New 1-(Heterocyclylalkyl)-4-(Propionanilido)-4-Piperidinyl Methyl Ester and Methylene Methyl Ether Analgesics

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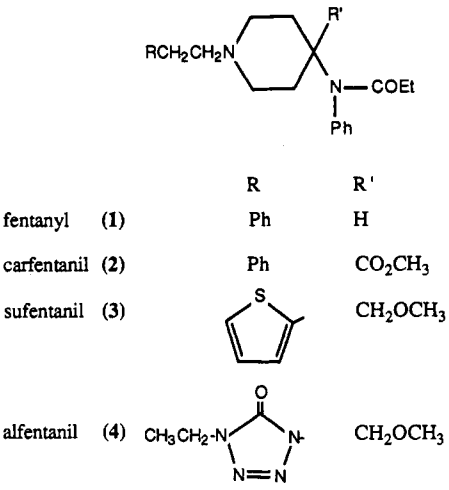
A series of new 1-(heterocyclylalkyl)-4-(propionanilido)-4-piperidinyl methyl esters and methylene methyl ethers have been synthesized and pharmacologically evaluated. In the mouse hot-plate test, the majority of compounds exhibited an analgesia (ED_{50} < 1 mg/kg) superior to that of morphine. These studies revealed a pharmacological accommodation for many more structurally diverse and far bulkier aromatic ring systems than the corresponding components of the arylethyl groups of the prototypic methyl ester (carfentanil, **2**) and methylene methyl ether (sufentanil, **3** and alfentanil, **4**) 4-propionanilido analgesics. Compound **9A** (methyl 1-[2-(1*H*-pyrazol-1-yl)-ethyl]-4-[(1-oxopropyl)phenylamino]-4-piperidinecarboxylate), which exhibited appreciable μ-opioid receptor affinity, was a more potent and short-acting analgesic, than alfentanil with less respiratory depression in the rat. On the other hand, the phthalimides **57A** and **57B**, which exhibited negligible affinity for opioid receptors associated with the mediation of nociceptive transmission (i.e., μ-, κ-, and δ-subtypes), displayed analgesic efficacy in all antinociception tests. In addition, while **57B**, compared to clinical opioids, showed a superior recovery of motor coordination after regaining of righting reflex from full anesthetic doses in the rat rotorod test, **57A** showed significantly less depression of cardiovascular function at supraanalgesic doses in the isoflurane-anesthetized rat.

Introduction

Some 30 years ago, Janssen and co-workers initiated the 4-anilidopiperidine class of opioid analgesics with the introduction of fentanyl (**1**) (Chart I).[1] It was found to be a significantly more potent analgesic than morphine with a faster onset and shorter duration of action.[2] Since then, **1** has become the agent of choice as the analgesic component of balanced anesthesia.[3] An advantage in the structure of such a compound is the lack of a need for an absolute asymmetric requirement for analgesic activity, unlike the more complex morphine alkaloid, benzomorphan, and morphinan analgesics.[4] Expansion of structure–activity relationships within the 4-anilidopiperidine class of analgesics has been reported.[5] The most notable advance in this field has been the simultaneous incorporation of small polar moieties with the propionanilido group at carbon-4 of the piperidine ring.[6] Carfentanil (**2**) and sufentanil (**3**) were found to be far more potent and of longer durations than **1** with **3** exhibiting an extraordinarily high margin of lethality in animals[7] and superior to **1** in clinical studies in stabilization of hemodynamic and hormonal responses to surgical stress.[8]

The latest entry to this class of analgesics was alfentanil (**4**). While four times less potent than **1**, it has a more rapid onset and shorter duration of analgesia.[9,10] In addition, the depressant effect on respiration was less severe than that of **1**.[10,11] The contrast in pharmacological profiles between **4** and analgesics **1–3** was explained as the result of marked differences in physicochemical properties.[12] The tetrazolinone ring with its concentration of electronegative atoms by electron withdrawal through the connecting ethylene chain render the piperidino nitrogen of **4** (pK_a = 6.5) far less basic than that of **1** (pk_a = 8.4). Thus at physiological pH (7.4), **4** is extensively un-ionized while **1** is extensively protonated and is regarded as the reason for its rapid onset of action.[12] In addition, the shorter duration of analgesia as well as the lowest overall tissue distribution of **4** than other opioid analgesics can be accounted for by the high affinity of **4** for plasma proteins.[12] With the growing popularity of outpatient

Chart I



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Current address: Cobe Laboratories, Inc., Arvada, CO.

(1) Janssen, P. A. J. *Brit. J. Anaesth.* **1962**, *34*, 260.
(2) Gardocki, J. K.; Yelnosky, J.; Kulhn, W. F.; Gunter, H. *Toxicol. Appl. Pharmacol.* **1964**, *6*, 593.
(3) Kitahata, L. M.; Collins, J. G. *Narcotics in Anesthesiology*; The Williams and Wilkins Co.: Baltimore, 1982.
(4) Lenz, G. R.; Evans, S. M.; Walters, D. E.; Hopfinger, A. J. *Opiates*; Harcourt, Bruce and Jovanovich; Academic Press, Inc.: New York, 1986; Chapters 3, 5, 6, and 7.
(5) Reference 5, Chapter 7.
(6) Van Daele, P. G. H.; DeBruyn, M. F. L.; Boey, J. M.; Sanczuk, S.; Agten, J. T. M.; Janssen, P. A. J. *Arzneim-Forsch. Drug Res.* **1976**, *26*, 1521.
(7) (a) Van Bever, W. F. M.; Niemeggers, C. J. E.; Schellenkens, K. H. L.; Janssen, P. A. J. *Arzneim-Forsch. Drug Res.* **1976**, *26*, 1548. (b) A recently reported procedure that allows a more facile access to the noramine **5** can be found in Feldman and Brackeen: Feldman, P. L.; Brackeen, M. F. *J. Org. Chem.* **1990**, *55*, 4207.
(8) Delange, S.; Stanley, T. H.; Boscoe, M. J. *Anesthesiology* **1980**, *53*, S64.
(9) Cookson, R. F.; Niemeggers, C. J. E.; Vanden Bussche, G. *Brit. J. Anaesth.* **1983**, *55*, 147S.
(10) Niemeggers, C. J. E.; Janssen, P. A. J. *Drug Dev. Res.* **1981**, *1*, 83.
(11) Scamman, F. L.; Ghoneim, M. M.; Kortilla, K. *Anesthesiology* **1982**, *57*, A364.

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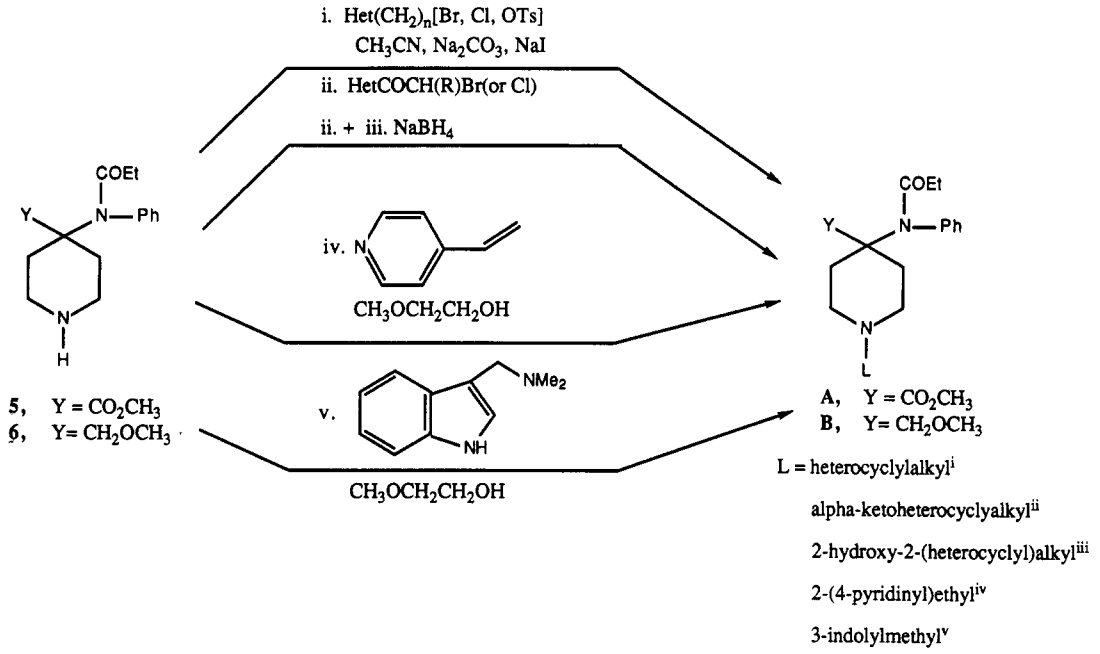
Scheme I



surgical procedures, analgesics with such a pharmacological profile are much in demand.

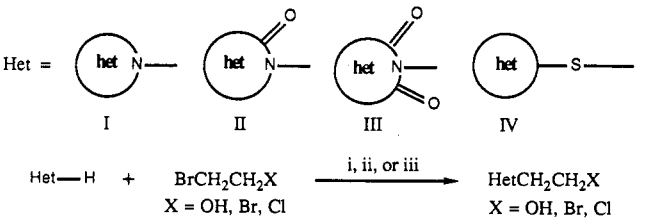
Therefore, a research program was initiated to prepare further novel analgesics A and B, structurally characterized by other heterocyclic substitutions (L) in an attempt to new find agents with therapeutically advantageous profiles. The rationale for this approach was based on the interesting fact that while heteroaromatic substitutions for the benzene ring of the phenethyl group at the basic nitrogen in the 4-(propionanilido)piperidine class of opioids have rarely been reported, these have yielded analgesics which have been more therapeutically advantageous than the class prototype 1.

Chemistry

The new 1-(heterocyclylalkyl)-4-(propionanilido)-4-piperidinyl methyl esters and methylene methyl ethers were prepared by the coupling of the noramines[7] **5** and **6** with the appropriate heterocyclic electrophiles (Scheme I). Virtually all were products of nucleophilic displacement of a bromine or chlorine atom or tosylate group in refluxing acetonitrile. In the case of α-halo ketones, stirring the reaction mixtures at room temperature was sufficient. Most of the amino ketones were evaluated for analgesia and all were subsequently reduced to the corresponding amino alcohols with sodium borohydride in absolute ethanol. Compounds **44A** and **52A** were synthesized by the coupling of **5** with 4-vinylpyridine and 3-[(dimethylamino)methyl]indole, respectively, in refluxing 2-methoxyethanol.

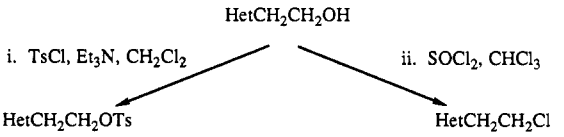
The heterocyclylalkyl intermediates, when not commercially available, were synthesized by three major routes of alkylation (Scheme II). Most involved reaction of an appropriate heterocyclic N–H (substructures I, II, and III) with 2-bromo-1-chloroethane, 1,2-dibromoethane, or 2-bromoethanol in sodium–ethanol, or sodium–dimethylformamide media, or via quaternary ammonium phase transfer catalysis. A few instances involved alkylation of a peripheral thio group (substructure IV). Alcohol intermediates were activated by chlorination with thionyl chloride or by tosylation (Scheme III).

Scheme II[a]



[a] (i) NaOEt, EtOH; (ii) NaH, DMF; (iii) $Bu_4N^+X^-$, KOH, organic solvent.

Scheme III



Preliminary Pharmacology

A. Results and Discussion. The compounds were evaluated for analgesia 1 min following injection into the lateral tail vein of the mouse by the 55 °C hot-plate assay. An initial dose of 1 mg/kg was administered, and if 100% analgesia was observed, then lower dosing was continued until an ED_{50} was generated. If less than 100% analgesia was observed, then 5 mg/kg was administered. Examination of the structures of the heterocycles depict a systematic variation from five-membered rings to large fused ring systems (Table I). No pharmacologically advantageous trend was observed whether the smaller functionality at C-4 was carbomethoxy or methoxymethyl.

1. The Azole Series (7–25). Compounds bearing pyrrole and pyrazole rings (**7–13**) exhibited analgesic activity with the simple pyrrole analogue **7A** being one of the most potent analgesics in the series. While methylation at the positions adjacent to the pyrazole nitrogens did not significantly change activity (**10** and **11**), introduction of larger ester functionalities drastically reduced activity (**13A**). The diester **13A** was an attempt to provide an analgesic of short duration due to rapid in vivo hydrolysis

(12) Janssens, F.; Torremans, J.; Janssen, P. A. J. *J. Med. Chem.* 1986, *29*, 2290.

of the ester groups by esterases present in the plasma and cytosol of mammalian red blood cells[13] to yield inactive metabolites. Generally, the 1-ethylimidazole analogues (**14**, **15**, and **17**) were inactive, except for those analogues (**16**) in which the ethyl connector at N′-1 was sandwiched between two peripheral substituents. The 4(5)-substituted imidazoles **18** were inactive, a finding consistent with the report that the substitution of the phenethyl group with the same 4-(2-ethyl)imidazole group in the potent *cis*-3-methylfentanyl also resulted in diminished analgesia.[14] The 2′-substituted imidazoles **19** were active, thus revealing an pharmacophore induction site of substitution in this otherwise placid ring system. The simple triazole analogues **20** were more active that the simple imidazoles while the substituted triazole **21B** was less active than its imidazole counterpart (**19B**), perhaps due to the presence of the additional trifluoromethyl substituent. The simple tetrazole analogues **22** were more active than the triazole congeners (**20**). The general loss of activity on proceeding from pyrrole to imidazole and reemergence of activity with triazole was an interesting phenomenon. Perhaps, introduction of a nitrogen adjacent to that bearing the ethyl connecting chain in **14** to yield **20** may result in an increase in activity due to the mimicing of the pyrazole ring. The further increase in activity on introduction of a nitrogen in an identical juxtaposition in the tetrazole analogues supported this hypothesis. Placement of large substituents at ring position 5 of **22** only rendered the inactive **23A** and **24B**. Of significance was the finding that identical juxtapositioning of a N'-CH_3 with an adjacent C'-SCH_2CH_2 group in the tetrazole **25A**, as in the imidazoles **19**, resulted in an identical degree of analgesia.

