oxazoline (2.50 g, 15.1 mmol) and $NiO_2 \cdot xH_2O$ (25 g, 10 equiv by wt)[38] were added to benzene (150 mL) and heated to reflux for 24 h. The reaction was cooled to rt and filtered (*Whatman*, glass microfibre filters, GF/F) and the solvent removed to give an oil (2.02 g, 12.4 mmol, 80%). The crude oil was used directly in the next step. *N*-Benzylpiperazine (5.1 g, 29.5 mmol) was dissolved in THF (20 mL) and cooled to 0 °C, and *n*-BuLi (11.8 mL, 29.5 mmol, 2.5 M/hexane) was slowly added. The mixture was stirred for 1 h followed by the addition of the above crude oxazole (1.20 g, 7.36 mmol) in THF (5 mL). The reaction was warmed to rt over 0.5 h, quenched with water, and extracted with Et_2O (100 mL, 3×). The combined organic fractions were washed with brine and dried ($MgSO_4$), and the solvent was removed to give a yellow oil. 10% Pd/C catalyst (400 mg) was suspended in MeOH and a solution of the above crude oil in MeOH added. The reaction was stirred under H_2 (1 atm) for 24 h. The mixture was filtered (*Whatman*, glass microfibre filter, GF/F) and the solvent removed to give an oil. The residue was purified by SGC (CH_2Cl_2/MeOH, 97:3, tr. Et_3N) to give a clear oil, **24j** (870 mg, 51%): ^{1}H NMR δ 2.82 (broad s, 1 H), 2.89−2.97 (m, 4 H), 3.02−3.10 (m, 4 H), 7.05−7.12 (m, 2 H), 7.26 (d, 1 H, J = 0.6 Hz), 7.36−7.45 (m, 1 H), 7.74 (d, 1 H, J = 0.6 Hz), 7.83−7.89 (m, 1 H); ^{13}C NMR δ 46.0, 53.2, 118.8, 119.1, 121.3, 122.3, 128.2, 131.4, 138.2, 151.7, 161.8; MS m/z 229 (M^+), 212, 199, 173. Anal. ($C_{13}H_{15}N_3O$) C, H, N.

1-[4-Fluoro-2-(oxazol-2-yl)phenyl]piperazine (24y) as an oil, 13% overall from 2,5-difluorobenzoyl chloride: ^{1}H NMR δ 2.41 (broad s, 1 H), 2.89−2.98 (m, 4 H), 3.03−3.10 (m, 4 H), 7.07−7.12 (m, 2 H), 7.27 (d, 1 H, J = 0.75 Hz), 7.59−7.64 (m, 1H), 7.75 (d, 1 H, J = 0.78 Hz); ^{13}C NMR δ 46.2, 53.9, 117.5 (d, J = 25 Hz), 117.7 (d, J = 22 Hz), 120.9 (d, J = 8.0 Hz), 123.0, 128.4, 138.6, 148.2, 157.5 (d, J = 241 Hz), 160.6; MS m/z 247 (M^+), 217, 191; HRMS calcd for $C_{13}H_{14}FN_3O$ 247.1121, found 247.1120.

1-(3-Methylpyrid-4-yl)piperazine (24l). 4-Chloro-3-methylpyridine[19] (2.32 g, 18.2 mmol) and *N*-formylpiperazine (4.7 mL, 45.5 mmol) were dissolved in NMP (10 mL) and heated to 90 °C for 16 h. The mixture was cooled, partitioned between water and EtOAc (8 × 30 mL), dried (Na_2SO_4), and purified by SGC (0−5% gradient MeOH/CH_2Cl_2) to give an oil (1.8 g, 46%): ^{1}H NMR δ 2.29 (s, 3 H), 2.96−3.04 (m, 4 H), 3.55 (dd, 2 H, J = 5.1, 6.6 Hz), 3.73 (dd, 2 H, J = 5.1, 5.4 Hz), 6.78 (d, 1 H, J = 5.4 Hz), 8.11 (s, 1 H), 8.34 (d with predominant s, 2 H, J = 5.7 Hz); ^{13}C NMR δ 17.7, 30.7, 40.1, 45.7, 50.0, 113.2, 126.2, 148.8, 152.3, 160.9, 175.4. The oil (1.75 g) was treated with MeOH (20 mL) and aqueous NaOH (2 mL, 5 M) and boiled for 5.5 h. The mixture was concentrated and used crude in subsequent alkylation chemistry: ^{1}H NMR δ 2.26 (s, 3 H), 2.96−3.07 (m, 8 H), 6.79 (d, 1 H, J = 5.4 Hz), 8.28 (s, 1 H), 8.31 (d, 2 H, J = 5.4 Hz).