2. The Thiophene, Furan, and Thiazole Series (26–34). The 3-thiophene analogue **30B** was equiactive to sufentanil (**3**), and the methyl ester **30A** was the most potent analgesic in the series. Within the thiophene family, the degree of analgesia declined in the β-hydroxyethyl derivatives **28** and **29** and this continued in the β-keto derivatives **26** and **27** indicating that a sp2 hybridized β-carbon and the resulting π-orbital electron conjugation was the least pharmacophorically conducive molecular geometry in this subseries. Methylation of the α-carbon (**27B** and **29B**) did not lead to enhancement of analgesia, unlike that reported in congeners of **1**.[15] The furan **31B** was as active as the corresponding thiophene **28B** and subsequent ring methylation (**32B**) reduced activity here as well. The 4-methyl thiazoles (**33**) showed a relatively high degree of potency. β-Methoxylation of the ethylene chain to yield **34** resulted in a decline in potency. Further, the diminished activity of **34** compared to **28**, **31B**, and **32B** may be due to the loss of a analgesic pharmacophore on methylation.

3. Other Heteropentacyclic Series (35–41). The lack of appreciable activity by **35A** was probably due to the lack of aromatic or flat structural features of the oxazolinone ring. Neither does compound **37A** have an arylethyl moiety attached to the piperidino nitrogen, however the N′-2 phenyl ring may be in a favorable recognition mode combined with the carfentanil piperidino substructure for the eliciting of an analgesic response. In the 4-propionanilido class of opioid analgesics, the significance of a certain juxtaposition between an aromatic feature and the piperidino nitrogen, to which it is linked, in optimizing analgesic activity has been established.[16] Compound **36B** was an analogue of alfentanil (**4**), lacking the nitrogens in the 2′- and 3′-positions, with twice the potency of **4**. The thiadiazole **39A** showed only modest activity. The C=S and/or large peripheral phenyl at 5′-position rendered the oxadiazole **40A** inactive in the mouse. The rationale for incorporation of the 4′-aminotriazolinone ring in **41B** was to provide a short-acting analgesic through relatively higher plasma compartmentalization due to the hydrophilic nature of the NH_2. Indeed, in subsequent rat tail-flick studies, where the blood–brain barrier was circumvented by intrathecal injection, a peak 99% maximum pharmacological effect was measured 30 min after **41B** (20 μg) was administered.

4. The Heterohexacyclic Series (42–51). Among the pyridines **42–44**, potency gradually diminished as the ethyl connector was moved from the 2′-position to the 4′-position. Thus these ring systems were not exact bioisosteres to the phenyl ring. A relative decline in potency was observed with compounds **45**, **46A**, and **49**. The simple pyrimidone **47A** was weakly active while the peripherally substituted derivatives **48** exhibited good analgesia, a substitution pattern with opposite results from that in the five-membered series. The uracil pair (**49**) were unique in one respect. Increasing supraanalgesic doses, up to 100 mg/kg, could not induce hypnosis (loss of righting) in the mouse. Attachment of the 3(2*H*)-pyridazinone ring, a pharmacophoric feature extensively employed in the synthesis of nonopioid analgesics,[17] to 4-anilido-4-(methoxymethyl)piperidine produced an opioid agonist (**50A**) as active as alfentanil (**4**). The triazolinone **51A** was $^1/_{10}$th as active as the pyridazinone **50A**.

5. The Benzo-Fused Heteropentacyclic Series (52–64). Among the compounds with fused ring substituents, all those with free N–H groups were inactive (**52A**, **59A**, and **64A**). The indolinones **53–55** were among the most potent analgesics in the series though small alkyl additions at the 3′-position of the indolinone ring of **53** reduced activity 10-fold. Transposition of the lactam features of **53** to give the isoindolinone **56B** resulted in a 500-fold reduction in activity. Incorporation of an additional C=O in the isoindolinone ring to yield the phthalimides **57** significantly restored analgesic potency. It is interesting that while the imidazole **14A** was inactive, the benzimidazole **58A** showed modest potency, and the indazole **60A** showed no activity in the mouse. The imidazolinones **61**, which were extended versions of **36B**, showed activities approximating that of the smaller compound. Like other examples previously mentioned, peripheral substitution (**63A**) on the simple 1,3-benzoxazolinone ring of **62** produced a less active agent.

6. The Benzo-Fused Heterohexacyclic Series (65–72). Compounds **65B** and **66A** were also efforts to provide analgesics of short durations due to rapid in vivo cleavage of the lactone functionalities by plasma esterases. However, these were inactive at doses up to 5 mg/kg. The 1,4-benzodioxanes **67** were analgesics, while the 1,3-derivative (**68B**) was not. The inactivity of the latter may be the result of the single methylene linkage between the benzene ring and the piperidino nitrogen, a juxtaposition which generally drastically reduced activity in other classes of piperidine analgesics.[15] The 1,4-benzothiazin-3-one **69A** exhibited appreciable analgesia; however, transposition of

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(14) Changying, C.; Lemin, L. *Int. J. Quantum Chem.* **1983**, *23*, 1597.
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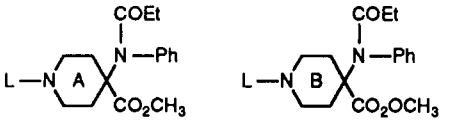
Table I. New 1-(Heterocycylylalkyl)-4-(Propionanilido)-4-Piperidinyl Methyl Esters (L-A) and Methylene Methyl Ethers (L-B). Preliminary Pharmacology (L group, ED_{50} (CL))



L = $-(CH_2)_n$–X–heterocycle (n = 1, 2; X = O, S, or direct bond)

1. Azoles

a. Pyrroles

	7	8
A	0.001[a] (0.00068–0.001)[b]	0.003 (0.0021–0.0032)
B	0.003 (0.002–0.004)	0.003 (0.002–0.004)

b. Pyrazoles

	9	10	11	12	13
A	0.009 (0.0072–0.0123)	0.004 (0.003–0.005)	0.007 (0.005–0.01)	0.017 (0.012–0.023)	>1
B	0.016 (0.011–0.021)	–	0.012 (0.010–0.014)	0.018 (0.014–0.023)	–

c. Imidazoles

	14	15	16	17	18	19
A	>5	>5	0.264 (0.201–0.399)	>5	>5	0.13 (0.09–0.19)
B	–	–	0.262 (0.203–0.344)	–	>5	0.13 (0.01–0.18)

d. Triazoles

	20	21
A	1.04 (0.76–1.43)	–
B	80% at 1 mg/kg[c] –	>1

e. Tetrazoles

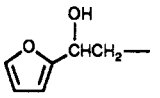
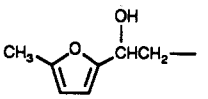
	22	23	24	25
A	0.19 (0.10–0.38)	>5	–	0.131 (0.077–0.222)
B	0.34 (0.02–0.73)	–	>5	–

2. a. Thiophenes

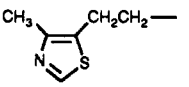
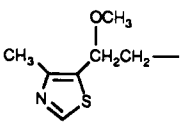
	26	27	28	29	30
A	0.044 (0.034–0.057)	–	0.0020 (0.0017–0.0024)	–	0.0006 (0.0004–0.0008)
B	–	>1	0.005 (0.003–0.008)	0.015 (0.012–0.019)	0.004 (0.003–0.005)

Table I (Continued)

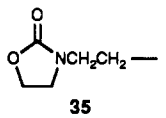
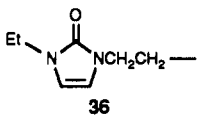
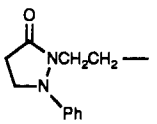
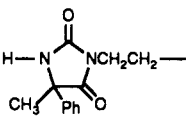
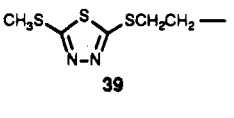
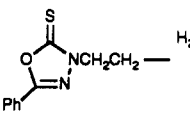
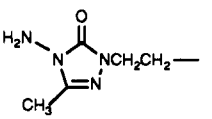
b. Furans

	 **31**	 **32**
A	–	–
B	0.003 (0.0026–0.0044)	0.009 (0.007–0.013)

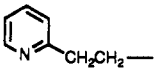
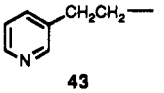
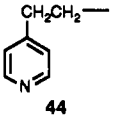
c. Thiazoles

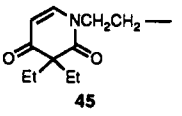
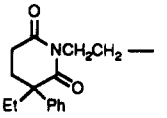
	 **33**	 **34**
A	0.0013 (0.0010–0.0020)	0.045 (0.037–0.057)
B	0.003 (0.002–0.006)	0.067 (0.050–0.077)

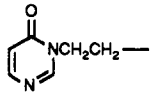
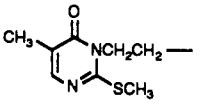
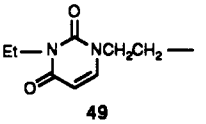
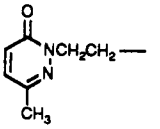
3. Other Heteropentacyclic Series

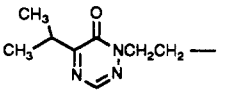
	 **35**	 **36**	 **37**	 **38**	 **39**	 **40**	 **41**
A	>1	–	0.50 (0.42–0.60)	>1	0.19 (0.16–0.22)	>5	–
B	–	0.09 (0.05–0.16)	>1	–	–	–	>1

4. Heterohexacyclic Series

	 **42**	 **43**	 **44**
A	0.005 (0.004–0.006)	0.005 (0.004–0.006)	0.061 (0.005–0.080)
B	0.005[d]	0.011 (0.009–0.013)	–

	 **45**	 **46**
A	0.156 (0.103–0.237)	0.462 (0.339–0.628)
B	0.176 (0.143–0.215)	–

	 **47**	 **48**	 **49**	 **50**
A	60% at 1 mg/kg[e]	0.037 (0.020–0.067)	2.67 (2.15–3.31)	0.05 (0.04–0.06)
B	–	0.055 (0.032–0.077)	0.60 (0.85–0.74)	–



51

0.621 (0.457–0.846)

–

Table I (Continued)

5. Benzo-Fused Heteropentacyclic Series

	52	53	54	55	56
A	>1	0.009 (0.005–0.016)	0.038 (0.028–0.052)	0.022 (0.010–0.046)	-
B	-	0.003 (0.002–0.004)	0.027 (0.021–0.036)	0.064 (0.049–0.082)	1.50 (0.98–2.40)

	57	58	59	60
A	0.19 (0.15–0.25)	0.22 (0.16–0.30)	>5	>5
B	0.80 (0.68–0.95)	-	-	-

	61	62	63	64
A	0.121 (0.024–0.669)	0.03 (0.002–0.004)	0.27 (0.19–0.39)	>5
B	0.092 (0.069–0.126)	0.10 (0.05–0.22)	-	-

6. Benzo-Fused Heterohexacyclic Series

	65	66	67	68
A	-	>5	0.05 (0.04–0.06)	-
B	>5	-	0.10 (0.08–0.12)	>1

	69	70	71	72
A	0.047 (0.039–0.056)	0.30 (0.03–0.539)	>1	0.19 (0.15–0.25)
B	-	0.42 (0.31–0.58)	-	0.15 (0.10–0.21)

7. a. Xanthines

	73	74
A	>5	>5
B	-	-

b. Naphthalimides

75	76	77

Table I (Continued)

		b. Naphthalimides	
A	–	0.22 (0.18–0.28)	>1
B	0.50 (0.40–0.62)	–	–

fentanyl (1)	carfentanil (2)	sufentanil (3)	alfentanil (4)	morphine
0.018 (0.025–1.50)	0.0008 (0.0006–0.0009)	0.00290 (0.00006–0.15100)	0.047 (0.034–0.065)	10.00 (0.01–108.00)

[a] Mouse hot-plate ED_{50} (mg/kg). [b] 95% confidence limits (mg/kg). [c] Percentage of maximum pharmacological effect detected at dose indicated. [d] Janssen, P. A. J.; Van Daele, G. H. P., U. S. Patent 3 998 834, 1976.

Table II. Pharmacological Results of Highlighted Compounds

	9A	9B	57A	57B	1	4
rat tail-flick ED_{50}[a]	0.0024 (0.0013–0.0048)	0.0039 (0.0030–0.0051)	0.032 (0.023–0.045)	0.045 (0.027–0.075)	0.004 (0.003–0.006)	0.011 (0.008–0.014)
rat hot-plate ED_{50}[a]	0.0099 (0.0072–0.0138)	0.0075 (0.0048–0.0098)	0.056 (0.044–0.071)	0.119 (0.060–2.17)	0.008 (0.006–0.010)	0.031 (0.011–0.084)
rat rotorod[b]						
a. immediately after regain of righting:						
succeeded/tested (s)[c]	2/5 (40.9)	2/5 (43.2)	3/5 (59.9)	4/5 (86.6)	0/5 (11.0)	1/5 (32.5)
b. 90 s later:						
succeeded/tested (s)[c]	1/3 (34.7)	1/3 (52.3)	1/2 (47.0)	0/1 (20.8)	2/5 (38.0)	1/4 (51.1)
c. 180 s later:						
succeeded/tested (s)[c]	1/2 (50.8)	0/2 (36.5)	0/1 (4.6)	0/1 (58.5)	1/3 (31.5)	0/3 (51.0)
rotorod index (ROI)	34.5	37.0	44.2	55.1	18.2	31.3
recovery of motor activity						
GRI, min[d]	10.8	not determined	4.7	6.7	17.3	6.8
opioid receptor binding:[e]						
IC_{50}, nM						
μ (^{3}H-DAGO)[f]	5.4	10.3	1200	1600	3.1	15
κ (^{3}H-EKC)[g]	29% at 10000	34% at 10000	>10000	>10000	5893	>10000
δ (^{3}H-DPDPE)[h]	809	1701	38% at 10000	35% at 10000	187.4	14% at 10000

[a] Injection at the lateral tail vein (mg/kg). [b] Recovery of motor coordination after intravenous injection of ED_{100} (loss of righting) of compound and regaining of righting (see Experimental Section). [c] Number of animals which succeeded/tested on the rotating rod (average duration in seconds). [d] GRI = general recovery index. The GRI is the mean recovery time of behavioral parameters defining locomotor activity (see Experimental Section). [e] Opioid receptors were isolated from guinea pig brain (see Experimental Section). [f] DAGO IC_{50} = 1.6 nM. [g] EKC IC_{50} = 5.0 nM. [h] DPDPE IC_{50} = 5.5 nM.

the lactam features to yield **70** and **72** resulted in diminished activity in the mouse. When compared to **72**, the free N–H at N′-1 of **71** was apparently detrimental to activity.

7. The Xanthine and Naphthalene Series (73–77). The purine analogues **73A** and **74A**, which were inactive in the mouse, were attempts to obtain compounds with opioid receptor mediated analgesia combined with the respiratory stimulation of a methylxanthine pharmacophore to physiologically antagonize opioid-induced apnea.[18,19] The compounds bearing the largest of the L heterocyclic groups in the series showed modest (**75B** and **76A**) to poor activity (**77A**) in this species.

B. Summary. In the mouse, a clear structure–activity relationship was observed. The most potent analgesics were found among the compounds bearing certain five-membered heterocyclic rings (e.g., pyrroles, pyrazoles, thiophenes, furans, and thiazole). By comparison, those compounds containing six-membered heterocyclic rings were less potent as analgesics, except for the pyridines. When azolinone (five-membered) rings were fused to a benzene ring, potent analgesia was detected (**53–55**), but potency was reduced on transposition of the nitrogen and C=O (**56B**), or on introduction of an additional C=O (**57**), and generally when an internal heteroatom was introduced (**61–63**). The benzo-fused six-membered counterparts (**69–72**) were generally shown to offer no advantage in analgesic potency. Thus heterocyclic L substituents, which were large relative to the corresponding groups of **1–4**, were analgesic pharmacophores in the mouse. Among these, optimal molecular design was seen in those compounds in which heterocycles were fused to only one benzene ring and the ethyl connector attached to a nitrogen, which was situated between the benzene ring and a C=O (e.g., **53** and **69**).

Highlighted Compounds. Many of the compounds (e.g., **9A**, **9B**, **16A**, **33A**, **45A**, **53A**, **53B**, **57A**, **57B**, **70B**, and **72A**) which exhibited appreciable analgesia (<1 mg/kg) or exhibited other interesting properties (e.g., short duration of action = $2XED_{50}$ dose < 6.0 min) in the mouse were further investigated in the rat primary overt effects (POE) screen. Primary overt effects of standard opioids (e.g., **1–4**) most often observed have been cyanosis, presumably due to increased blood CO_2 levels, trunk and limb skeletal muscle rigidity, decrease or loss of reflexes, hypothermia, miosis, decreased heart rate, as well as loss of righting and analgesia to the paw pinch (see Experimental Section). Two structural groups of analgesics which emerged with favorable syndromes were the pyrazoles **9** and the phthalimides **57**. All the compounds showed better recoveries of motor coordination in varying degrees than the clinical analgesics **1** and **4** in the rat rotorod test (Table II). In this test for recovery of motor coordination, rats were trained to maintain their balance on a revolving rotorod. Following intravenous injection of the ED_{100} (loss of righting) dose, groups of animals were subjected to the rotorod immediately, 90 s, and 180 s after regaining of righting reflex and then a rotorod index (ROI) was calculated for each compound over the three time intervals (see

(18) Bellville, J. W.; Escarraga, L. A.; Wallenstein, S. L.; Wang, K. C.; Howland, W. S.; Houde, R. W. *J. Pharmacol. Exp. Ther.* **1962**, *136*, 38.
(19) Stirt, J. A. *Anesthesia* **1983**, *38*, 275.

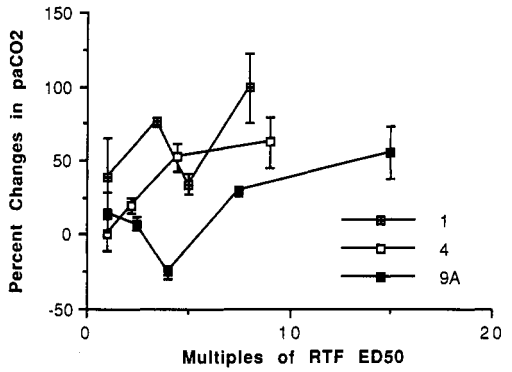


Figure 1. Effects on respiration in conscious freely moving rats after iv fentanyl (1), alfentanil (4), and **9A**. $PaCO_2$ = pressure in millimeters of mercury of CO_2 gas in arterial blood. Respiratory effects were measured as percent changes in $paCO_2$ after control blood samples were taken and each animal served as its own control. Data points are mean values (±SEM), N = 2–5.

Experimental Section). A perfect score of 60.0 is received when all the animals remain on the rotorod for 90 s after immediate regaining of righting.

When the analgesia of the pyrazoles **9** was compared to 1 and 4, both were more potent than 4 against thermal nociception in rodents (Table I and II). In these tests, **9A** was consistently a shorter-acting analgesic than **9B**. Following injection in mice of $2XED_{50}$ and $16XED_{50}$ doses **9A** exhibited respective durations of 4.42 and 11.52 min, while respective durations of 1.73 and 10.36 min were recorded for 4. The $2XED_{50}$ duration for **9B** in the mouse was 8.35 min. In the rat tail-flick test, the $8XED_{50}$ durations for **9A** and **9B** were 14.1 and 33.0 min, respectively, while in the rat hot-plate test, the $8XED_{50}$ durations for **9A** and **9B** were 21.21 and 30.5 min, respectively. For 4, $8XED_{50}$ durations of 20.0 and 17.7 min were measured in the rat tail-flick and hot-plate tests, respectively. The analgesia of **9A** (rat tail flick) was significantly reversed by 0.01 mg/kg of naloxone. The general recovery index (GRI), the mean time in minutes to recovery of locomotor activity from loss of righting doses of a drug (see Experimental Section), for **9A** was slower than 4, but far superior to 1. In the rotorod test, both **9A** and **9B** were not appreciably superior to 4 in recovery of motor coordination, but were significantly better than 1. In the freely moving, conscious rat model, **9A** showed less respiratory depression at analgesic doses than the clinically employed opioids 1 and 4 (Figure 1). Only at a dose of $15XED_{50}$ (rat tail flick), did **9A** produce a slightly greater than 50% increase in arterial blood carbon dioxide levels. One can observe from the graph that this dose is approximately 3–4 times the ED_{50} multiples of 1 and 4 which also produced the same effect. Also noteworthy was the apparent absence of hypercapnia with **9A** between ED_{50} and $5XED_{50}$. Since alfentanil (4) caused the least respiratory depression of the standard opioids, comparison of therapeutic indices between 4 and **9A** was made. The relative safety of a drug can be measured by the determination of its therapeutic index. This is calculated by dividing the side effect or toxicity dose which elicits a 50% response from control for a specific pharmacological parameter (as determined graphically), by the measured therapeutic response such as analgesia, i.e., rat tail-flick or hot-plate ED_{50}. The respective therapeutic indices for 4 and **9A** were the following: (rat tail flick) 6.0 and 13.5, (rat hot plate) 3.6 and 3.3, and (rat loss of righting) 2.7 and 4.1. Thus, it would appear that replacement of the phenethyl group of the long-acting 4-(carbomethoxy)piperidine, carfentanil (**2**),[7] with a simple pyrazolylethyl system to yield **9A** has provided an agent capable of eliciting high dose analgesia of similar duration to alfentanil with a higher margin of safety in the rat.

Between the two phthalimides **57A** and **57B**, the former was consistently a superior analgesic in rodents (Tables I and II). In the rat primary overt effects screen, the ED_{50} of analgesia (paw pinch) for **57A** was 0.052 (0.0516–0.0524) mg/kg and for **57B** was 0.061 (0.055–0.067) mg/kg, respectively. Further studies of the **57** pair in rabbits and dogs continued to show the profile of a short-acting iv analgesic, with anesthetic possibilities as well (data not shown). It was extraordinary that while the analgesia (rat tail flick) of **57A** was significantly reversed with a dose of 0.01 mg/kg of naloxone, which suggested that the mode of action of these phthalimides was occupancy of the opioid receptor, no appreciable binding to those opioid receptor subtypes (μ, κ, and δ) associated with antinociception was detected at concentrations of up to 10000 nM (Table II). In the POE screen, **57B** caused less central nervous system depression than **57A** as evident by the quick response of the animals to touch and noise stimuli during loss of righting. In the rat rotorod test, both compounds exhibited better recoveries of motor coordination after regaining of righting than 1 and 4 with **57B** rendering a near maximal score (60.0). In the computerized screen for recovery of locomotor activity, recovery time for **57A** was quicker than that from 1 and 4 (Table II). These tests can be predictive of the quality of recovery after administration of drugs in the clinic. The greater safety of **57A**, especially on cardiovascular function, was most evident in the isoflurane-anesthetized rat (see Experimental Section). Respective therapeutic indices for 1, **57A**, and **57B** for depression of mean arterial blood pressure were the following: (rat tail flick) 0.7, 22.8, 5.1; (rat hot plate) 0.2, 13.0, 1.9. Therapeutic indices for **57A** in depression of heart rate could not be calculated since a 24% ceiling effect relative to control was observed in this screen. Therapeutic indices could not be calculated for **57B** as well, since the decreases in heart rate versus dose generated a nonlinear curve. However, a depression of heart rate of 51% was observed for **57B** in these experiments. Respective therapeutic indices for 1, **57A**, and **57B** for depression of respiration were the following: (rat tail flick) 1.9, 6.3, 5.6; (rat hot plate) 0.6, 3.4, 2.0.

Conclusion

Many compounds displayed analgesia superior to that of morphine. Noteworthy was the finding that **9A** showed potent μ opioid receptor affinity and analgesia, but displayed a superior respiratory depression profile compared to clinically used opioids in the freely moving, conscious rat model. On the other hand, the phthalimides **57** while exhibiting profound analgesia in rodents, showed no significant affinity for receptors associated with mediation of pain transmission, i.e., μ-, κ-, and δ-opioid subtypes, in in vitro binding studies. Nevertheless, an opioid receptor link for the mechanism of analgesia was suggested by naloxone reversibility. Such pharmacodynamic properties are atypical of compounds that one may regard as structurally related to the opioid agonists 2–4. In addition the 4-anilidopiperidine structure is not known to confer blockade of antinociceptive impulse transmission through indirect means as stimulation of the release of endogenous opioids or inhibition of enkephalinase.[20] The consistency in the eliciting of analgesia in all the tests for antinociception, the improvements in the onset and quality of

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recovery of motor function, and the greater cardiovascular safety associated with the presence of the phthalimide ring system offers a new pharmacophoric tool for the development of more efficacious central analgesics.

Experimental Section

General Information. Melting points were recorded on a Thomas–Hoover melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian EM 360 (60 mHz) spectrometer. IR spectra were recorded on a Perkin-Elmer 197 spectrophotometer. Conventional and flash column chromatography were performed with fine silica (EM Sciences, 230–400 mesh). Reaction progress and purity of products were checked by analytical TLC using Analtech (GHLF) silica-coated glass plates. Spots were visualized with UV_{254} light or iodine. Tetrahydrofuran (THF) was freshly distilled from $LiAlH_4$, dimethylformamide (DMF) from CaH_2, and triethylamine (TEA) from KOH. All other solvents were used without further caution. Air-sensitive reactions were carried out under dry nitrogen or argon.

I. Heterocyclylalkyl Bromides, Chlorides, and Tosylates [Het–CH_n–[Br,Cl,OTs] (n = 1,2) and Het–[O,S]–CH_2CH_2–[Br,Cl]. For convenience these intermediates are designated with the letter C following the number assigned each heterocyclic unit illustrated in Table I.

A. Commercially available: 3-(2-chloroethyl)-2-oxazolidinone (**35C**, Aldrich), 4-vinylpyridine (**44C**, Aldrich), 3-[(dimethylamino)methyl]indole (**52C**, Aldrich), *N*-(2-bromoethyl)phthalimide (**57C**, Aldrich), 2-(chloromethyl)benzimidazole (**59C**, Aldrich), 4-(bromomethyl)-7-methoxycoumarin (**66C**, Aldrich), 8-(chloromethyl)-2-fluorobenzo-1,3-dioxane (**68C**, Maybridge), 3-(2-bromoethyl)-1,2,3,4-tetrahydro-2,4-dioxoquinazoline (**71C**, Maybridge), 7-(2-chloroethyl)theophylline (**73C**, Aldrich), and *N*-(2-chloroethyl)-1,8-naphthalimide (**77C**, Aldrich).

B. Available from previously published procedures: 1-(2-chloroethyl)-1*H*-pyrrole[21] (**7C**), 1-(2-tosylethyl)-1*H*-pyrazole[22] (**9C**), 1-(2-chloroethyl)-1*H*-imidazole hydrochloride[23] (**14C**), 5-nitro-1-(2-bromoethyl)-1*H*-imidazole[24] (**15C**), 2-methyl-5-nitro-1-(2-chloroethyl)-1*H*-imidazole[25] (**16C**), 4-(2-chloroethyl)-1*H*-imidazole hydrochloride[26] (**18C**), 1-methyl-2-[(2-chloroethyl)-thio]-1*H*-imidazole[27] (**19C**), 2-(bromoacetyl)thiophene[28] (**26C**), 2-(2-bromopropionyl)thiophene[29] (**27C**), 2-(bromoacetyl)furan[30] (**31C**), 5-methyl-2-(chloroacetyl)furan[31] (**32C**), 4-methyl-5-(1-methoxy-2-bromoethyl)thiazole[32] (**34C**), 1-(2-bromoethyl)-3-methyl-4-amino-5(1*H*)-triazolinone[33] (**41C**), 3-methyl-1-(2-bromoethyl)-1,6-dihydro-1*H*-pyridazin-6-one[34] (**50C**), (1′-(2-bromoethyl)spiro[cyclopropane-1,3′-[3*H*]-indole-2′(1′*H*)-one[35] (**55C**), 1-(2-chloroethyl)-1*H*-benzimidazole[36] (**58C**), 6-(2-bromoacetyl)-1,3-benzoxazolin-2(3*H*)-one[37] (**64C**), 7-(2-bromoethoxy)-coumarin[38] (**65C**), and 2-methyl-3-(2-chloroethyl)-3,4-dihydroquinazolin-4-one[39] (**70C**).