1-[4-Methyl-2-(1-pyrrolyl)phenyl]piperazine (24x). 4-Chloro-3-nitrotoluene (29.2 g, *ca.* 170 mmol) and *N*-formylpiperazine (22.8 mL, 221 mmol) were dissolved in DMF (50 mL) and heated to 100 °C for 16 h. The mixture was cooled, partitioned between water and EtOAc (8 × 100 mL), dried (Na_2SO_4), and purified by SGC (50−100% gradient hexanes/EtOAc) to give an oil (11.2 g, 26%): ^{1}H NMR δ 2.37 (s, 3 H), 2.96−3.04 (m, 4 H), 3.51 (t, 2 H, J = 5.1 Hz), 3.71 (t, 2 H, J = 5.1 Hz), 7.08 (d, 1 H, J = 8.4 Hz), 7.33 (dd, 1 H, J = 1.5, 8.4 Hz), 7.60 (d, 1 H, J = 1.2 Hz), 8.08 (s, 1 H). The oil (6.2 g) was sequentially treated with 1 atm of H_2 [10% Pd/C (1 g), EtOH (70 mL), 20 h, rt] and 2,5-dimethoxy-THF [(4.4 mL, 33.6 mmol), glacial HOAc (20 mL), 2 h, 105 °C]. The residue was subjected to SGC (2:1 hexanes:acetone, tr. Et_3N) to yield a pyrrole (2.5 g, 39%): ^{1}H NMR δ 2.32 (s, 3 H), 2.59−2.72 (m, 4 H), 3.32 (t, 2 H, J = 5.1 Hz), 3.55 (t, 2 H, J = 5.4 Hz), 6.29 (t, 2 H, J = 2.1 Hz), 6.89 (d, 1 H, J = 8.7 Hz), 7.02 (t, 2 H, J = 2.1 Hz), 7.06−7.20 (m, 2 H), 8.00 (s, 1 H); MS m/z 269 (M^+), 240, 197, 183. The pyrrole (512 mg, 1.90 mmol) was treated with NaOH (8 mL, 1 M MeOH) and stirred at 50 °C for 2.7 d. **24x** was obtained upon extraction from water and CH_2Cl_2 (4 × 20 mL), drying ($MgSO_4$), filtration, and concentration as an oil (452 mg, 10% yield overall): ^{1}H NMR δ 2.06 (broad s, 1 H), 2.31 (s, 3 H), 2.61 (t, 4 H, J = 4.5 Hz), 2.85 (t, 4 H, J = 4.5 Hz), 6.27 (t, 2 H, J = 2.4 Hz), 6.92 (d, 1 H, J = 8.7 Hz), 7.02−7.07 (m, 4 H).

Compounds Reported in Table 3. *N,N*-Dimethyl-2-[[3-(4-phenylpiperazin-1-yl)propyl]amino]nicotinamide oxalate (25a): mp 104.4−104.9 °C. Anal. ($C_{21}H_{29}N_5O \cdot (C_2H_2O_4)_{1.5} \cdot (H_2O)_{0.25}$) C, H, N.

***N,N*-Dimethyl-2-[[3-[4-(2-cyanophenyl)piperazin-1-yl]-propyl]amino]nicotinamide hydrochloride (25b)** from a HCl/EtOH solution: mp 129 °C dec. Anal. ($C_{22}H_{28}N_6O \cdot (HCl)_3 \cdot (EtOH)_{0.15} \cdot (EtOAc)_{0.15} \cdot (H_2O)_{1.3}$) C, H, N.

***N,N*-Dimethyl-2-[[3-[4-(2-hydroxyphenyl)piperazin-1-yl]propyl]amino]nicotinamide fumarate (25c):** mp 181.2−183.9 °C. Anal. ($C_{21}H_{29}N_5O_2 \cdot (C_4H_4O_4)_{0.5} \cdot H_2O$) C, H, N.

***N,N*-Dimethyl-2-[[3-[4-(2-ethoxyphenyl)piperazin-1-yl]-propyl]amino]nicotinamide oxalate (25d):** mp 138.0−140.0 °C. Anal. ($C_{23}H_{33}N_5O_2 \cdot C_2H_2O_4$) C, H, N.

***N,N*-Dimethyl-2-[[3-[4-[2-(trifluoromethoxy)phenyl]piperazin-1-yl]propyl]amino]nicotinamide oxalate (25e):** mp 142.5−145.0 °C. Anal. ($C_{22}H_{28}F_3N_5O_2 \cdot C_2H_2O_4$) C, H, N.

***N,N*-Dimethyl-2-[[3-[4-[2-(2,2,2-trifluoroethoxy)phenyl]-piperazin-1-yl)propyl]amino]nicotinamide hydrochloride (25f):** mp 122 °C dec. Anal. ($C_{23}H_{30}F_3N_5O_2 \cdot (HCl)_{2.5} \cdot (EtOAc)_{0.1}$) H, N; C: 49.70; found, 50.26.

***N,N*-Dimethyl-2-[[3-[4-[2-(cyclopropylmethoxy)phenyl]-piperazin-1-yl]propyl]amino]nicotinamide oxalate (25g):** mp 117.5−123.0 °C. Anal. ($C_{25}H_{35}N_5O_2 \cdot C_2H_2O_4 \cdot (H_2O)_{0.65}$) C, H, N.

***N,N*-Dimethyl-2-[[3-[4-[2-[(2,2-dimethylpropyl)oxy]phenyl]piperazin-1-yl]propyl]amino]nicotinamide hydrochloride (25h):** mp 111−125 °C. Anal. ($C_{23}H_{39}N_5O_2 \cdot (HCl)_{1.6}$) C, H, N.

***N,N*-Dimethyl-2-[[3-[4-(2-biphenylyl)piperazin-1-yl]propyl]amino]nicotinamide hydrochloride (25i):** mp 195.8−196.8 °C. Anal. ($C_{27}H_{33}N_5O \cdot (HCl)_2 \cdot (H_2O)_{0.25}$) C, H, N.

***N,N*-Dimethyl-2-[[3-[4-(2-oxazol-2-ylphenyl)piperazin-1-yl]propyl]amino]nicotinamide hydrochloride (25j):** mp 102−104 °C. Anal. ($C_{24}H_{30}N_6O_2 \cdot (HCl)_2$) C, H, N.

***N,N*-Dimethyl-2-[[3-[4-(2-methylphenyl)piperazin-1-yl]-propyl]amino]nicotinamide hydrochloride (25k):** mp 67 °C dec. Anal. ($C_{22}H_{31}N_5O \cdot (HCl)_3$) C, H, N.

***N,N*-Dimethyl-2-[[3-[4-(2-methylpyrid-4-yl)piperazin-1-yl]propyl]amino]nicotinamide hydrobromide (25l):** mp 178.4−183 °C. Anal. ($C_{21}H_{30}N_6O \cdot (HBr)_3 \cdot H_2O$) C, H, N.