Synthesis. For the intermediates listed below, purification was usually accomplished by column chromatography (A = $CHCl_3$; B = $CHCl_3$–MeOH–TEA, 19:1:0.1; C = $CHCl_3$–MeOH–TEA, 80:1:0.1; D = $CHCl_3$–MeOH, 19:1; E = $CHCl_3$–MeOH, 40:1; F = hexane–EtOAc–TEA, 4:1:0.1; G = hexane–EtOAc–TEA, 5:1:0.1; H = hexane–EtOAc–TEA, 5:5:0.1; I = hexane–EtOAc–NH_4OH, 3:1:0.1; J = hexane–EtOAc, 1:1; K = hexane–EtOAc, 3:1; L = hexane–EtOAc, 7:1; M = $CHCl_3$–MeOH–NH_4OH, 80:1:0.1)). Confirmation of purity was achieved by detection of homogeneity on TLC analysis. Confirmation of structure of the intermediates was achieved by ^{1}H NMR analysis wherein characteristic resonances of the heterocyclic moiety (in this report contained in NMR data of target compounds) were compared to that of the immediate precursor and usually the observation of two prominent triplets at approximately 3.70 ppm (hetCH_2CH_2X) and at approximately 4.20 ppm (hetCH_2CH_2X). These intermediates were used directly in the synthesis of target compounds without further characterization. A typical workup consisted of partitioning of the crude concentrate, after evacuation of reaction solvent, between CH_2Cl_2 or $CHCl_3$ (50 mL) and water (50 mL), further extraction with additional organic solvent, washing of the combined organic extract with water (50 mL) and brine (30 mL), and drying over Na_2SO_4. Pertinent data is presented below in the following format after each general method: compound number (precursor, source of precursor, % yield, letter designation for column chromatography solvent system). The following procedures are outlined in Schemes II and III.

Via Sodium Ethoxide in Ethanol. Example. Sodium pieces (0.79 g, 34.3 mmol) were dissolved in absolute ethanol (150 mL) and the solution cooled to room temperature. 3,5-Bis(ethoxycarbonyl)-1*H*-pyrazole[40] (7.3 g, 34.3 mmol) was added in one portion, and the reaction mixture was stirred at room temperature for 20 min. 1,2-Dibromoethane (34.3 mL, 69.6 mmol) was added in one portion, and the reaction mixture was stirred under reflux for 24 h. The reaction mixture was cooled and concentrated in vacuo and the residue worked up as described above. Purification was achieved with column chromatography (400 g fine silica; $CHCl_3$–MeOH, 40:1) yielding 3.9 g (31%) of **13C**. Other heterocyclylethyl bromides synthesized by this method were the following: **17C** (4,5-bis(ethoxycarbonyl)-1*H*-imidazole, ref 41, 52%, D). Heterocyclylethyl chlorides were the following: **20C** (1,2,4-triazole, Aldrich, 43%, used directly after workup), **21C** (3-(trifluoromethyl)-4-methyl-4*H*-1,2,4-triazole-3-thiol, Aldrich, 88%, used without further purification), **23C** (5-phenyl-2*H*-tetrazole, ref 42, 48%, from EtOH, mp 52–56 °C), **24C** [5-(4-

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morpholinyl)-2*H*-tetrazole, Maybridge, 45%, A], **25C** (1-methyl-1*H*-tetrazole-5-thiol, Aldrich, 59%, A), **38C** (5-methyl-5-phenylhydantion, Aldrich, 83%, used without further purification), **39C** (5-(methylthio)-1,3,4-thiadiazole-2(3*H*)-thione, ref 43, 41%, C), and **40C** (5-phenyl-1,3,4-oxadiazole-2(3*H*)-thione, ref 44, 59%, EtOAc then MeOH).

Via Sodium Hydride in Dimethylformamide. Example. Sodium hydride (3.9 g, mmol, 50% mineral oil dispersion) was washed of mineral oil with hexane (3 × 10 mL) under a nitrogen stream. A solution of 1,3-benzoxazolin-2(3*H*)-one (Aldrich, 10 g, 74 mmol) in DMF (70 mL) was then added dropwise with stirring until hydrogen evolution ceased. The reaction flask was immersed in an ice bath and 2-bromo-1-chloroethane (12.3 mL, 148 mmol) in DMF (30 mL) was added dropwise. The reaction mixture stirred at room temperature for 30 min then at reflux for 3 days. At this time TLC analysis showed virtual consumption of starting material. The reaction mixture was cooled and the solvent evaporated in vacuo. Workup was as described above. Column chromatography (400 g fine silica, $CHCl_3$–MeOH–NH_4OH, 80:1:0.1) yielded 11.7 g (80%) of pure 3-(2-chloroethyl)-1,3-benzoxazolin-2(3*H*)-one (**62C**, mp 77–79 °C) as pale orange solid. Heterocyclylethyl bromides synthesized by this method were the following: **36C** (1-ethyl-2-imidazolone, ref 45, 17%, A), **72C** (1-ethyl-1,2,3,4-tetrahydro-2,4-quinazolinedione, ref 46, 55%, crystallized from CH_2Cl_2). Heterocyclylethyl chlorides were the following: **8C** (2-pyrrolecarboxaldehyde, Aldrich, 48%, I), **49C** (3-ethyluracil, ref 47, 60%, C), **53C** (oxindole, Aldrich, 15%, L), **54C** (1,3-dihydro-3,3-dimethyl-2*H*-indol-2-one, ref 48, 50%, used without further purification), and **69C** (1,4-benzothiazin-3(4*H*)-one, Aldrich, 8%, G).

Via Phase-Transfer Catalysis. Example. To stirring suspension of crushed KOH (1.1 g, 16.7 mmol, 85.5%), tetrabutylammonium bromide (1.4 g, 4.4 mmol), 1,2-dibromoethane (4.2 g, 29 mmol), and THF (5 mL), was added, in one portion, a solution of 1-(ethoxycarbonyl)-2*H*-indazolin-3-one[49] (3 g, 14.5 mmol) in THF–DMF (25 mL:5 mL). Stirred under reflux for 3 days at which time TLC analysis showed absence of starting material and the emergence of two new spots. Workup was as described above. Purification consisted of gradient elution column chromatography (200 g of fine silica; hexane–EtOAc, 7:1, to elute the first component; then 3:1 to 1:1 to obtain pure the second component). The former was spectroscopically identified as 3-(2-chloroethoxy)-1-(ethoxycarbonyl)-1*H*-indazole (**60C**) [2.2 g, 56%; IR 1705 (carbamate C=O); NMR 3.92, t, 2 H, OCH_2CH_2Cl; 4.75, t, 2 H, OCH_2CH_2Cl; R_f 0.34, hexane–EtOAc, 3:1] and the latter as 1-(ethoxycarbonyl)-2-(2-chloroethyl)-2*H*-indazolin-3-one [0.6 g, 15%; IR 1700 (carbamate C=O), 1735 (lactam C=O); NMR 3.92, t, 2 H, N′-2-CH_2CH_2Cl; 4.52, t, 2 H, N′-2-CH_2CH_2Cl); R_f 0.16). The former was employed in the synthesis of **60A** while attempts to utilize the latter isomer ended in extensive decomposition by TLC. Other reaction solvents were employed and are included in the below data. Heterocyclylethyl bromides synthesized by this method were the following: **45C** (pyrithyldione, Aldrich, THF, 52%, F), **51C** (5-isopropyl-1,6-dihydro-1,2,4-triazolin-6(1*H*)-one, ref 50, toluene, 49%, J), **75C** (1,8-naphthalimide, Aldrich, benzene, 18%, C), **76C** (1,8-naphthosultam, Aldrich, toluene, 79%, C). Heterocyclylethyl chlorides were the following: **10C** (3-methylpyrazole, Aldrich, toluene, 36%, C), **11C** (3,5-dimethylpyrazole, Aldrich, THF, 24%, C), **12C** (4-iodopyrazole, Aldrich, toluene, 41%, C), **37C** (1-phenyl-3(2*H*)-pyrazolinone, Aldrich, THF, 79%, J), **46C** (3-ethyl-3-phenylglutarimide, ref 51, THF, 84%, C), **47C** (4-pyrimidone, Aldrich, 34%, B), **48C** (2-(methylthio)-5-methyl-1,3-pyrimidin-6-one, ref 52, THF, 26%, J), **61C** (3-ethyl-2-benzimidazolin-2-one, Aldrich, THF, 6%, A), **63C** (5-chloro-3-(2-chloroethyl)-1,3-benzoxazolin-2(3*H*)-one, Aldrich, toluene, 35%, mp 82–85 °C (EtOH).

Procedure for Tosylation. Example. To a solution of 2-(hydroxymethyl)-1,4-benzodioxane (Maybridge, 5 g, 30 mmol) in CH_2Cl_2 (50 mL) was added, in one portion, triethylamine (4.2 mL, 30 mmol), and then, in portions, *p*-toluenesulfonyl chloride (5.7 g, 30 mmol). A mild exothermic reaction ensued. A suitable solvent system for separation of the sulfonyl chloride and the starting alcohol was hexane–EtOAc–TEA (100:100:1). The reaction was stirred overnight. Precipitated TEA·HCl was separated by filtration and washed with CH_2Cl_2 (50 mL). The organic medium was washed with 10% HCl (50 mL), water (50 mL), and brine (30 mL) and dried over Na_2SO_4. Purification by column chromatography (400 g fine silica, hexane–EtOAc) yielded pure tosylate **67C** (66%). Other heteroalkyl tosylates prepared were the following: **22C** (2-(2-hydroxyethyl)tetrazole, ref 53, 64%, mp 103–104 °C, from EtOAc–hexane (1:1), **30C** (3-(2-hydroxyethyl)thiophene, Aldrich, 100%, M), **56C** (2-(2-hydroxyethyl)-2,3-dihydro-3(2*H*)-isoindolinone, ref 54, 66%, mp 75–77 °C, from Et_2O).

Chlorination with $SOCl_2$.[55] Example. To an ice-chilled solution of 2-(2-hydroxyethyl)pyridine (Aldrich, 10 g, 81 mmol) in $CHCl_3$ (10 mL) was added, in a slow dropwise fashion, $SOCl_2$ (6.2 mL) in $CHCl_3$ (15 mL). On completion of addition, the reaction mixture was stirred for 15 h. Solvent and excess $SOCl_2$ was removed via rotary evaporator pressure followed by a 90-min high-vacuum (0.5 mmHg, 80 °C) exposure. Recrystallization of the crude brown solid from 2-PrOH–2-Pr_2O yielded 10.8 g of pure **42C**·HCl (mp 124–125 °C, lit.[55] mp ca. 120 °C) as light tan beads. Other heterocyclylethyl chlorides synthesized by this method were the following: **33C**·HCl [4-methyl-5-(2-hydroxyethyl)thiazole, Aldrich, in benzene, 71%, mp 135–137 °C, from 2-PrOH], **43C**·HCl [3-(2-hydroxyethyl)pyridine, ref 56, 65%, mp 154–155 °C].

II. Synthesis of Target Compounds 7–77. The following procedures are outlined in Scheme I.

Analogues of carfentanil (**2**) are designated with A and contain within their NMR spectra a triplet at approximately 0.90 ppm (3 H, $COCH_2CH_3$), a singlet at approximately 3.70 ppm (3 H, CO_2CH_3), and a singlet at approximately 7.30 ppm (5 H, phenyl H). Analogues of alfentanil (**4**) are designated with B and contain within their NMR spectra the above propionamide triplet and phenyl singlet as well as a singlet at approximately 3.30 ppm (3 H, CH_2OCH_3) and a singlet at approximately 4.00 ppm (2 H, CH_2OCH_3). *These proton resonances are generally not included in the following physical and spectral data except where they overlap with other prominent resonances. Additionally, since pairs of analogues have in common resonances caused by the particular heterocyclic ring system, NMR information will be included in only one of the summaries of data. Atoms designated by prime sign and number (e.g., N′-1) are members of the heterocyclic ring system of the particular L group.* Elemental analyses were obtained from the Analytical Services Division, BOC Technical Center, Murray Hill, NJ, Galbraith Laboratories,

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Knoxville, TN, and Robertson Analytical Services, Berkeley Heights, NJ. Compounds were analyzed for the presence of carbon, hydrogen, and nitrogen. Results were within ±0.4% of theoretical values unless otherwise indicated. TLC R_f values were recorded after elution in $CHCl_3$–MeOH–NH_4OH (19:1:0.1) unless otherwise indicated by a number in parenthesis denoting a different $CHCl_3$ composition. Solvents of crystallization, following the melting point data (°C) for the salt form, were the following: A = 2-PrOH–2-Pr_2O–MeOH, B = acetone–2-Pr_2O, C = 2-PrOH–2-Pr_2O, D = 2-PrOH, E = H_2O–MeOH–2-PrOH–2-Pr_2O, F = MeOH–H_2O, G = MeOH–2-PrOH, H = acetone, I = 2-PrOH–2-Pr_2O–acetone.

General Method for Synthesis of Amino Alcohols 28, 29, 31, and 32. To a stirring solution of the amino ketone (2 mmol) and absolute ethanol (10 mL) was added $NaBH_4$ (100 mg). Generally after 30 min at room temperature, TLC analysis showed completion reaction. The reaction mixture was then concentrated in vacuo and worked up as described above. Purification consisted of gravity elution through a column of fine silica with $CHCl_3$–MeOH–NH_4OH.

Synthesis of 44B. A mixture of **6**[7] (1.15 g, 4.2 mmol), 4-vinylpyridine (0.67 g, 6.3 mmol), and 2-methoxyethanol (10 mL) was stirred under reflux overnight. TLC analysis showed completion of reaction by the absence of **6**. The reaction was concentrated in vacuo and the crude concentrate partitioned between 10% HCl (40 mL) and ether (40 mL). The acidic aqueous layer was extracted with additional ether and then basified with 6 N NaOH. The liberated free base was extracted with CH_2Cl_2 (2 × 40 mL) and the organic extract was washed with water (50 mL) and brine (30 mL), and dried over Na_2SO_4. Purification consisted of gravity column chromatography (135 g of fine silica; $CHCl_3$–MeOH–NH_4OH, 40:1:0.1 to elute faster, excess 4-vinylpyridine) followed by flash chromatography (same column, $CHCl_3$–MeOH–NH_4OH, 30:1:0.1) to elute pure **44B** (1.22 g, 74%) as a golden oil.

Synthesis of 52A. A mixture of **5**[7] (0.94 g, 3.2 mmol), 3-[(dimethylamino)methyl]-1*H*-indole (0.62 g, 3.6 mmol), NaI (ca. 100 mg), and 2-methoxyethanol (9 mL) was stirred under reflux for 2 h. A prominent odor of dimethylamine was detected. TLC analysis showed completion of reaction by the absence of **5**. The reaction was concentrated in vacuo and worked up as described above for **44B**. Purification consisted of flash column chromatography (100 g fine silica; $CHCl_3$–MeOH–NH_4OH, 30:1:0.1 to 20:1:0.2) to yield pure **52A** (0.95 g, 70%) as a cream-colored solid.

General Method for Remainder of Target Compounds. A mixture of 1 g of **5** (or **6**), heterocyclylalkyl bromide, chloride, or tosylate (10% excess), 1.5 g of Na_2CO_3, NaI (ca. 100 mg), and acetonitrile (10 mL), was stirred under reflux until TLC analysis indicated completion of reaction. Stirring at room temperature was the practice when α-haloketoheterocycles (**26C**, **27C**, **31C**, and **32C**) were employed. The reaction mixture was filtered of insolubles, these were washed with CH_2Cl_2, and the filtrate concentrated in vacuo. Workup was as described for **44B**. Purification was achieved with column chromatography on fine silica with $CHCl_3$–MeOH–NH_4OH.

Spectroscopic and Physical Data for All Target Compounds. Compound 7A: 44% [L = 2-(1*H*-pyrrol-1-yl)ethyl]; NMR 3.80 (t, 2 H, N′-1-CH_2), 6.00 (br d, 2 H, C′-3-H and C′-4-H), 6.52 (br s, 2 H, C′-2-H and C′-5-H); R_f 0.52 (40); oxalate, mp 191–192.5 °C (C). Anal. ($C_{22}H_{29}N_3O_3\cdot C_2H_2O_4$) C, H, N; C: calcd, 60.87; found, 60.44.

Compound 7B: 42% [L = 2-(1*H*-pyrrol-1-yl)ethyl]; R_f 0.67; oxalate, mp 191–196 °C (C). Anal. ($C_{22}H_{31}N_3O_2\cdot C_2H_2O_4$) C, H, N; C: calcd, 62.73; found, 63.19; N: calcd, 9.14; found, 8.69.

Compound 8A: 40% [L = 2-(2-formyl-1*H*-pyrrol-1-yl)ethyl]; R_f 0.59 (17); oxalate, mp 175–176 °C (D). Anal. ($C_{23}H_{29}N_3O_4\cdot C_2H_2O_4$) C, H, N; C: calcd, 61.59; found, 61.17.

Compound 8B: 62% [L = 2-(2-formyl-1*H*-pyrrol-1-yl)ethyl]; NMR 4.35 (t, 2 H, N′-1-CH_2), 6.16 (m, 1 H, C′-4-H), 6.92 (br s, 2 H, C′-3-H and C′-5-H), 9.42 (s, 1 H, *CHO*); R_f 0.37 (40); oxalate, mp 172–175 °C (C). Anal. ($C_{23}H_{31}N_3O_3\cdot C_2H_2O_4$) C, H, N; H: calcd, 8.59; found, 8.13.

Compound 9A: 80% [L = 2-(1*H*-pyrazol-1-yl)ethyl]; NMR 4.18 (t, 2 H, N′-1-CH_2), 6.22 (br s, 1 H, C′-4-H), 7.20–7.65 (m, 7 H, ArH); R_f 0.40; oxalate, mp 184–187.5 °C (C). Anal. ($C_{21}H_{28}N_4O_3\cdot C_2H_2O_4$) C, H, N.

Compound 9B: 82% [L = 2-(1*H*-pyrazol-1-yl)ethyl]; R_f 0.41; oxalate, mp 169–170 °C (C). Anal. ($C_{21}H_{30}N_4O_2\cdot C_2H_2O_4$) C, H, N.

Compound 10A: 87% [L = 2-(3-methyl-1*H*-pyrazol-1-yl)ethyl]; NMR 2.20 (s, 3 H, C′-3-CH_3), 4.10 (t, 2 H, N′-1-CH_2), 6.00 (br s, 1 H, C′-4-H), 7.42 (br s, 6 H, ArH); R_f 0.28; oxalate, mp 170–173 °C (C). Anal. ($C_{21}H_{28}N_4O_3\cdot C_2H_2O_4$) C, H, N; C: calcd, 59.00; found, 58.56.

Compound 11A: 52% [L = 2-(3,5-dimethyl-1*H*-pyrazol-1-yl)ethyl]; oxalate, mp 204.5–205.5 °C (D). Anal. ($C_{23}H_{32}N_4O_3\cdot C_2H_2O_4$) C, H, N.

Compound 11B: 59% [L = 2-(3,5-dimethyl-1*H*-pyrazol-1-yl)ethyl]; NMR 2.25 (s, 6 H, C′-3 and C′-5-CH_3), 4.04 (t, 2 H, N′-1-CH_2), 5.72 (s, 1 H, C′-4-H); R_f 0.50; oxalate, mp 167–167.5 °C (A). Anal. ($C_{23}H_{34}N_4O_2\cdot C_2H_2O_4\cdot 1.25H_2O$) C, H, N; N: calcd, 10.96; found, 10.46.

Compound 12A: 64% [L = 2-(4-iodo-1*H*-pyrazol-1-yl)ethyl]; NMR 4.16 (t, 2 H, N′-1-CH_2), 7.40 (br s, 7 H, ArH); R_f 0.44; oxalate, mp 163–164.5 °C (C). Anal. ($C_{21}H_{27}N_4IO_3\cdot C_2H_2O_4$) C, H, N.

Compound 12B: 71% [L = 2-(4-iodo-1*H*-pyrazol-1-yl)ethyl]; R_f 0.30 (40); oxalate, mp 184–186 °C (C). Anal. ($C_{21}H_{29}N_4IO_2\cdot C_2H_2O_4$) C, H, N.

Compound 13A: 68% [L = 2-(3,5-bis(ethoxycarbonyl)-1*H*-pyrazol-1-yl)ethyl]; NMR 1.30 (2 t, 6 H, $CO_2CH_2CH_3$), 4.08–4.84 (m, 6 H, N′-1-CH_2 and $CO_2CH_2CH_3$), 7.28 (s, 1 H, C′-4-H); R_f 0.43 (40); oxalate, mp 123–127 °C (D). Anal. ($C_{27}H_{36}N_4O_7\cdot C_2H_2O_4$) C, H, N.

Compound 14A: 72% [L = 2-(1*H*-imidazol-1-yl)ethyl]; NMR 3.98 (t, 2 H, N′-1-CH_2), 7.05 (br d, 2 H, C′-4-H and C′-5-H), 7.38 (br s, 6 H, ArH); R_f 0.27; oxalate, mp 104–108 °C (C followed by trituration in Et_2O). Anal. ($C_{21}H_{28}N_4O_3\cdot C_2H_2O_4\cdot 0.5H_2O$) C, H, N.

Compound 15A: 72% [L = 2-(5-nitro-1*H*-imidazol-1-yl)ethyl]; NMR 4.14 (t, 2 H, N′-1-CH_2), 7.55 (s, 1 H, C′-2-H), 7.95 (s, 1 H, C′-3-H); R_f 0.34; oxalate, mp 187–188 °C (D). Anal. ($C_{21}H_{27}N_5O_5\cdot C_2H_2O_4$) C, H, N.

Compound 16A: 29% [L = 2-(2-methyl-5-nitro-1*H*-imidazol-1-yl)ethyl]; R_f 0.61; oxalate, mp 186.5–188.5 °C (G). Anal. ($C_{22}H_{29}N_5O_5\cdot C_2H_2O_4$) C, H, N.

Compound 16B: 59% [L = 2-(2-methyl-5-nitro-1*H*-imidazol-1-yl)ethyl]; NMR 2.48 (s, 3 H, C′-2-CH_3), 4.38 (t, 2 H, N′-1-CH_2), 7.55 (s, 1 H, C′-2-H), 7.95 (s, 1 H, C′-4-H); R_f 0.31; oxalate, mp 201–202 °C (C). Anal. ($C_{22}H_{31}N_5O_4\cdot C_2H_2O_4$) C, H, N.

Compound 17A: 55% [L = 2-(4,5-bis(ethoxycarbonyl)-1*H*-imidazol-1-yl)ethyl]; NMR 1.34 (t, 6 H, $CO_2CH_2CH_3$), 4.12–4.58 (m, 6 H, $CO_2CH_2CH_3$ and N′-1-CH_2), 7.66 (s, 1 H, C′-2-H); R_f 0.59; oxalate, mp 152–153 °C (C). Anal. ($C_{27}H_{36}N_4O_7\cdot C_2H_2O_4$) C, H, N.

Compound 18A: 69% [L = 2-(1*H*-imidazol-4-yl)ethyl]; R_f 0.08; maleate, mp 139.5–140 °C (C). Anal. ($C_{21}H_{28}N_4O_3\cdot 2C_4H_4O_4$) C, H, N.

Compound 18B: 35% [L = 2-(1*H*-imidazol-4-yl)ethyl]; NMR 3.62 (t, 2 H, N′-1-CH_2), 6.70 (s, 1 H, C′-5-H), 7.46 (s, 1 H, C′-2-H); R_f 0.08; maleate, mp 152–153 °C (H). Anal. ($C_{21}H_{30}N_4O_2\cdot 2C_4H_4O_4$) C, H, N.

Compound 19A: 68% [L = [2-(1-methyl-1*H*-imidazol-2-yl)-ethyl]thio]; NMR 3.55 (s, 3 H, N′-1-CH_3), 4.08 (t, 2 H, C′-2-S-CH_2), 6.68 (m, 2 H, C′-4-H and C′-5-H); R_f 0.47; oxalate, mp 168–172 °C (C). Anal. ($C_{22}H_{30}N_4O_3S\cdot C_2H_2O_4\cdot H_2O$) C, H, N.

Compound 19B: 57% [L = [2-(1-methyl-1*H*-imidazol-2-yl)-ethyl]thio]; R_f 0.30 (50) oxalate, mp 163.5–164.5 °C (A). Anal. ($C_{22}H_{32}N_4O_2S\cdot C_2H_2O_4\cdot 0.25H_2O$) C, H, N.

Compound 20A: 41% [L = 2-(1*H*-triazol-1-yl)ethyl]; NMR 4.20 (t, 2 H, N′-1-CH_2), 7.90 (s, 1 H, C′-5-H), 8.16 (s, 1 H, C′-3-H); R_f 0.36; oxalate, mp 171–172 °C (A). Anal. ($C_{20}H_{27}N_5O_3\cdot C_2H_2O_4$) C, H, N; C: calcd, 55.57; found; 56.18.

Compound 20B: 82% [L = 2-(1*H*-triazol-1-yl)ethyl]; R_f 0.27; oxalate, mp 132.5–134.5 °C (A). Anal. ($C_{20}H_{27}N_5O_3\cdot C_2H_2O_4\cdot H_2O$) C, H, N; H: calcd, 6.94; found, 6.54.

Compound 21B: 53% [L = [2-[5-(trifluoromethyl)-4-methyl-4*H*-triazol-3-yl]ethyl]thio]; NMR 3.36 (s, 3 H, C′-4-CH_3); R_f 0.25; oxalate, mp 171.5–173.5 °C (A). Anal. ($C_{22}H_{30}N_5F_3O_2\cdot C_2H_2O_4$) C, H, N.

Compound 22A: 82% [L = 2-(2*H*-tetrazol-2-yl)ethyl]; NMR 2.96 (t, 2 H, N′-2-CH_2CH_2), 4.70 (t, 2 H, N′-2-CH_2CH_2), 8.50 (s,

1 H, C′-5-H); R_f 0.68; oxalate, mp 198–200 °C (E). Anal. ($C_{19}H_{26}N_6O_3 \cdot C_2H_2O_4$) C, H, N; N: calcd, 17.64; found, 17.08.

Compound 22B: 23% [L = 2-(2*H*-tetrazol-2-yl)ethyl]; R_f 0.55; oxalate, mp 193 °C (D). Anal. ($C_{19}H_{28}N_6O_2 \cdot C_2H_2O_4$) C, H, N.

Compound 23A: 33% [L = 2-(5-phenyl-2*H*-tetrazol-2-yl)ethyl]; NMR 2.88 (t, 2 H, N′-2-CH_2CH_2), 4.70 (t, 2 H, N′-2-CH_2CH_2), 7.25–8.28 (m, 10 H, ArH); R_f 0.53; oxalate, mp 130–140 °C softens (C). Anal. ($C_{25}H_{30}N_6O_3 \cdot C_2H_2O_4$) C, H, N.

Compound 24B: 33% [L = 2-(5-morpholino-2*H*-tetrazol-2-yl)ethyl]; NMR 3.62–3.88 (m, 4 H, morpholine-CH_2), 4.45 (t, 2 H, N′-2-CH_2CH_2); R_f 0.54; oxalate, mp 153–154 °C (A). Anal. ($C_{23}H_{35}N_7O_3 \cdot C_2H_2O_4$) C, H, N.

Compound 25A: 69% [L = [2-(1-methyl-1*H*-tetrazol-5-yl)-ethyl]thio]; NMR 3.86 (s, 3 H, C′-5-N-CH_3); R_f 0.26 (40); oxalate, mp 144–147 °C (C). Anal. ($C_{22}H_{28}N_6O_3S \cdot C_2H_2O_4 \cdot 0.25H_2O$) C, H, N.