***N,N*-Dimethyl-2-[[3-[4-[2-(methylthio)phenyl]piperazin-1-yl]propyl]amino]nicotinamide hydrochloride (25m):** mp 137−143 °C. Anal. ($C_{22}H_{31}N_5OS \cdot (HCl)_2$) C, H, N.

***N,N*-Dimethyl-2-[[3-[4-(2-*n*-propylphenyl)piperazin-1-yl]propyl]amino]nicotinamide oxalate (25n):** mp 127.1−127.5 °C. Anal. ($C_{24}H_{35}N_5O \cdot C_2H_2O_4$) C, H, N.

***N,N*-Dimethyl-2-[[3-[4-(2-benzylphenyl)piperazin-1-yl]-propyl]amino]nicotinamide oxalate (25o):** mp 127−130 °C. Anal. ($C_{28}H_{35}N_5O \cdot C_2H_2O_4$) C, H, N.

***N,N*-Dimethyl-2-[[3-[4-(2-cyclopropylphenyl)piperazin-1-yl]propyl]amino]nicotinamide hydrochloride (25p):** mp 124−133 °C. Anal. ($C_{24}H_{33}N_5O \cdot (HCl)_2$) C, H, N.

***N,N*-Dimethyl-2-[[3-[4-(2-isopropylphenyl)piperazin-1-yl]propyl]amino]nicotinamide oxalate (25q):** mp 119.0−121.0 °C. Anal. ($C_{24}H_{35}N_5O \cdot (C_2H_2O_4)_{2.5}$) C, H, N.

***N,N*-Dimethyl 2-[[3-[4-[2-(trifluoromethyl)phenyl]piperazin-1-yl]propyl]amino]nicotinamide oxalate (25r):** mp 132.5−133.5 °C. Anal. ($C_{22}H_{28}F_3N_5O \cdot (C_2H_2O_4)_{1.5}$) C, H, N.

***N,N*-Dimethyl-2-[[3-[4-(2,6-dimethylphenyl)piperazin-1-yl]propyl]amino]nicotinamide hydrochloride (25s):** mp 98−125 °C. Anal. ($C_{23}H_{33}N_5O\cdot HCl\cdot(H_2O)_{0.5}$) C, H, N.

***N,N*-Dimethyl-2-[[3-[4-(4-fluoro-2-methoxyphenyl)piperazin-1-yl]propyl]amino]nicotinamide hydrochloride (25t):** mp 228.4−229.1 °C; ^{1}H NMR δ 1.95−2.10 (m, 2 H), 2.94 (s, 3 H), 3.08−3.55 (m, 12 H), 3.80 (s, 3 H), 6.36 (s, broad, 1 H), 6.58 (dd, 1 H, J = 4.95, 7.29 Hz), 6.70 (dt, 1 H, J = 2.80, 8.46 Hz), 6.90 (m, 2 H), 7.37 (dd, 1 H, J = 1.83, 7.29 Hz), 8.08 (dd, 1 H, J = 1.85, 4.97); ^{13}C NMR δ 23.5, 37.8, 47.1, 51.1, 53.6, 55.8, 100.3 (d, J = 26.90 Hz), 106.0 (d, J = 21.52 Hz), 111.1, 115.9, 118.9 (d, J = 9.91 Hz), 135.6, 136.0, 148.2, 153.0 (d, J = 10.12 Hz), 154.4, 157.2, 160.3, 167.9; ^{19}F NMR δ −117.6; EIMS m/z 415 (M^+), 235, 209, 192. Anal. ($C_{22}H_{30}FN_5O_2\cdot HCl$) C, H, N.

***N,N*-Dimethyl-2-[[3-[4-(4-hydroxy-2-methoxyphenyl)-piperazin-1-yl]propyl]amino]nicotinamide Hydrochoride (25u).** An aqueous solution of 40% HBr (30 mL) and (2,4-dimethoxyphenyl)piperazine (3.1 g, 13.9 mmol) was heated to reflux[39] for 30 h and cooled, and the volatiles were removed. The residue (4.6 g) was dissolved in 20 mL each of saturated $NaHCO_3$ and THF while N_2 was bubbled into the mixture. Di-*tert*-butyl dicarbonate (3.3 g, 15 mmol) was added in one portion and stirred at rt for 5 h. The mixture was partitioned between EtOAc (5 × 50 mL) and water. 1-(*tert*-Butylcarbonyl)-4-(4-hydroxy-2-methoxyphenyl)piperazine was obtained following drying, filtration, and removal of volatiles (oven temperature *ca.* 50 °C) as a solid (1.40 g, 4.56 mmol, 33%): 213.6−214.3 °C; ^{1}H NMR δ 1.41 (s, 9 H), 2.44−2.51 (m, 4 H), 3.37−3.42 (m, 4 H), 3.71 (s, 3 H), 6.25 (dd, 1 H, J = 2.4, 8.4 Hz), 6.37 (d, 1 H, J = 2.4 Hz), 6.70 (d, 1 H, J = 8.4 Hz), 9.05 (broad s, 1 H); MS m/z 308 (M^+), 252 (M^+ loss of Bu + H). The phenol (1.26 g, 4.1 mmol) was dissolved in DMF (20 mL), treated with BnBr (0.54 mL, 4.5 mmol) and Cs_2CO_3 (1.46 g, 4.5 mmol), and stirred at rt for 18 h. The benzyl ether (1.59 g) was isolated by standard workup and SGC (elute with 2:1 hexanes:EtOAc). It was subsequently treated with TFA [(10 mL) in CH_2Cl_2 (20 mL), rt, 1 h], *N*-(3-bromopropyl)phthalimide [(1.57 g, 5.9 mmol), K_2CO_3 (660 mg, 7.2 mmol) in DMF (9 mL), 80 °C, 16 h], $N_2H_4\cdot H_2O$ [(1 mL, 18 mmol), EtOH (25 mL), 80 °C, 1 h], **14ii** [(660 mg, 3.6 mmol), K_2CO_3 (510 mg, 3.7 mmol) in xylene (12 mL) 140 °C, 21 h], and 10% Pd/C (150 mg) with NH_4CO_2H (550 mg, 8.7 mmol) in boiling MeOH. The title compound was isolated by filtration and SGC (eluant: 6% MeOH/CH_2Cl_2, 420 mg, 22%) and formed an amorphous solid with HCl/EtOH: mp 165 °C dec. Anal. ($C_{22}H_{31}N_5O_3\cdot(HCl)_3$) C, H, N.

***N,N*-Dimethyl-2-[[3-[4-(2,4-dimethoxyphenyl)piperazin-1-yl]propyl]amino]nicotinamide hydrochoride (25v):** mp 80 °C dec. Anal. ($C_{23}H_{33}N_5O_3\cdot(HCl)_2\cdot(EtOAc)_{0.5}\cdot(H_2O)_{1.3}$) C, H, N.

***N,N*-Dimethyl-2-[[3-[4-(2-methoxy-4-methylphenyl)piperazin-1-yl]propyl]amino]nicotinamide oxalate (25w):** mp 89.5−96.5 °C. Anal. ($C_{23}H_{33}N_5O_2\cdot C_2H_2O_4\cdot(H_2O)_{1.1}$) C, H, N.

***N,N*-Dimethyl-2-[[3-[4-(4-methyl-2-pyrrol-1-ylphenyl)piperazin-1-yl]propyl]amino]nicotinamide fumarate (25x):** mp 125−148 °C. Anal. ($C_{26}H_{34}N_6O\cdot(C_4H_4O_4)_{3.25}\cdot(H_2O)_2$) C, H, N.

Compounds Prepared in Scheme 4. 2-[2-(2,2,2-Trifluoroethoxy)phenoxy]ethanol (27a). A mixture of catechol (28.45 g, 259 mmol), ethylene carbonate (22.76 g, 259 mmol), and *n*-BuN_4Br (1.7 g, 5.2 mmol) was heated to 180 °C until gas evolution subsided (about 3.5 h). The mixture solidified upon cooling and was recrystallized from hot water. A tan solid was collected after sitting overnight at rt and furnished 25.8 g of the desired phenol upon being dried *in vacuo* at 70 °C. The phenol (5 g, 32 mmol), K_2CO_3 (4.9 g, 35.6 mmol), and 2,2,2-trifluoroethyl methanesulfonate (4.2 mL, 35.6 mmol) were suspended in DMF (65 mL) and heated to 100 °C for 18 h. Upon cooling, the mixture was partitioned between water (200 mL) and 1:1 hexanes:EtOAc (3 × 150 mL). The organic extract was washed with water and brine and stored over Na_2SO_4. **27a** was obtained as an oil (3.8 g, 16 mmol) after SGC, eluant 4:1 hexanes:EtOAc: R_f (3:2 hexanes:acetone) 0.34; ^{1}H NMR δ 2.27 (t, 1 H, J = 6.3 Hz, O*H*), 3.95−4.00 (m, 2 H, CH_2OH), 4.14 (t, 2 H, J = 4.9 Hz, OCH_2CH$_2$), 4.38 (q, 2 H, J = 8.3 Hz, OCH_2CF$_3$), 6.96−7.09 (m, 4 H, C$_6H_4$); EIMS m/z 236 (M^+), 192 (M^+ loss of CH_2CH_2OH), 109.

2-[2-(Pyrimid-5-yl)phenoxy]ethanol (27b). A suspension of 2-iodophenol (6.22 g, 28.0 mmol), 2-bromoethyl acetate (3.72 mL, 33.6 mmol), NaI (4.24 g, 28 mmol), and Cs_2CO_3 (9.6 g, 29.5 mmol) in DMF (70 mL) was stirred at rt for 10 d. The mixture was partitioned between H_2O and Et_2O:hexanes (1:1 4 × 100 mL), dried (brine wash and Na_2SO_4), concentrated, and subjected to SGC (eluant 7:1 hexanes:EtOAc) to obtain an oil (5.93 g). The ester (2.71 g, 8.8 mmol) was treated with MeOH (10 mL) and NaOH (1.4 g, 35 mmol in 5 mL H_2O) at 40 °C for 1 h. The mixture was cooled, partitioned between aqueous NH_4Cl and EtOAc (3 × 50 mL), dried ($MgSO_4$), filtered, and concentrated. The residue was dissolved in THF (25 mL), cooled to 0 °C, and treated with NaH (60% with oil, 350 mg, 8.8 mmol). After 2 h of stirring, the resulting solution was cooled to −78 °C and treated sequentially with *t*-BuLi (10.7 mL, 1.5 M, 16.0 mmol for 40 min) and $(MeO)_3B$ (1.8 mL, 16.0 mmol) and allowed to warm to rt overnight. The dark suspension was quenched with 10% aqueous HOAc, stirred 10 min, and extracted with Et_2O (2 × 50 mL). Upon drying (Na_2SO_4) and concentration, half of the residue (*ca.* 4.2 mmol) was treated with dioxane (25 mL), 5-bromopyrimidine (572 mg, 3.6 mmol), $[Ph_3P]_4Pd$ (105 mg, 0.09 mmol), and K_3PO_4 (1.53 g, 7.2 mmol) and heated to 85 °C for 20 h.[27] The title compound was obtained following extraction with aqueous NH_4Cl and EtOAc (4 × 50 mL), drying (Na_2SO_4), concentration, and SGC (eluant 2:1 to 1:1 gradient of hexanes:acetone) as a white solid: mp 88.4−89.8 °C; ^{1}H NMR δ 3.38 (t, 1 H, J = 6.0 Hz), 3.91−3.97 (m, 2 H), 4.16 (t, 2 H, J = 5.7 Hz), 7.05 (d, 1 H, J = 8.1 Hz), 7.08 (dt, 1 H, J = 0.9, 7.5 Hz), 7.31 (dd, 1 H, J = 1.5, 8.1 Hz), 7.42 (dt, 1 H, J = 1.8, 7.5 Hz), 8.91 (s, 2 H), 9.03 (s, 1 H); MS m/z 216 (M^+), 172 (M^+ loss of CH_2CH_2OH).