Compound 26A: 60% [L = 2-oxo-2-(2-thienyl)ethyl]; NMR 3.60 (s, 2 H, NCH_2CO), 6.92–7.46 (m, 8 H, ArH); R_f 0.71; oxalate, mp 196–199 °C (D). Anal. ($C_{22}H_{26}N_2O_4S \cdot C_2H_2O_4$) C, H, N.

Compound 27B: 76% [L = 1-methyl-2-oxo-2-(2-thienyl)ethyl]; NMR 1.22 (d, 3 H, N(CH_3)CHCO), 3.68 (q, 1 H, N(CH_3)CHCO), 7.10–7.90 (m, 8 H, ArH); R_f 0.76; oxalate, mp 74 °C (C followed by trituration in Et_2O). Anal. ($C_{23}H_{30}N_2O_3S \cdot C_2H_2O_4 \cdot H_2O$) C, H, N; H: calcd, 6.56; found, 6.13.

Compound 28A: 57% [L = 2-hydroxy-2-(2-thienyl)ethyl]; NMR 4.90 (t, 1 H, -CH_2CH(OH)-), 6.92–7.62 (m, 8 H, ArH); R_f 0.64; oxalate, mp 179–180 °C (C). Anal. ($C_{22}H_{28}N_2O_4S \cdot C_2H_2O_4$) C, H, N.

Compound 28B: 44% [L = 2-hydroxy-2-(2-thienyl)ethyl]; R_f 0.28 (40); oxalate, mp 169–170.5 °C (C). Anal. ($C_{22}H_{30}N_2O_3S \cdot C_2H_2O_4$) C, H, N.

Compound 29B: 67% [L = 1-methyl-2-hydroxy-2-(2-thienyl)ethyl]; NMR 0.84 (d, 3 H, NCH(CH_3)CH(OH)), 4.46 (d, 1 H, -$CH(CH_3)CH$(OH)-), 6.72–7.40 (m, 8 H, ArH); R_f 0.54 (50); oxalate, mp 171–174 °C (C). Anal. ($C_{23}H_{32}N_2O_3S \cdot C_2H_2O_4$) C, H, N.

Compound 30A: 42% [L = 2-(3-thienyl)ethyl]; R_f 0.66; NMR 6.85–7.50 (m, 8 H, ArH); oxalate, mp 192.5–193 °C (C). Anal. ($C_{22}H_{28}N_2O_3S \cdot C_2H_2O_4$) C, H, N.

Compound 30B: 37% [L = 2-(3-thienyl)ethyl]; R_f 0.59; oxalate, mp 177–179 °C (C). Anal. ($C_{22}H_{30}N_2O_2S \cdot C_2H_2O_4$) C, H, N; H: calcd, 6.77; found, 6.24.

Compound 31B: 50% [L = 2-hydroxy-2-(2-furyl)ethyl]; NMR 4.62 (d, 1 H, -NCHC*H*(OH)-), 6.25 (s, 1 H, C′-4-H), 7.36 (s, 7 H, ArH); R_f 0.52; oxalate, mp 175–177 °C (C). Anal. ($C_{22}H_{30}N_2O_4 \cdot C_2H_2O_4$) C, H, N.

Compound 32B: 32% [L = 2-hydroxy-2-(5-methyl-2-furyl)-ethyl]; NMR 3.32 (s, 3 H, C′-5-CH_3), 4.62 (d, 1 H, -NCHC*H*-(OH)-), 5.78 (br d, 1 H, C′-3-H), 6.12 (br d, 1 H, C′-4-H); R_f 0.55; oxalate, mp 150–156 °C (C). Anal. ($C_{23}H_{32}N_2O_4 \cdot C_2H_2O_4$) C, H, N.

Compound 33A: 63% [L = 2-(4-methylthiazol-5-yl)ethyl]; NMR 2.35 (s, 3 H, C′-4-CH_3), 8.55 (s, 1 H, C′-2-H); R_f 0.34; oxalate, mp 218.5–220 °C (D). Anal. ($C_{22}H_{29}N_3O_3 \cdot C_2H_2O_4$) C, H, N.

Compound 33B: 63% [L = 2-(4-methylthiazol-5-yl)ethyl]; R_f 0.21; oxalate, mp 203.5–204.5 °C (C). Anal. ($C_{22}H_{31}N_3O_2 \cdot C_2H_2O_4 \cdot 0.25H_2O$) C, H, N; C: calcd, 57.60; found, 57.16.

Compound 34A: 56% [L = 1-methoxy-2-(4-methylthiazol-5-yl)ethyl]; NMR 2.42 (s, 3 H, C′-4-CH_3), 3.20 (s, 3 H, $CHOCH_3$), 4.58 (t, 1 H, CH_2CH(OCH_3)), 8.68 (s, 1 H, C′-2-H); R_f 0.29 (40); oxalate, mp 163–164 °C (C). Anal. ($C_{23}H_{31}N_3O_4 \cdot C_2H_2O_4$) C, H, N.

Compound 34B: 48% [L = 1-methoxy-2-(4-methylthiazol-5-yl)ethyl]; R_f 0.24 (40); oxalate, mp 147–149.5 °C (C). Anal. ($C_{23}H_{31}N_3O_4 \cdot C_2H_2O_4$) C, H, N.

Compound 35A: 51% [L = 2-(2,3,4,5-tetrahydro-2-oxo-oxazol-3-yl)ethyl]; NMR 3.30 (t, 2 H, N′-3-CH_2), 4.30 (t, 2 H, C′-5-H); R_f 0.16; oxalate, mp 160–163 °C (C). Anal. ($C_{21}H_{29}N_3O_5 \cdot C_2H_2O_4$) C, H, N.

Compound 36B: 69% [L = 2-(3-ethyl-2,3-dihydro-2-oxo-1*H*-imidazol-1-yl)ethyl]; NMR 1.22 (t, 3 H, N′-3-CH_2CH_3), 3.56 (q, 2 H, N′-3-CH_2CH_3), 3.76 (t, 2 H, CH_2CH_2-N′-1), 6.28 (br s, 2 H, C′-4 and C′-5); R_f 0.42; oxalate, mp 122–124 °C (A). Anal. ($C_{23}H_{34}N_4O_3 \cdot C_2H_2O_4 \cdot 1.5H_2O$) C, H, N; H: calcd, 7.39; found, 6.72; N: calcd, 10.54; found, 10.03.

Compound 37A: 56% [L = 2-(2,3,4,5-tetrahydro-2-phenyl-5-oxo-1*H*-pyrazol-1-yl)ethyl]; NMR 3.38 (t, 2 H, N′-1-CH_2CH_3; CH_2CH_2-N′-1), 6.74–7.40 (m, 10 H, ArH); R_f 0.67; oxalate, mp 163.5–164.5 °C (C). Anal. ($C_{27}H_{34}N_4O_4 \cdot C_2H_2O_4$) C, H, N.

Compound 37B: 69% [L = 2-(2,3,4,5-tetrahydro-2-phenyl-5-oxo-1*H*-pyrazol-1-yl)ethyl]; R_f 0.57; oxalate, mp 86–89 °C (C). Anal. ($C_{27}H_{36}N_4O_3 \cdot C_2H_2O_4 \cdot 0.5H_2O$) C, H, N; N: calcd, 9.94; found, 9.51.

Compound 38A: 53% [L = 2-(2,3,4,5-tetrahydro-2,4-dioxo-5-methyl-5-phenyl-1*H*-imidazol-3-yl)ethyl]; NMR 3.54 (t, 2 H, N′-1-CH_2), 7.18–7.62 (m, 10 H, ArH); R_f 0.49; oxalate, mp 138–141 °C (A). Anal. ($C_{28}H_{34}N_4O_5 \cdot C_2H_2O_4$) C, H, N.

Compound 39A: 36% [L = [2-[5-(methylthio)-1,3,4-thiadiazol-2-yl]ethyl]thio]; NMR 2.74 (s, 3 H, SCH_3), 3.38 (t, 2 H, SCH_2CH_2N); R_f 0.70; oxalate, mp 144.5–147 °C (C). Anal. ($C_{21}H_{28}N_4O_3S_3 \cdot C_2H_2O_4$) C, H, N.

Compound 40A: 57% [L = 2-(2,3-dihydro-2-thioxo-5-phenyl-1,3,4-oxadiazol-3-yl)ethyl]; NMR 3.40 (t, 2 H, N′-3-CH_2), 7.28–8.12 (m, 10 H, ArH); R_f 0.73; oxalate, mp 140.5–142 °C (A). Anal. ($C_{26}H_{30}N_4O_4S \cdot C_2H_2O_4$) C, H, N.

Compound 41B: 37% [L = 2-(4,5-dihydro-3-methyl-4-amino-5-oxo-1*H*-triazol-1-yl)ethyl]; NMR 2.28 (s, 3 H, C′-3-CH_3), 3.84 (t, 2 H, N′-1-CH_2), 7.28–8.12 (m, 10 H, ArH); R_f 0.16; oxalate, mp 95 °C (A). Anal. ($C_{21}H_{33}N_6O_4 \cdot C_2H_2O_4 \cdot H_2O$) C, H, N; N: calcd, 16.02; found, 15.56.

Compound 42A: 68% [L = 2-(2-pyridinyl)ethyl]; NMR 7.00–7.65 (m, 8 H, ArH), 8.52 (d, C′-4-H); R_f 0.26; oxalate, mp 95 °C (A). Anal. ($C_{23}H_{29}N_3O_3 \cdot C_2H_2O_4$) C, H, N; H: calcd, 8.66; found, 8.25.

Compound 43A: 66% [L = 2-(3-pyridinyl)ethyl]; R_f 0.44; oxalate, mp 142–145 °C (C). Anal. ($C_{23}H_{29}N_3O_3 \cdot 2C_2H_2O_4 \cdot 0.5H_2O$) C, H, N.

Compound 43B: 59% [L = 2-(3-pyridinyl)ethyl]; NMR 7.02–7.62 (m, 8 H, ArH), 8.44 (br s, 1 H, C′-4-H); R_f 0.46; oxalate, mp 156.5–159.5 °C (D). Anal. ($C_{23}H_{31}N_3O_2 \cdot 2C_2H_2O_4 \cdot 0.5H_2O$) C, H, N.

Compound 44A: 49% [L = 2-(4-pyridinyl)ethyl]; NMR 7.10 (d, 2 H, C′-3,5-H), 8.50 (d, 2 H, C′-2,6-H); R_f 0.34; maleate, mp 108–111 °C (C). Anal. ($C_{23}H_{31}N_3O_2 \cdot 2C_4H_4O_4 \cdot H_2O$) C, H, N.

Compound 45A: 77% [L = 2-(1,2,3,4-tetrahydro-2,4-dioxo-3,3-diethylpyridin-1-yl)ethyl]; NMR 0.75 (t, 6 H, C(CH_2CH_3)$_2$), 3.75 (t, 2 H, N′-1-CH_2), 5.52 (d, 1 H, C′-5-H), 7.12 (d, 1 H, C′-6-H); R_f 0.67; oxalate, mp 172–174 °C (C). Anal. ($C_{27}H_{37}N_3O_5 \cdot C_2H_2O_4$) C, H, N.

Compound 45B: 68% [L = 2-(1,2,3,4-tetrahydro-2,4-dioxo-3,3-diethylpyridin-1-yl)ethyl]; R_f 0.25 (50); oxalate, mp 159–161.5 °C (C). Anal. ($C_{27}H_{39}N_3O_4 \cdot C_2H_2O_4$) C, H, N.

Compound 46A: 33% [L = 2-(2,6-dioxo-3-ethyl-3-phenylpiperidin-1-yl)ethyl]; NMR 0.85 (t, 3 H, C(Ph)CH_2CH_3), 7.35 (br s, 10 H, ArH); R_f 0.79; oxalate, mp 121–124 °C (A). Anal. ($C_{31}H_{39}N_3O_5 \cdot C_2H_2O_4$) C, H, N.

Compound 47A: 25% [L = 2-(1,6-dihydro-6-oxopyrimidin-1-yl)ethyl]; NMR 3.84 (t, 2 H, N′-1-CH_2), 6.40 (d, 1 H, C′-4-H), 7.80 (d, 1 H, C′-5-H), 8.16 (s, 1 H, C′-2-H); R_f 0.16; oxalate, mp 182–183 °C (A). Anal. ($C_{22}H_{28}N_4O_4 \cdot C_2H_2O_4$) C, H, N.

Compound 48A: 50% [L = 2-[2-(methylthio)-1,6-dihydro-4-oxo-5-methylpyrimidin-1-yl]ethyl]; NMR 1.86 (s, 3 H, C′-5-CH_3), 2.54 (s, 3 H, SCH_3), 4.12 (t, 2 H, N′-1-CH_2), 7.62 (s, 1 H, C′-4-H); R_f 0.54; oxalate, mp 165–166.5 °C (A). Anal. ($C_{24}H_{32}N_4O_4S \cdot C_2H_2O_4 \cdot H_2O$) C, H, N; C: calcd, 53.78; found, 53.33; H: calcd, 6.96; found, 6.50.

Compound 48B: 65% [L = 2-[2-(methylthio)-1,6-dihydro-4-oxo-5-methylpyrimidin-1-yl]ethyl]; R_f 0.63; oxalate, mp 168.5–169.5 °C (A). Anal. ($C_{24}H_{34}N_4O_3S \cdot C_2H_2O_4$) C, H, N.

Compound 49A: 83% [L = 2-(1,2,3,4-tetrahydro-2,4-dioxo-3-ethylpyrimidin-1-yl)ethyl]; R_f 0.55; oxalate, mp 193.5–196 °C (C). Anal. ($C_{24}H_{32}N_4O_5 \cdot C_2H_2O_4$) C, H, N.

Compound 49B: 87% [L = 2-(1,2,3,4-tetrahydro-2,4-dioxo-3-ethylpyrimidin-1-yl)ethyl]; NMR 1.16 (t, 2 H, N′-3-CH_2CH_3), 3.78 (t, 2 H, N′-1-CH_2), 3.93 (t, 2 H, N′-3-CH_2), 5.70 (d, 1 H, C′-5-H), 7.15 (d, 1 H, C′-6-H); R_f 0.32; oxalate, mp 158–160 °C (A). Anal. ($C_{24}H_{34}N_4O_4 \cdot C_2H_2O_4 \cdot H_2O$) C, H, N; C: calcd, 56.71; found, 56.12.