4-[[2-[2-(2,2,2-Trifluoroethoxy)phenoxy]ethyl]amino]-3,4,5,6-tetrahydro-2*H*-[1,2′]bipyridinyl-3′-carboxylic Acid Dimethylamide Fumarate (28a). 27a (2.13 g, 9.0 mmol) was sequentially treated with MsCl [(0.84 mL, 10.8 mmol) CH_2Cl_2 (30 mL), Et_3N (2.5 mL, 18.0 mmol), 15 min, 0 °C], 4-amino-1-benzylpiperidine [(740 mg, 3.8 mmol), K_2CO_3 (536 mg, 3.88 mmol), CH_3CN (25 mL), reflux, 18 h], 1 atm of H_2 [wet, Degussa type E101 10% Pd/C (250 mg), MeOH (20 mL), 4 h], and **14ii** [(286 mg, 1.55 mmol), K_2CO_3 (214 mg, 1.55 mmol), xylenes (10 mL), 140 °C, 6 h]. The title compound was obtained (400 mg, 9% overall) following SGC (eluant CH_2Cl_2: MeOH, 95:5) and treatment with an Et_2O:MeOH solution of fumaric acid: mp 152−153 °C; ^{1}H NMR δ 1.32−1.48 (m, 2H), 1.91−2.06 (m, 2 H), 2.78−2.96 (m with predominant s, 8 H), 2.99 (s, 3 H), 3.10 (t, 3 H, J = 5.3 Hz), 3.64−3.84 (m, 2 H), 4.15 (t, 2 H, J = 5.3 Hz), 4.66 (q, 2 H, J = 9.0 Hz), 6.52 (s, 1 H), 6.84 (dd, 1H, J = 4.9, 7.4 Hz), 6.90−7.10 (m, 4 H), 7.46 (dd, 1H, J = 1.7, 7.3 Hz), 8.20 (dd, 1H, J = 1.7, 4.7 Hz); ^{13}C NMR δ 30.8, 34.2, 37.5, 44.1, 46.0, 54.1, 66.4 (q, J = 33 Hz), 67.5, 114.6, 114.9, 116.6, 121.1, 121.2, 122.1, 123.4, 126.5 (q, J = 277.5 Hz), 134.7, 137.2, 146.8, 147.9, 148.6, 156.4, 169.2; EIMS m/z 466 (M^+). Anal. ($C_{23}H_{29}F_3N_4O_3\cdot(C_4H_4O_4)_{0.5}$) C, H, N.

4-[[2-[2-(Pyrimid-5-yl)phenoxy]ethyl]amino]-3,4,5,6-tetrahydro-2*H*-[1,2′]bipyridinyl-3′-carboxylic acid dimethylamide hydrobromide (28b): mp 229.0−233.0 °C dec. Anal. ($C_{25}H_{30}N_6O_2\cdot(HBr)_{0.75}$) C, H, N.

4-[[2-(2-Ethoxyphenoxy)ethyl]amino]-3,4,5,6-tetrahydro-2*H*-[1,2′]bipyridinyl-3′-carboxylic acid dimethylamide hydrochloride (28c): mp 129.1−132.1 °C. Anal. ($C_{23}H_{34}F_3N_4O_3\cdot(HCl)_2\cdot(H_2O)_{2.5}$) C, H, N.

Representative Procedure for the Annulation of Anilines (and Aminoheterocycles) to Quinoline-3-carboxamides, Scheme 5: *N,N*-Dimethyl-4-chloro-8-iodoquinoline-3-carboxamide (34). A flask containing 2-iodoaniline (2.9 g, 13.2 mmol) and diethyl (ethoxymethylene)malonate (2.7 mL, 14.0 mmol) was equipped with a short-path distillation head and heated to 120 °C. Over 0.2−4 h, ethanol is collected. The pot residue was cooled and recrystallized from hot *n*-heptane. Diethyl *N*-amino-(2-iodophenyl)methylenemalonate (4.86 g, 12.5 mmol, 94%) was obtained as a flakey white