Compound 50A: 80% [L = 2-(1,6-dihydro-6-oxo-3-methylpyridazin-1-yl)ethyl]; NMR 2.30 (s, 3 H, C′-3-CH_3), 4.22 (t, 2 H, N′-2-CH_2), 6.95 (dd, 2 H, C′-4-H and C′-5-H); R_f 0.53; oxalate,

mp 158–160 °C (A). Anal. ($C_{23}H_{30}N_4O_4 \cdot C_2H_2O_4 \cdot 1.5H_2O$) C, H, N; C: calcd, 55.24; found, 55.68.

Compound 51A: 69% [L = 2-(1,6-dihydro-5-isopropyl-6-oxo-1,2,4-triazin-1-yl)ethyl]; NMR 1.24 (d, 6 H, $CH(CH_3)_2$), 3.48 (septet, 1 H, $CH(CH_3)_2$), 4.16 (t, 2 H, N′-1-CH_2), 8.16 (s, 1 H, C′-3-H); R_f 0.67; oxalate, mp 148–152 °C (C). Anal. ($C_{24}H_{33}N_5O_4 \cdot C_2H_2O_4$) C, H, N.

Compound 52A: 70% [L = 1*H*-indol-3-ylmethyl]; NMR 3.60 (s, 2 H, C′-3-CH_2), 6.84–7.70 (m, 10 H, ArH); R_f 0.32 (17); oxalate, mp 188.5–190 °C (F). Anal. ($C_{25}H_{29}N_3O_3 \cdot C_2H_2O_4$) C, H, N; C: calcd, 64.01; found, 63.06; H: calcd, 6.08; found, 6.49; N: calcd, 8.25; found, 7.78.

Compound 53A: 51% [L = 2-(2,3-dihydro-2-oxo-1*H*-indol-1-yl)ethyl]; NMR 3.46 (s, 2 H, C′-3-H), 3.85 (s, N′-1-CH_2), 6.70–7.50 (m, 9 H, ArH); R_f 0.72; oxalate, mp 166–171 °C (C). Anal. ($C_{26}H_{31}N_3O_4 \cdot C_2H_2O_4$) C, H, N.

Compound 53B: 54% [L = 2-(2,3-dihydro-2-oxo-1*H*-indol-1-yl)ethyl]; R_f 0.54; oxalate, mp 108.5–112 °C (C). Anal. ($C_{26}H_{33}N_3O_3 \cdot C_2H_2O_4 \cdot H_2O$) C, H, N.

Compound 54A: 69% [L = 2-(3,3-dimethyl-2,3-dihydro-2-oxo-1*H*-indol-1-yl)ethyl]; NMR 1.30 (s, C′-3-$(CH_3)_2$), 3.72 (br s, 5 H, N′-1-CH_2 and CO_2CH_3), 6.72–7.45 (m, 9 H, ArH); R_f 0.60 (40); oxalate, mp 184–185 °C (C). Anal. ($C_{28}H_{35}N_3O_4 \cdot C_2H_2O_4$) C, H, N.

Compound 54B: 69% [L = 2-(3,3-dimethyl-2,3-dihydro-2-oxo-1*H*-indol-1-yl)ethyl]; R_f 0.50 (50); oxalate, mp 186.5–190 °C (C). Anal. ($C_{28}H_{37}N_3O_3 \cdot C_2H_2O_4$) C, H, N.

Compound 55A: 62% [L = 2-(2,3-dihydro-2-oxo-3,3′-spiropropane-1*H*-indol-1-yl)ethyl]; R_f 0.50 (50); oxalate, mp 186.5–190 °C (C). Anal. ($C_{28}H_{37}N_3O_3 \cdot C_2H_2O_4$) C, H, N.

Compound 55B: 80% [L = 2-(2,3-dihydro-2-oxo-3,3′-spiropropane-1*H*-indol-1-yl)ethyl]; NMR 3.88 (t, 2 H, N′-1-CH_2), 6.88–7.35 (m, 9 H, ArH); R_f 0.44 (50); oxalate, mp 194.5–196.5 °C (C). Anal. ($C_{28}H_{35}N_3O_3 \cdot C_2H_2O_4$) C, H, N.

Compound 56B: 96% [L = 2-(1,3-dihydro-1-oxo-2*H*-isoindol-2-yl)ethyl]; NMR 3.75 (t, 2 H, N′-2-CH_2), 4.48 (s, 2 H, C′-3-H), 7.22–8.00 (m, 9 H, ArH); R_f 0.32 (40); oxalate, mp 160–163 °C (A). Anal. ($C_{26}H_{33}N_3O_3 \cdot C_2H_2O_4$) C, H, N.

Compound 57A: 47% [L = 2-(1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)ethyl]; R_f 0.57; oxalate, mp 150–152.5 °C (C). Anal. ($C_{26}H_{29}N_3O_5 \cdot C_2H_2O_4$) C, H, N; C: calcd, 60.75; found, 60.31.

Compound 57B: 43% [L = 2-(1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)ethyl]; NMR 3.78 (t, 2 H, N′-2-CH_2), 7.82 (br s, 4 H, C′-4,5,6,7-H); R_f 0.68; oxalate, mp 172.5–174.5 °C (A). Anal. ($C_{26}H_{31}N_3O_4 \cdot C_2H_2O_4$) C, H, N.

Compound 58A: 75% [L = 2-(1*H*-benzimidazol-1-yl)ethyl]; NMR 4.10 (t, 2 H, N′-1-CH_2), 7.20–7.95 (m, 10 H, ArH); R_f 0.49 (40); oxalate, mp 160–163 °C (A). Anal. ($C_{25}H_{30}N_4O_3 \cdot 2C_2H_2O_4 \cdot 0.5H_2O$) C, H, N.

Compound 59A: 72% [L = (1*H*-benzimidazol-2-yl)methyl]; NMR 3.72 (s, 5 H, CO_2CH_3 and C′-2-CH_2), 7.12–7.68 (m, 9 H, ArH); R_f 0.14; oxalate, mp 153–155 °C (A). Anal. ($C_{24}H_{28}N_4O_3 \cdot C_2H_2O_4 \cdot H_2O$) C, H, N; C: calcd, 59.08; found, 59.51.

Compound 60A: 53% [L = 2-[1-(ethoxycarbonyl)-1*H*-benzopyrazol-3-yl]ethoxy]; NMR 1.50 (t, 3 H, $CO_2CH_2CH_3$), 4.30–4.72 (m, 4 H, $CO_2CH_2CH_3$ and OCH_2CH_2N), 7.10–8.25 (m, 9 H, ArH); R_f 0.62; oxalate, mp 153–155 °C (A). Anal. ($C_{24}H_{28}N_4O_3 \cdot C_2H_2O_4 \cdot H_2O$) C, H, N; C: calcd, 58.81; found, 58.33; H: calcd, 9.15; found, 9.58.

Compound 61A: 73% [L = 2-(3-ethyl-2,3-dihydro-2-oxo-1*H*-benzimidazol-1-yl)ethyl]; NMR 1.30 (t, 3 H, N′-3-CH_2CH_3), 3.92 (br t, 4 H, N′-3-CH_2CH_3 and N′-1-CH_2CH_2N), 7.12 (s, 4 H, C′-4,5,6,7-H); R_f 0.38; oxalate, mp 188–190 °C (C). Anal. ($C_{27}H_{34}N_4O_4 \cdot C_2H_2O_4$) C, H, N; C: calcd, 61.25; found, 61.66.

Compound 61B: 52% [L = 2-(3-ethyl-2,3-dihydro-2-oxo-1*H*-benzimidazol-1-yl)ethyl]; R_f 0.57; oxalate, mp 191.5–192.5 °C (A). Anal. ($C_{27}H_{36}N_4O_3 \cdot C_2H_2O_4$) C, H, N.

Compound 62A: 78% [L = 2-(2,3-dihydro-2-oxobenzoxazol-3-yl)ethyl]; NMR 3.84 (t, 2 H, N′-3-CH_2), 7.12, 7.46 (2s, 9 H, ArH); R_f 0.67 (17); oxalate, mp 134–138 °C (C). Anal. ($C_{25}H_{29}N_3O_5 \cdot C_2H_2O_4 \cdot 0.5H_2O$) C, H, N.

Compound 62B: 38% [L = 2-(2,3-dihydro-2-oxobenzoxazol-3-yl)ethyl]; R_f 0.56 (40); oxalate, mp 194–195 °C (C). Anal. ($C_{25}H_{31}N_3O_4 \cdot C_2H_2O_4$) C, H, N.

Compound 63A: 61% [L = 2-(5-chloro-2,3-dihydro-2-oxobenzoxazol-3-yl)ethyl]; NMR 3.65–4.05 (m, 5 H, CO_2CH_3 and N′-3-CH_2), 7.08 (s, 3 H, C′-4, 6, 7 H); R_f 0.63 (17); oxalate, mp 180–181 °C (C). Anal. ($C_{25}H_{28}N_3ClO_5 \cdot C_2H_2O_4$) C, H, N.

Compound 64A: 42% [L = 2-oxo-2-(2,3-dihydro-2-oxobenzoxazol-6-yl)ethyl]; NMR 3.88 (br s, 5 H, CO_2CH_3 and C′-6-$COCH_2$), 7.05–8.10 (m, 8 H, ArH), 8.35 (br s, 1 H, NH); R_f 0.10; oxalate, mp 215–217 °C (C). Anal. ($C_{25}H_{28}N_3ClO_5 \cdot C_2H_2O_4$) C, H, N.

Compound 65B: 32% [L = 2-(2-oxo-2*H*-benzopyran-7-oxy)ethyl]; NMR 3.14 (br m, 4 H, CH_3OCH_2 and NCH_2CH_2O), 6.30 (d, 1 H, C′-3-H), 6.60–7.50 (m, 8 H, ArH), 7.72 (d, 1 H, C′-4-H); R_f 0.58; oxalate, mp 110–113 °C (C). Anal. ($C_{27}H_{32}N_2O_5 \cdot C_2H_2O_4 \cdot 0.5H_2O$) C, H, N.

Compound 66A: 47% [L = (7-methoxy-2-oxo-2*H*-benzopyran-4-yl)methyl]; NMR 3.15 (s, C′-4-CH_2), 3.82 (2s, 6 H, CO_2CH_3 and C′-7-OCH_3), 6.32 (s, 1 H, C′-3-H), 6.86–7.78 (m, 8 H, ArH); R_f 0.68 (40); oxalate, mp 184–186 °C (C). Anal. ($C_{27}H_{30}N_2O_6 \cdot C_2H_2O_4 \cdot 0.5H_2O$) C, H, N.

Compound 67A: 52% [L = (1,4-benzodioxan-2-yl)methyl]; NMR 3.86 (s, 5 H, C′-2, 3 H, and C′-2-CH_2N), 6.85 (s, 4 H, C′-5,6,7,8-H); R_f 0.62; oxalate, mp 213.5–214 °C (D). Anal. ($C_{25}H_{30}N_2O_5 \cdot C_2H_2O_4$) C, H, N.

Compound 67B: 82% [L = (1,4-benzodioxan-2-yl)methyl]; R_f 0.45; oxalate, mp 200–202 °C (C). Anal. ($C_{25}H_{32}N_2O_4 \cdot C_2H_2O_4 \cdot 0.25H_2O$) C, H, N.

Compound 68B: 68% [L = (6-fluoro-1,3-benzodioxan-8-yl)methyl]; NMR 3.43 (s, 5 H, CH_2OCH_3, and C′-8-CH_2N), 4.84 (s, 2 H, C′-4-H), 5.18 (s, 2 H, C′-2-H), 6.46–7.18 (2d, 2 H, C′-5,7-H); R_f 0.64; oxalate, mp 196–197 °C (D). Anal. ($C_{25}H_{31}N_2FO_4 \cdot C_2H_2O_4$) C, H, N.

Compound 69A: 34% [L = 2-(2,3-dihydro-3-oxo-4*H*-1,3-benzothiazin-4-yl)ethyl]; NMR 3.30 (s, 2 H, C′-2-H), 4.02 (t, 2 H, N′-4-CH_2), 7.02–7.62 (m, 9 H, ArH); R_f 0.30 (40); oxalate, mp 215–218.5 °C (D). Anal. ($C_{26}H_{31}N_3O_4S \cdot C_2H_2O_4$) C, H, N.

Compound 70A: 89% [L = 2-(2-methyl-3,4-dihydro-4-oxo-3*H*-quinazolin-3-yl)ethyl]; NMR 2.62 (s, 3 H, C′-2-CH_3), 4.15 (t, 2 H, N′-3-CH_2), 7.45–8.22 (m, 9 H, ArH); R_f 0.62; oxalate, mp 210–211 °C (C). Anal. ($C_{27}H_{32}N_4O_4 \cdot C_2H_2O_4 \cdot 0.5H_2O$) C, H, N.

Compound 70B: 56% [L = 2-(2-methyl-3,4-dihydro-4-oxo-3*H*-quinazolin-3-yl)ethyl]; R_f 0.46; oxalate, mp 214.5–216.5 °C (C). Anal. ($C_{27}H_{34}N_4O_3 \cdot C_2H_2O_4$) C, H, N.

Compound 71A: 85% [L = 2-(1,2,3,4-tetrahydro-2,4-dioxo-3*H*-quinazolin-3-yl)ethyl]; NMR 4.18 (t, 2 H, N′-3-CH_2), 6.96–8.20 (m, 9 H, ArH); R_f 0.31; oxalate, mp 190–193 °C (C). Anal. ($C_{26}H_{30}N_4O_5 \cdot C_2H_2O_4 \cdot 0.5H_2O$) C, H, N.

Compound 72A: 28% [L = 2-(1-ethyl-1,2,3,4-tetrahydro-2,4-dioxo-3*H*-quinazolin-3-yl)ethyl]; R_f 0.56; oxalate, mp 224–228 °C (C). Anal. ($C_{28}H_{34}N_4O_5 \cdot C_2H_2O_4 \cdot 0.5H_2O$) C, H, N.

Compound 72B: 72% [L = 2-(1-ethyl-1,2,3,4-tetrahydro-2,4-dioxo-3*H*-quinazolin-3-yl)ethyl]; NMR 1.30 (t, 3 H, N′-1-CH_2CH_3), 3.90–4.36 (m, 6 H, CH_2OCH_3 and N′-1,3-CH_2), 7.12–7.84 (m, 8 H, ArH), 8.20 (d, 1 H, C′-5-H); R_f 0.50; oxalate, mp 189–190 °C (D). Anal. ($C_{28}H_{36}N_4O_4 \cdot C_2H_2O_4$) C, H, N.

Compound 73A: 28% [L = 2-(1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo-7*H*-purin-7-yl)ethyl]; NMR 3.42 (s, 3 H, N′-3-CH_3), 3.60 (s, 3 H, N′-1-CH_3), 7.60 (s, 1 H, C′-6-H); R_f 0.40; oxalate, mp 194–195 °C (I). Anal. ($C_{25}H_{32}N_6O_5 \cdot C_2H_2O_4$) C, H, N.

Compound 74A: 70% [L = 2-(1,2,3,6-tetrahydro-3,7-dimethyl-2,6-dioxo-1*H*-purin-1-yl)ethyl]; NMR 3.50 (s, 3 H, N′-7-CH_3), 3.75 (s, 3 H, N′-1-CH_3), 4.00 (t, 2 H, N′-3-CH_2), 7.52 (s, 1 H, C′-6-H); R_f 0.45; oxalate, mp 95 °C (C). Anal. ($C_{25}H_{32}N_6O_5 \cdot C_2H_2O_4 \cdot 1.5H_2O$) C, H, N.

Compound 75B: 71% [L = 2-[2-oxobenz[*c*,*d*]indolyl]ethyl]; NMR 3.87–4.20 (m, 4 H, CH_2OCH_3 and N′-CH_2), 6.76–8.10 (m, 11 H, ArH); R_f 0.40 (40); oxalate, mp 95 °C (C). Anal. ($C_{29}H_{33}N_3O_3 \cdot C_2H_2O_4 \cdot 0.5H_2O$) C, H, N.

Compound 76A: 44% [L = 2-[1,1-dioxo-2*H*-naphth[1,8-*c*-*d*]isothiazol-2-yl]ethyl]; NMR 3.42–4.16 (m, 5 H, CO_2CH_3 and N′-CH_2), 6.62–8.16 (m, 11 H, ArH); R_f 0.64; oxalate, mp 212–214 °C (C). Anal. ($C_{28}H_{31}N_3O_5S \cdot C_2H_2O_4$) C, H, N.

Compound 77A: 62% [L = 2-[*N*-(1,8-naphthylenedicarboxamido]ethyl]; NMR 4.30 (t, 2 H, N′-CH_2), 7.66–8.78 (m, 6 H, naphthalene ArH); R_f 0.57; oxalate, mp 140–143 °C (E). Anal. ($C_{28}H_{31}N_3O_5S \cdot C_2H_2O_4 \cdot H_2O$) C, H, N.

Pharmacological Methods. In Vivo. Analgesic. A. 55 °C Mouse Hot Plate (MHP).[57] The hot-plate assay utilized

nonfasted male mice (Swiss-Webster) weighing between 18 and 22 g. The surface of the hot-plate apparatus was maintained at 55 ± 0.5° C. To determine the percentage of maximum pharmacological effect (MPE) using the MHP assay, vehicle (saline) or drug solution (10 mL/kg) was injected into the lateral tail vein of groups of 10 mice and placed on the hot plate after 1 min. An initial dose of 1 mg/kg of compound was administered. If antinociception was observed in 100% of the mice, then lower dosing was continued until an ED_{50} was generated. If antinociception was not observed in 100% of the mice, then 5 mg/kg was administered. In addition to analgesia, side effects were noted. These were chiefly categorized as rigidity, sedation, respiratory depression, tremors, convulsions, and cyanosis. For each experiment, control latency times were determined in 10 mice and treatment latency times determined in additional groups after each dose of compound. The response latency was the time between the initial contact on the hot surface and the first paw-lick response. Animals were removed from the hot plate immediately after a response or until the cut-off time of 30 s was reached. Antinociceptive effect was defined as a doubling of the latency time to paw-lick over control times.

The ED_{50} and 95% confidence limits were calculated with use of a standard computer program of the method of Litchfield and Wilcoxon[58] fitted to a minicomputer.[59] Calculation of the ED_{50} (95% confidence limits) was corrected for base content of the salts.

Duration of Analgesia. Two times the ED_{50} was administered to 10 mice and the hot-plate latencies were determined at various times after injection in the lateral tail vein. The mean MPE was calculated for each time period, and a time effect curve was generated.

$$\% \text{ MPE} = (\text{test time} - \text{control time}/30 \text{ s} - \text{control time})100$$

A test compound was defined to be short acting if the duration of action to 50% MPE was less than 6 min, intermediate duration was 6.1–15 min, and long acting was a duration greater than 15.1 min.

B. 55 °C Rat Hot Plate. This assay was performed similarly to the above using six male Sprague-Dawley rats weighing between 300 and 400 g.

C. Rat Tail Flick. A modification of the D'Amour–Smith tail-flick method was employed in the evaluation of analgesic activity.[60] Male Sprague-Dawley rats weighing between 150 and 200 g were given thermal stimulus challenges 5 min before and 1 min after iv administration of the test compounds. Analgesia was defined by post-injection tail-flick latencies greater than or equal to twice pre-injection latencies. Groups of at least six animals were used in the determination of ED_{50} values, which were calculated in a manner similar to that described above.

D. Intrathecal Experiments. Intrathecal preparation and administration of test compounds were performed according to previously published procedures.[61,62]

Screen for Primary Overt Effects for Hypnotics–Analgesics in the Rat. Primary detrimental effects most often associated with hypnotics–analgesics in this species model have been auricular cyanosis, presumably due to increased blood CO_2 levels and another indicator of respiratory depression, trunk and limb skeletal muscle rigidity, decrease or loss of reflexes to touch and sound, hypothermia, miosis, and decreased heart rate. Therapeutic potential for anesthesia (loss of righting) and for analgesia, which is determined by the response to the paw pinch, an intense nociceptive stimulus, are sought in this screen. Six Sprague-Dawley rats (230–290 g) are used. Immediately following iv drug administration, the animal is removed from the restrainer and observed along with a control (i.e., the next test animal) for 20 min. Righting is lost when the animal remains supine for at least 30 s. Analgesia is present when there is no vocalization or overt movements in response to supramaximal paw pinch delivered with a pair of Kelly clamps. The ED_{50} for analgesia was determined by linear regression. The confidence limits were determined as previously described.[63] Core temperature is obtained rectally prior to and during the 5 min post-drug period and the difference is recorded. Other primary overt effects are scored from 0 to ±3 (0 = normal, 1 = mild, 2 = moderate, 3 = marked) and recorded at 5-min intervals for 30 min.

Rat Rotorod Test for Recovery of Motor Coordination. This is a modification of the method described by Kinnard and Carr.[64] Five male Sprague-Dawley rats are trained to maintain their balance for 90 s on a rotorod revolving at a constant 10 rpm. The animals are allowed to rest for 5 min, then are retrained to the 90 s criterion. Following an additional 5 min the ED_{100} for loss of righting of the test drug is injected intravenously. When the animals regain their righting they are placed on the rotorod 0, 90, and 180 s later and tested for 90 s at each interval. However, animals that stayed on the rotorod for the full 90 s are not tested further. The durations for maintaining balance are averaged and the number of animals tested and meeting the 90 s criterion are recorded for each time interval. The rotorod data was compared first by the Kruskall–Wallis H statistic for group difference and then the Mann–Whitney U test for individual differences followed by calculation of the rotorod index (ROI).[65]

Computerized Screen for Recovery of Locomotor Activity. This method was designed to measure the recovery of various parameters of motor activity following loss of righting (LOR) induced by the administration of hypnotic–analgesic drugs.[66]

Male Sprague-Dawley rats are maintained as previously described in the primary overt effects screen and tested for LOR with one of the following doses (N = 6/dose per drug): ED0, ED50, ED100, or ED150. The ED0 and ED100 are determined experimentally, whereas the ED50 and ED150 are calculated from linear regression analysis. Animals are injected iv and the duration of LOR is recorded. They are placed in the activity monitors as soon as righting is regained. Control rats (N = 6/drug), treated in a similar manner, are injected with vehicle and tested along with drugged animals. Data for horizontal, vertical, and stereotypic parameters of motor activity are collected automatically and recorded every minute for 30 min. From these raw data, means, standard deviations, and percent control are calculated for each time interval using RS-1 statistical procedures. Mean recovery times for each behavioral parameter at each dose and a "general recovery index" (GRI) consisting of a single mean of all behavioral parameters across all four doses are then calculated.

Cardiorespiratory Measurements in the Conscious Freely Moving Rat.[67] In the method described direct recordings of arterial blood pressure, heart rate, electrocardiograph (ECG), arterial blood gases (CO_2 and O_2), and pH were used. Male Sprague-Dawley rats about 300–400 g were allowed free access to food and water and housed five per cage in a vivarium with a light–dark cycle of 12 h. Prior to testing (24 h) the animals were chronically implanted with heparinized catheters in the left internal jugular vein and right common carotid artery under 2% isoflurane anesthesia. The catheters were exteriorized through the nap of the neck and secured with surgical silk. Two braided strands of aluminum wire were threaded subcutaneously on either

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side of the chest in the shoulder area for the ECG recording. On the day of the experiment, the catheters were flushed with heparinized saline and the arterial catheter was connected to a P-50 pressure transducer. The pressure signal was displayed as systolic, diastolic, and mean blood pressure on a physiological recorder. Heart rate was recorded from the pulse pressure signal and channeled through a tachograph for recording. Two standard limb leads were connected to the subcutaneous electrodes for lead(II) ECG recording through a 7P4G Grass preamplifier. Control blood samples were taken prior to the test drug administration for measurement of arterial blood gases, i.e., each animal served as its own control. Therapeutic indices of a compound for the rat tail-flick, hot-plate, and loss-of-righting tests were determined by calculating the ratio of the dose producing a 50% increase in arterial blood carbon dioxide levels to the ED_{50} in the test.

Cardiorespiratory Measurements in the Isoflurane Anesthetized Rat. This method is used to determine the cardiovascular and respiratory measurement of the action of a drug in the absence of any significant behavior normally accompanied in conscious freely moving rats. These experiments are not unlike the "operating room" setting.

Anesthesia was induced for 1 min by means of a vaporizer (Ohmeda Fortec) with 3% isoflurane in 100% O_2. A small midline incision was made along the ventral surface of the neck to expose the trachea. In between the third and fourth cartilage ring, caudal to the larynx, an incision was made with a cautery, 2–3-mm wide and maintained at 1.8% (1.25 minimum alveolar concentration). A P-50 transducer was connected to a PE-50 cannula placed in the left femoral artery for direct measurement of arterial blood pressure and heart rate. For the intravenous administration of drugs, a PE-50 catheter was threaded into the left femoral vein. Blood pressure and heart rate were recorded off instruments as described in the preceding method. Respiration was monitored through a pneumotachograph connected to the tracheal cannula and intergrated through a recorder. An 18-gauge needle-tipped catheter was placed in the tracheal cannula to continuously sample end-tidal volume CO_2 concentrations (150 mL/min, CO_2 monitor). The control values of blood pressure and heart rate were recorded for a minimum period of 15 min to insure stable baseline recordings before drugs were injected. Drugs were injected into the femoral vein through the exteriorized venous cannula, connected to a three-way stopcock via a 20-cm length of PE-50 tubing filled with 0.9% saline. The injections were made slowly (10–15 s) and subsequently flushed with 0.4 mL of 0.9% saline. The above measurements were made except for monitoring the isoflurane concentration via the anesthetic agent monitor. Dose–response curves were constructed using any of the physiological parameters as the y values and time as the x values. Therapeutic indices of a compound for depression of blood pressure, heart rate, and respiration for the rat tail-flick and hot-plate tests were determined by calculating the ratio of the side-effect dose producing a 50% response from control (as determined graphically) to the measured ED_{50} in the tail-flick and hot-plate tests.

In Vitro. Opioid Receptor Binding. Modifications of previously published procedures for assay of ^{3}H-[D-Ala^2, N-Me-Phe^4, Gly^5-OH] (DAGO) displacement for determination of μ, of ^{3}H-ethylketocyclazocine (EKC) for κ, and of ^{3}H-[D-Pen^2, D-Pen^5] (DPDPE) for δ opioid receptor binding were employed.[68-70]

Male guinea pigs (Hartley, 300–350g) were sacrificed by decapitation and the brains rapidly removed. After removing the brainstem and cerebellum, the remaining brain tissue was homogenized in 20 volumes of cold Tris, pH 7.4. The homogenates were centrifuged at 4000g for 15 min at 5 °C and the supernatants decanted. The pellets were resuspended in the original volume of Tris and homogenized, and the supernatants were decanted. The pellets were again in the same volume of Tris and the homogenates incubated at 37 °C for 45 min to remove endogenous opioids. The homogenates were centrifuged a third time and the supernatants decanted. The pellets were stored at −50 °C until the day of assay. Briefly, 0.25 mL of homogenate (ca. 10 mg of the original weight of tissue) was incubated with either 0.2 nM [^{3}H]DAGO, 2.0 nM [^{3}H]EKC or 2.0 nM [^{3}H]DPDPE (final concentrations) in a final volume of 0.5 mL. Nonspecific binding was defined in the presence of 10 μM levorphanol. DAGO (100 nM final concentration) and [D-Ala^2, D-Leu5]-enkephalin (DADLE, 100 nM final concentration) were added to the [^{3}H]EKC assay to mask μ- and δ-binding sites, respectively. All assays were carried out at room temperature; [^{3}H]DAGO and [^{3}H]DPDPE for 40 min and [^{3}H]EKC for 2 h. Test compounds (0.1 mL) were added to incubates where appropriate. Bound ligand was separated from unbound ligand by filtration and quantitated by using liquid scintillation spectrophotometry. IC_{50} values were calculated for all test compounds.

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