solid: mp 112.2−112.5 °C; IR 3436, 1682, 1641, 1597 cm^{-1}; ^1H NMR δ 1.33 (t, 3 H, J = 7.2 Hz), 1.39 (t, 3 H, J = 7.2 Hz), 4.26 (q, 2 H, J = 7.2 Hz), 4.36 (q, 2 H, J = 7.2 Hz), 6.88 (dt, 1 H, J = 1.2, 7.5 Hz), 7.22 (dd, 1 H, J = 1.5, 8.1 Hz), 7.39 (dt, 1 H, J = 1.5, 8.4 Hz), 7.84 (dd, 1 H, J = 1.5, 7.8 Hz), 8.44 (d, 1 H, J = 13.2 Hz), 11.09 (d, 1 H, J = 12.9 Hz); MS m/z 389 (M^+), 343 (M^+ loss of OEt). The adduct (3.76 g, 9.7 mmol) was treated with (*i*-Pr)$_2$NEt (2.0 mL, 11.6 mmol) and $POCl_3$ (6.8 mL, 73 mmol) and heated to reflux in xylenes (35 mL). After 14 h, the dark mixture was distilled to *ca*. 10 mL of residue, cooled to rt, poured into ice, extracted with Et_2O (5 × 30 mL), washed with saturated $NaHCO_3$ and then brine, and stored over Na_2SO_4. Ethyl 4-chloro-8-iodoquinoline-3-carboxamide was obtained following SGC (eluant: 8:1 hexanes:EtOAc) as tan powder (2.304 g, 66%): mp 81.5−82.9 °C; ^1H NMR δ 1.46 (t, 3 H, J = 7.2 Hz), 4.51 (q, 2 H, J = 7.2 Hz), 7.42 (t, 1 H, J = 7.5 Hz), 8.43 (dd, 1 H, J = 1.2, 8.1 Hz), 8.46 (dd, 1H, J = 0.9, 7.2 Hz), 9.31 (s, 1 H); MS m/z 363 (M^+ with ^{37}Cl), 361 (M^+ with ^{35}Cl), 318 (M^+ with ^{37}Cl loss of OEt), 316 (M^+ with ^{35}Cl loss of OEt). Anal. ($C_{12}H_9ClINO_2$) C, H, N. The ester (2.72 g, 7.5 mmol) was dissolved in DME (35 mL), treated with NaOH (900 mg, 23 mmol), dissolved in 7 mL of water, and heated to reflux for 40 min. Upon cooling, the solution was treated with HOAc (3.0 mL, 53 mmol), solids formed, and the volatiles were removed by the aid of toluene azeotrope (3 × 25 mL). The resulting white solids were treated with $(COCl)_2$ [(0.98 mL, 11.25 mmol), DCE (15 mL), 80 °C, 2 h] and Me_2NH [(12 mL, 24 mmol, 2 M THF), −10 °C, 0.5 h]. The title compound was obtained following aqueous workup and SGC (eluant: 3:2 hexanes:EtOAc) as a waxy solid (985 mg, 2.7 mmol, 36%): ^1H NMR δ 2.93 (s, 3 H), 3.23 (s, 3 H), 7.41 (t, 1 H, J = 7.5 Hz), 8.29 (dd, 1H, J = 1.2, 8.4 Hz), 8.43 (dd, 1 H, J = 1.2, 7.5 Hz), 8.86 (s, 1 H); MS m/z 362 (M^+ with ^{37}Cl), 360 (M^+ with ^{35}Cl), 318 (M^+ with ^{37}Cl loss of NMe_2), 316 (M^+ with ^{35}Cl loss of NMe_2).

***N,N*-Dimethyl-4-chloro-8-cyanoquinoline-3-carboxamide (35).** Following the report of Piers[16] as modified for **14vi**, **34** (2.3 g, 6.4 mmol) was treated with 12-crown-4 (0.1 mL, 0.64 mmol), LiCN (12.7 mmol), and $[Ph_3P]_4Pd$ (910 mg, 0.8 mmol) in benzene (60 mL) at rt for 10 d and gave **35** (280 mg, 1.08 mmol) as a powder: mp 194−200 °C; ^1H NMR δ 2.95 (s, 3 H), 3.24 (s, 3 H), 7.79 (dd, 1 H, J = 7.2, 8.7 Hz), 8.24 (dd, 1 H, J = 1.2, 7.2 Hz), 8.54 (dd, 1 H, J = 1.2, 8.7 Hz), 8.94 (s, 1 H); MS m/z 260 (M^+ with ^{37}Cl), 258 (M^+ with ^{35}Cl), 217 (M^+ with ^{37}Cl loss of NMe_2), 215 (M^+ with ^{35}Cl loss of NMe_2).

***N*-Methyl-4-chloro-1,3-dimethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid (36)** was prepared from 4-chloro-1,3-dimethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonyl chloride[28] (1.38 g, 4.9 mmol), Et_3N (2.4 mL, 17.2 mmol), and $MeNH_2$ (0.42 mL, 40% aqueous, 5.4 mmol) in THF (10 mL) at −10 °C and obtained as a white powder (247 mg, 1.03 mmol, 20%): mp 219.7−221.2 °C; ^1H NMR δ 2.73 (s, 3 H), 3.08 (d, 3 H, J = 4.8 Hz), 4.07 (s, 3 H), 6.05 (broad s, 1 H), 8.74 (s, 1 H); MS m/z 240 (M^+ with ^{37}Cl), 238 (M^+ with ^{35}Cl), 210 (M^+ with ^{37}Cl loss of NHMe), 208 (M^+ with ^{35}Cl loss of NHMe).

***N,N*-Dimethyl-4-chloro-1,3-dimethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid (37)** was prepared from 4-chloro-1,3-dimethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonyl chloride[28] (4.81 g, 19.7 mmol), Et_3N (7 mL, 50 mmol), $Me_2NH\cdot HCl$ (1.77 g, 21.7 mmol) in DCE (25 mL) at −10 °C and obtained as a white solid (3.15 g, 63%): mp 143.3−143.8 °C; ^1H NMR δ 2.73 (s, 3 H), 2.93 (s, 3 H), 3.20 (s, 3 H), 4.08 (s, 3 H), 8.36 (s, 1 H); ^{13}C NMR δ 14.4 (q), 33.9 (q), 34.9 (q), 38.3 (q), 112.5 (s), 135.0 (s), 141.1 (s), 147.5 (d), 151.5 (s), 167.0 (s); MS m/z 254 (M^+ with ^{37}Cl), 252 (M^+ with ^{35}Cl), 210 (M^+ with ^{37}Cl loss of $CONMe_2$), 208. Anal. ($C_{11}H_{13}ClN_4O$) C, H, N.

A Representative Procedure for Target Preparation in Scheme 6. *N,N*-Dimethyl-8-chloro-4-[[3-[4-[2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl]propyl]amino]quinoline-3-carboxamide Hydrobromide (30f). A toluene (15 mL) suspension of ethyl 4,8-dichloroquinoline-3-carboxylate (982 mg, 3.64 mmol), K_2CO_3 (550 mg, 3.9 mmol), and 3-amino-1-propanol (0.29 mL, 3.8 mmol) was heated to reflux for 3.5 h. The mixture was filtered hot, the filter cake was washed with EtOAc, and the filtrate was concentrated. Some of the resulting powder (650 mg) was dissolved in CH_2Cl_2 (9 mL) and Et_3N (0.41 mL, 2.84 mmol), cooled to 0 °C, and treated with MsCl (0.21 mL, 2.52 mmol). After 0.5 h, the solution was partitioned between aqueous $NaHCO_3$ and CH_2Cl_2, dried (Na_2SO_4), concentrated, and subjected to **24f** (700 mg, 2.69 mmol), NaI (165 mg, 1.1 mmol), and K_2CO_3 (400 mg, 2.9 mmol) in DMF (22 mL) at 40 °C for 18 h. The ester was isolated by standard extraction and SGC (eluant: 3:2 hexanes:EtOAc, tr. Et_3N) as a foam (650 mg, 1.2 mmol, *ca*. 55%) and partially characterized: ^1H NMR δ 1.41 (t, 3 H, J = 7.2 Hz), 1.97 (quin, 2 H, J = 6.9 Hz), 2.51−2.68 (m, 6 H), 3.03−3.10 (m, 4 H), 3.85 (q, 2 H, J = 5.7 Hz), 4.40 (dq, 4 H, J = 7.2, 8.4 Hz), 6.87−7.07 (m, 4 H), 7.26 (dd, 1 H, J = 7.7, 8.4 Hz), 7.77 (dd, 1 H, J = 1.2, 7.5 Hz), 8.17 (dd, 1 H, J = 1.2, 8.7 Hz), 9.20 (s, 1 H), 9.27 (broad t, 1 H, J = 5.1 Hz). The foam (650 mg, 1.2 mmol) was dissolved in MeOH (10 mL) and treated with KOH (270 mg, 4.8 mmol) and water (1 mL). The solution was heated to 40 °C for 16 h, allowed to cool, and treated with HCl (10 mL, 1 M Et_2O, 10 mmol). White solids formed and were collected and dried *in vacuo* (6 h, 50 °C). They were suspended in DMF (15 mL), treated with CDI (215 mg, 1.32 mmol), and stirred at 60 °C for 2 h, at which time, *i*-Pr_2NEt (1.0 mL, 6.0 mmol) and $Me_2NH\cdot HCl$ (145 mg, 1.8 mmol) were added and heating continued for 2.6 d. The resulting suspension was concentrated *in vacuo* and partitioned between aqueous $NaHCO_3$ and CH_2Cl_2 (5 × 20 mL), dried (Na_2SO_4), and concentrated. The title compound was isolated by SGC (eluant 2% MeOH/CH_2Cl_2, trace Et_3N) as a foam (405 mg, 63%) and formed a solid from HBr/EtOH: mp 185−192 °C; IR 3430, 2955, 1635 cm^{-1}; ^1H NMR δ 2.19 (quin, 2 H, J = 5.7 Hz), 3.02−3.32 (m with 2 predominant s, 12 H), 3.41−3.70 (m, 6 H), 4.73 (q, 2 H, J = 9.0 Hz), 6.98−7.11 (m, 4 H), 7.76 (t, 1 H, J = 8.7 Hz), 8.19 (d, 1 H, J = 7.8 Hz), 8.45 (s, 1 H), 8.74 (d, 1 H, J = 8.4 Hz), 9.28 (broad s, 1 H); ^{13}C NMR δ 23.0 (t), 34.8 (q), 38.6 (q), 42.1 (t), 46.9 (t), 51.3 (t), 53.1 (t), 65.0 (t, J = 34 Hz), 109.6 (s), 114.8 (d), 118.8 (d), 119.7 (s), 122.9 (d), 123.2 (d), 123.4 (d), 124.0 (q, J = 142 Hz), 126.9 (d), 133.6 (d), 134.1 (s), 139.9 (d),143.1 (s), 149.4 (s), 152.7 (s), 165.2 (s); MS m/z 551 (M^+ with ^{37}Cl), 549 (M^+ with ^{35}Cl), 321, 319. Anal. ($C_{27}H_{31}F_3ClN_5O_2\cdot(HBr)_2\cdot(H_2O)_{2.5}$) C, N; H: calcd, 5.06; found, 4.60.

***N,N*-Dimethyl-4-[[3-[4-[2-(2,2,2-trifluoroethoxy)phenyl]-piperazin-1-yl]propyl]amino]quinoline-3-carboxamide hydrobromide (30f′):** mp 120 °C dec. Anal. ($C_{27}H_{32}F_3N_5O_2\cdot(HBr)_{2.5}$) C, H, N.

A Representative Procedure for Target Preparation in Scheme 6. 4-[[3-[4-[4-Fluoro-2-(oxazol-2-yl)phenyl]-piperazin-1-yl]propyl]amino]-1,3-dimethyl-1*H*-pyrazolo-[3,4-*b*]pyridine-5-carboxylic Acid Dimethylamide, Oxalate (37y). Piperazine **24y** (300 mg, 1.21 mmol) was homologated to its aminopropyl derivative **43y** [*N*-(3-bromopropyl)phthalimide (358 mg, 1.33 mmol), K_2CO_3 (200 mg, 1.45 mmol), DMF (10 mL), then SGC and $N_2H_4\cdot H_2O$ (0.5 mL, 0.82 mmol) in boiling EtOH (15 mL)] as described for Scheme 1. Crude **43y** was treated with **37** (190 mg, 0.69 mmol) and K_2CO_3 (114 mg, 0.83 mmol) in xylene (10 mL) and heated to 120 °C for 16 h. The desired **37y** was obtained following SGC (eluant: 3% MeOH/CH_2Cl_2, 211 mg, 59%) and formed a solid with oxalic acid/EtOAc/MeOH: mp 88−96 °C; ^1H NMR δ 1.93 (quin, 2 H, J = 6.7 Hz), 2.64 (s, 3 H), 2.88 (t, 2 H, J = 7.0 Hz), 2.97−3.29 (m with predominant s, 16 H), 3.84 (s, 3 H), 5.97 (broad s, 1 H), 7.21−7.36 (m, 2 H), 7.41 (d, 1 H, J = 0.9 Hz), 7.89 (s, 1 H), 8.22 (d, 1 H, J = 0.9 Hz); ^{13}C NMR δ 15.3 (q), 24.7 (t), 32.9 (q), 41.6 (t), 50.0 (t), 51.8 (t), 53.9 (t), 103.5 (s), 107.3 (s), 116.4 (d, J = 24.7 Hz), 117.7 (d, J = 21.7 Hz), 121.9 (d, J = 8.3 Hz), 122.3 (d, J = 8.5 Hz), 128.3 (d), 138.9 (s), 140.0 (d), 146.4 (s), 146.6 (s), 149.1 (d), 151.8 (s), 157.3 (d, J = 240 Hz), 163.5 (s), 169.5 (s). Anal. ($C_{27}H_{33}FN_8O_2\cdot C_2H_2O_4\cdot(H_2O)_{0.2}$) C, H, N.

4-[[3-[4-(4-Fluoro-2-methoxyphenyl)piperazin-1-yl]propyl]amino]-8-methylquinoline-3-carboxylic acid dimethylamide hydrobromide (33t): mp 174−180 °C. Anal. ($C_{27}H_{34}FN_5O_2\cdot(HBr)_3\cdot H_2O$) C, H; N: calcd, 9.45; found, 8.99.

4-[[3-[4-(4-Fluoro-2-methoxyphenyl)piperazin-1-yl]propyl]amino]-8-cyanoquinoline-3-carboxylic acid dimethylamide oxalate (35t): mp 118−133 °C. Anal. ($C_{27}H_{31}FN_6O_2\cdot(C_2H_2O_4)_{1.5}$) C, H, N.

4-[[3-[4-(4-Fluoro-2-methoxyphenyl)piperazin-1-yl]pro-

pyl]amino]-8-quinoline-3-carboxylic acid dimethylamide hydrobromide (35t′): mp 163.5−170.0 °C. Anal. ($C_{27}H_{33}FN_6O_3$·HBr·$(EtOAc)_{0.33}$·$(H_2O)_3$) C, N; H: calcd, 6.39; found, 5.64.

4-[[3-[4-[2-(2,2,2-Trifluoroethoxy)phenyl]piperazin-1-yl]propyl]amino]-1,3-dimethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid methylamide oxalate (36f): mp 189.3−189.5 °C. Anal. ($C_{25}H_{32}F_3N_7O_2$·$(C_2H_2O_4)_2$) C, H, N.

4-[[3-[4-[2-(2,2,2-Trifluoroethoxy)phenyl]piperazin-1-yl]propyl]amino]-1,3-dimethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid dimethylamide hydrochloride (37f): mp 206.5−207.8 °C. Anal. ($C_{26}H_{34}F_3N_7O_2$·HCl) C, H, N.

4-[[3-[4-(4-Fluoro-2-methoxyphenyl)piperazin-1-yl]propyl]amino]-1,3-dimethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid dimethylamide citrate (37t): mp 100−110 °C. Anal. ($C_{25}H_{34}FN_7O_2$·$C_6H_8O_7$) C, H, N.

4-[[3-[4-[2-(2,2,2-Trifluoroethoxy)phenyl]piperazin-1-yl]propyl]amino]-3-*tert*-butyl-1-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid dimethylamide hydrobromide (38f): mp 178.2−181.0 °C. Anal. ($C_{29}H_{40}F_3N_7O_2$·$(HBr)_{2.5}$·$(EtOH)_{0.15}$·$(H_2O)_{0.65}$) C, H, N.

4-[[3-[4-[2-(2,2,2-Trifluoroethoxy)phenyl]piperazin-1-yl]propyl]amino]-3-methyl-1*H*-isoxazo[3,4-*b*]pyridine-5-carboxylic acid dimethylamide hydrochloride (39f): mp 113 °C dec. Anal. ($C_{25}H_{31}F_3N_6O_3$·HCl·$(H_2O)_{0.5}$) C, H, N.

4-[[3-[4-(4-Fluoro-2-methoxyphenyl)piperazin-1-yl]propyl]amino]-1,2-dimethyl-1*H*-imidazo[4,5-*b*]pyridine-5-carboxylic acid dimethylamide hydrochloride (40t): mp 160−168 °C. Anal. ($C_{25}H_{34}FN_7O_2$·$(HCl)_3$·$(H_2O)_{1.5}$) C, H, N.

7-[[3-[4-(4-Fluoro-2-methoxyphenyl)piperazin-1-yl]propyl]amino]pyrazolo[1,5-*a*]pyrimidine-6-carboxylic acid dimethylamide oxalate (41t): mp 77.5−105 °C. Anal. ($C_{23}H_{30}FN_7O_2$·$(C_2H_2O_4)_{2.5}$) C, H, N.

7-[[3-[4-(4-Fluoro-2-methoxyphenyl)piperazin-1-yl]propyl]amino]-3-chloropyrazolo[3,4-*b*]pyrimidine-6-carboxylic acid dimethylamide, oxalate (41t′): mp 128.5−138.5 °C. Anal. ($C_{23}H_{29}FClN_7O_2$·$(C_2H_2O_4)_2$·H_2O) C, H, N.

***N,N*-Dimethyl-4-[[3-[4-(4-fluoro-2-methoxyphenyl)piperazin-1-yl]propyl]amino]-7-methyl-1,8-naphthyridine-3-carboxamide fumarate (42t):** mp 130−133 °C. Anal. ($C_{26}H_{33}FN_6O_2$·$C_4H_4O_4$·$(H_2O)_{1.5}$) C, H, N.

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